The Misdiagnosis Casebook in Clinical Medicine

A Case-Based Guide

Hassaan Tohid
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Editors

Springer

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A L G r a w a n y

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Editors

Bilal Haider Malik
Associate Editor

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Editors
Hassaan Tohid
California Institute of Behavioral
Neurosciences and Psychology LLC
Fairfield, CA, USA

Howard Maibach
University of California - San Francisco
San Francisco, CA, USA

Larry G. Baratta
Dean of Medical Education
California Institute of Behavioral
Neurosciences and Psychology LLC
Fairfield, CA, USA

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I dedicate this book to my wife Sidra and daughters Ayla & Inara for their unconditional support and love.

Dr. Hassaan Tohid

I dedicate this book to my mother Mrs. Anne Marie Baratta and my Tita Ms. Luz Evangelista who always offer their guidance, counsel, wisdom, and unwavering love.

Dr. Larry G. Baratta

We dedicate this book to Dr. Howard I. Maibach, who is an esteemed mentor and adviser to whom we are eternally grateful.

Dr. Hassaan Tohid
Dr. Larry G. Baratta

Preface

"There is still an eraser at the end of my pencil".

The editors felt compelled to journey down a less traveled road in medicine to address an esoteric topic where clinicians are taciturn, which is a misdiagnosis. A misdiagnosis can result in grave consequences to the patient, their family, and the clinician. The book addresses a vital issue by balancing practicing defensive versus dangerous medicine. It is the first book of its kind to take a modular approach that covers all of the significant fields of medicine to offer the reader a wholesome representation. Each chapter contains evidence-based knowledge carefully chosen to depict intricate details of typical manifestations of rare and common diseases. We have included an exceptional and dedicated chapter addressing misdiagnosis's legal perspective.

The editors want to underscore a critical message that we are human beings prone to making mistakes and errors. Alexander Pope, in 1711 aptly said, "To err is human." His words have resonated throughout history, identifying the inherent attribute of being human, that is, prone to making mistakes. One of the dividends of striving for human perfection is recognizing one's mistakes, accepting and correcting them, and preventing them from repeating during one's life journey. This is why we wanted to write this book to mitigate errors in diagnosis.

We also intend that this book will serve clinicians, practitioners, and medical students who face the daily challenges of diagnosing complex clinical cases.

The ultimate goal is always for the patient's benefit and the preservation of their well-being.

The editors sincerely thank Springer Nature Publishing Co. for supporting this writing journey and making this book a reality. We are also grateful to have assembled a talented, dynamic, and passionate research and writing team represented by esteemed faculty members and medical students who served as chapter authors.

We hope you, as a reader, will enjoy this book and use it while practicing and providing good medicine.

Fairfield, CA — Hassaan Tohid
Fairfield, CA — Larry G. Baratta
San Francisco, CA — Howard Maibach

Contents

Contributors

Akhil Ansary St. Martinus University Faculty of Medicine, Willemstad, Curacao

Fatima Anwer, MD PGY-1, Internal Medicine, Harlem Hospital, New York, NY, USA

Anthony V. Baratta Jr., MD Gastroenterology Associates of Rochester, Rochester, NY, USA

John Michael Baratta, MD, MBA Department of Physical Medicine and Rehabilitation, Medical Director of Stroke Rehabilitation, University of North Carolina School of Medicine, Chapel Hill, NC, USA

Adedamola Bello, MD St. Martinus University Faculty of Medicine, Willemstad, Curacao

Pushpa Bhatt, MBBS, DDV, MPH St. Martinus University Faculty of Medicine, Willemstad, Curacao

Ivan Cancarevic, MD Icahn School of Medicine at Mount Sinai, New York, NY, USA

Jose Luis Ferrero, MD St. Martinus University Faculty of Medicine, Willemstad, Curacao

Allison Foster, MD Icahn School of Medicine at Mount Sinai, New York, NY, USA

Kosha Geslaghi St. Martinus University Faculty of Medicine, Willemstad, Curacao

Mohammad J. Ghosheh, MBBS Al-Faisal University College of Medicine, Riyadh, Saudi Arabia

Momina Shahid Hameed, MBBS, MRCGP Partner GP, Strathmore Medical Practice, Wrexham, Wales

Junaid Hassan, MBBS, FCPS M. Islam Medical & Dental College, Gujranwala, Pakistan

Department of Surgery, M. Islam Medical & Dental College, Gujranwala, Pakistan

Katarzyna Karpinska-Leydier, MD Internal Medicine, Florida State University - Cape Coral Hospital, Cape Coral, FL, USA

Sirving Keli, MD, PhD St. Martinus University Faculty of Medicine, Willemstad, Curacao

Abdulla Khan St. Martinus University Faculty of Medicine, Willemstad, Curacao

Safeera Khan, MBBS California Institute of Behavioral Neurosciences and Psychology, Fairfield, CA, USA

Arseni Khorochkov, MD California Institute of Behavioral Neurosciences and Psychology, Fairfield, CA, USA

Brandon Krout, MD St. Martinus University Faculty of Medicine, Willemstad, Curacao

Bilal Haider Malik, MBBS, MRCP Dermatology, Betsi Cadwaladr University Health Board, Mold, Wales

Mohammed Mohammed, MBBS, MD St. Martinus University Faculty of Medicine, Willemstad, Curacao

Revathi Myneni, MD St. Martinus University Faculty of Medicine, Willemstad, Curacao

Aemil Palm St. Martinus University Faculty of Medicine, Willemstad, Curacao

James M. Ringer, Esq. Meister Seelig & Fein LLP, New York, NY, USA

Carla Rodriguez, MD St. Martinus University Faculty of Medicine, Willemstad, Curacao

Rupanshu St. Martinus University Faculty of Medicine, Willemstad, Curacao

Jonathan Seok St. Martinus University Faculty of Medicine, Willemstad, Curacao

Prakrut Nishamanish Sethi St. Martinus University Faculty of Medicine, Willemstad, Curacao

Srushti Shahi St. Martinus University Faculty of Medicine, Willemstad, Curacao

Maria Mohammed Javed Shaikh, MD St. Martinus University Faculty of Medicine, Willemstad, Curacao

Akshay K. Shetty St. Martinus University Faculty of Medicine, Willemstad, Curacao

Shashwat Shrivastava, MD St. Martinus University Faculty of Medicine, Willemstad, Curacao

Shitij Shrivastava, MD PGY-1, Internal Medicine, BronxCare Health System, Bronx, NY, USA

St. Martinus University Faculty of Medicine, Willemstad, Curacao

Danna Soria, MD, MSc St. Martinus University Faculty of Medicine, Willemstad, Curacao

Hassaan Tohid, MBBS, SUDCC, CCATP California Institute of Behavioral Neurosciences and Psychology, Fairfield, CA, USA

Alluri Vasu, MD, Dip Card St. Martinus University Faculty of Medicine, Willemstad, Curacao

Sathish Venugopal, MD St. Martinus University Faculty of Medicine, Willemstad, Curacao

Ravi Vintha, MBBS, MD St. Martinus University Faculty of Medicine, Willemstad, Curacao

Part I
Allergy and Immunology

Chapter 1
Allergic Bronchopulmonary Aspergillosis Masquerading as Recurrent Bacterial Pneumonia

Katarzyna Karpinska-Leydier

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Assess the overlapping features between allergic bronchopulmonary aspergillosis and the two most common differentials: bacterial pneumonia and pulmonary tuberculosis.
2. Recall allergic bronchopulmonary aspergillosis as a differential for common presenting pulmonary symptoms.
3. Choose appropriate testing to best manage patients presenting with respiratory complaints regardless of geographic region.
4. Minimize the time needed for accurate diagnosis and treatment of allergic bronchopulmonary aspergillosis.
5. Apply the knowledge gained from this and similar cases where appropriate in future clinical settings.

Introduction

The clinical presentation of allergic bronchopulmonary aspergillosis (ABPA) is indistinguishable from other infectious pulmonary conditions [1]. *Aspergillus fumigatus* through airborne conidia is the most common pathogen, although colonization is dependent on the host's immune system competence [2]. Similarly, there is a distinction between colonization, the benign isolation of *Aspergillus* from the lower respiratory tract, and disease as per clinical judgment [3]. Interactions between the host and fungus are unfavorable in conditions where patients are

K. Karpinska-Leydier (✉)
Internal Medicine, Florida State University - Cape Coral Hospital, Cape Coral, FL, USA

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immunocompromised, critically ill, on steroids, or with underlying lung conditions [3]. Furthermore, ABPA is relatively uncommon compared with bacterial pneumonia and pulmonary tuberculosis (TB), depending on the geographic region [4].

Cystic bronchiectasis and mucus plugs are frequently overlapping features between ABPA and cavitating pulmonary TB, which are seen on chest computed tomography (CT.) [4, 5] Asthma and cystic fibrosis (CF) patients are predisposed to ABPA if *Aspergillus* exposure occurs and results in hypersensitivity to *Aspergillus* antigens, involving eosinophilic infiltration of the bronchial wall, mucoid impaction, or granulomatous inflammation [4, 6]. Patients with asthma and ABPA often have hemoptysis, fever, malaise, and eosinophilia, which mimic TB; it is common for misdiagnosed ABPA patients to receive anti-TB therapy even with smear-negative testing [4, 6, 7]. Productive cough and a suggestive chest X-ray (CXR) are common manifestations of bacterial pneumonia and may show temporary clinical improvement with antibiotic therapy; however, suspicion for ABPA and evaluation for eosinophilia are needed to avoid potential misdiagnosis [1].

Patients with an extensive history of asthma complicated by misdiagnosis and poor respiratory function are more likely to exhibit acute exacerbations [8]. However, treatment with glucocorticoids and antifungal agents may prolong event-free periods [8]. Contributing factors to the misdiagnosis of ABPA include atypical presentations, interference of tumor markers in diagnostic testing, misunderstandings of screening indicators, and significant overlap with other pulmonary pathologies [9]. The high misdiagnosis rate of ABPA and lack of standardized treatment contribute to diagnostic delays and suboptimal prognosis [10].

Clinical Case Presentation

A man aged 74 years sought medical attention for a cough and was found to have a chest X-ray (CXR) showing right perihilar airspace opacities 4 months ago. His past medical history includes hypertension, allergic rhinitis, and diabetes mellitus. He is a nonsmoker and denies alcohol. He was treated for bacterial pneumonia, improving his cough and CXR by day 30 and almost normal by 3 months. Successively, he was admitted due to a 10-day history of productive cough with viscous, white-cloudy sputum. His initial presentation in the emergency department was with dyspnea and fatigue. Physical exam was significant for tachycardia, respiratory rate of 28/min, temperature of 37 °C, and peripheral capillary oxygen saturation (Sp2) of 88% breathing room air. A pulmonary exam revealed scattered rhonchi and the use of accessory respiratory muscles. On workup, eosinophilia was 3400/mm3, and blood glucose was 336 mg/ml. Bilateral perihilar airspace opacities were present on admission. Serologic tests and direct fecal smear ruled out parasitic infections on day +1. Acid-fast bacilli (AFB) testing was negative in three consecutive sputum samples; however, *Klebsiella pneumoniae* (2.106 cfu/ml) was positive on hospital day +3. He started antibiotic therapy for the presumed diagnosis of bacterial pneumonia. Evaluation of the total serum IgE level revealed 5110 IU/m, and serum

level-specific IgG to *Aspergillus* was 1000 U/ml. Skin prick testing with a standard *Aspergillus* mix was negative despite the elevated serum IgE specific to *Aspergillus* spp. (38 LU). On hospital day +6, high-resolution contrast-enhanced chest computed tomography (CT) showed scattered nodules and halo signs without bronchiectasis. However, mucus plugs occluding the central bronchi contained infiltrated eosinophils on bronchoscopy. 30% of the cell count was eosinophil on bronchoalveolar lavage (BAL). AFB testing of BAL fluid was negative, but it was positive for *Aspergillus* sp.; therefore, serologic allergic bronchopulmonary aspergillosis (ABPA-S) was confirmed.

Further spirometry showed respiratory function compatible with asthma. The patient was managed with inhaled corticosteroids (ICS) using a combination of salmeterol/fluticasone 25/250 with a dose of fluticasone of 1000 micrograms daily. Within 1 month, the eosinophil count was 206/mm3, and his CXR showed the disappearance of air space opacities, achieving remission at 1 year.

Differential Diagnosis

1. Allergic Bronchopulmonary Aspergillosis – ABPA is a syndrome caused by a type 1 hypersensitivity to *Aspergillus* species. Features include asthma, eosinophilia, bronchiectasis, and recurrent bronchopulmonary infiltrates. Patients with an atopic history or lung disease are at increased risk, particularly those afflicted with asthma, hyper-IgE syndrome, or cystic fibrosis. Patients may present with chronic asthma, productive cough, hemoptysis, or fatigue. Chest CT is necessary to assess for central bronchiectasis or mucoid impaction. Skin prick testing is helpful for diagnosis of ABPA; however, it may be negative in serologic ABPA, and further lab testing for total and specific IGE and eosinophil count is necessary.
2. Bacterial Pneumonia – Bacterial pneumonia is a pulmonary parenchymal infection of the lower respiratory tract. Patients at risk may have an underlying lung disease such as COPD or other compromising conditions, including smoking, alcohol consumption, aspiration, or diabetes. The most common implicated bacterial organism is *Streptococcus pneumoniae*. Presenting symptoms may include fatigue, dyspnea, pleuritic chest pain, and cough, which may be either productive or nonproductive. Diagnosis is supported by imaging or sputum culture. Empiric antibiotics are first-line therapy.
3. Pulmonary Tuberculosis – *Mycobacterium tuberculosis* is the agent responsible for pulmonary tuberculosis. Patients at risk are in close contact with Tb patients or patients with immunosuppression. Presenting symptoms are productive or nonproductive cough, hemoptysis, fever, anorexia, night sweats, and weight loss. Chest imaging is useful in identifying lobar consolidation, but cavitary lesions or hilar adenopathy may also be seen. Sputum is positive for acid-fast bacilli. Treatment is with a regimen of rifampin, isoniazid, and ethambutol.
4. Bronchial Asthma – Bronchial asthma is characterized by inflammation causing a reversible and intermittent obstructive respiratory disease of the small airways.

It is most common in children and patients with a history of atopy, family history, obesity, or smoking. Presenting symptoms include wheezing, productive cough, chest tightness, and dyspnea. Chest imaging may be normal, but pulmonary function tests are the mainstay of diagnosis. First-line treatment is with inhaled beta-2 agonists.

What Was Misdiagnosed in This Case and Why?

Serologic allergic bronchopulmonary aspergillosis (ABPA-S) was misdiagnosed as recurrent bacterial pneumonia after a nonspecific clinical presentation and sequelae before a bronchoalveolar lavage confirmed the presence of *Aspergillus*.

Discussion

Nonspecific clinical presentations, such as a productive cough with pulmonary infiltrates on imaging, often obtain an initial diagnosis based on disease prevalence within a population. Cases of ABPA are considered rare and often mistaken for either bacterial pneumonia or pulmonary TB [1]. The estimated prevalence of ABPA in asthma and CF patients is 1–2% and 2–9%, respectively; however, rarer cases may occur in lung transplant recipients or other coexisting disorders, including hyper-IgE syndrome and chronic granulomatous disease [11]. ABPA is the leading cause of pulmonary fungal pathology but maintains a high rate of misdiagnosis [11]. However, diagnostic algorithms targeted to the most accurate and sensitive diagnostic criteria could alter the prevalence of ABPA; nevertheless, a simple periodic screening in patients with asthma for skin prick testing of *Aspergillus*-specific IgE may be sufficient in some instances [11–13].

The chosen case describes a patient diagnosed with bacterial pneumonia [1]. Antibiotic treatment resulted in an initial improvement followed by recurrence of productive cough and worsening condition; this is typical in the misdiagnosis of allergic bronchopulmonary aspergillosis (ABPA) [1]. Eosinophilia was confirmed; however, *Klebsiella pneumoniae,* isolated from sputum, appeared to confirm the initial diagnosis, and the patient continued with antibiotic treatment [1]. Despite a negative skin prick test, total serum IgE and specific IgG to *Aspergillus* were positive [1]. However, it was not until a bronchoscopy showing mucous plugging and culture from bronchoalveolar lavage (BAL) that serologic ABPA (ABPA-S) was confirmed [1].

It is common for patients in TB endemic areas to undergo multiple courses of TB treatment regimens even if acid-fast bacteria testing is negative [14]. A study in Nepal showed that 40% of ABPA patients are misdiagnosed and treated for TB despite eosinophilia and high total serum IgE [15]. In some instances, a high total IgE and positive anti-*Aspergillus* IgE and IgG antibodies may be found but not

recognized as clinically significant due to the low prevalence of ABPA [14]. Patients may present with mediastinal lymphadenopathy suggesting TB; however, ABPA should be considered and not ruled out based on this finding. Further overlap of features between ABPA and TB may include miliary mottling. In these settings, subtleties of eosinophilia should prompt vigilance in ABPA investigation [16]. Among patients with chronic or idiopathic bronchiectasis, many are sensitized to *Aspergillus fumigatus* or have a sputum culture supporting ABPA [17]. An allergic background, most commonly with asthma, is a predisposing factor for ABPA, although not always necessary [10].

Antibiotic therapy may lead to an initially favorable clinical and radiologic response, further masking a fungal cause, and the presence of a bacterial co-infection, as seen in this case, may further distract from diagnostic accuracy. This patient was ultimately treated with high-dose inhaled steroids; relevant medical history precluded the use of systemic corticosteroids. The patient had significant clinical improvement with remission of the CXR lesions and a normal eosinophil count [1]. ABPA is a hypersensitivity reaction more common in atopic patients or those with underlying lung pathology such as CF; however, patients without a history of asthma are susceptible [18]. Skin prick testing to *A. fumigatus* has a sensitivity of 90%, but the demonstration of specific IgE has a sensitivity of 100% [19]. In this case, the skin prick testing was negative [1]. A lack of standardized testing and improper technique regarding skin prick testing may contribute to missed clinical recognition [18]. Overlapping features and low prevalence contribute to the easy misdiagnosis of ABPA. Patients with asthma and pulmonary CF should be under careful consideration for ABPA, especially with new-onset wheezing, sputum, fleeting infiltrations, or elevated eosinophils [20].

Conclusion

ABPA is an allergic hypersensitivity to a species of fungus, most commonly *Aspergillus fumigatus* which is generally considered rare but most commonly occurs in patients with asthma or CF. Many of the clinical features of ABPA overlap with bronchopulmonary pneumonia and TB. The rarity of ABPA and ambiguity of clinical presentation contribute to widespread misdiagnosis. Close attention to eosinophilia, specific and total IgE, and skin prick testing standardization are proposed to improve the accurate and early diagnosis of ABPA. High-risk patients with a history of allergy or asthma, immunocompromised, or structural lung pathologies require particular vigilance for ABPA in the presence of *Aspergillus* sensitization and new-onset or worsening pulmonary symptoms.

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Chapter 2
Angioedema Bowel Blockade: The Misdiagnosis of Hereditary Angioedema as a Rare Cause of Small Bowel Obstruction

Arseni Khorochkov

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Raise clinical awareness of hereditary angioedema.
2. Familiarize clinicians with the history and presentation of hereditary angioedema.
3. Recommend the use of the "Hereditary AngioEdema Rapid Triage" (HAE-RT) tool for assessing angioedema.
4. Suggest the addition of C1-INH and C4 levels to the lab analysis in cases of acute abdominal pain or angioedema swelling with no discernible cause.
5. Appropriately manage patients with HAE to reduce the need for unnecessary procedures and improve the overall patient quality of life.
6. Apply the knowledge gained from this case presentation to identify and treat patients with HAE.

Introduction

Acute abdominal pain can have a wide array of differentials. In the case of bowel obstruction caused by hereditary angioedema (HAE), it easily can be misdiagnosed as a more common disorder such as gastroenteritis or acute appendicitis [1–6].

Hereditary angioedema (HAE) is an autosomal dominant disorder characterized by the deficiency or dysfunction of complement 1 (C1) inhibitor (C1-INH) [2, 7–10]. This can eventually lead to episodes of bradykinin-induced non-pitting angioedema of subcutaneous and submucosal tissues [7]. In the case of intestinal submucosal angioedema, it can lead to obstruction of the bowel lumen and

A. Khorochkov (✉)
California Institute of Behavioral Neurosciences and Psychology, Fairfield, CA, USA

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bradykinin-mediated acute abdominal pain that can be easily misdiagnosed as various other more common conditions affecting the abdomen [2, 3]. Due to the eclectic nature of the HAE episodes, symptoms can have a wide array of differentials [1, 2]. Physicians unfamiliar with HAE or the patient's medical history may then proceed to treat the patient improperly and may subject them to unnecessary surgical procedures such as appendectomy, exploratory laparotomy, or hysterectomy [2, 4, 8, 11]. The angioedema of HAE can occur in the subcutaneous regions of the face, upper and lower extremities, and genitalia, and the submucosa commonly involved is the respiratory and gastrointestinal tracts. Although painful abdominal manifestations are the most common, it is essential to note that in the respiratory tract, laryngeal swelling may occur and is an emergency as it can be fatal due to asphyxiation [7, 8, 11]. These angioedema episodes can be triggered by physical stressors (e.g., trauma, infection, surgical procedures, etc.) and emotional stressors [11, 12].

Other known triggers include certain medications and hormonal changes; however, episodes can also be triggered idiopathically [11, 12]. If left untreated, the swelling can usually last up to 5 days before beginning to resolve [7]. Since this is bradykinin-mediated angioedema, treatment typically involves antagonism of bradykinin receptors or reduction of bradykinin production [7, 13]. In the clinical setting, angioedema is commonly caused by the mast cell-mediated type and, as such, is treated with antihistamines, glucocorticoids, and epinephrine [3, 13]. However, these treatments are ineffective in the treatment of the bradykinin variant [3, 13].

Clinical Case Presentation

In this case, a 52-year-old man presented to the surgery department with a 2-day history of acute abdominal pain. The pain was gradual and located in the right upper quadrant (RUQ), epigastric, and central abdominal regions. The patient reported three episodes of vomiting the day before presenting and constipation and lack of flatus.

The patient's medical history includes hereditary angioedema (HAE), an open appendectomy in his youth, and hypercholesterolemia. His family history includes HAE and myocardial infarction on his paternal side. His current medications are danazol, a mild androgen as prophylaxis for his HAE, and atorvastatin for hypercholesterolemia.

Upon examination, the patient was alert, oriented, afebrile, and normotensive. Tenderness was present in the RUQ, epigastric, and paraumbilical regions. Bowel sounds were decreased, and Murphy's sign was negative. The patient's urinalysis showed a minor elevation in amylase (938 U/L) and C-reactive protein (17.3 mg/L). His complete blood count (CBC), liver function test (LFT), electrolytes, and urea levels were normal. The chest X-ray was noncontributory, and the abdominal X-ray showed the presence of air-fluid level and a visible jejunal loop. A contrast

computed tomography (CT) scan of the abdomen and pelvis indicated proximal and mid-small bowel obstruction, circumferential thickening with edema of the distal ileum, and sigmoid diverticulosis, but no signs of diverticulitis. There was a modest amount of free fluid in the abdomen and pelvis but no signs of free air. The initial differential diagnoses pointed towards acute pancreatitis or acute cholecystitis and bowel obstructions due to adhesion secondary to appendectomy. However, after the appropriate work-up, it was determined that the obstruction was caused by angioedema of the small bowel. The patient was treated with C1 esterase inhibitors, and after 24 h, a repeat abdominal and pelvic CT showed complete resolution of the obstruction and free fluid levels. Following successful treatment, the patient admitted to a history of previous episodes of similar but mild abdominal pain that resolved without intervention. During his gastroenterology follow-up appointment, the patient underwent an esophagogastroduodenoscopy and a colonoscopy to rule out other conditions such as Crohn's disease or malignancy and was found to have chronic gastritis. He also followed up with an immunologist for further management of his HAE. His final diagnosis was small bowel obstruction due to HAE and chronic gastritis.

Table of Lab Results for HAE Case

Laboratory Parameters	Results	Reference Range
Urine		
Amylase	938 U/L	1-17 U/hr.
Blood		
Hemoglobin (Hb)	16.6 g/dL	14-18 g/dL
White Blood Cell (WBC)	10.8 x 10^9/L	4.0-11.0 x 10^9/L
Alanine Aminotransferase (ALT)	Normal	10-40 U/L
Aspartate Aminotransferase (AST)	Normal	10-40 U/L
Urea	Normal	8-20 mg/dL
C-Reactive Protein	1.73 mg/dL	≤0.8 mg/dL

Differential Diagnosis

1. Acute pancreatitis – The patient presented with a 2-day history of progressively worsening abdominal pain as well as nausea and vomiting.
2. Acute cholecystitis – The patient presented with RUQ, epigastric, and central abdominal pain as well as nausea and vomiting.
3. Small bowel obstruction – Secondary to adhesions from a previous appendectomy, decreased bowel sounds.

4. Ischemic bowel – A 2-day history of abdominal pain with decreased bowel sounds.
5. Diverticulosis – A history of abdominal pain, nausea, vomiting, abdominal distension, and constipation.
6. Renal colic – Right-sided abdominal pain with episodes of nausea and vomiting.
7. Gastritis – The patient presented with a 2-day history of progressively worsening abdominal pain as well as nausea and vomiting.
8. Crohn's disease – A history of abdominal pain, nausea, vomiting, and constipation.

What Was Misdiagnosed in This Case and Why?

This case was misdiagnosed due to the symptomatically nonspecific disease presentation and the lack of physician familiarity with hereditary angioedema.

Discussion

In the case, a 52-year-old man presented with a 2-day history of right upper quadrant pain combined with episodes of nausea and vomiting. Despite the patient's known history of HAE, the initial differentials included acute pancreatitis and acute cholecystitis due to the location of the pain. Bowel obstruction due to adhesions from an appendectomy was also considered. After further investigation, it was eventually determined to be intestinal obstruction secondary to HAE and treated with C1 esterase inhibitors, resulting in a full recovery. Even with the patient's history, obstruction secondary to HAE was not considered a differential until further investigation, thus delaying appropriate treatment [1]. Inherited HAE is subdivided into a deficiency (type 1), in which there are low levels of C1-INH, or a defect (type 2), which has nonfunctional but normal levels of C1-INH [2, 11]. Both variants will have a depletion of complement 2 (C2) and complement 4 (C4) proteins since they are consumed by the uninhibited action of C1 and can serve as an excellent initial diagnostic indicator of HAE [8, 11, 12, 14–18]. Other less common variants of HAE can have both normal function and amount of C1-INH [1, 11]. These types involve mutations of Factor XII, kininogen-1, or can even be unknown, but ultimately will lead to the unchecked generation of bradykinin [1].

Under normal conditions, the classical complement cascade begins with C1 activation via antigen-antibody complexes. In turn, C1 will activate subsequent complement signals until, ultimately, the membrane attack complex is formed. C1-INH also suppresses FXII and Kallikrein and is involved in other processes. Thus, the

lack of inhibitor leads to uncontrolled activation of FXIIa and kallikrein, which results in increased bradykinin production [7, 12]. This vasodilatory peptide can increase pain and relaxes the vascular smooth muscles, causing increased capillary permeability [7, 12].

Uninhibited bradykinin release manifests as angioedema and can involve upper and lower extremities, the face, trunk, and genitalia [19, 20]. Furthermore, angioedema can involve submucosal tissue such as the respiratory and gastrointestinal tracts [3]. The angioedema of HAE can present in many ways leading to a differing array of symptoms. This presentation makes it challenging to identify and may require physicians to pay close attention to the patient's medical history for episodes of unexplained abdominal pain since it is one of the most common presenting symptoms [11]. Depending on the location, the abdominal symptoms can be easily misdiagnosed as more common gastrointestinal maladies (e.g., gastroenteritis, appendicitis, cholecystitis, acute pancreatitis, diverticulosis, etc.) [3, 9]. This misdiagnosis can lead to unnecessary procedures such as appendectomy, exploratory laparotomy, and even hysterectomy [2, 4]. Swelling of subcutaneous tissue may mimic the more common presentation of mast cell-induced allergic reactions (e.g., non-pruritic skin rash, urticaria, etc.) [14]. Other indicators to look out for are a history of endemic episodes of unknown cause or even inconclusive procedures [1, 11]. In addition, medications such as ACE inhibitors or oral contraceptives can increase the overall levels of bradykinin and lead to increased frequency or increase in the severity of angioedema attacks, so consideration should be taken when prescribing these [1, 15, 16]. It is essential to be aware of HAE as a possible differential diagnosis since, if identified to be the cause, the treatment plan can focus on the regulation of bradykinin and functional C1-INH levels to reduce the frequency and severity of the angioedema episodes [1, 8, 19]. One quick identification method is the Hereditary AngioEdema Rapid Triage tool. Using this tool can help identify a cause for recurrent idiopathic angioedema [3, 7]. During acute HAE episodes, prompt and early treatment can decrease the subsequent duration and pain intensity compared to delayed treatment [7]. Medications used for the acute episodes include human-purified plasma-derived C1 inhibitors, kallikrein inhibitors (i.e., ecallantide), or bradykinin B2 receptor antagonists (i.e., icatibant) [3]. After the HAE exacerbation resolves, first-line prophylaxis involves the administration of C1 inhibitors, monoclonal antibodies against kallikrein that prevent its function (i.e., lanadelumab) [21, 22]. Second-line treatment options include attenuated androgens (i.e., danazol) or tranexamic acid [3, 12, 21–23]. Early diagnosis and treatment will significantly improve quality of life [1, 7]. and prevent the patient from being subjected to further investigation [1, 8]. Following treatment of the acute episode and subsequent long-term prophylactic management of HAE, the prognosis is generally favorable [12] Fig. 2.1.

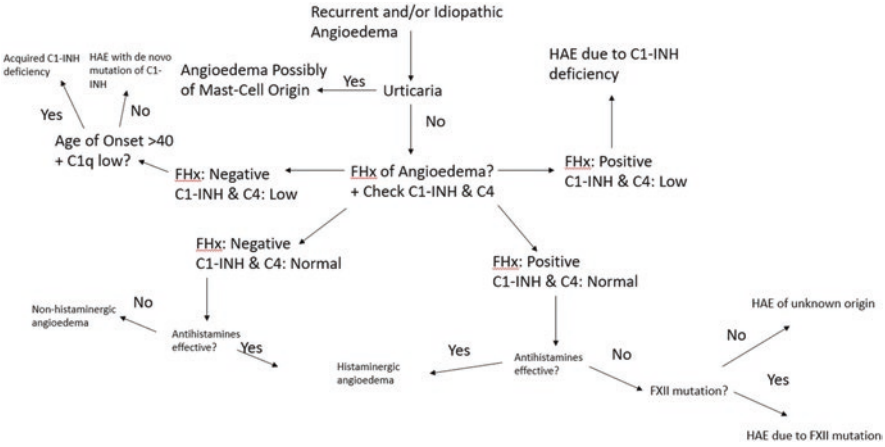

Fig. 2.1 A quick step-by-step method to assess a patient that arrives with angioedema of unknown origin [3, 7]. HAE, hereditary angioedema; C1-INH, C1 inhibitor; FHx, family history; FXII, Factor 12

Conclusion

Due to the broad range of tissue that can be affected and its nonspecific presentation, hereditary angioedema can mimic a range of other conditions. Subcutaneous presentation of angioedema can resemble a cutaneous allergic reaction. If the angioedema exacerbation occurs in the submucosa of the GI, it can present as any number of diseases in that location. Although not as common as conditions (e.g., diverticulosis, cholecystitis), physicians should be aware of HAE as a differential for gastrointestinal symptoms, especially in situations where symptoms have no identifiable cause or when the patient has a history of previously diagnosed HAE.

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Chapter 3
Bullous Fixed Drug Eruption Due to Fluconazole Imitating Herpes Simplex

Fatima Anwer

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Discuss what fixed drug eruptions are.
2. Enumerate the drugs that are most likely to cause fixed drug eruptions and understand their pathogenesis.
3. Describe how to diagnose and treat fixed drug eruptions.
4. Differentiate the mucosal fixed drug eruptions from recurrent herpes simplex.
5. Elaborate on the importance of taking a thorough drug history to prevent misdiagnosis.

Introduction

Fixed drug eruptions (FDEs) are recurring erythematous plaques that occur at the exact anatomical location due to drug allergy. They happen every time after the drug is administered [1]. It is supposed to be caused by the activation of epidermal CD8(+) T cells that produce plenty of interferon-gamma (IFN-gamma) [2]. Antibiotics and analgesics are the leading cause of FDE [3]. Oral fluconazole is most frequently associated with FDE around the mouth, which resembles the recurrent herpes simplex lesion and has been misdiagnosed [4]. We discuss a misdiagnosed case of FDE after fluconazole.

F. Anwer (✉)
PGY-1, Internal Medicine, Harlem Hospital, New York, NY, USA

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Clinical Case Presentation

A 25 year-old-female reported a history of recurrent vesicles in the perioral area. They appeared on the third day of every cycle with burning and tingling in the affected area. There was no fever or systemic symptoms. She was diagnosed with recurrent herpes simplex virus (HSV) infection by a few dermatologists she has visited previously. She started taking oral acyclovir followed by oral valacyclovir as prophylaxis for recurrent HSV. The problem persisted despite taking the medication, and she kept visiting doctors. The patient had redness, burning sensation and pain in the affected area. They suspected the HSV was resistant to medication.

Physical examination revealed a bunch of vesicles, 2–3 mm in size, in the perioral area. Labs including complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), urine analysis, serum IgM, IgG, and IgA came back normal. Syphilis and HIV screening came back negative, and polymerase chain reaction (PCR) for herpes and cultures from vesicles came back negative.

The patient later revealed that she had been taking fluconazole monthly for recurrent vaginal candidiasis. This led to the final diagnosis, which was a fixed drug eruption due to fluconazole, as the blisters always appeared a few hours after taking the drug. Fluconazole was discontinued, and she didn't report any recurrence on her 3-month follow-up.

Differential Diagnosis

1. Erythema Multiforme – Erythema multiforme presents as tiny, evenly distributed lesions that mainly involve acral areas. On the other hand, FDE is distributed primarily to the trunk. There is no hyperpigmentation after the lesions resolve, and FDE recurs at the same spot. Both can involve mucosa [5]. When compared to FDE, histopathology is incredibly different. There could be liquefactive basal epidermal cell degeneration, necrotic keratinocytes, and lymphocyte exocytosis. Necrosis is prominent in the dusky center of the targetoid lesion [6].
2. Stevens-Johnson Syndrome (SJS) – Stevens-Johnson lesions begin as a morbilliform rash and are less well-defined than FDE lesions. In addition, systemic findings are always present in SJS patients, and the disease spreads rapidly [5]. SJS occurs 6–21 days after inciting the drug. It has mucosal involvement in >90% of the cases. Histology consists of pauci-inflammatory infiltrate with many eosinophils and total thickness epidermal necrosis [7].
3. Toxic Epidermal Necrolysis—Toxic epidermal necrolysis is a therapeutic emergency. It is caused by drugs or infections and damages the keratinocytes. It leads to various hydroelectric disorders and systemic infections. Greater than 30% of the body area has mucocutaneous detachment. Histology shows necrotic keratinocytes [8].

4. Herpes Simplex Virus—FDE is frequently misdiagnosed as a herpes simplex virus infection. In the case of FDE, a hyperpigmented patch appears after the lesion has healed, and drug history is invariably present. Furthermore, if antiviral treatment fails, a biopsy of the lesion should be performed, and PCR for herpes simplex should be ordered to look for the virus [9].

What Was Misdiagnosed in This Case and Why?

FDE was misdiagnosed as the patient forgot to mention the fluconazole she used once a month for vaginal candidiasis. Moreover, the lesions were recurrent and occurred at the same spots, which resembles Herpes Simplex lesions.

Discussion

Fixed drug eruptions are a cutaneous adverse effect of a drug defined by lesions that reappear in the same spot after the patient takes the offending medication [10]. FDE is responsible for 10% of cutaneous drug reactions, and it can occur at any site but mainly on hands, lips, and genitalia [11].

Pathogenesis and Presentation of Fixed Drug Eruptions

FDE is a delayed-type cellular hypersensitivity response [12]. FDE presents as a single or a small number of itchy, red macules with distinct margins that later evolve into edematous plaques. Once the triggering medicine is discontinued, the lesion disappears, leaving hyperpigmentation. The lesion flares up within 30 mins to 8 h after drug intake [13]. The lesions last for around 1–3 weeks after discontinuing the drug [11]. The pathogenesis is caused by intraepidermal CD8+ T cells. These cells are not cytolytic in general, but once triggered by CD3-T-cell receptor complex, they start killing natural killer sensitive or NK-resistant tumor cells and keratinocytes. CD8+ T cells cause direct cytolysis by perforins. Additionally, they release lots of interferon-gamma (IFN-γ). IFN-γ recruits unchecked CD4+, CD8+ T cells and neutrophils and enhances tissue damage. These intradermal CD8 + T cells are abundant in the FDE lesions [13].

The most characteristic finding of FDE is recurrence at the same site. Although most lesions have persistent hyperpigmentation in the afflicted region, some uncommon variants leave no residual hyperpigmentation. Several distinctive forms have been reported, including erythema multiforme-like FDE, toxic epidermal necrolysis-like FDE, linear FDE, etc. [14]. Mahboob A and Haroon TS studied 450 cases of FDE. 72% of the patients had no symptoms, while 24% reported itching,

burning, or combination. Rest 3.8% reported local pain. 84% had lesions on multiple sites of the body. Lips were the most involved site. 31% reported back to the hospital within 1 year due to missed diagnosis on their first visit and lack of awareness led to multiple episodes. The lesions were hyperpigmented primarily. Some distinctive forms, including urticaria, dermatitis, periorbital, and generalized hyper melanosis, were also reported. Clotrimazole was the most common cause of FDE [15].

Diagnostic Approach Toward Fixed Drug Eruptions

The patch test is the most common method to diagnose FDE, and it is less damaging, but it is less realistic. Positive outcomes rely on the causative medication, and it was more accurate when contrast medium or antiepileptics were the culprits [16]. A biopsy is recommended in undiagnosed cases or those with systemic symptoms or atypical appearance [17]. Clotrimazole was the most common cause of FDE. Localized lesions are caused by trimethoprim-sulfamethoxazole (TMP-SMX) and NSAIDs. Oral mucosa is involved with naproxen and TMP-SMX. Antibiotics cause generalized bullous variants [15, 17].

Treatment of Fixed Drug Eruptions

Treatment involves removing the harmful medication and providing supportive care. Oral antihistamines and medium to high dosage of topical corticosteroids could be administered for pruritus. Oral steroids are of no benefit. Cyclosporine has also shown a favorable response in some patients [13]. We have discussed a case of FDE after fluconazole. The FDE mainly involves mucosa and recurs every time the drug is readministered, and it was mistaken for recurrent herpes. Mucosal FDE can masquerade as herpes. Many cases of FDE are mistaken for herpes simplex lesions, and it is critical to establish a correct diagnosis by knowing the difference between lesions. Most patients respond to itraconazole, so it can be used to treat the fungal infection instead [9, 18, 19].

Conclusion

Fixed drug eruptions are the type 4 hypersensitivity reaction to drugs. It develops as an allergic response to medication and can manifest as various lesions, ranging from mucosal vesicles that mirror herpes simplex to bullous lesions that imitate different bullous disorders. It's vital to get the correct diagnosis to avoid recurrent reactions.

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Chapter 4
Deficiency of Adenosine Deaminase Type 2 (DADA2) Masquerading as GATA-Binding Factor 2 (GATA2) Deficiency

Fatima Anwer

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Discuss the phenotypic overlap between certain primary immunodeficiency disorders.
2. Identify the various hematologic, autoimmune and vasculitis manifestations of DADA2.
3. Correctly diagnose DADA2 and know the role of whole-exome sequencing in diagnosing DADA2.
4. Classify the various treatment modalities available to treat the disease effectively.
5. Articulate the value of early detection and therapy in reducing mortality and improving prognosis.

Introduction

Adenosine is produced within or on the surface of cells by breaking adenine, a purine nucleotide. It is important for anti-inflammatory effects, boosting the oxygen supply/demand ratio, preconditioning, and angiogenesis promotion. It acts through G-coupled receptors, and it's more active when there's tissue injury or stress [1, 2]. Deficiency of adenosine deaminase 2 (DADA2) is an autosomal recessive condition caused by a loss of function mutation in the adenosine deaminase 2 gene, originally known as cat eye syndrome critical region protein 1 (CECR1 gene). Neutrophils play an important role in DADA2 pathogenesis by forming neutrophil extracellular traps (NET) [3]. NET, in turn, leads to vasculopathy and direct endothelial injury

F. Anwer (✉)
PGY-1, Internal Medicine, Harlem Hospital, New York, NY, USA

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leading to vascular plaque formation and thrombosis [4]. DADA2 commonly affects children. However, sometimes it can also appear in adults and is expressed as a multiorgan disease. The disease can manifest as immunodeficiency, medium vessel vasculitis, hematologic disease, or even stroke [5].

Clinical Case Presentation

A 20-year-old Hispanic female presented for the evaluation of febrile neutropenia, anemia, and invasive *Fusarium proliferatum* sinusitis. She was diagnosed with common variable immune deficiency (CVID) at seven and had low Immunoglobulin G (IgG). She has also been admitted at the age of 19 due to febrile neutropenia, right maxillary sinusitis due to *Fusarium proliferatum*, sepsis, and respiratory failure secondary to extended-spectrum β-lactamase-producing *Escherichia coli*. She required ICU care, broad-spectrum antibiotics, and corticosteroids at that time. For the patient's laboratory results, see Table 4.1.

Her bone marrow was mildly hypocellular and showed no neutrophils or neutrophil precursors (promyelocytes, myelocytes, and/or metamyelocytes). It showed erythroid predominance, myeloid hypoplasia, very low CD20+ B cells, and increased T cells with lymphohistiocytic aggregates. There was no evidence of dysplasia.

Flow cytometric analysis (FCA) of bone marrow aspirate revealed 4% myeloblasts, absent maturing neutrophil precursors, monocytopenia, severe B-cell lymphopenia, and increased T cells with a CD4:CD8 ratio of 0.48 (normal >1). She also developed monocytopenia and *Mycobacterium avium* infection (MonoMAC) syndrome. The patient's history and bone marrow findings were consistent with MonoMAC syndrome due to GATA2 deficiency. But when tested, they found no mutation of GATA2. Additionally, in GATA2 deficiency, the dendritic cells and B-cell precursors are absent in the bone marrow. However, cytogenetic analysis of the patient's bone marrow was normal with both dendritic cells and B-cell precursors. Whole-exome sequencing depicted a unique, homozygous change leading to a

Table 4.1 Patient's laboratory results

Cell type	Results	Reference range
White blood cells	**0.7** ↓ cells/μl	4.2–9.0 × 10^3 cells/μl
Absolute neutrophil count	**0** ↓ cells/μl	1.7–5.3 × 10^3 cells/μl
Absolute monocytes count	**0** ↓ cells/μl	0.3–0.8 × 10^3 cells/μl
CD20+ B cells	**0** ↓ cells/μl	1121 100–600 cells/μl
Hemoglobin Hb	**10.2** ↓ g/dl	11.2–15.7 g/dL
Platelets	**125** ↓ cells/μl	173–369 × 10^3 cells/μl
ABS CD19+	**0** ↓ cells/μl	61–321 cells/μl
ABS NK(CD56+)	**32** ↓ cells/μl	126–729 cells/μl
ABS CD3+	**645** ↓ cells/μl	714–2266 cells/μl

premature stop codon, c.794C > G, p. Gln265Stop, in CECR1-encoding adenosine deaminase 2 (ADA2). Sanger sequencing of parents and siblings was done, and it showed all to be heterozygous for the mutation. Although they originate from a remote town, the family claimed no consanguinity, and a homozygous area of 650 kb surrounding CECR1 suggests a shared ancestral allele. No one else in the family had any signs or symptoms of the condition. However, the neutrophil counts of both the father and two twin sisters were somewhat low.

Plasma ADA 2 levels were undetectable in the patient while intermediate in parents and siblings. The patient underwent a haploidentical hematopoietic stem cell transplant HSCT from her 17-year-old sister, who had normal blood counts and no history of immunodeficiency. On post-op day 8, she caught methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia and bacteremia and was put on mechanical ventilation. She had neutrophil engraftment on post-op day 19 and was extubated on post-op day 20. The invasive *Fusarium* infection was resolved. After 1 month, her CD3+ and myeloid chimerism were precisely the same as the donor, and her monocyte count and NK cell count returned to normal. CD19+ B cells normalized after 1 year. Immunosuppression was gradually stopped after about 6 months. A 2-year follow-up showed a completely normal blood count and no clinical abnormalities. The plasma ADA2 levels also normalized after the transplant [6].

Differential Diagnosis

1. Immunodeficiency mimics CVID.
2. GATA2 deficiency.
3. MonoMAC syndrome.
4. Polyarteritis nodosa.
5. Sneddon syndrome.
6. Diamond-Blackfan anemia.
7. Stroke.

What Was Misdiagnosed in This Case and Why?

In this case, the DADA2 was misconstrued as CVID first, and GATA2 deficiency later as the peripheral blood count and bone marrow findings pointed toward GATA2 deficiency. Additionally, the patient had immunodeficiency and multiple infections, including MonoMAC syndrome, further supporting the GATA2 deficiency. However, the GATA2 levels were normal, ruling out the possibility. The whole-exome sequencing led to the final diagnosis of DADA2 due to premature stop codon in the CECR1 gene.

Discussion

DADA2 is a monogenic disorder that affects multiple organs [7]. The syndrome is mainly characterized by medium vessel vasculitis, resembling polyarteritis nodosa, early stroke, recurrent fever, and slight immunodeficiency. The phenotypic appearance varies considerably. The illness generally shows up in childhood. However, some people go unidentified until adulthood [8]. DADA2 should be suspected in the patient presenting with recurrent fever, rash, and strokes even in the absence of family history. The patients exhibit hematological problems, including pure red cell aplasia (PRCA), hypogammaglobulinemia, thrombocytopenia, and neutropenia [9]. Patients presenting with hematologic manifestations like PRCA and bone marrow failure present with severe disease and complete loss of function of ADA2. In contrast, those who suffer from vasculitis presented late in the course of the disease and had missense mutation with roughly 3% residual enzyme function. The hematologic symptoms do not respond to treatment with tumor necrotic factor (TNF) inhibitors. On the other hand, vasculitis symptoms usually respond well to TNF inhibitors [10]. The clinical manifestations of the DADA2 are shown in Fig. 4.1.

The skin and central nervous systems are most involved. Approximately 50% of patients have constitutional symptoms like fever and high erythrocyte sedimentation rate or elevated C-reactive proteins. Musculoskeletal symptoms are reported less often [9].

DADA2 is sometimes misdiagnosed as common variable immunodeficiency (CVID) or deficiency of antibodies. Schepp J et al. in 2017 conducted a study on a cohort of 181 patients with deficient antibodies and used next-generation

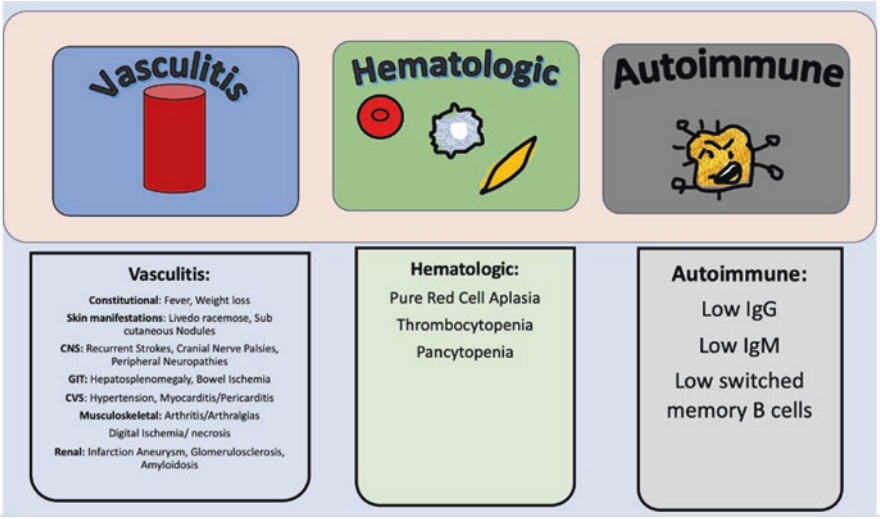

Fig. 4.1 Clinical manifestation of adenosine deaminase deficiency type 2. (There can be an overlap of vasculitis, hematologic, and autoimmune symptoms)

sequencing and Sanger sequencing to diagnose mutation in the CECR1 gene. They confirmed the mutations using ADA2 enzymatic activity in dried plasma. Eleven patients had mutations in the CERC1 gene, and the median age of patients was 22 years. They concluded that DADA2 not only presents with vascular pathology but can sometimes also present as low antibodies. Therefore, all patients with dec antibodies should be screened for DADA2 to prevent missed diagnosis [11]. To diagnose DADA2 cost-effectively, we should measure plasma adenosine deaminase levels before genetic studies [12]. Next-generation sequencing, Sanger sequencing, or whole-exome sequencing can confirm most cases. However, some variants can be missed and need molecular diagnosis using multiplex ligation-dependent probe amplification (MLPA) [13]. Treatment is determined by disease phenotype. TNF inhibitors lower the risk of stroke and decrease inflammation. However, it does appear to be effective in patients with bone marrow failure [10]. ADA2 enzyme replacement using fresh frozen plasma was investigated as a treatment option. However, it was not cost-effective due to its short half-life and frequent large volume infusions required to maintain effectiveness. Anti-TNF therapy shows dramatic improvement in symptoms [14]. Anti-TNF started early in the course of the disease and can decrease mortality. Delayed diagnosis and delayed anti-TNF therapy are the leading cause of mortality [15]. When to start treatment in asymptomatic patients and when to stop once symptoms resolve is unknown and must be explored [16]. Hematopoietic stem cell transplant is the definitive treatment. Indications for HSCT are bone marrow failure, immunodeficiency, and severe unresponsive vasculitis [17].

Conclusion

DADA2 presents recurrent infections due to immunodeficiency, medium vessel vasculitis, and hematologic problems. It is frequently misdiagnosed as CVID, GATA2 deficiency, or polyarteritis nodosa. Treatment and early diagnosis can help to reduce mortality. Thus, investigations should be done as early as possible.

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Chapter 5
Hypereosinophilic Syndrome Misdiagnosed as Asthma

Fatima Anwer

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Create a differential diagnosis for patients who have symptoms that could indicate hypereosinophilic syndrome.
2. Define hypereosinophilic syndrome and changes in the criteria that have been used to diagnose it in the past.
3. Evaluate the medical history and physical examination components in the appropriate sequence.
4. Discuss the various disorders that can lead to hypereosinophilia and investigations needed to reach a definitive diagnosis.
5. Discuss the consequences of a misdiagnosis or delay in getting a correct diagnosis for the individual patient's prognosis.

Introduction

Hypereosinophilia consists of multiple disorders that can present in various ways; one thing common is the increased number of eosinophils that accumulate in different body organs [1]. Three criteria have been used to diagnose hypereosinophilic syndrome, including the following:

1. Blood eosinophil count >1500/mm^3 for 6 months.
2. Plausible organ involvement.
3. No other causes like allergic, parasitic, or else that could explain the increase in eosinophils [2]. It is now defined as a peripheral eosinophil count greater than

F. Anwer (✉)
PGY-1 Internal Medicine, Harlem Hospital, New York, NY, USA

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1500/mm that might lead to tissue damage. Prognosis depends on early diagnosis and treatment, so we must exclude secondary causes of hypereosinophilia (including neoplasms) as soon as the disease is suspected. Physicians should order blood and bone marrow morphology, cytogenetics, fluorescent in situ hybridization, flow immunocytometry, and T-cell clonality [3]. Additionally, some cases of the hypereosinophilic syndrome as Fip1-like-1 (FIP1L1)/platelet-derived growth factor receptor α (PDGFRA)-associated HES have a pathogenic mutation explaining the increase in eosinophils. Hence, the diagnostic criteria used in the past need to be revised [2]. Hypereosinophilic syndrome is classified as the following:

1. Myeloproliferative neoplasm/HES
2. Myeloproliferative syndrome/chronic eosinophilic leukemia, not otherwise categorized
3. Myeloid neoplasm associated with the eosinophilia and abnormalities of platelet-derived growth factor receptor alpha (PDGFRA), platelet-derived growth factor receptor-beta (PDGFRB), or fibroblast growth factor receptor 1 (FGFR1)
4. T-cell neoplasm/lymphoma, unclassifiable [2]

The organ involvement depends on the type of hypereosinophilic syndrome and mutation. Treatment also depends on the type of mutation. Glucocorticoids can keep eosinophils under check in idiopathic variants. Tyrosine kinase inhibitors can treat secondary hypereosinophilic form [4]. In this case report, we will discuss the scenario where the patient with hypereosinophilia due to myeloid and lymphoid neoplasia was misinterpreted as cough variant asthma.

Clinical Case Presentation

A 41-year-old male presented to the clinic with a complaint of dry cough for more than 2 years. He has also had shortness of breath for the past 6 months. The cough aggravated at night, especially in the supine position. He had a 20 pack-years smoking history. On examination, he had bilateral pitting edema in his lower limbs. Lungs were clear on auscultation. Additionally, grade 3 systolic murmur was present at the apex and tricuspid valve. His eosinophils count was 7510/uL. Computed tomography revealed enlarged cardiac shadow and small pericardial effusion. Pulmonary function tests showed forced expiratory volume in the first second (FEV1) at 97.63% of the predicted value. The FEV1/forced vital capacity ratio (FEV1/FVC) was 100.97%, and the peak expiratory variability over the next week was 27%. Bronchoscopy results came back normal. However, the bronchoalveolar lavage fluid (BALF) had 28% eosinophils. The total IgE level was 26.1 kU/L. The respirologist diagnosed the patient with cough variant asthma (CVA) as the patient had airway eosinophilia and airway reversibility. He got 80 mg/dl of intravenous methylprednisolone and bronchodilators. The patient did not respond to treatment,

and the eosinophil count rose from 7510/uL to 10,700/uL. The patient was moved to the hospital for extensive testing. They evaluated the patient for the cardiac causes of shortness of breath during the hospital stay. Cardiac magnetic resonance imaging revealed hypertrophic cardiomyopathy. Brain natriuretic peptide (BNP) was 4766 ng/ml. The antineutrophil cytoplasmic antibody (ANCA) came back negative. Coronary angiography did not show any narrowing. Abdominal ultrasound revealed splenomegaly and ascites. Inhaled corticosteroids (ICS), cardiotonic drugs, and diuretics were administered. The patient improved a bit. He tested positive for antibodies against liver flukes and paragonimiasis. Subsequently, praziquantel (anthelmintics) was used; however, no improvement was seen. Bone marrow cytology showed eosinophilia (37.5%). The patient was then evaluated for primary hypereosinophilic syndrome. Platelet-derived growth factor receptor alpha fusion gene came back positive. Fluorescence in situ hybridization analysis further depicted Fip1-like1-platelet-derived growth factor receptor alpha gene fusion on one of the chromosomes 4. Myeloid and lymphoid neoplasm with eosinophilia and PDGFRA rearrangement was the ultimate diagnosis. Dexamethasone 10 mg and imatinib 100 mg tablets were given. With medication, the cough and shortness of breath subsided. The heart issue responded to a mitral tricuspid angioplasty [5].

Differential Diagnosis

1. Idiopathic Hypereosinophilic Syndrome—To diagnose the hypereosinophilic syndrome, one must rule out the causes of eosinophilia, and there must be some end-organ damage. If there is no end-organ damage, it is idiopathic hypereosinophilia, not idiopathic HES [6].
2. Cough Variant Asthma—Cough variant asthma is often confused with hypereosinophilia. However, cough variant asthma improves promptly with corticosteroids, and as per the WHO guidelines, we cannot diagnose HES if eosinophilia is explained by other causes.
3. Churg-Strauss Syndrome—Churg-Strauss syndrome presents with eosinophilia and elevated IgE. Antinuclear cytoplasmic antibodies (ANCA) are positive in only 50% of the cases [7].
4. Reactive Eosinophilia—Eosinophilia due to parasitic infections, Cushing's disease.

What Was Misdiagnosed in This Case and Why?

The patient with hypereosinophilia due to myeloid and lymphoid neoplasm had a dry cough and shortness of breath. It was confused with cough variant asthma due to eosinophilia and airway reversibility.

Discussion

Eosinophils make up 1–5% of human leukocytes [8]. Paul Ehrlich first coined the term "eosinophils" in 1879 while describing blood film staining techniques. Eosinophils are found in blood and infiltrate tissue during various allergic and parasitic disorders. They are considered immune cells, and their arsenal of protein, receptors, and interaction with other cells has shown that they play a vital role in innate and acquired immunity. Their presence is associated with several disorders, and they play an essential role in disease pathogenesis [9]. Eosinophilia can be mild absolute eosinophil count (AEC) ranging from 500 to 1500/mm^3, moderate AEC 1500–5000 mm^3, and severe AEC > 5000 mm^3 [1].

Classification of Hypereosinophilia

Chusid et al. first described the criteria for diagnosing hypereosinophilic syndrome in 1975, including three requirements as described in Table 5.1. This diagnosis did not cover the secondary causes of eosinophilia. Additionally needed, the multiple organ damage to diagnose HES [10].

We could not diagnose most reactive eosinophilic illnesses until the 1990s, and they were categorized as idiopathic hypereosinophilic syndrome. With molecular pathophysiology advancements, we could better analyze the diseases due to genetic mutations activating tyrosine kinases. Fip1-like-1 (FIP1L1)/platelet-derived growth factor receptor alpha gene fusion resulted in systemic mast cell disease with eosinophilia. PDGFA and PDGFB rearrangement cause eosinophilic myeloproliferative disorders. Lymphocytes secrete interleukin 5 and cause lymphocyte-mediated hypereosinophilia [11].

The classification of eosinophilic disorders was revised recently in 2016 by the World Health Organization.

To diagnose idiopathic hypereosinophilic syndrome, one must exclude the following:

1. Reactive eosinophilia
2. Lymphocytic variant hypereosinophilic
3. Chronic eosinophilic leukemia not otherwise specified WHO-defined myeloid malignancies

Table 5.1 Criteria used in the past to diagnose hypereosinophilic syndrome

Chusid et al. criteria have been used to diagnose the hypereosinophilic syndrome [10]
1. Blood eosinophil count > 1500/mm^3 for 6 months
2. Multiple organ involvement
3. No other causes (allergic, parasitic, etc.) could explain the increase in eosinophils.

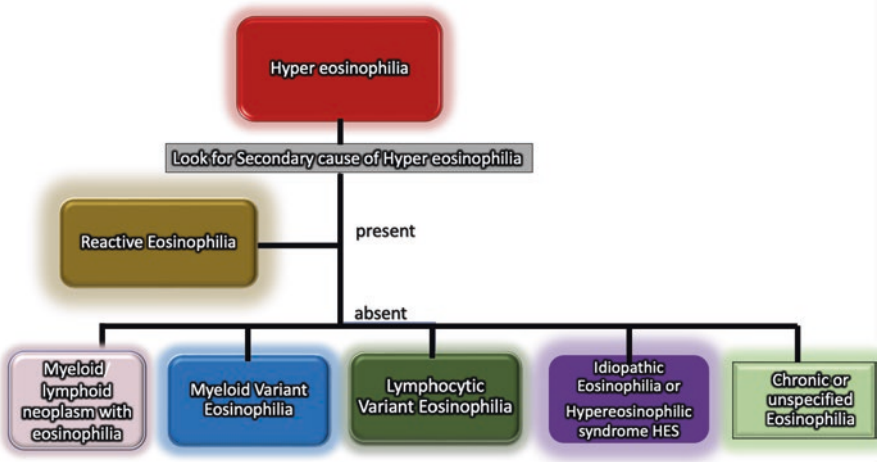

Fig. 5.1 Classification of hypereosinophilia [11]

Table. 5.2 Ogbogu et al. initial and subsequent clinical manifestations of hypereosinophilia [12]

Organ involved	Initial clinical presentation	Subsequent clinical manifestations
Dermatologic	37%	69%
Pulmonary	25%	44%
Gastrointestinal	14%	38%
Neurologic	<5%	20%
Cardiac	<5%	20%
Constitutional/asymptomatic	6%	None
Splenomegaly	No data	10%
Hematologic	<5%	No data

Eosinophilia is due to myeloproliferative disorders. The absolute eosinophil count must stay persistently elevated for 6 months, and tissue damage must be present. If there is no tissue damage, the diagnosis is idiopathic hypereosinophilia, not idiopathic hypereosinophilic syndrome [6] (Fig. 5.1).

Clinical Manifestations of Hypereosinophilia

Multiple organs can be involved in hypereosinophilia. A study was conducted to determine the clinical and laboratory characteristics of HES. Ogbogu et al. studied 188 patients between 2001 and 2006 in various US and European institutions. The clinical manifestations were recorded at the initial presentation and after some time. The organ involvement is described in the Table 5.2 below [12].

The cutaneous lesions are the most common clinical manifestations of the disease. They include pruritic, tender, erythematous, or edematous papules on

extremities and trunk [13]. Pulmonary symptoms such as dyspnea and cough are common in hypereosinophilic syndrome and are further supported by the histologic presence of eosinophils in the tissue. Sometimes the pulmonary presentation is confused with cough variant asthma [5, 14]. Cardiac manifestations of hypereosinophilia range from asymptomatic cardiac involvement to fatal necrotic myocarditis or irreversible cardiomyopathy. A cardiac biopsy is the only way to confirm the diagnosis. On the other hand, cardiovascular MRI and echocardiography are practical diagnostic tools [15]. Cerebrovascular accidents are the most common pathology associated with hypereosinophilia. Eosinophils can't cross the blood-brain barrier easily, so the deposition of eosinophils in the brain is rare [16].

Diagnostic Approach to Hypereosinophilia

A shotgun approach can pinpoint the cause of hypereosinophilia, but it would be costly. Therefore, we need a step-by-step approach to ruling out common diseases first. Once you suspect hypereosinophilic syndrome, stop all nonessential drugs the patient is taking and rule out allergic and parasitic causes. The physician should order a radioallergosorbent test (RAST) and stool for ova parasite and serology to check for parasitic diseases. Then, using antineutrophil cytoplasmic antibody titers, look for autoimmune reasons. Additionally, check morning cortisol levels to screen for Cushing's disease, and refer to the dermatologist for skin lesions. Checking thymus activation-related chemokine (TARC) levels will help rule out allergic asthma. After that, rule out reactive and malignant clonal causes. Order bone marrow biopsy, flow cytometry, and routine karyotyping, FISH, and PCR, and check for translocations of PDGFRB and FGFR1. If no other cause can explain eosinophilia, the diagnosis of idiopathic hypereosinophilia is confirmed [17].

Hypereosinophilic Syndrome Treatment Options

Treatment of the disease depends on the cause of the hypereosinophilia, end-organ damage, and tyrosine kinase activation [4]. Most patients respond to corticosteroids, but they cannot be used for long due to side-effect profiles. Apart from steroids, mepolizumab can also be used in FIP-PDGFRA-negative patients [18]. In cardiac involvement, early diagnosis and treatment are crucial to prevent permanent cardiac damage [15]. Prompt treatment with high-dose steroids is indicated in patients with hypereosinophilia. If eosinophil count is >100,000, leukostasis or end-organ damage is suspected. In case of myeloid hypereosinophilic syndrome with PDGFR positive status, treat with imatinib [19]. The lymphocytic variant responds to pegylated interferon-alpha 2a, which decreases secretion of interleukin 5 and hence lower eosinophil count [20].

Plan of Action: The Points Clinician Should Consider: Pitfalls to Avoid and Pearls of Knowledge to Consider

The following basics should not be overlooked:

1. Instead of going with the shotgun diagnostic approach, rule out the common causes of eosinophilia before diagnosing hypereosinophilic syndrome.
2. Myeloid and lymphoid neoplasm can also be associated with eosinophilia, and treatment is based on pathophysiology. Therefore rule out the clonal proliferation of eosinophils as it can change the treatment plan.
3. Start corticosteroids early in the course of disease for better outcomes and to prevent irreversible damage.

Conclusion

When idiopathic hypereosinophilia is suspected, corticosteroids should be administered as soon as possible. This is to avoid irreversible organ damage, especially to the heart. A time period requirement of 6 months in the criteria of the hypereosinophilic syndrome will delay the treatment. Hence, the definition needs revision.

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Chapter 6
Misdiagnosis of Common Variable Immune Deficiency

Katarzyna Karpinska-Leydier

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Assess the overlapping features between common variable immune deficiency with granulomatous features and sarcoidosis.
2. Recall that sarcoidosis is a diagnosis of exclusion and identify steps necessary to arrive at a confident diagnosis.
3. Interpret clinical findings as features present over an indolent course to aim for early detection and treatment of CVID.
4. Distinguish between coexisting immunodeficiency and autoimmune disorders where CVID is present and immunoglobulin replacement therapy is needed.
5. Apply the knowledge gained from this and similar cases where appropriate in future clinical settings.

Introduction

Common variable immune deficiency (CVID) and sarcoidosis may share the common feature of granulomatous inflammation [1]. CVID is a primary immunodeficiency disorder where impaired B-cell differentiation results in reduced serum IgG with low IgA and IgM, resulting in a blunted response to immunizations and a higher risk of recurrent bacterial infection [1–3]. It is the most common primary immunodeficiency, with a prevalence ranging from 1:25,000 to 1:50,000 [3]. Granulomatous features are seen in 8–22% [3]. Despite this, CVID is not always a distinct and clear presentation which may lead to misdiagnosis, resulting in

K. Karpinska-Leydier (✉)
Internal Medicine, Florida State University - Cape Coral Hospital, Cape Coral, FL, USA

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treatment delays and complications, including mortality [3]. Sarcoidosis is a multisystem granulomatous disease diagnosed by exclusion [1, 4]. It may be either erroneously diagnosed without proper workup or coexist with other immune-mediated diseases (IMDs) [1, 4]. Among IMDs associated with sarcoidosis, CVID shows the strongest relationship compared with the general population, further adding to misdiagnosis in complex clinical presentation [4]. Moreover, CVID may present with features similar to sarcoidosis, such as arthralgia and granulomatous lymphocytic interstitial lung disease (GLILD) [5, 6]. Immunodeficiency disorders among themselves also have a considerable overlap of features such as GLILD seen in approximately 10–30% of CVID cases and can specifically impact prognosis and therapeutic options [7, 8]. Sarcoidosis usually requires the demonstration of granulomatous inflammation, most commonly affecting the lungs and can involve the skin, lymph nodes, and eyes [1]. The granulomatous variant of CVID may closely mimic sarcoidosis; therefore, clinical discernment is necessary to ensure early detection and treatment for the appropriate diagnosis [9].

Clinical Case Presentation

In 1981, a 29-year-old male patient presented with cervical and axillary lymphadenopathy, transient thrombocytopenia, and splenomegaly. A lymph node biopsy from the axilla demonstrated granulomatous inflammation, interpreted as sarcoidosis. His past medical history is significant for employment as a farmer and agricultural salesman and status as a lifelong nonsmoker. In 1998, he developed conjunctivitis, cough, breathlessness, and recurrent peripheral lymphadenopathy. Nodular interstitial pulmonary shadowing and bilateral hilar lymphadenopathy were present. Several investigations were performed at this time, including an elevated ACE level. Hypogammaglobulinemia was demonstrated with low IgG 3.3 g/L (normal 6–16), IgM 0.7 g/L (0.5–3), and IgA 0.5 g/L (0.8–2.8) levels; however, this was not documented as being clinically relevant.

He began oral steroid therapy in 1999 for the treatment of sarcoidosis. In 2009, he returned with increasing splenomegaly and thrombocytopenia, thought to be due to idiopathic thrombocytopenic purpura (ITP). Bone marrow trephine showed the presence of granulomas and unremarkable megakaryocyte numbers. Within the year, left vocal cord palsy developed and was considered related to sarcoidosis. Over the next several years, he suffered from treatment-resistant ITP, systemic malaise, and increasing splenomegaly. In 2011, a prolonged right upper lobe cavitating pneumonia prompted further workup, including a bronchoalveolar lavage growing *Haemophilus influenzae* on bronchoalveolar lavage and now recognized for agammaglobulinemia (serum IgG, IgA, and IgM all <0.3 g/L). Sarcoidosis was initially misdiagnosed and revised 30 years later to common variable immune deficiency, complicated by disseminated granulomatous disease, splenomegaly, and idiopathic (autoimmune) thrombocytopenia.

Differential Diagnosis

1. Common variable immune deficiency (granulomatous variant) – CVID is a primary immunodeficiency disorder with phenotypically normal B cells that under or fail to produce immunoglobulins. Presentation is typically between ages 20–40 with an indolent history of recurrent pyogenic respiratory infection affecting both men and women equally. Granulomas may be a feature of some variants. Diagnosis involves serologic testing for low IgG, IgA, IgM, and plasma cells and insufficient response to immunizations. Flow cytometry is normal for subsets of both B and T cells. It is pertinent to treat early with IVIG replacement and manage infections.
2. Sarcoidosis – This multisystem disorder primarily affects the lung with noncaseating granulomatous inflammation features. It commonly affects African American women. A chest X-ray is appropriate to assess for hilar lymphadenopathy; however, sarcoidosis is a diagnosis of exclusion. Biopsy showing granulomatous inflammation and lab findings of increased CD4/CD8 ratio and increased ACE are supportive. Treatment involves glucocorticoid therapy and is aimed at preventing progression.

What Was Misdiagnosed in This Case and Why?

Sarcoidosis was misdiagnosed in this case because of overlapping clinical features with the granulomatous variant of CVID and unrecognized agammaglobulinemia early in the clinical course.

Discussion

Allergy and immunology specialists are well versed in the nuances of common variable immune deficiency (CVID) and its variants; however, typical disease hallmarks of sarcoidosis may be misleading, and a diagnosis may be reached without appropriate investigation. Here, the patient was initially diagnosed with sarcoidosis in the presence of nodular granulomatous inflammation and telltale bilateral hilar lymphadenopathy; however, panhypogammaglobulinemia, which would indicate CVID, was initially overlooked [1]. It is typical for manifestations of CVID to develop over several years; however, serum immunoglobulins are necessary to distinguish between these two differentials, as hypergammaglobulinemia is more likely in sarcoidosis, but hypogammaglobulinemia is suspicious for a primary immunodeficiency [1, 5]. After the development of idiopathic thrombocytopenic purpura (ITP), increasing splenomegaly, and cavitating pneumonia with confirmed *Haemophilus influenzae,* the serum IgG, IgA, and IgM were reassessed [1]. Although these

symptoms could fit into a clinical picture of sarcoidosis, CVID must be suspected in patients with recurrent infections and immunodeficiency; furthermore, concomitant autoimmunity, including ITP, may offer further support but is not specific enough to exclude sarcoidosis [1, 4–6] (Fig. 6.1).

Bronchoalveolar lavage (BAL) in granulomatous variants of CVID with interstitial lung disease (ILD) has a comparably high CD4:CD8 ratio to sarcoidosis; however, the "sarcoid-like" presentation is distinct from pulmonary sarcoidosis when considering the entirety of clinical history and investigations [10–12]. Patients suspected of sarcoidosis may receive a diagnosis through radiological and histological examination even with sufficient clinical observation but still may lack a full clinical picture without serological testing [13]. Further overlap between sarcoidosis and CVID may be seen in the co-occurrence of chronic granulomatous disease (CGD) with CVID, which is rare but documented [14]. Granulomas are histologically identical; however, a higher level of tumor necrosis factor (TNF) in these patients may account for granuloma development [14]. A less common presentation of tonsillar granulomas raises suspicion for etiologies of malignancy, infection, or sarcoidosis; however, in a setting of B-cell deficiency, this may be the only presenting symptom of CVID [15]. It is significant to highlight that even in patients with CVID who develop the co-occurrence of sarcoidosis, hypogammaglobulinemia is present, and they are more likely to have recurrent infections, splenomegaly, and thrombocytopenia [16].

Routine assessment of serum immunoglobulins in patients with suspected sarcoidosis can lead to early disease recognition and immunoglobulin replacement (IVIG), thereby reducing complications and mortality of CVID patients [1]. Granulomatous features do not respond to IVIG and usually require corticosteroids; however, additional immunosuppressive protocols with azathioprine or rituximab may be necessary for remission [3]. This regimen may increase the risk of infection,

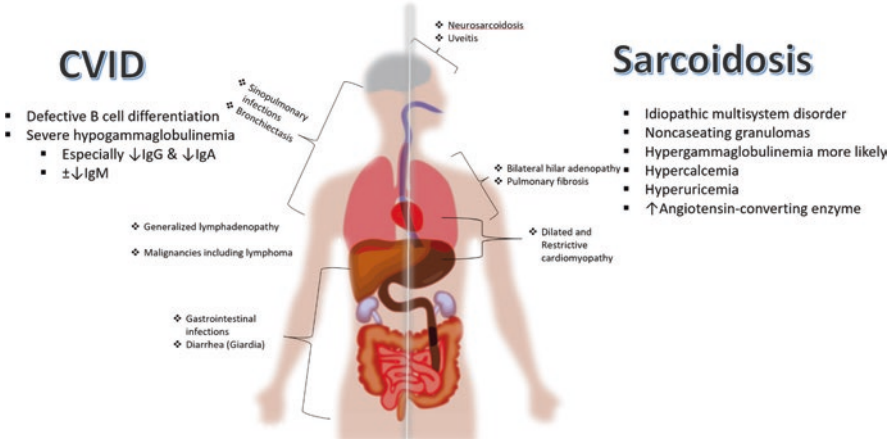

Fig. 6.1 Comparison of CVID and sarcoidosis [3, 5]. CVID, common variable immune deficiency; Ig, immunoglobulin

but because the presence of granulomas is a result of an independent process, they will not respond to IVIG alone [3]. Bronchiectasis is prevalent in the CVID population and is associated with poor prognosis; azathioprine improves the quality of life in these patients [3]. Serum immunoglobulin measurement is an inexpensive initial test that should be considered routine in patients suspected of sarcoidosis regardless of infection history; this ensures that CVID is correctly identified at an earlier clinical presentation and allows for prompt IVIG replacement [1].

Conclusion

Both immunodeficiency and autoimmune conditions may take several years of clinical evolution before diagnosis. Nevertheless, the arrival at a diagnosis is not an infallible step to the correct treatment, as described here. Serum immunoglobulin levels should be evaluated in suspected sarcoidosis, and granulomatous variants of CVID should be properly excluded before a final diagnosis is achieved. Patients with CVID should start IVIG early to avoid recurrent infections and resulting sequelae.

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Chapter 7
Confusion of Cutaneous Reactions: A Misdiagnosis of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome

Katarzyna Karpinska-Leydier

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Assess the overlapping presentation of drug reaction and eosinophilia with systemic symptoms (DRESS) syndrome and red man syndrome.
2. Recall the clinical timeline and risk factors of DRESS syndrome presentation.
3. Relate adverse drug reactions involving vancomycin or cross-reacting glycopeptide antibiotics with the onset of DRESS syndrome.
4. Recommend the use of the European Registry of Severe Cutaneous Adverse Reaction Criteria (RegiSCAR) clinical score in the assessment of vancomycin-associated drug reactions.
5. Apply the knowledge gained from this and similar cases where appropriate in future clinical settings.

Introduction

Rare and potentially fatal drug-induced reactions may not be immediate and can be challenging to connect with the inciting substance [1]. This creates a conundrum where the timing of drug administration, visual similarities between types of drug reactions, and rarity of certain conditions lead to misdiagnosis [1]. Drug reaction and eosinophilia with systemic symptoms (DRESS) syndrome commonly emerges between 2 and 8 weeks after drug administration with features of widespread rash,

K. Karpinska-Leydier (✉)
Internal Medicine, Florida State University - Cape Coral Hospital, Cape Coral, FL, USA

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fever, lymphadenopathy, transaminitis, and end-organ damage including kidney injury [1, 2]. Drug-induced hypersensitivity reactions are relatively common among hospitalized patients at approximately 3%; however, rarer conditions such as DRESS syndrome must be considered in patients receiving vancomycin [2].

Vancomycin is widely used in US hospitals and produces a range of drug reactions ranging from the reasonably common red man syndrome to rarer DRESS syndrome [3]. It is the first-line therapy for methicillin-resistant *Staphylococcus aureus* (MRSA) infections and an effective alternative for patients with contraindications to beta-lactam agents and active against gram-positive anaerobes [4]. However, only approximately 10% of hypersensitivity reactions to vancomycin are IgE-mediated [4]. RMS is a comparatively more common vancomycin hypersensitivity reaction, and often the first differential considered [5]. However, it can be distinguished from DRESS syndrome by a limited presentation with cutaneous eruptions more typical in the upper body and onset within minutes or hours of vancomycin administration [5]. RMS does not require prior sensitization to vancomycin as it is mediated through MAS-related G protein-coupled receptor X2 [4]. Likewise, vancomycin can be readministered without desensitization since it is not an IgE-dependent reaction [4]. Another similar differential to consider is Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), where features are consistent with cutaneous eruptions of the face and thorax, including blistering mucosal involvement, sparing the palms and soles [5].

Risk factors for vancomycin hypersensitivity reactions are those that increase the possibility of systemic absorption: these are often renal insufficiency, high dose (over 500 mg/day), prolonged exposure (longer than 10 days), and severe *Clostridium difficile* infection, including age over 65 years [6]. Some patients may be more prone to vancomycin-related reactions leading to multisystem compromise due to genetic variations in human leukocyte antigen (HLA) [7]. The case discussed here illustrates the difficulty in diagnosing DRESS syndrome linked with vancomycin administration [1].

Clinical Case Presentation

A female patient aged 44 years in a skilled nursing facility presented with a pruritic, diffuse, erythematous facial rash and a high fever persisting for 2 weeks. The course of the rash was waxing and waning over the course of the day with sudden progression every morning. Over the next week, she was given a trial of oral antihistamines without improvement. The rash grew to involve the patient's legs and evolved to encompass the upper extremities and trunk. Upon questioning, it was determined that she had received intravenous vancomycin for osteomyelitis 4 weeks before the onset of the rash. This prompted suspicion for red man syndrome

(RMS); however, no improvement was noted on the antihistamine trial. Physical exam revealed bilateral conjunctival injection, facial edema, fissuring of lips, and lymphadenopathy. The rash appeared diffuse and erythematous to violaceous patches with periorbital sparing, discrete patches on the extremities, and trunk without blistering. Initial labs showed leukocytosis with 13% eosinophilia, elevated creatinine, and electrolyte abnormalities which prompted suspicion for acute kidney injury, indicating organ involvement. Punch biopsies confirmed spongiosis with small Langerhans abscesses, interface dermatitis in lichenoid pattern with cellular infiltrates in the upper dermis, and eosinophils. The cumulative presentation of the patient's history, physical examination, and histopathological findings determined that DRESS syndrome (drug reaction with eosinophilia and systemic symptoms) is the correct diagnosis. This realization further explained why treatment with antihistamines was ineffective and why it was ultimately discontinued in favor of management with high-dose oral prednisone and fluids. She showed significant clinical improvement in cutaneous eruption and acute kidney injury. The patient was discharged on an oral prednisone taper with outpatient follow-up.

Differential Diagnosis

1. Drug reaction and eosinophilia with systemic symptoms syndrome (DRESS) – DRESS syndrome is a potentially fatal delayed hypersensitivity caused by a handful of medications. Onset is between 2 and 8 weeks after exposure, and symptoms including diffuse rash, facial edema, lymphadenopathy, fever, and organ involvement may follow. Eosinophilia may be present. Diagnosis is clinical and may include a skin biopsy but must meet RegiSCAR criteria. Prompt withdrawal of the inciting medication is necessary, in addition to supportive care and corticosteroids, as was done in the resolution of this case.
2. Red Man Syndrome – Red man syndrome is a vancomycin infusion-related anaphylactoid reaction that presents almost immediately on exposure with pruritis, an erythematous rash of the upper body, and may include angioedema and chest pain. The histamine release is proportionate to the vancomycin dose received. Management is the immediate discontinuation of vancomycin, and it responds well to H1 or H2 antihistamines. Management with antihistamines did not improve the condition of this patient.
3. Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis –These are clinically similar severe drug hypersensitivity reactions afflicting the skin. Antibiotics, anti-seizure medications, and sulfur-containing drugs are most commonly implicated. Lesions are widespread and macular, which coalesce, causing blis-

tering and necrosis. Diagnosis is clinical, and treatment is supportive in addition to plasmapheresis, IVIG, or corticosteroids. In SJS, less than 10% of the body is affected; in TEN, up to 30% of the body area is affected. This presentation did not meet the criteria for SJS/TEN as it was nonblistering.

What Was Misdiagnosed in This Case and Why?

Drug reaction and eosinophilia with systemic symptoms syndrome was initially misdiagnosed as red man syndrome and given antihistamines without improvement until DRESS syndrome was recognized and treatment was started with high-dose oral prednisone.

Discussion

Hospitalized patients present a complex scenario where several medications, an unclear timeline, and varied clinical presentation convolute arrival at an accurate diagnosis. The case discussed here exemplifies the difficulty of diagnosing DRESS syndrome [1]. The patient was notably given intravenous vancomycin for more than 10 days to treat osteomyelitis prior to rash onset [1]. Antihistamines, the typical therapy for RMS, were ineffective, and the rash spread to cover the legs, trunk, and upper extremities [1]. Rash morphology included diffuse erythema to violaceous patches with periorbital sparing and bilateral conjunctival injection, lymphadenopathy, facial edema, and mucosal fissuring [1]. Initial labs showed leukocytosis, eosinophilia, electrolyte abnormalities, and elevated creatine, while a punch biopsy demonstrated morphology suspicious morphology for DRESS syndrome, including eosinophils [1]. Although vancomycin is implicated in DRESS syndrome, more common inciting agents include antiepileptics, sulfonamides, and allopurinol [1]. Furthermore, cross-reactivity between vancomycin and other glycopeptide antibiotics such as teicoplanin and telavancin is shown to induce DRESS syndrome [8, 9]. The common heptapeptide core present in all glycopeptide antibiotics is implicated in cross-reactivity; however, this remains controversial due to demonstrated tolerability to vancomycin post-teicoplanin-induced DRESS [9]. Genetic predisposition contributes to the risk of these reactions; specifically, the HLA-A*32:01 variant in European populations is strongly linked with vancomycin-associated DRESS syndrome [9, 10]. HLA testing could improve patient safety and prevent high-risk drug reactions [10].

DRESS syndrome is a clinical diagnosis of exclusion using the European Registry of Severe Cutaneous Adverse Reaction Criteria (RegiSCAR) clinical

score; however, many reported cases do not report a RegiSCAR score and, therefore, lack a standardization across patient records [11]. RegiSCAR is an accurate tool that can improve the diagnosis of DRESS syndrome by considering eosinophilia, lymphadenopathy, organ involvement, rash morphology, fever, and atypical lymphocytes [7]. Objective scoring is beneficial for diagnostic certainty, which is the purpose of assessing cases such as those discussed here where the initial treatment reflects misdiagnosis of DRESS syndrome [11]. When RegiSCAR is used in drug reactions with an unusual presentation, the path to diagnosis and treatment is clearer [12]. This has been demonstrated in presentations with multiorgan dysfunction, including metabolic encephalopathy, which is considerably underreported in literature [12]. Prompt identification is necessary for the management of DRESS syndrome [12]. An association between DRESS syndrome and intravenous vancomycin is recognized in the literature despite a lack of awareness in clinical settings; however, vancomycin through other administration routes has also been implicated in these reactions [13]. A recognition of the specific drugs implicated in DRESS syndrome and the use of these drugs through different methods of administration must be considered as part of the diagnostic picture [13].

Antihistamines are effective against RMS as it is a syndrome related to histamine release seen in rapid vancomycin infusions [13]. DRESS syndrome is widespread and associated with eosinophilia, with a reversible course dependent on discontinuation of the implicated drug and therapy with topical or systemic corticosteroids [14]. However, in steroid-resistant cases, immunosuppressive agents include cyclosporine or cyclophosphamide [14]. Intravenous immunoglobulin replacement or plasma exchange may also be used in severe DRESS [14]. The patient discussed in this chapter was initially treated with antihistamines ineffectively, which delayed necessary treatment with high-dose oral prednisone and supportive care [1].

Nevertheless, withdrawal of the offending agent is the only proven step to decrease mortality [1]. Early recognition through careful review of medications and timing of symptoms could have improved diagnostic accuracy and punctuality in this case [1]. Furthermore, genetic testing, where feasible, can further categorize vancomycin-related reactions in sensitive HLA populations [10]. Standardization of RegiSCAR to determine the probability of DRESS syndrome in similarly presenting cases may be useful in minimizing the occurrence of misdiagnoses and may still be valuable in the revision of information where initial treatment is ineffective, as seen in this case [1, 11] (Table 7.1).

Table 7.1 RegiSCAR Criteria for the diagnosis of DRESS

Criteria	Criteria has been met?	Criteria not met	Unknown if Criteria has been met	Comments
Fever ≥38.5° C	0	−1	−1	
Enlarged lymph nodes	1	0	0	>1cm size in ≥2 different areas
Eosinophilia	1 or 2	0	0	≥700/μL or >10% = 1
				≥1500/μL or ≥20% = 2
Atypical Lymphocytes	1	0	0	
Rash	1	0	0	≥50% of body surface area
Rash suggestive for DRESS	1	−1	0	≥2 symptoms of facial edema, purpuric changes, infiltration, desquamation
Skin biopsy suggestive for DRESS	0	−1	0	
Duration	0	−1	−1	Disease lasting >15 days
Organ involvement	1 or 2	0	0	1 organ involved = 1
				≥2 organs involved = 2
Investigations to exclude other	1	0	0	≥3 negative results for tests including: Blood cultures, antinuclear
Likelihood of DRESS	**Excluded**	**Possible**	**Probable**	**Definite**
Total Score	<2	2-3	4-5	≥6

RegiSCAR European registry of severe cutaneous adverse reactions, *DRESS* drug reaction with systemic symptoms, *HAV* hepatitis A virus, *HBV* hepatitis B virus, *HCV* hepatitis C virus

Conclusion

Vancomycin is associated with several distinct adverse drug reactions involving a skin rash. Nevertheless, prompt and accurate identification is necessary for precise treatment. The offending agent must be immediately discontinued to minimize potential mortality. Appropriate treatment is dependent on the specific diagnosis. RegiSCAR is important in the diagnosis of DRESS syndrome; however, it is not currently standardized and often neglected in recorded case descriptions. Symptom chronology, HLA genetic testing, and RegiSCAR scores are considerations for improving the identification of DRESS syndrome.

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Chapter 8
The Dish with the Fish: Scombroid Poisoning Misdiagnosed as Food Allergy

Arseni Khorochkov

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Raise clinical awareness of scombroid poisoning.
2. Familiarize clinicians with the history and presentation of scombroid poisoning.
3. Suggest the addition of allergy testing for patients presenting with scombroid poisoning.
4. Differentiate between food allergies and scombroid poisoning.
5. Appropriately manage patients with scombroid poisoning to reduce the need for unnecessary treatments and unwarranted avoidance of fish.
6. Apply the knowledge gained from this case presentation to identify and treat patients with scombroid poisoning.

Introduction

The public generally recognizes common food allergies; however, even frequent seafood diners may not be aware of scombroid poisoning. Scombroid poisoning or histamine fish poisoning is a foodborne histamine toxicity caused by the consumption of improperly handled fish such as tuna or mackerel and can easily be mistaken for an allergic reaction to fish [1–4].

When ingested, these toxic histamine levels may manifest clinically within minutes to hours with symptoms resembling, which is often misdiagnosed as a type 1 hypersensitivity food allergic reaction [1, 3]. The typical presentation includes rash, flushing, gastrointestinal abnormalities, and headaches [3]. More serious

A. Khorochkov (✉)
California Institute of Behavioral Neurosciences and Psychology, Fairfield, CA, USA

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symptoms, such as hypotensive shock, bronchospasm, or cardiac arrhythmia, have also been reported, especially in patients with underlying comorbidities [3, 5]. Due to its presentation, scombroid poisoning can be easily misdiagnosed as a seafood allergy, resulting in patients avoiding certain foods unnecessarily [6].

Histamine is a heat-stable amino acid product from the decarboxylation of histidine by anaerobic bacteria typically found in fish flora [3]. It can generate histamine rapidly, usually reaching toxic levels in under a few hours [3, 5, 6]. This histamine generation can occur due to inadequate handling or storage conditions [7]. Furthermore, signs of spoilage, such as color change or foul smell, do not have to be present for the fish to be hazardous, and after the histamine has formed, it will not be broken down from cooking [6, 7]. The following case demonstrates how the similar presentation of scombroid toxicity to an allergic reaction can easily lead to an improper diagnosis of seafood allergy [1].

Clinical Case Presentation

A 53-year-old male presented to the emergency department with a sudden onset of nausea, vomiting, diarrhea, headache, and skin flushing that began an hour ago. The patient reported feeling well before having an ahi tuna salad for lunch which he stated had a "peppery" taste, but he still ate the entire meal. After approximately 10–15 mins, he experienced a sudden onset of headache, fatigue, diaphoresis, pruritus, nausea, and abdominal cramping, followed by voluminous non-bloody diarrhea. He denied having any recent sick contacts and recent travel. On presentation, the patient was afebrile, hypotensive (88/57 mmHg), tachycardic (130 beats/min), and tachypneic (24 breaths/min). Physical exam showed cutaneous flushing with diaphoresis and reported some nausea and feeling warm. The patient was initially given a 1-liter bolus of saline, and further work-up was done. The echocardiogram (ECG) showed sinus tachycardia with ST-segment depression in the inferior and lateral leads and a slight elevation in the aVR lead. The patient denied any chest pain. His labs indicated elevated lactate, glucose, blood urea nitrogen (BUN) levels, and decreased hematocrit and potassium levels, raising the suspicion of acute kidney injury (AKI). Normal troponin levels helped to rule out myocardial infarction. Differential diagnoses included anaphylaxis, allergic reaction to seafood, acute coronary syndrome, staphylococcal food poisoning, ciguatera toxicity, and scombroid poisoning. Although the patient did not display any respiratory symptoms or compromised airway, epinephrine was ordered. Treatment included the administration of corticosteroids, H1 and H2 antagonists, and 2 L of intravenous saline. Shortly after treatment, the patient's condition improved, and his heart rate decreased to 100 beats/min. Repeat ECG and troponins came back normal. The patient remained under cardiac observation overnight due to his initial ECG presentation. After 24 h, the patient's AKI resolved, his blood work-up returned to normal, and he was discharged. The restaurant where the patient had the ahi tuna salad was informed of scombroid poisoning.

Differential Diagnosis

1. Anaphylaxis – The patient presented with hypotension, tachycardia, palpitations, tachypnea, flushing, pruritus, urticaria, diaphoresis, nausea, abdominal cramps, diarrhea, and dizziness shorty after consuming fish. However, there was no previous history of anaphylaxis when consuming seafood.
2. Allergic reaction to fish/seafood – The patient presented with flushing, pruritus, urticaria, diaphoresis nausea, abdominal cramps, diarrhea, and dizziness shortly after consuming fish. The patient did not have a history of previous fish allergy.
3. Acute coronary syndrome – The patient presented with hypotension, tachycardia, palpitations, tachypnea, flushing, diaphoresis, nausea, and dizziness. This is unlikely due to normal troponins.
4. Staphylococcal food poisoning – The patient presented with nausea, abdominal cramps, and diarrhea after consuming fish. Pruritus and urticaria are unusual symptoms with this differential.
5. Ciguatera toxicity – The patient presented with pruritus, urticaria, nausea, abdominal cramps, diarrhea, and dizziness shortly after consuming fish. However, the patient does not have a history of recent fish consumption known to cause ciguatera toxicity.
6. Scombroid poisoning – The patient presented with hypotension, flushing, pruritus, urticaria, diaphoresis, nausea, abdominal cramps, diarrhea, and dizziness shortly after consuming fish.

What Was Misdiagnosed in This Case and Why?

This case was misdiagnosed due to the lack of clinical awareness of histamine fish toxicity in non-maritime areas combined with the general presentation, including a history of fish consumption followed by sequelae of allergy-like symptoms.

Discussion

In this case, a 53-year-old male presented with headache, pruritus, diaphoresis, nausea, vomiting, and diarrhea shortly after consuming a tuna fish salad at lunchtime. Vital signs showed hypotension, tachycardia, and tachypnea, so initial differentials included anaphylaxis, seafood allergy, acute coronary syndrome, staphylococcal food poisoning, ciguatera toxicity, or scombroid poisoning. After further investigation, the patient was treated with epinephrine, steroids, and antihistamines resulting in a rapid recovery [1].

Scombroid poisoning results from the massive influx of histamine produced by bacteria in oily fish [4]. When present at temperatures above 39.2° C Fahrenheit

(4° C Celsius), these bacteria enzymatically convert histidine found in the fish's muscles into heat-stable histamine, which, when ingested, leads to the activation of histamine receptors throughout the body [5, 6, 8]. This results in allergy-like symptoms such as those seen in the case report (e.g., pruritus, flushing, headache, palpitations, vomiting, diarrhea, etc.) [5, 6]. In more severe cases, anaphylactic-like reactions such as hypotensive shock, bronchospasm, respiratory distress, and cardiac arrhythmia have been reported [5, 8]. Due to its similar presentation, scombroid poisoning is often mistaken for an IgE-mediated allergic reaction to fish and, more commonly so, in situations where only one person has been poisoned [4]. Since patients would be misdiagnosed with food allergies, they are often told to avoid fish unnecessarily [1, 5, 7, 9].

As previously mentioned, the pathogenesis behind scombroid poisoning is the significant and sudden increase in histamine levels [1–13]. In this aspect, IgE-mediated allergic reactions and scombroid poisoning are relatively similar; both have elevated histamine levels, with the difference lying in the origin of the histamine [6]. IgE-mediated allergic reactions release histamine and other chemical mediators via degranulation of mast cells and basophils [6]. Therefore treatment options can potentially target these cells to prevent further histamine release. In scombroid poisoning, treatment would focus mainly on the sequestration of the exogenous histamine and its effects as mast cells and basophils are not involved [10].

In the case described, the patient's presentation was akin to an allergic reaction and, as such, can easily be misdiagnosed as a food allergy without diligence in obtaining a history [2, 3, 11]. Although the fish implicated in scombroid poisoning will not show any signs of spoilage (i.e., no change in color, taste, or smell), some patients may report oral burning or numbness with a peppery or metallic taste shortly after consuming the fish meat [1, 5, 7, 10]. Physicians should pay close attention to these initial symptoms as they tend to be more specific to scombroid poisoning [1, 6].

Ideally, the diagnosis would be made from the clinical evaluation, serum histamine levels, and detection of toxic levels of histamine in an uneaten sample of the fish However, since extracellular histamine has a relatively short half-life, serum testing must be done within 24 h of the initial exposure [5]. Under safe conditions, an oral challenge test or skin prick test can determine whether seafood elimination is necessary [12, 13]. ECG and troponins can also help narrow down the differentials by ruling out the possibility of myocardial infarction since patients may present with coronary artery vasospasms [1, 4, 10].

Fortunately, the H1 and H2 receptor blockage with antihistamines is the appropriate initial treatment for both allergic reactions and scombroid poisoning [9]. However, unlike in IgE-mediated allergic reactions, further treatment of scombroid poisoning with glucocorticoids, or epinephrine, does not directly affect the extracellular histamine levels and will not be beneficial [5]. Scombroid toxicity is self-limiting and usually resolves completely within 24 h but in some cases can last longer [5, 11]. Patients will typically make a full recovery and can resume eating fish without further concern for similar reactions, provided the fish is appropriately handled [4] (Fig. 8.1).

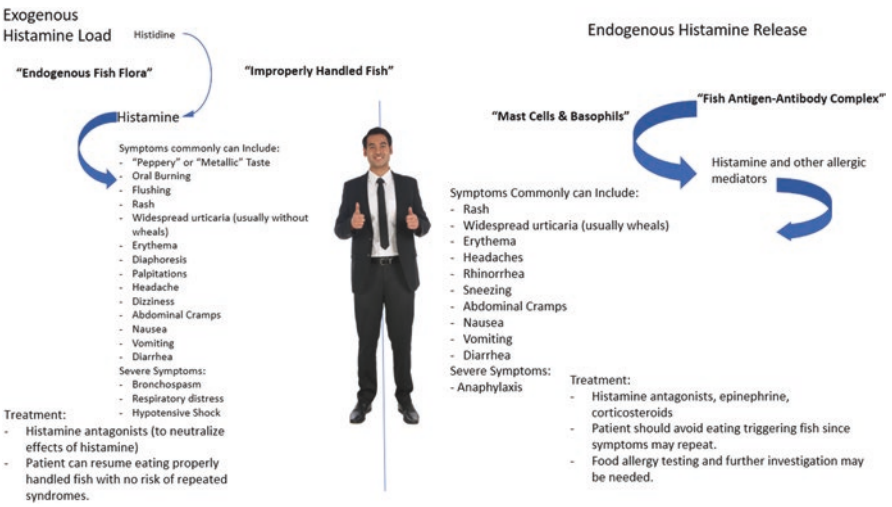

Fig. 8.1 Comparing scombroid poisoning with fish allergies [6, 7, 14]

Conclusion

When scombroid poisoning is misdiagnosed, it is most commonly mistaken for an allergic reaction to fish, a condition with a prevalence of 0.6% for newly manifested fish allergies in adults. However, since food allergies are commonplace, they are more likely to be considered [6]. Scombroid poisoning is not IgE-mediated and will not result in worse symptomatology with subsequent antigen exposure. It, therefore, does not activate a type 1 hypersensitivity reaction in the patient. As a result, future consumption of dark-meat fish will not lead to a similar sequela of symptoms, provided the fish was adequately handled [10, 11].

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Chapter 9
Using Indirect Immunofluorescence in Unveiling Unknown Pemphoids and Avoiding Misdiagnosis

Arseni Khorochkov

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Assess the differential diagnoses for unusually presenting bullous pemphigoid, including anti-p200 pemphigoid and epidermolysis bullosa acquisita.
2. Review the available substrates for indirect immunofluorescence.
3. Recommend that further work be done to obtain commercially available tests for anti-p200, anti-p105, and anti-laminin 332.
4. Propose the use of indirect immunofluorescence as part of a standard autoimmune bullous disease workup.
5. Apply this knowledge to similar cases in future clinical settings to minimize the likelihood of misdiagnosis.

Introduction

It is somewhat of a coin flip for patients presenting with a rash as to whether the referral trajectory will lead them to specialists in allergy and immunology or dermatology. Bullous pemphigoid (BP) is the most diagnosed autoimmune bullous disease (AIBD) with histological characteristics of subepidermal blisters, eosinophils, and direct immunofluorescence (DIF) features of immunoglobulin G (IgG) or C3 basement membrane zone (BMZ) depositions [1]. BP presents with an extremely pruritic rash consisting of urticarial plaques and subepidermal blisters that may affect the mucosa [2]. It more commonly affects older female patients, and approximately one in five patients may have an initial non-bullous phase [3]. Furthermore,

A. Khorochkov (✉)
California Institute of Behavioral Neurosciences and Psychology, Fairfield, CA, USA

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some studies show that autoantibodies for AIBD among the healthy population are generally low, suggesting that these diseases may develop over time [4].

However, less common subsets of AIBD are often overlooked; anti-p200 pemphigoid is a rarer form with IgG antibodies directed against laminin gamma-1, a 200 kDa protein within the basement membrane lamina lucida [5]. BP is recognized by autoantibodies against BP180 and BP 230 [6]. While these and many other variants of pemphigoid may afflict patients presenting with cutaneous symptoms, the standard workup for BP remains limited, which in the case chosen here for discussion can lead to initial treatment failure as a result of misdiagnosis [1]. Anti-p200 pemphigoid shares the BP200 target with epidermolysis bullosa acquisita (EBA), which is considered another close differential but additionally targets anti-laminin 332 [7]. IIF microscopy with salt-split human skin in BIOCHIP can distinguish between floor-binding and roof-binding immune reactants, as well as offer a form of fluid blister testing standardization [7–9].

Immunofluorescence is an essential tool for the diagnosis of autoimmune blistering disease; direct immunofluorescence (DIF) is the current standard; however, the higher sensitivity for salt-split skin methodology in indirect immunofluorescence (IIF) is necessary in suspected BP refractory to treatment and may reflect an initial inaccuracy in diagnosis [1, 10]. Here we see a case where the initial misdiagnosis of BP due to incomplete workup was rectified by further investigation with IIF confirming anti-p200 pemphigoid [1]. The current gold standard of BP diagnosis is DIF visualization of membrane-bound autoantibodies in the skin or mucosa, together with clinical features [11]. However, DIF without further workup with IIF is not capable of differentiating between entities of pemphigoid disease as demonstrated here [7].

Clinical Case Presentation

A male patient aged 60 years sought medical assistance for a generalized, blistering rash. It was erythematous with papules and herpetiform vesicles on the trunk, axillae, palms, upper extremities, buttocks, inner thighs, toes, and ulcers on the tongue palate.

Punch biopsies for routine histopathology and direct immunofluorescence (DIF) showed a subepidermal blister with neutrophils, a linear band of C3, and IgG at the dermal-epidermal junction suspicious for unusual bullous pemphigoid (BP). However, further histopathology and DIF were consistent with BP. The patient started oral dapsone without improvement despite taking 50 mg prednisone daily for over a month with persistent flaring.

He was then started on dupilumab; however, the presentation was concerning for an AIBD other than BP, warranting further workup. Repeat biopsies showed a subepidermal blister with a mixed dermal infiltrate and a smooth band of IgG and C3 with an n-serration pattern consistent with BP.

Nevertheless, enzyme-linked immunosorbent assay (ELISA) for BP antibodies was not supportive. ELISA was negative for antinuclear antibodies, as was ELISA for antibodies which ruled out paraneoplastic pemphigus, pemphigus vulgaris, pemphigus foliaceus, and epidermolysis bullosa acquisita. Indirect immunofluorescence (IIF) on rat bladder epithelium and monkey esophagus was negative, thus eliminating pemphigus vulgaris and paraneoplastic pemphigus. However, IIF on salt-split skin showed strong binding of IgG4 and IgG antibodies to the dermal floor, consistent with EBA, anti-laminin 332 mucous membrane pemphigoid (MMP), anti-p105 pemphigoid, and anti-p200 pemphigoid. There is a lack of commercially available tests for anti-p200 (laminin gamma-1), anti-laminin 332, or anti-p105, which could ease this diagnostic process. By exclusion, the patient was diagnosed with anti-p200 pemphigoid, the most common pemphigoid that shows serum antibodies binding to the dermal floor of human salt-split skin IIF, thus revising the initial diagnosis of BP. Furthermore, in contrast to BP, anti-p200 pemphigoid exhibits prominent mucosal, palmoplantar, and cephalic involvement. This was seen in the patient with an earlier onset age than BP. Anti-p105 pemphigoid is less likely due to the clinical presentation, as it clinically resembles toxic epidermal necrolysis or pemphigus vulgaris. Dupilumab was discontinued in favor of an increased dose of prednisone to 100 mg daily, two infusions of rituximab separated by 2 weeks, and initiation of dapsone 100 mg daily. He experienced promising improvement and continued on prednisone 60 mg daily 1 month after the last dose of rituximab.

Differential Diagnosis

1. Anti-p200 Pemphigoid – Is a rare subepidermal condition belonging to autoimmune bullous disease. It is diagnosed by indirect immunofluorescence through the identification of a 200-kd protein. Clinical characteristics include urticarial plaques and tense blisters with erosions that mimic bullous pemphigoid and epidermolysis bullosa acquisita.
2. Bullous Pemphigoid—Is a disorder of autoimmune blistering where bullae are fluid-filled, larger than 1 cm, and pruritic. It more commonly affects patients above age 70. Autoantibodies target hemidesmosomes in the epidermal-dermal junction, mainly at BP180 and BP 230, which distinguishes it from even rarer forms of pemphigoid. Direct immunofluorescence shows a linear band. Topical steroids are first-line management.
3. Epidermolysis Bullosa Acquisita – Is a chronic blistering autoimmune disease affecting the cutaneous and mucosal regions. Autoantibodies target type VII collagen in the dermal-epidermal junction. It presents as blisters, erosions, fragile skin, and nail loss. Supportive care and maintenance of the skin barrier are mainstays for management.

What Was Misdiagnosed in This Case and Why?

The patient was misdiagnosed with bullous pemphigoid confirmed by direct immunofluorescence which was later corrected to the diagnosis of anti-p200 pemphigoid after an unsuccessful course of treatment and further workup with indirect immunofluorescence.

Discussion

AIBD encompasses various entities of BP, including anti-p200 pemphigoid [1]. However, the initial workup with DIF is not sufficient to distinguish these subsets and can lead to a treatment-resistant course due to initial misdiagnosis [1]. The patient discussed in the highlighted case had DIF and histopathology results concerning for a rare BP [1]. No further workup was done at this time, and treatment was started on oral dapsone without improvement despite receiving prednisone for 1 month [1]. Additional trials with dupilumab and prednisone were ineffective [1]. Eventually, enzyme-linked immunosorbent assay (ELISA) for BP antibodies were inconsistent with the clinical presentation; IIF showed strong binding of IgG and IgG4 BMZ antibodies to the dermal floor, and it was eventually determined to be anti-p200 pemphigoid despite a lack of commercially available screening tools for anti-p105 also present in this subset [1]. The patient continued to have flares until management was revised to a higher dose of prednisone, two infusions of rituximab, and dapsone daily [1].

The diagnosis of AIBD starts with the clinical characteristics and a patient encounter detailing the disease [12]. Next, histopathology may provide information differentiating between pemphigus and pemphigoid disease [12]. Currently, DIF microscopy is the gold standard for detecting tissue-bound antibodies, with a specificity of 98% and a sensitivity of 91%; however, there is a limit to the antigens that can be targeted [12]. Characteristic linear binding of IgG and C3 at the dermal-epidermal junction is typical of pemphigoid disease, while further pattern differentiation determines the subset [12]. Nevertheless, serological detection of circulating antibodies is minimally invasive and does not require a biopsy [12]. It relies on IIF used in conjunction with DIF for a complete clinical picture [12]. Recombinant antigens can also be used in ELISA, which has added value in monitoring disease activity [12].

Further complicating the presentation of AIBD, not all patients with BP form blisters [14]. Unusual AIBD presentations are still largely uncategorized: BP may be mimicked by unique forms of bullous eczema and only identified by biopsies showing eosinophilic spongiosis [13]. The diagnosis of both bullous and non-bullous pemphigoid variants necessitates a full workup including both DIF and IIF; ELISA is valuable for monitoring the activity of the disease [14]. Specifically, clinicians should be aware that IIF can differentiate between BP and epidermolysis bullosa acquisita, as in the discussed case, they performed several tests, and a diagnosis was

determined by process of elimination [1, 15]. The use of rat bladder epithelium as a substrate in IIF has been shown to be a more sensitive substrate for the diagnosis of BP as compared to monkey esophagus, although it is comparatively lacking in specificity; nevertheless, it is easier and faster than the salt-split skin technique which is a benefit in the timely distinction of BP from EBA [16]. However, the predictive values of IIF have not yet been standardized [17]. Alternative studies suggest that monkey esophagus may be a more reliable substrate if pemphigus vulgaris or pemphigus foliaceus are suspected [17]. Conversely, normal human skin in some literature is preferred to monkey esophagus because it is at least as sensitive for serological BP diagnosis, and BP180 is genetically different in humans and monkeys [18].

Full diagnosis workup for AIBD includes a clinical examination, lesional skin biopsy for histology, DIF of a perilesional sample, and IIF of serum on monkey esophagus [18]. With the standardization of this process, fewer misdiagnoses are likely in suspected AIBD; IIF is a necessary component to distinguish BP from other rarer conditions, including anti-p200 pemphigoid [1]. Commercially available tests for anti-p200 (laminin gamma-1), anti-p105, and anti-laminin 332 would be assets in the diagnostic clarity of AIBD [1]. The awareness of rarer AIBD types, including anti-p200 pemphigoid and epidermolysis bullosa acquisita, availability of these commercial tests, and standard practice of IIF in the diagnostic workup can minimize delays in finding appropriate treatment strategies [1]. The patient in the assessed case arrived at the diagnosis of anti-p200 pemphigoid; however, there is continued suspicion for other yet undiscovered forms of pemphigoid; nevertheless, the original misdiagnosis of BP was excluded [1]. Clinicians can benefit from increased awareness of AIBD types and the use of IIF in the diagnostic strategy [1].

Conclusion

Subsets within AIBD often have similar presentations within this group, and BP is primarily the most diagnosed. However, BP may appear similarly clinically and with partial workup, including DIF microscopy. It is only on further investigation with IIF that a distinction is evident between BP, anti-p200, and epidermolysis bullosa acquisita. Increased clinical awareness for rare AIBD presentations, the standardization of IIF, and the development of targeted commercial tests will reduce the likelihood of misdiagnosis.

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Part II
Cardiology

Chapter 10
Infective Endocarditis Misdiagnosed as Community-Acquired Pneumonia

Ravi Vintha and Prakrut Nishamanish Sethi

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Discuss the important facts about community-acquired pneumonia.
2. Differentiate between community-acquired pneumonia and aortic valve endocarditis.
3. Compare and contrast between aortic valve endocarditis and noninfective endocarditis.
4. Differentiate clinically between aortic valve endocarditis and prosthetic valve thrombosis.
5. Analyze the consequences of a misdiagnosis or delay in reaching a correct diagnosis for the individual patient prognosis, for the transmission of bacterial endocarditis, and for public health.

Introduction

The diagnosis and treatment options for community-acquired pneumonia have been widely addressed by healthcare experts for decades, but unfortunately, the diagnostic errors still occur often in clinical practice. Community-acquired pneumonia, according to many authors, is one of the most misdiagnosed illnesses, with diagnostic mistakes ranging from 7% to 67% [1, 2].

R. Vintha (✉) · P. N. Sethi
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: ravi.vintha@martinus.edu; prakrut.sethi@martinus.edu

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On the one hand, various illnesses have been identified as "masks of pneumonia." Community-acquired pneumonia, on the other hand, can resemble a variety of conditions, including neurological problems and acute abdomen. Any illness with a high incidence of respiratory symptoms is extremely likely to be diagnosed as community-acquired pneumonia in clinical practice [3–6].

Making a diagnosis of community-acquired pneumonia or ruling it out may appear simple due to clear guidelines and diagnostic criteria. However, when patients are in a severe state, especially if they have a fever and/or respiratory failure, ruling out pneumonia can be challenging [6, 7].

Differential Diagnosis

1. Noninfective endocarditis/nonbacterial thrombotic endocarditis (NBTE) – Nonbacterial thrombotic endocarditis is a rare, noninfective form of endocarditis due to sterile platelet thrombus formation on the heart valves (usually mitral and aortic valves). There can be many causes for the disease like malignancy, hypercoagulable states, underlying trauma, previous rheumatic fever, and autoimmune conditions like systemic lupus erythematosus, rheumatoid arthritis, and antiphospholipid syndrome. Chronic infections like tuberculosis, pneumonia, and osteomyelitis can also lead to nonbacterial thrombotic endocarditis. The clinical features compared to infective endocarditis, vegetations are easily dislodged, and embolization is common, leading to hemorrhages under the nails, skin, and retina. Most affected individuals are asymptomatic until embolization occurs. In infective endocarditis, the body's response is inflammation, whereas nonbacterial thrombotic endocarditis does not cause an inflammatory response. Biopsy is the definitive diagnosis:
    - Sterile vegetations on either surface of the valve are composed of immune complexes, mononuclear cells, and thrombi interwoven with fibrin strands.
    - Not always feasible, therefore diagnosis is mostly made based on the clinical findings, no response to antibiotic treatment, negative blood cultures, and echocardiography findings. Treatment: anticoagulation with heparin [8–10].
2. Prosthetic valve thrombosis (PVT) – It usually affects mechanical valves and is rare if anticoagulation is adequate. It is caused mainly due to insufficient anticoagulation therapy after valve replacement. The clinical features shows signs of acute heart failure:
    - Left heart failure: difficulty breathing and cough
    - Right heart failure: jugular venous distention and edema
    - Other signs and symptoms include deterioration of general condition, cardiac arrhythmias, and cerebral emboli, i.e., stroke.

- Prosthetic valve thrombosis is diagnosed by transesophageal echocardiography while it is treated by
- Anticoagulation and fibrinolysis
- Surgical valve replacement [11]

Clinical Case Presentation

A 48-year-old man was admitted to intensive care in a critical condition with the primary diagnosis of severe community-acquired pneumonia of both lower lobes of both lungs. The patient complains of shortness of breath at rest, exhaustion, chest pain that worsens with deep breathing, and a fever of up to 40 °C. On admission: patient is awake but disoriented, with pale skin, marked dyspnea at rest, respiratory rate of 32, oxygen saturation of 92 percent, temperature of 40 °C, heart rate of 90 per minute, and blood pressure of 90/60 mm hg. The lungs were examined and found to have weak vesicular breathing in both lower lobes. Heart auscultation reveals a modest systolic murmur at the apex, and leukocytosis on the complete blood count.

Past Medical History: He has been sick for the past 11 days. Fever and exhaustion were the first signs. He began taking an antibiotic (can't recall the name of the prescription) on the first day of his illness, but it had no clinical effect. The fever remained, and chest pain had happened 2 days before admission.

Concomitant diseases:

- Spontaneous coronary artery dissection (SCAD): class III
- Myocardial infarction (2016)
- Persistent atrial fibrillation (AF)
- CHADS2-VASC score: 0 (*c*ongestive heart failure, *h*ypertension, *a*ge ≥ 75 years, *d*iabetes mellitus, prior *s*troke, *v*ascular disease, *a*ge 65–74 years, *s*ex *c*ategory) [12]
- Congestive Heart Failure: CHF,II A with preserved ejection fraction (EF) (58%)
- He took aspirin 100 mg and bisoprolol 5 mg regularly for these ailments. In the intensive care unit, the patient was given intravenous ceftriaxone 2,0 g + levofloxacin 500 mg, as well as oxygen. The patient did not demonstrate any clinical improvement after 48 hours of treatment. The patient's vital signs were temperature up to 40 °C, chest pain, leukocytosis, C-reactive protein 239 mg/l, T2 levels 96 ng/ml. Atrial fibrillation paroxysm on electrocardiography (ECG). Troponin testing was negative.

Discussion

The computed tomography scan revealed no infiltration in the lung tissue, but it did reveal minor hydrothorax and hydropericardium. Hence, bacterial endocarditis was suspected in the patient. As a result, he had echocardiography, which revealed only aortic valve fibrosis and mitral and tricuspid valve regurgitation, and ejection fraction was retained (58%). As these tests confirmed that the earlier diagnosis and treatment administered for community-acquired pneumonia were incorrect, the course of treatment was changed to an antibacterial treatment (vancomycin 1,5 g + meropenem 3 g daily), and an antiarrhythmic drug was introduced (amiodarone 600 mg daily). The patient showed mild clinical improvement but deteriorated again on the sixth day of treatment. Another echocardiography was conducted, and this time there was evidence of possible aortic valve vegetation. The patient was sent to the department of cardiac surgery for further evaluation (transesophageal echocardiography) and treatment. Unfortunately, he deteriorated and died 24 h after the move. Aortic valve endocarditis was established by autopsy. The absence of clinical symptoms of pneumonia as well as infiltrative alterations on computed tomography scan helped to rule out community-acquired pneumonia in this patient. High levels of indicators of systemic inflammation and disease progression, on the other hand, were suggestive of a septic process, and paroxysms of atrial fibrillation, as well as episodes of left ventricular failure, helped to suspect and diagnose bacterial endocarditis. However, the pathological process continued for much too long before the diagnosis was verified, resulting in multiple organ insufficiency.

Conclusion

In conclusion, we wanted to use this clinical case to emphasize the significance of differential diagnosis in severe patients who are first suspected of pneumonia but later lack adequate clinical proof. In order to achieve an accurate diagnosis as quickly as possible, it's vital to keep in mind a variety of potentially fatal diseases that look like pneumonia, especially the ones discussed earlier. Despite advancements in diagnostic and microbiological methods, infectious endocarditis is still associated with severe morbidity and mortality. Measures that have been proven to improve patient outcomes include early diagnosis, early participation of a focused infective endocarditis team, and rapid surgical surgery when necessary [7].

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Chapter 11
Cardiac Amyloidosis Misdiagnosed as Monoclonal Gammopathy of Undetermined Significance

Shitij Shrivastava

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Discuss the root causes which led to the false diagnosis of monoclonal gammopathy of undetermined significance (MGUS).
2. Describe the diagnostic steps involved in diagnosing cardiac amyloidosis.
3. Interpret the autopsy report of the patient.
4. Explain the history of amyloidosis.
5. Identify and enumerate the elements physicians must avoid when forming a differential for abnormal protein tests.

Introduction

In 1838, Matthias Schleiden first used the term "amyloid" to describe the composition of a type of starch in plants. Before the word amyloid came into practice, "lardaceous" or "waxy" was used to describe amyloid disease processes in the human body [1]. In 1856, Dr. Samuel Wilks, a British physician, biographer, and an avid user of the phrase "lardaceous disease," described a 52-year-old male patient with lardaceous kidneys, heart, and spleen. This was most likely the first case of primary amyloidosis reported in literature [1, 2]. However, the term "amyloid" persisted because of Virchow's experiment. He added iodine to the sulfated glycosaminoglycans (corpora amylacea) from brain tissue and what resulted was a color reaction from brown to blue, similar to starch [3].

S. Shrivastava (✉)
PGY-1, Internal Medicine, BronxCare Health System, Bronx, NY, USA

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A high index of suspicion for amyloidosis, positive family history, and biopsy are essential for the correct diagnosis of amyloidosis [4]. There are various types of amyloidosis, affecting different and multiple organs [5]. The majority of patients are affected by either AL (acquired monoclonal immunoglobulin light chain) or ATTR (transthyretin-related) type [6, 7].

Clinical Case Presentation

A 62-year-old female arrived at the hospital with fatigue, dyspnea, an abnormal mammogram, and pulmonary edema for at least 3 months. Her medical history included bilateral carpal tunnel syndrome (CTS), and her family history was positive for breast cancer. The EKG revealed a previous myocardial infarct and a single run of supraventricular tachycardia with normal sinus rhythm. Her chest X-ray was significant for mild bilateral pleural effusions and increased pulmonary congestion, which explained the orthopnea experienced by the patient. Laboratory tests showed highly elevated brain natriuretic peptide (BNP) (NT-proBNP, 2959 pg/ml) and troponin I of less than 0.3 ng/ml. The patient was hospitalized. An echocardiogram performed during hospitalization was notable for right and left ventricular (LV) systolic dysfunction, decreased ejection fraction (EF) (<20%), and right and left atrial dilation. Other echo findings were within normal limits. Former echocardiograms were unavailable. Cardiac index measured in the cardiac catheterization laboratory was 2.2 L/min/kg^2 (N: 2.5–4.0). 99 m technetium-pyrophosphate scan did not reveal any tracer uptake by the myocardium. Cardiac magnetic resonance imaging (CMR) revealed a normal LV wall thickness of 1.3 cm without late gadolinium enhancement (LGE) in the basal short-axis cine view. Urine protein electrophoresis turned out to be 62 mg/dl; however, serum protein electrophoresis with immunofixation (SPIE) was within normal limits. The clinicians considered a diagnosis of monoclonal gammopathy of undetermined significance. Serum-free light chain assay (SFLC) and bone marrow biopsy were taken into consideration as MRI and SPIE were normal, and the patient was negative for CRAB criteria for multiple myeloma. The authors never consulted hematology and oncology services [8]. Despite aggressive medical management, her initial symptoms continued to worsen, and she required hospital admission after 8 months for severe cardiogenic shock. Repeated measurement of the cardiac index was done, and it had gone down from 2.2 L/min/kg^2 to 1.6 L/min/kg [2]. The patient finally underwent a breast biopsy due to her abnormal mammogram and family history. Pink, amorphous substance was observed under the microscope, and a diagnosis of light chain (AL) amyloidosis was entertained. Hematology/oncology service was consulted, and SFLC assay, repeat echocardiogram, and urine protein immunofixation (UPIE) tests were performed. This time, the echocardiogram showed an interventricular thickness of 1.1 cm (vs. 0.8 cm previously), global hypokinesis, and mild dilation. Serum kappa and lambda levels were 22.1 mg/dl and 880 mg/dl, respectively (ratio: 0.03), and

urine immunofixation showed abnormal free lambda light chains. Subsequent tests (cardiac and bone marrow biopsies) could not be performed as the patient, unfortunately, passed away. Her clinical status had faded very rapidly [8].

Differential Diagnosis

1. Monoclonal gammopathy of undetermined significance
2. Breast cancer
3. Light chain amyloidosis

What Was Misdiagnosed in This Case and Why?

In this ill-fated cardiology case, cardiac amyloidosis was misdiagnosed as MGUS due to normal apparent imaging and lack of resources [8]. Multiple reasons come into play when we dig deeper into the root causes.

Discussion

There are nine types of amyloidosis that have cardiac involvement. Usually, invasive and noninvasive diagnostic tests are combined to assist in diagnosing cardiac amyloidosis. It typically presents with both cardiac and extracardiac organ involvement. Such symptoms and signs are known as red flags. They include but are not limited to skin bruising, macroglossia, proteinuria, vitreous deposits, and unexplained elevated troponin. The current position statement published by the European Society of Cardiology (ESC) states that if the clinical picture, EKG, echocardiogram, and CMR point toward cardiac amyloidosis, then scintigraphy and monoclonal protein assessment must be made. If both are positive, histological analysis is the next step to confirm the subtype. Histological confirmation should also be done if both CMR and hematologic tests are positive (or CMR is inconclusive) and scintigraphy is negative. If tests reveal no monoclonal spike and grade 1 uptake on scintigraphy, a biopsy becomes necessary for diagnosis. Grade 2–3 on scintigraphy indicates ATTR amyloidosis, and the patient must undergo genetic testing to distinguish between acquired and hereditary forms (Fig. 11.1) [9].

Endomyocardial biopsy showing amyloid fibrils in the heart is the gold standard of diagnosis. Red flag signs are not always there, but when present, they can dramatically help in adding amyloidosis to the differential. One such finding is reduced longitudinal strain with apical sparing on echocardiogram [9]. In this case, the authors state that strain imaging was unavailable as they hadn't updated their

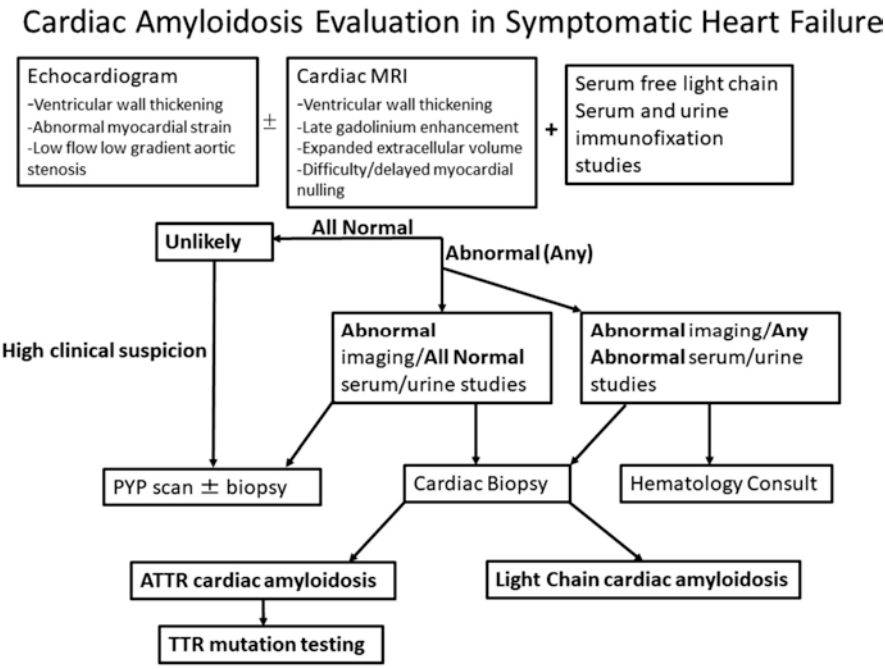

Fig. 11.1 Approach to cardiac amyloidosis evaluation in symptomatic heart failure [8]

software. After upgrading their system, a second look at the images showed longitudinal strain of −2 without apical sparing. It is interesting to note that LGE was nearly absent, and left ventricular wall thickness was normal in this patient despite having advanced disease. Septal thickness was also within normal limits initially. Although unlikely, the patient might have had recent AL amyloidosis on top of preexisting dilated cardiomyopathy. One can argue against this assumption due to the abrupt clinical decline and heart failure progression. Lack of LGE could have been falsely absent due to the high amyloid burden and small cellular volume. Due to the fact that profound heart failure due to amyloidosis could not have occurred until there was myocardial infiltration, CMR was rechecked, and difficulty in nulling the myocardium was seen, which was earlier reasoned to be a motion artifact. The characteristic above is seen explicitly in infiltrative disorders. In the presence of normal wall thickness, absence of LGE, and normal SPIE, labeling the nulling as a motion artifact seemed appropriate [8].

Additionally, T1 mapping equipment was not available in the hospital, and the patient never underwent T1 mapping for diagnosis [8]. In approximately 17% of patients, a free light chain might be the only protein present, leading to a negative serum protein electrophoresis result. Combined UPIE, SPIE, and SFLC quantification have a sensitivity of 99% to detect AL amyloidosis. SFLC assay can pick up minute amounts of kappa and lambda chains [10].

Plan of Action: The Points Clinician Should Consider – Pitfalls to Avoid

Don't delay a biopsy in cases with abnormal protein tests, and make sure that the patient is compliant with follow-up appointments. Comprehensive care and high clinical suspicion of cardiac amyloidosis are vital for early diagnosis and management. Atypical presentations of amyloidosis may be seen in a few cases which require meticulous attention to detail, clinical history, and imaging studies. If needed, a referral to a quaternary center must be made for advanced imaging to take place. A difficulty in nulling the myocardium is most commonly seen in infiltrative disorders [8] such as cardiac amyloidosis, hemochromatosis, etc.

Pearls of Knowledge to Consider

AL-type amyloidosis is an aggressive systemic disease that can affect the heart. The threshold for diagnosis must be low, especially in patients with carpal tunnel syndrome, troponin elevation with normal left and right heart catheterization, and oncology must be consulted. Cardiac MRI must be carefully read and analyzed for nulling of myocardium and thickness of the interventricular septum. Serum and urine protein tests, cardiac imaging, and tissue biopsy are able to provide a definitive diagnosis in uncertain cases.

If Misdiagnosed, Was It Realized Later?

Sadly, the patient died before endomyocardial and bone marrow biopsies could be obtained and appropriate therapy could be started. On autopsy, amyloid deposits were discovered in the heart and lungs. Interventricular septum thickness had increased from 1.1 cm to 2.3 cm since the last echocardiogram. Hypercellular bone marrow, cardiomegaly, plasma cell infiltration, and LV wall thickness of 2.0 cm were observed [8].

Conclusion

Cardiac amyloidosis requires a prompt diagnosis as the disease can progress rapidly and eventually be fatal. Endomyocardial biopsy must not be deferred, regardless of circumstances, and a team approach must be used while diagnosing and interpreting abnormal protein studies.

Original Article Link: https://www.cureus.com/articles/77219-slip-ups-in-the-diagnosis-of-cardiac-amyloidosis-a-case-fatality-in-point

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Chapter 12
Metastatic Heart Cancer Misdiagnosed as Acute Myocardial Infarction

Ravi Vintha and Prakrut Nishamanish Sethi

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Discuss facts about acute myocardial infarction.
2. Explain about metastatic cancer of the heart.
3. Distinguish between the cardiac and noncardiac conditions that can mimic the electrocardiography changes similar to those seen in ST elevation myocardial infarction.
4. Differentiate metastatic cancer of the heart from other conditions.
5. Discuss conditions to be considered as a differential diagnosis for metastatic cancer of the heart.

Introduction

The most common cause of ST-elevation myocardial infarction is atherosclerosis, which leads to coronary blockage. Since the positive effects of reperfusion therapy are maximum when performed rapidly, early coronary reperfusion is required for ST elevation myocardial infarction. Electrocardiography (ECG) alterations comparable to those found in ST elevation myocardial infarction have been seen in a range of cardiac and noncardiac diseases. Central nervous system disease, perforated duodenal ulcer, esophageal rupture, acute pancreatitis, pneumothorax,

R. Vintha (✉) · P. N. Sethi
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: ravi.vintha@martinus.edu; prakrut.sethi@martinus.edu

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pneumomediastinum, hyperkalemia, hypocalcemia, hypercalcemia, pheochromocytoma, and normal variations are all noncardiac diseases that mimic ST elevation myocardial infarction. Early repolarization, pericarditis, myocarditis, hypertrophic cardiomyopathy, Brugada syndrome, and patients with left ventricular hypertrophy and left bundle branch block have all been linked to electrocardiography abnormalities that mirror ST elevation myocardial infarction [1]. However, there have been a few reports of ST elevation myocardial infarction mimics in patients with cardiac tumors. When compared to metastatic cardiac tumors, primary cardiac tumors are quite rare. Despite this, antemortem detection of cardiac metastases is uncommon due to the fact that the majority of them are clinically silent [2]. In this case report, an electrocardiography alteration simulating acute anterior ST elevation myocardial infarction was documented in a patient undergoing therapy for tongue cancer.

Clinical Case Presentation

A 63-year-old man was taken to the emergency room after experiencing an immediate onset of chest pain. The patient was diagnosed with tongue cancer 2 years ago. The tumor was completely resected, and radiotherapy was used to finish the procedure. There were no reported symptoms for the last 3 years. He had no previous history of serious systemic disorders like diabetes, hypertension, or cardiovascular disease.

On examination, he appeared to be in good health, with the following vital signs:

Blood pressure: 129/74 mm Hg
Pulse rate: 74 beats per minute
Respiratory rate: 17 breaths per minute
Body temperature: 36.5 degrees Celsius
Oxygen saturation: 95%

The heart sounds were normal, and no abnormalities were discovered during the chest examination. A repeat surface 12-lead electrocardiogram revealed sinus rhythm with ST segment elevation in all anterior leads, which was consistent with an acute anterior wall myocardial infarction. An urgent coronary angiography was performed on the patient, which indicated noncritical stenosis of the coronary artery.

An X-ray of the chest revealed a clear pulmonary examination and a moderately dilated heart. A large tumor affecting the free wall of the right ventricle and filling the hollow was discovered using standard transthoracic echocardiography.

Furthermore, echocardiography indicated right ventricle wall hypokinesia from the middle to the apex, confirming tumoral invasion. Transthoracic echocardiography revealed a D-shaped left ventricle in the short-axis view. To obtain precise information about the mass, computed tomography scan with contrast and magnetic resonance imaging were used. Finally, the presence of a tumor in the right ventricle was established.

Serial cardiac troponin readings were consistently negative, despite ST elevations on the electrocardiogram remaining static. Based on the tumor's echocardiographic features and the patient's past history, we assumed it was a metastasis from primary tongue cancer. The patient sought further consultation to the oncology department after a referral was made. Sepsis occurred during the follow-up, and the patient died 2 months after metastatic heart malignancy was discovered.

Differential Diagnosis

Other than metastasis, a differential diagnosis to consider is a primary cardiac tumor, such as myxoma, vegetation, or thrombus. Taking into account the position of the mass, as well as its echogenicity, and integrating all of this information with the patient's medical history, can often lead to an appropriate diagnosis.

Discussion

A case of tongue cancer with cardiac involvement was reported, with electrocardiography alterations that resembled acute myocardial infarction. Before the echocardiography was in use, only sporadic case reports diagnosed the right-sided cardiac tumors by angiography and diagnosed the right-sided cardiac tumors by angiography, and, however, detecting a tumor in the heart by echocardiography is not always straightforward [3].

For best imaging of heart morphology, most clinicians consider transesophageal echocardiography to be the procedure of choice. Due to swallowing difficulties and a history of neck irradiation, our patient did not undergo transesophageal echocardiography. Additional imaging modalities, such as computed tomography scan and magnetic resonance imaging, can aid in determining the exact location and amount of extracardiac extension, as well as demonstrating the lesion's impact on adjacent structures [4].

A thoracic computed tomography scan was used to discover cancer involvement in the myocardium that had previously gone undetected. To examine neoplastic infiltration of the heart, diagnostic methods such as echocardiography, magnetic resonance imaging, and computed tomography can be used. Such patients have a very high surgical death rate. Cardiac metastases are a difficult clinical problem due to their rarity and poor prognosis [2, 5]. Individualized treatment plans should be implemented in a multidisciplinary manner, taking into account the patient's functional capacity, tumor features, and past treatment.

Despite the fact that surgery appears to be the best option at this time, cardiovascular metastasis has a terrible prognosis, with an average life expectancy of fewer than 6 months after diagnosis [6]. In our case, the electrocardiography revealed a typical anomaly. The exact etiology of this electrocardiogram abnormality is

unknown; however, it could have been caused by myocardial injury to the RV apex wall caused by the metastatic tumor [7]. Similarly, metastasis, tumor invasion into the heart, tumor emboli within a coronary artery, or a metastatic lesion around a coronary artery can all cause a neoplastic process.

This patient did not have the typical enzyme and electrocardiography changes associated with acute myocardial infarction. A metastatic tumor had infiltrated the pericardium and myocardium, causing the ST segment elevation. Continuous myocardial injury, which prevents the formation of new cardiac cell membranes, stretched adjacent muscle fibers, inflammatory reaction, ionic potassium transfer from necrotic tissue to the adjacent myocardium, and potassium transfer from damaged tissue to the adjacent myocardium, all of which produce electric potential differences, are suggested mechanisms for these pseudo-infarction electrocardiography patterns [8]. An electrocardiography anomaly comparable to ST segment elevation in myocardial infarction was reported by Na et al. in a case of mimicking ST segment elevation in myocardial infarction [9]. In another example, it was reported that the electrocardiogram revealed a specific anomaly (ST segment).

With metastatic heart disease, there is an increase and T inversion in leads V1–V6. Detailed history, physical examination, basic laboratory testing, or imaging studies can all help diagnose urothelial carcinoma [10]. In such circumstances, acute myocardial infarction should be ruled out [11]. As a result, invasive procedures can be avoided.

Conclusion

In conclusion, this is a case of metastatic cancer of the heart that was identified primarily as an acute myocardial infarction. However, this diagnosis was refuted by the clinical presentation, serial cardiac enzyme values, and persistent ST elevation observations. When electrocardiography alterations without classic angina are seen in a patient with malignancy and negative cardiac enzymes in the blood, metastatic myocardial infiltration due to the tumor should be suspected.

Especially in patients with unusual presentations, such as loss of consciousness and no chest pain, echocardiography is essential for confirming the diagnosis of myocardial infarction or ischemia when patients show electrocardiography alterations that are suggestive of these conditions. Patients with chronic ST elevation and unexplained hypercalcemia, particularly those with known or suspected malignancies, should have metastatic malignancy considered in the differential diagnosis. Furthermore, coronary catheterization was recommended to distinguish between true coronary occlusion and fake infarction electrocardiogram patterns in patients with high cardiac enzyme levels, notwithstanding the rarity of myocardial infarction caused by cancer.

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Chapter 13
Primary Cardiac Synovial Sarcoma Misdiagnosed as Tuberculoma

Shitij Shrivastava

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Discuss the reasons which led to a false diagnosis of a tuberculoma.
2. Describe and explain the histopathology of primary cardiac synovial sarcoma.
3. Learn about the epidemiology of cardiac tumors.
4. Enumerate the diagnostic methods used to diagnose cardiac sarcomas.
5. Distinguish the clinical signs in patients with primary cardiac synovial sarcomas.

Introduction

Primary cardiac synovial sarcoma comprises 1 in every 20 cardiac sarcomas and less than 0.1% of all primary cardiac tumors [1]. Synovial sarcomas (or malignant synovioma) are seen in all age groups in males and females but usually present in young males. The distal extremities are most commonly involved. It is a rare disease and not understood very well. The predominant literature on cardiac tumors comprises case reports rather than their microscopic profile [2]. Case reports on cardiac synovial sarcomas (including those of secondary origin) date back to 1958 on PubMed [3].

In 1988, Sheffield et al. described a case of a primary cardiac synovial sarcoma arising from a benign mesothelioma of the atrioventricular (AV) node [4]. Until April 1997, only six cases of primary synovial sarcomas of the heart had been described [5]. They most commonly arise from the right side of the heart, and most patients have general, unclear symptoms which coincide with other cardiac

S. Shrivastava (✉)
BronxCare Health System, Bronx, NY, USA

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pathologies. This makes diagnosing primary cardiac synovial sarcomas challenging. They can be either biphasic or monophasic. The mean age of presentation is 32.5 years, and age ranges from 13 to 66 years [6, 7].

Clinical Case Presentation

A 31-year-old, female, Caucasian, presented to the emergency department complaining of fatigue and increasingly severe dyspnea for 2 weeks. Her past medical history was insignificant. The patient reported anorexia, 8 kg weight loss, and physical weakness during the last 3 months. The patient started having New York Heart Association Class IV dyspnea and general fatigue in the previous 10 days. Her brother, whom she lived with, had been receiving medical treatment for pulmonary tuberculosis (TB), although the patient was not taking prophylactic drugs. The patient required admission for her symptoms. Vital signs were as follows: heart rate, 130 bpm; blood pressure, 100/64 mmHg; and oxygen saturation, 94%. On the physical exam, muffled heart sounds were heard. No murmurs, bruits, rubs, or gallops were audible. Jugular venous pressure was normal and peripheral edema was absent. Chest X-ray, echocardiogram, and electrocardiogram (EKG) were ordered on Day 1. Chest X-ray revealed a cardiothoracic ratio of 0.7, along with striking cardiomegaly. The EKG was significant for diffuse T-wave inversion with normal sinus rhythm. A mass with the dimensions of 27 mm × 35 mm was observed in the right atrium. Echocardiogram also showed large-sized pericardial effusion. The left ventricular ejection fraction (LVEF) was 65%, and the inferior vena cava (IVC) measured 18 mm. The IVC vessel was compliant. Antinuclear antibody (ANA) and rheumatoid factor (RF) were negative. Additional routine blood tests were within normal limits except for serum C-reactive protein, which was elevated to 24.5 mg/L. Given the shortness of breath in light of pericardial effusion, pericardiocentesis was performed. One liter of bloody, exudative fluid was removed. The pericardial fluid was lymphocytic predominant and protein-rich (66 g/L). Adenosine deaminase (ADA) level was 17 UI/L. However, neoplastic cells were lacking in cytologic analysis [8]. On the third day of admission, cardiac magnetic resonance imaging (CMR) demonstrated an immobile intracavitary solid mass of the right atrium, measuring 39 mm × 28.5 mm (Fig. 13.1). The mass displayed lobulated contours and was fixed to the wall opposite the emergence of the IVC. CMR was negative for vascular, local, or systemic infiltration. The authors presumptively diagnosed the mass as tuberculoma, owing to the patient's history of living with her brother and not receiving TB preventive treatment (TBT). The next day she was scheduled for a surgical biopsy. Numerous metastatic lesions and vesicles were discovered on the heart, large vessels, and pericardium. Further surgery was deferred after frozen examination established their neoplastic origin. Pathological examination of biopsy specimens of neoplastic masses was notable for monophasic cardiac synovial sarcoma. A translocation investigation was not done; she died 3 days later from cardiac tamponade [8].

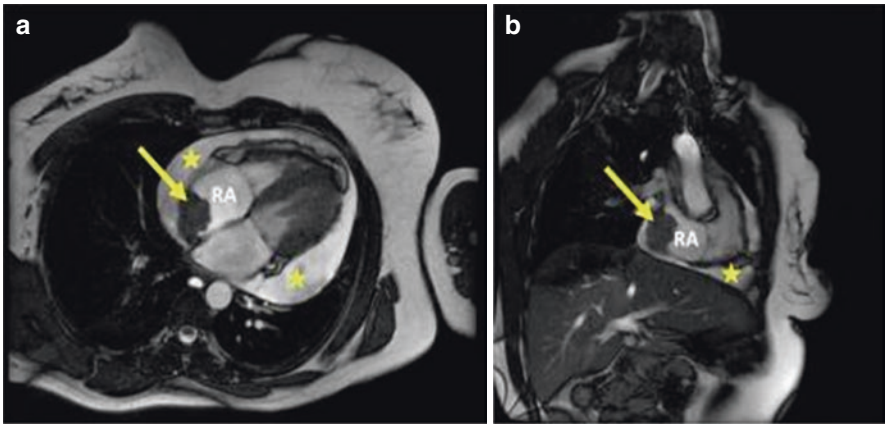

Fig. 13.1 CMR in axial T2 FIESTA (**a**) and sagittal T2 FIESTA (**b**) showing an intracavitary right atrial (yellow arrows) mass with pericardial effusion (yellow stars) [8]

Differential Diagnosis

1. Primary cardiac synovial sarcoma
2. Tuberculoma

What Was Misdiagnosed in This Case and Why?

In this case, a synovial cell carcinoma of the heart was misdiagnosed as a tuberculoma. The authors were fixated on the diagnosis suggested by the patient's social history and, therefore, never conducted a complete diagnostic workup [8].

Discussion

In the heart, secondary lesions are more frequently encountered than primary masses and are seen in 95% of cases. The most common histopathological subtype of benign cardiac tumors is myxoma. It is seen in 50% of patients, followed closely by cardiac fibromas, lipomas, hemangiomas, rhabdomyomas, papillary fibroelastomas, teratomas, pericardial cysts, or cystic tumor of the AV node. CMR and computed tomography scans can be employed as adjuvant imaging modalities. Transthoracic echocardiogram (TTE) and transesophageal echocardiogram (TEE) remain the gold-standard diagnostic tools [9].

Patients usually present with shortness of breath, signs of heart failure, and chest pain [10]. This patient, in our case, presented with dyspnea, fatigue, and weight loss

[8]. Such nonspecific symptoms make the diagnosis of primary cardiac synovial sarcoma very challenging. Like synovial sarcoma, a tuberculoma may also present with vague features such as arrhythmia or congestive heart failure [11]. In this particular case, the patient's brother was being treated for tuberculosis, and the patient was living with him without taking prophylaxis herself. Therefore, the diagnosis of tuberculoma was reinforced, given the patient's social and family histories [8]. Fewer than 70 primary cardiac synovial sarcomas have been reported in the literature [12]. Pericardiocentesis was negative for neoplastic cells. However, the absence of malignant cells does not exclude malignancy. In 2016, Ma et al. published a prospective cohort study evaluating the causes of moderate to large pericardial effusion requiring pericardiocentesis in 140 Chinese patients. They found that neoplastic cells might be missing in 25% of malignant effusions. There was no statistically significant difference noted in the ADA level in the TB subset (39.56 ± 27.05) compared to the malignant subset (41.61 ± 37.52) [13]. The ADA level of 17U/I was not high enough to classify the pericardial effusion as tuberculous. A cut-off level of 40 UI/L results in a sensitivity, specificity, and positive predictive value of 84.0%, 80.0%, and 91.0%, respectively. ADA synthesis in the body results from the factors associated with the immune response against TB antigens [14].

There are three subtypes of synovial sarcomas: biphasic, monophasic, and undifferentiated. The architecture of biphasic type is made up of gland-like epithelial structures and spindle cells. The epithelial part consists of amphophilic cytoplasm. Monophasic synovial sarcomas have infiltrative borders and scant amphophilic cytoplasm, whereas the poorly differentiated subtype has high mitotic activity, round cells, and hyperchromatic nuclei [15]. In the histological sections of the biopsy specimens, hematoxylin and eosin staining showed spindle cell proliferation, and immunohistochemistry revealed focal expression of epithelial membrane antigen and diffuse expression of cluster of differentiation – 99 antigen and B-cell lymphoma 2 protein [8]. CMR and echo are not very useful in discerning a tuberculoma from a cardiac synovial sarcoma [12], but CMR may help with surgical plantification [16]. A biopsy followed by histologic analysis, immunohistochemistry, and genetic investigation is the key to diagnosis [12].

Proper guidelines for treating primary cardiac synovial sarcoma are yet to be established. Further research is suggested in this area, but the rarity of the disease is a limitation for research. Although rarely possible, complete surgical excision is the gold standard of treatment [17]. Orthotopic heart transplantation may be performed, and its role continues to be discussed [18]. Bench surgery can be useful in accomplishing a more thorough tumor excision [19]. The authors note that their approach to diagnosis could have been different. TEE might have provided more insight on the tumor's connection to the pericardium, epicardium, or the endocardium. Positron emission tomography would have given some clues on additional masses and lymph node involvement, while coronary angiography would have detected the extent of vascularization of the mass. In this case, the mass could not be resected due to local invasion, and the resulting cardiac tamponade proved fatal [8].

Plan of Action: The Points Clinician Should Consider – Pitfalls to Avoid

It is crucial to have a thorough medical history when dealing with intracardiac masses. Subsequent imaging must not be delayed. The most important kinds of imaging are TTE, TEE, coronary angiography, and cardiac MRI. Then, a biopsy must be ordered to diagnose cardiac synovial cell carcinoma. Surgical resection is the mainstay of treatment.

Pearls of Knowledge to Consider

Elevated ADA levels are seen in cardiac sarcomas as well as tuberculomas. Neoplastic disease should not be ruled out in the absence of neoplastic cells in the pericardial fluid.

Conclusion

This case speaks volumes on the importance of having an extensive scale of differential diagnoses from the start when confirming the etiology of cardiac masses. Of special note, attention must be paid to the location of the tumor, the age of the patient, and clinical symptoms, and a team approach must be utilized. Though hard to think of, rare pathologies can prove to be fatal, especially if not recognized early. Local invasion can make it impossible to resect a primary cardiac synovial cell sarcoma, hence reinforcing the need for prompt diagnosis.

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Chapter 14
Severe Eccentric Mitral Regurgitation Misdiagnosed as Severe Aortic Stenosis

Shitij Shrivastava

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Discuss the cause of the misdiagnosis of mitral regurgitation as aortic stenosis.
2. Describe how transesophageal and transthoracic echocardiography can be used to identify mitral regurgitation and aortic stenosis.
3. Identify the factors responsible for the improvement in mitral regurgitation post-surgical aortic valve replacement.
4. Enumerate the causes of mitral regurgitation.
5. Describe and list the hemodynamic changes in patients with mitral regurgitation.

Introduction

Aortic stenosis gradients are often underestimated in presence of severe mitral regurgitation on echocardiography [1]. Rheumatic mitral regurgitation may present with mixed valvular pathology including severe AS. However, the hemodynamic interplay between the two may lead to improper estimation of the severity of cardiac echocardiography [2]. Transesophageal echocardiography or transcatheter assessment should be considered for proper measurement of gradients or MR gradings. Mitral valve regurgitation, simply known as mitral regurgitation, is the most common valvular heart disease followed by aortic stenosis in the western population [3]. Rheumatic pathology is the most common cause of multivalvular disease involving younger people. Degenerative disease affects the older population involving the mitral and aortic

S. Shrivastava (✉)
BronxCare Health System, Bronx, NY, USA

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valves. MR increases the volume overload of the left ventricle and also decreases the cardiac output and stroke volume. This creates a low-flow and low-gradient situation misleading the correct gradient across the aortic valve [4]. Aortic stenosis causes pressure overload of the left ventricle thus overestimating regurgitant volume of MR jet. The aortic valve area may provide better information about coexisting AS in presence of severe MR. In our case, the patient was a 75-year-old female with chronic asthma and progressive dyspnea. She was misdiagnosed with severe aortic stenosis and moderate mitral regurgitation of degenerative etiology. Transthoracic echocardiography (TTE) also confirmed the same diagnosis. However, TEE carried out in the operating room (OR) revealed a normal aortic valve without any gradients and showed severe MR with flail posterior mitral leaflet due to ruptured chordae tendineae [5].

Clinical Case Presentation

In this publication by Kumar et al., an elderly female presented with long-standing asthma and ongoing dyspnea. She was referred to the authors as a diagnosed case of severe aortic stenosis and moderate mitral regurgitation. She was not in failure.

On TTE, her peak vs mean gradients across the aortic valve were 113 vs 75 mmHg. The patient also had moderate mitral regurgitation with normal left ventricular function and moderate pulmonary artery hypertension. Auscultatory findings revealed a systolic murmur at the apex and right second intercostal space radiating to the left axilla. Before surgery, coronary angiography was done which revealed normal coronaries.

The patient was planned for aortic valve replacement after due consent. In the OR, TEE was performed for a detailed evaluation of the pathology. Unexpectedly, the TEE showed flail posterior mitral leaflet and ruptured chordae causing severe eccentric mitral regurgitation. The aortic leaflets were opening well with good coaptation, and the gradients measured were peak/mean as 57/41 mmHg. TTE was repeated to understand the reason for misdiagnosis. The position of the continuous wave (CW) Doppler was adjusted diligently to avoid the MR jet while calculating the AS gradient. This time the true gradient could be measured which turned out to be low with near-normal aortic valve hemodynamics. Hence the surgical plan was revised after providing the new information to the patient's family and mitral valve replacement was carried out. Post-surgery, a TEE was done which demonstrated normal functioning of the mitral prosthesis, and no significant aortic valve gradients were observed. Her post-op course was unremarkable and she was discharged after 1 week [5].

Differential Diagnosis

1. Mitral valve regurgitation
2. Aortic valve stenosis

What Was Misdiagnosed in This Case and Why?

In this case, the patient's severe mitral regurgitation was misdiagnosed and reported as severe aortic stenosis. This was because of the nature and direction of the regurgitant jet which was toward the anterior mitral leaflet causing left ventricle outflow gradients. The authors didn't consider transesophageal echocardiography with multiple views in this patient preoperatively which could probably have assisted in reaching the proper diagnosis.

Discussion

Multivalvular heart diseases possess a diagnostic challenge in terms of their correct assessment of the severity of their hemodynamic intermingling causing variable effects on the heart. Rheumatic AS is commonly associated with MR of varying degrees. Mostly, severe MR causes low-flow-low-gradient aortic stenosis which falsely underpredicts the aortic valve gradients [1]. On the other hand, severe eccentric mitral regurgitation can mislead us to high trans-aortic gradients which may be normal [5]. The inaccuracy in proper diagnosis in patients with multivalvular heart disease is a challenge. The complexity of pathophysiology of the affected valves causes the valves to behave differently in different patients, affecting the heart function variably and often misleading the diagnosis. In this particular case, the MR jet was eccentric, hugging the anterior mitral leaflet and interfering with the reading of the aortic valve gradient. Abnormally high gradients were observed on CW which picked up the MR jet toward the LV outflow tract. Additionally, this patient had long-standing asthma causing a poor echocardiographic window contributing to the error in interpretation. The CW Doppler picks up systolic signals which are away from the probe, and both MR and AS have a systolic murmur which makes the assessment difficult. Electrocardiography gating during echocardiography is essential for excellent correlation with the cardiac cycle. Numerous views were obtained to establish the correct diagnosis and for accurate quantification of the images. A mid-esophageal long-axis view revealed smooth blood flow across the aortic valve without any turbulence. The short-axis images showed good coaptation of the aortic leaflets. Deep trans-gastric findings stated the peak and mean gradients as 4 mmHg and 2 mmHg, respectively [5]. Degenerative AS is frequently associated with MR in the west. The mixed lesions affect the dynamics of the heart chambers in a complex way. The antagonistic effects on the left ventricle with AS and MR dubiously estimate the ejection fraction as normal. The CW Doppler overestimates the MR and underreads the AS severity [6]. MR causes increased volume load on the LV, whereas AS causes pressure overload resulting in LV hypertrophy and reduced stroke volume. Consequently, there is a false estimation of low flow and low gradients with conserved LV function [7]. Transesophageal or transthoracic real-time

three-dimensional echocardiography with color Doppler images may deliver better judgment than 2D echocardiography [8]. Measurement of regurgitant volume can be more specific when Doppler quantification lacks accuracy. Though the "gold-standard" imaging type is still not defined, volumetric analysis is considered better than 2D Doppler as it overestimates the MR [9]. Cardiac magnetic resonance imaging (CMR) can be used as an additional modality for the proper identification of the structure and function of the cardiac chambers and heart valves. The immediate and long-term outcomes are poor if moderate to severe mitral regurgitation is left behind during surgical aortic valve replacement [10]. MR magnitude post-SAVR is unpredictable. SAVR reduces LV pressure load thereby reducing the transmitral pressure and gradient. There are multifactorial predictors of MR severity improvement post-SAVR such as LV dimensions and volumes, ejection fraction, wall motion abnormalities, bundle branch block, etc. [11] A heart team approach for the best treatment plans and better short- and long-term outcomes should be recommended.

Plan of Action: The Points Clinician Should Consider – Pitfalls to Avoid

This patient was misdiagnosed with severe aortic stenosis in presence of moderate mitral regurgitation. The transthoracic echocardiography couldn't pick up the mitral regurgitation severity due to the eccentricity of the jet toward the left ventricle outflow tract. In this patient, multiple views of echocardiographic images with different measurements should have been contemplated to arrive at a certain diagnosis. Moreover, whenever such situations arise, a transesophageal echocardiography should always be considered before wheeling the patient to the OR. This will avoid surprises that are cumbersome and inappropriate for the patient and the family. Also, sudden changes in operating plans may not turn up with the desired results.

Pearls of Knowledge to Consider

In severe aortic stenosis associated with varying degrees of mitral regurgitation, a definitive diagnosis should be sought. Multiple views, several readings, and combinations of various measurements must always be observed. A detailed examination with transesophageal echocardiography with different views should be mandatory to avoid a misleading diagnosis. The direction of the MR jet should be analyzed intricately, especially when toward the anterior mitral leaflet to avoid misinterpretations as left ventricle outflow gradients.

Conclusion

Mixed valvular pathology is a common occurrence in rheumatic or degenerative diseases. Unerring quantification of the severity of stenotic or regurgitant lesions is a diagnostic predicament. Surgeons often land up in surprises in the OR which causes the change of operating plans. The precise determination of aortic stenosis gradients with concomitant severe mitral regurgitation can be misjudged. The position of the transducer probe during TTE can also lead to a false evaluation of the disease. Sometimes the transducer picks up the MR jet velocity and reads it as abnormally high aortic gradients. In this case, a similar thing happened as the regurgitant jet was directed eccentrically toward the anterior mitral leaflet close to the left ventricular outflow tract. Hence the initial TTE was reported as severe aortic stenosis along with moderate mitral regurgitation. TEE in the OR on various views ruled out any AS and reported a normally functioning aortic valve. On the contrary, the MR turned out to be severe, and the treatment approach was switched to mitral valve replacement. These diagnostic shortcomings can be overcome with a combination of various paradigms of echocardiography images. The application of 3D imaging techniques and transesophageal echocardiography with color Doppler quantification can curb the difficulties to a large extent. The use of CMR and the recent advances in technology can serve better results. This can provide meticulous and detailed information about LV function and volumes, valve morphology and their diseases, and other necessary calculations. In this case report, the patient underwent mitral valve replacement. The postoperative TEE showed good prosthetic valve function and a normally functioning aortic valve. Mixed lesions need to be evaluated carefully for better patient outcomes.

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Part III
Emergency Department

Chapter 15
A Case of Misdiagnosis of Hepatic Encephalopathy

Mohammad J. Ghosheh

Learning Objectives
By the end of this presentation, the clinician should be able to:

1. Discuss the classical presentation of hepatic encephalopathy and its variations in clinical practice.
2. Enumerate the processes of how to diagnose hepatic encephalopathy in the emergency department and know what the most appropriate investigations are.
3. Manage the different causes of hepatic encephalopathy and the precipitating factors.
4. Describe the grading of hepatic encephalopathy and know how to implement it in a clinical setting.
5. Summarize the pathophysiology of hepatic encephalopathy and apply the knowledge clinically.
6. Learn how to avoid misdiagnosing hepatic encephalopathy to facilitate a better treatment approach to reduce complications and get better outcomes.

Introduction

Hepatic encephalopathy (HE) is a disorder that presents with reversible neuropsychiatric impairment, usually accompanied by severe liver dysfunction. It manifests as fluctuations in mental and cognitive function that may progress to stupor and coma [1]. A diagnosis of hepatic encephalopathy may only be made after the

M. J. Ghosheh (✉)
Al-Faisal University College of Medicine, Riyadh, Saudi Arabia

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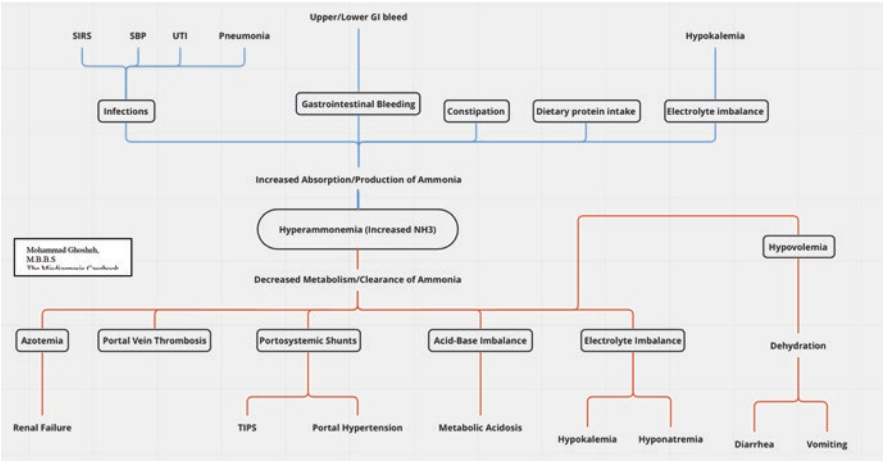

Fig. 15.1 Causes of hyperammonemia

exclusion of any other cause of cerebral dysfunction. Hepatic encephalopathy is believed to be caused by an abnormal accumulation of neurotoxic metabolites (i.e., ammonia, NH_3) in the systemic circulation [2]. Several studies have suggested that increased concentrations of ammonia have been directly associated with astrocyte swelling and cerebral edema, due to the excess glutamine produced as a result. Cerebral edema would cause an increase in the intracranial pressure and subsequently result in the neurological deterioration seen in hepatic encephalopathy patients [1, 3]. The diagnosis of hepatic encephalopathy is primarily based on both the patient's medical history and clinical presentation. A psychiatric assessment can be made by performing a mini-mental state examination. Moreover, laboratory studies should be done to evaluate serum ammonia levels. Hepatic encephalopathy most commonly presents due to a precipitating factor in patients with underlying liver dysfunction (i.e., cirrhosis). Avoidance and correction of the underlying factor and preventing the development of further complications are generally the mainstay of treatment. When considering the appropriate treatment for patients with hepatic encephalopathy, other serious concurrently present medical conditions such as hepatorenal syndrome, portal vein thrombosis, and portal hypertension should also be investigated. General treatment measures for hepatic encephalopathy patients depend on the precipitant factor. Hepatic encephalopathy due to hyperammonemia can be precipitated by two main factors [3–7]. Figure 15.1 illustrates the causes of hyperammonemia.

Table 15.1 Patient's vital signs

Parameters	Results
Blood pressure	106/48 mmHg
Heart rate	122
Temperature (Celsius)	37.2
Respiratory rate	20
O_2 saturation %	95

Clinical Case Presentation

A 53-year-old gentleman was admitted to the emergency department accompanied by his wife due to epigastric abdominal pain, confusion, and irritability that has been increasing for the past 2 days. His wife states that her husband has been acting strange recently and is unable to care for himself anymore and spends most of his time sleeping. She also mentions that he has been shouting at her recently and is "getting very frustrated with things we would normally enjoy doing together." The patient is drowsy, oriented to person only, and only arousable in response to pain. His Glasgow coma scale score is 11/15. The patient's vital signs are in Table 15.1.

The patient has lost his appetite for food and refuses to eat. He has lost 3 kg in the past 2 weeks. He has a known medical history of hypertension, gastroesophageal reflux disease, peptic ulcer disease, and alcoholic cirrhosis. His medications include esomeprazole, ramipril, and a laxative for when he occasionally gets constipated. He is a 20-pack-year smoker and has been drinking 4–6 beers a day for the past 30 years. He works in construction and is married with 2 children. His family history is only significant for diabetes and hypertension in his mother. General physical examination shows jaundice and multiple small bruises on his arms and legs. Neurological examination shows an altered level of consciousness, increased muscle tone, and rigidity in all extremities. His gait is abnormal, and he falls to the side when attempting to walk (Tables 15.2 and 15.3) [8].

Table 15.2 Patient's laboratory results

Parameters	*Results*	*Reference range*
Hemoglobin	9.4 g/dL	13.5–17.5
Hematocrit	31%	41%–53%
ESR	25	4.3–5.9
CRP	8	<10
Platelet count	131,000/mm^3	150,000–400,000
Leukocyte count	3800/mm^3	4500–11,000
Albumin	3.5 g/dL	3.5–5.5
Total bilirubin	2.2 mg/dL	0.1–1.0
AST	96	12–38
ALT	68	10–40
α-Fetoprotein	8	10–20
Creatinine	1.1	0.6–1.2
BUN	22	7–18
Anti-HAV IgG antibody	Positive	Negative
Anti-HBs antibody	Positive	Negative
Sodium	138	136–146
Potassium	3.6	3.5–5.0
Chloride	99	95–105
Bicarbonate	27	22–28
Urinalysis	*Results*	*Reference range*
Blood	1+	Negative
WBC	0	0–5 per high-power field
Protein	Negative	Negative
RBC	N/A	0–4 per high-power field
Nitrite	Negative	Negative
Ketone	Negative	Negative

Table 15.3 Differential diagnosis and associations

Differential diagnoses	Associations
Infections	Meningitis, encephalitis, intracranial abscess
Metabolic encephalopathy	Hypoglycemia, electrolyte imbalance, anoxia, hypercarbia, uremia, ketoacidosis
Alcohol-related encephalopathy	Acute alcohol intoxication, alcohol withdrawal, Wernicke's encephalopathy
Toxic encephalopathy	Sedatives, antidepressants/antipsychotics, salicylates
Hyperammonemia	Hepatic encephalopathy, urea cycle disorders
Intracranial lesions	Intracranial bleeds, stroke, tumor

Differential Diagnosis

Considering this patient's presentation, a devised list of differential diagnoses should have been formulated. An accurate list of differentials is a vital factor in

determining an accurate diagnosis and the most appropriate next step in management [9]. The table below summarizes the list of differential diagnoses and their associations based on the patient's history, physical exam, and laboratory evaluations [1, 2, 4, 9, 10].

Discussion

Based on the patient's medical/surgical history, clinical presentation, and laboratory evaluation, a diagnosisof hepatic encephalopathy remains only one of several other possible diagnoses. This patient's hemodynamic instability with cognitive disturbances and a history of chronic alcohol abuse may hold the emergency physician in doubt. Further investigations are the next best step in determining an accurate diagnosis.

This patient was suspected to have an episode of Wernicke's encephalopathy due to vitamin B1 deficiency. The patient was initially stabilized with IV fluids and a banana bag containing thiamine, folic acid, and magnesium sulfate. The patient showed slight improvement, and a diagnosis of hepatic encephalopathy was missed. The slight initial cognitive improvement might have been due to the nutritional and vitamin deficiencies that might have precipitated the encephalopathy in this patient. After further investigations, elevated serial ammonia measurements with an abdominal CT scan confirming alcoholic liver cirrhosis were sufficient to diagnose hepatic encephalopathy. Imaging of the brain may also be necessary for ruling out any important intracranial lesions that might cause similar symptoms [4, 5].

There are many important hepatic encephalopathy clinical features that every physician should be aware of, to prevent a potential misdiagnosis. Disorientation, alterations in consciousness, confusion, irritability, fatigue, memory loss, abnormal sleeping patterns, cognitive disturbances, slurring of speech, asterixis, and muscle rigidity are important clinical features that can support diagnosing hepatic encephalopathy [3, 4, 6, 7, 10].

The symptoms of hepatic encephalopathy have been graded into a well-known classification system. The West Haven classification system is divided into five grades, Grade 0 to Grade 4 in ascending order of severity [2, 3, 7]. After the diagnosis was established, this patient was assigned a Grade 2 on the West Haven scale. Subsequent to investigations, it was evident that the reason behind this patient's exacerbated hepatic encephalopathy was a bleeding peptic ulcer that increased the production of ammonia by the gut bacteria and ultimately its absorption into the systemic circulation [1]. The increase in ammonia levels with a cirrhotic liver that is unable to degrade the excess ammonia through the urea cycle precipitated the symptoms observed in this patient [4].

Ammonia is believed to induce hepatic encephalopathy in several ways. Increased levels of ammonia alter the transport of amino acids and impair their metabolism in the brain [3]. The altered amino acid metabolism results in increased levels of glutamine that ultimately results in astrocyte swelling and cerebral edema [3, 4]. The

treatment of hepatic encephalopathy is usually based on correcting the precipitating factor. In this patient, the precipitating factor was the increased production of ammonia in the gut from the bacteria due to the bleeding gastric ulcer. In general, rifaximin and lactulose are used as first-line pharmacotherapy for hepatic encephalopathy [3]. Lactulose is a synthetic disaccharide laxative that decreases the absorption of ammonia by acidifying the gut. This results in the conversion of ammonia to ammonium (NH_4^+) which is excreted in the feces, instead of being reabsorbed [3]. Rifaximin is a broad-spectrum oral antibiotic that kills ammonia-producing intestinal bacteria, resulting in less ammonia being produced [2].

Conclusion

Patients presenting with cognitive impairment and confusion with suspected liver cirrhosis should be evaluated for hepatic encephalopathy. A thorough diagnostic workup with precise laboratory investigation and imaging modalities should be conducted to rule out any other causes of encephalopathy. Hepatic encephalopathy is observed in more than 70% of patients with liver cirrhosis, and the accompanying symptoms are usually reversible [2, 10]. As discussed above, proper investigations and correct examination are essential to prevent misdiagnosis and further complications.

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Chapter 16
A Case of Misdiagnosis of Rhabdomyolysis

Mohammad J. Ghosheh

Learning Objectives
By the end of this presentation, the clinician should be able to:

1. Recite the clinical presentation of rhabdomyolysis and its variations in clinical practice.
2. Discuss how to diagnose rhabdomyolysis in the emergency department and know what the most appropriate investigations are.
3. Enumerate the different causes of rhabdomyolysis and the complications associated with it.
4. Recite the pathophysiology of rhabdomyolysis and apply the knowledge clinically.
5. Explain how to avoid misdiagnosing rhabdomyolysis to facilitate a better treatment approach to reduce complications and get better outcomes.

Introduction

Rhabdomyolysis is a clinical syndrome that results in the breakdown of skeletal muscle. The destruction of the muscle tissue results in the release of intracellular components into the bloodstream [1]. The intracellular components such as myoglobin, creatinine, and potassium that get released are primarily responsible for the symptoms observed in rhabdomyolysis. The acute tubular necrosis and intrinsic acute kidney injury that occurs in patients with rhabdomyolysis are a result of the released myoglobin and creatinine kinase into the bloodstream, directly causing obstruction of the intrinsic tubules and pigment nephropathy. Potassium and lactic

M. J. Ghosheh (✉)
Al-Faisal University College of Medicine, Riyadh, Saudi Arabia

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Table 16.1 Categories and causes of rhabdomyolysis

Traumatic	Non-traumatic
Crush injury	Ischemic necrosis
Prolonged immobilization	Drug-induced
Overexertion	Infections
Heat stroke	Autoimmune
Electrical injury	Intoxication

acid are similarly released into the bloodstream, and their increased concentrations consequently result in fatal cardiac arrhythmias and metabolic acidosis, respectively. Crush syndrome due to crush injury from trauma can cause hypovolemia and shock, both resultantly contributing to further kidney injury and azotemia. A classic diagnostic finding that is found specifically in acute kidney injury associated with myoglobinuria is the presence of blood on urine dipstick in the absence of red blood cells in the urine sediment. Prolonged untreated rhabdomyolysis can result in serious life-threatening complications such as kidney failure, compartment syndrome, and fatal arrhythmias. Therefore, an accurate diagnosis of rhabdomyolysis and its management all in a timely manner is necessary.

The causes of rhabdomyolysis can vary significantly and can present differently depending on the cause. It is essential to understand and distinguish the different causes of rhabdomyolysis and appreciate the different ways they can present.

The causes of rhabdomyolysis can be divided into two main categories as seen in Table 16.1 [2–4].

Clinical Case Presentation

A 26-year-old lady was admitted to the emergency department due to generalized muscle pain. She has recently started working out at the gym a total of 4 hours every day and eats a well-balanced diet.

She has a known medical history of recurrent kidney stones and urinary tract infections. She takes no medications, except for when she was hospitalized for a urinary tract infection 6 months ago. She is single and does not smoke and only drinks alcohol on occasions. She has no significant family history. General physical examination shows diffuse tenderness on palpation of both her arms and legs. Neurological examination is normal, and the patient is oriented to place, time, and person. She was discharged home on painkillers and was advised to refrain from exercising until her symptoms subsided. Later that day the patient was readmitted to the emergency department with worsening of her symptoms, vomiting, and blood in her urine. Her labs are shown below (Tables 16.2 and 16.3) [5].

Table 16.2 Patient's vital signs

Parameters	Results
Blood pressure	124/76 mmHg
Heart rate	67
Temperature (Celsius)	37.8
Respiratory rate	16
O_2 saturation %	96

Table 16.3 Patient's laboratory results

Parameter	*Results*	*Reference range*
Hemoglobin	12.4 g/dL	12.0–16.0
Hematocrit	42%	36%–46%
ESR	22	0–20
CRP	4	<10
Platelet count	250,000/mm^3	150,000–400,000
Leukocyte count	6900/mm^3	4500–11,000
Creatinine	1.8	0.6–1.2
BUN	27	7–18
Creatine kinase (CK)	5600	10–70
Lactate dehydrogenase	322	45–200
Sodium	142	136–146
Potassium	6.8	3.5–5.0
Phosphate	5.8	3.0–4.5
Calcium	7.8	8.4–10.2
Chloride	114	95–105
Bicarbonate	18	22–28
Urinalysis	*Results*	*Reference range*
Blood	3+	Negative
WBC	1–2	0–5 per high-power field
Protein	1+	Negative
RBC	N/A	0–4 per high-power field
Nitrite	Negative	Negative
Ketone	Negative	Negative

Differential Diagnosis

Based on the patient's initial symptoms upon arrival at the emergency department [6], a wide range of reasonable differential diagnoses could've been formulated. Listed below are the most important ones [6].

1. Myalgia – myalgia is a term used to describe muscle pain or discomfort. It is a very common symptom associated with rhabdomyolysis, yet it can be absent in many cases. Although myalgia is associated with rhabdomyolysis, it is only diagnosed independently in uncomplicated cases to describe simple muscle pain

due to strain, overuse, or tension. In this case, the presentation of myalgia is due to an underlying cause of rhabdomyolysis.
2. Infection – even though this patient's temperature is high, the absence of an elevated leukocyte count and localized symptoms such as redness and edema makes this diagnosis unlikely. Moreover, this patient's normal vital signs and absence of hemodynamic instability rules out the possibility of a septic shock due to a disseminated infection.
3. Inflammatory myositis – this patient's acute onset of symptoms without any previous complaints of muscle pain or weakness makes this diagnosis unlikely.
4. Congenital diseases (carnitine deficiency, glycogen storage diseases) – this patient's onset and age of presentation with previous normal functionality and an absence of similar family history makes this diagnosis unlikely.

Discussion

This patient's nonspecific initial presentation of myalgia is unclear. Her diffuse muscle pain is an alarming symptom signifying a more serious underlying condition. The extraordinary time spent at the gym with sudden-onset diffuse pain and fever should've been further investigated. The early complications associated with rhabdomyolysis are very important for a physician to be aware of. Electrolyte abnormalities such as hyperkalemia, hyperphosphatemia, and hypocalcemia due to their release from the myocytes can pose a serious threat to the patient [7]. Cardiac arrhythmias and potentially cardiac arrest can be serious manifestations of electrolyte abnormalities. This patient's electrolytes were tested for after readmission and were abnormal. Late complications such as acute kidney injury due to the myoglobin released from the myocytes are a serious complication that presents with oliguria and darkening of the urine, as seen in this patient [7, 8]. These symptoms can be reversed if the appropriate treatment was delivered in a timely fashion [9].

Understanding the pathophysiology behind rhabdomyolysis is very important. The myocyte injury that occurs in rhabdomyolysis results in cell membrane injury and hence the release of intracellular components, adenosine triphosphate phosphate (ATP) depletion, and generation of free radicals [10]. This results in the activation of cellular destructive processes through the activation of cellular proteases and proteolytic enzymes. Ultimately, cellular destruction causes the release of mainly potassium and myoglobin; both are largely the main triggers of arrhythmias and acute kidney injury, respectively [11, 12].

The workup for patients with suspected rhabdomyolysis should mainly include, complete blood count, serum chemistry (BUN, creatinine, uric acid, and liver function tests), lactate dehydrogenase, creatine kinase, and serum electrolytes (potassium, phosphate, calcium, and sodium) [9, 11]. The latest evidence-based approach to treating patients with a confirmed diagnosis of rhabdomyolysis after targeting the underlying cause is aggressive fluid resuscitation and correction of the electrolytes and acid-base abnormalities [10]. This essentially prevents end-organ complications

that may develop. Electrocardiogram monitoring is also advised if the levels of potassium get significantly high. Alongside active management, monitoring the patient for other complications like compartment syndrome, disseminated intravascular coagulation, and severe hypokalemia is very important. Finally, repeat creatinine kinase assays every 6–12 h are recommended to determine the peak creatinine kinase levels [11, 12]. The incidence of rhabdomyolysis in the United States has been reported to be as high as 26,000 cases annually, as of 2015 [7]. Considering the relatively high number of misdiagnosed cases of rhabdomyolysis, a complete understanding of the presentation and potential complications is very important.

Conclusion

Rhabdomyolysis is a serious clinical syndrome that should be managed promptly. It is commonly misdiagnosed in the emergency department due to its wide range of nonspecific symptoms. A misdiagnosis would potentially put a patient at an increased risk of developing severe and possibly fatal complications. Alarming symptoms such as kidney injury, compartment syndrome, darkening of the urine, and arrhythmias should be further investigated and managed. Rhabdomyolysis can arise due to a wide range of causes; all can be classified under traumatic or nontraumatic causes. Traumatic causes of rhabdomyolysis and specifically crush injuries are the most common. In this case, this patient was misdiagnosed early on with myalgia not related to rhabdomyolysis resulting in delayed treatment and consequently the development of serious complications of rhabdomyolysis. Therefore, patients presenting with acute-onset diffuse muscle pain should be promptly tested for creatinine kinase levels and electrolytes to rule out rhabdomyolysis.

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Chapter 17
Acute Coronary Syndrome Misdiagnosed as Anxiety

Alluri Vasu

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Thoroughly evaluate patients presenting with pain anywhere in the region of the chest.
2. Discuss the rationale of ordering serial ECG depending on the necessity to rule out noncardiac from cardiac chest pain.
3. Rationalize additional investigations in patients with other comorbid conditions.
4. Discuss the justification of referring for expert care and management, for all patients diagnosed with chest pain.

Introduction

Out of the several reasons for an emergency room (ER) visit, perhaps chest pain happens to be among the top 5 [1]. On a given day, depending on how busy the day was, doctors often find it very difficult to come to a diagnosis of chest pain that could be life-threatening vis-à-vis musculoskeletal. Pain in the region of the chest can be as a result of several reasons and does not necessarily point toward cardiac in origin. A casual review of medical literature will bring to light several instances where chest pain was incorrectly assumed to be cardiac in origin leading to an unpleasant situation for both the patient and the treating doctors often ending in

A. Vasu (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: alluri.vasu@martinus.edu

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lawsuits. More often than not, the symptoms associated with diseases of the gastrointestinal tract present with symptoms in the region of the chest which the patients assume to be pain that actually might have been heartburn, a common symptom of reflux esophagitis. Musculoskeletal pain in the region of the chest following a blunt injury to the chest or a fall is one of the several reasons for patients seeking medical attention. Women and patients who are anxious are a challenging group of patients who often present with ambiguous symptoms and require additional efforts from the treating physician to come to a reasonable diagnosis in the ER setup. If the first point of contact is a weak link in the chain of events, there is every possible reason for that patient ending up treated inappropriately. In that particular group of patients like smokers, diabetics, and the elderly, the symptoms and signs of many diseases are masked or overlapped, and it becomes particularly challenging to come to an appropriate diagnosis in the ER given the paucity of time. It is the responsibility of the senior doctors to train the new doctors in the nuances of the art of medical practice to come to a reasonable diagnosis in the shortest time possible, and it goes a long way in establishing confidence in the doctors undergoing training. Medical practice does not permit any room for misdiagnosis, and mistakes that occur unintentionally often end up as tragedy for all those involved. Misdiagnosis of chest pain and the associated implication for that patient can be life-changing [2]. Many a time doctors take the help of additional diagnostic tools to differentiate between relevant and irrelevant [3] chest pain. It is always a good practice to take a second look or seek additional help from a senior colleague when in doubt about the diagnosis, and that goes a long way in helping both the patients and as well as the medical fraternity. Chest pain should get the evaluation it deserves as any lapse can be life-changing, regardless of its origin, and it should always be evaluated by a medical doctor. Many times, most patients with chest pain are treated in the ER without the need for additional tests or physician visits. The only problem is in deciding if chest pain can wait till the next physician appointment. The patients should not take chances and make it possible, to at least, visit a medical doctor who can further advise them on treatment and diagnosis. There have been several groundbreaking diagnostic tests to diagnose chest pain of cardiac origin, but their use is based on the suspicion of cardiac chest pain at presentation. The diagnosis or misdiagnosis of chest pain in the ER is largely dependent on the presence of trained staff who can differentiate cardiac from noncardiac chest pain. Today, many point-of-care devices as well as elevated levels of enzymes are being used to diagnose cardiac chest pain within the "golden hour," as suggested by recent data from several large clinical trials; treatment done within that golden hour salvages the myocardium to a large extent. Statistically, most misdiagnosis occurs in those patients presenting to ER either late into the night or while changing shifts. The reasons are obvious. Many hospitals have brought about standard operating protocols to overcome these difficulties and minimize misdiagnosis. But despite the many advances in medical sciences, chest pain happens to be a frequently misdiagnosed medical emergency. We

bring forward one such case which was almost misdiagnosed as noncardiac chest pain.

Clinical Case Presentation

A 40-year-old, obese male presented to the ER with a brief history of ongoing chest pain of 1 h duration. The patient was recently diagnosed with diabetes and was struggling to give up smoking. He had on arrival at the ER confessed about the binge drinking party during the long weekend and having to enjoy a wide variety of food. The patient denied any injury or trauma to the chest. The patient was evaluated by the ER physician who after a careful history and examination concluded that the patient was having acid reflux disease as the chest pain was atypical; however, more for the sake of completion, he advised an ECG for the patient, who with great reluctance complied with the request. ECG was done and reported to be normal. He was reassured and advised proton pump inhibitors for 6 weeks, and an appointment with his family physician was fixed. The patient, although not fully relieved of the pain, nonetheless decided to go with the doctor's advice. But an hour later, he presented again with worsening pain and cold clammy extremities. This time he was seen by a different ER physician, who after spending a brief time with the patient and quick history was convinced that he was dealing with a psychiatric patient who was having atypical chest pain, nothing more than a gastric esophageal disease, and was desperate to seek medical attention. This time he was administered some intravenous painkillers and advised to return if there wasn't any relief of symptoms. This patient visited the ER a third time with ongoing chest pain of 5 h duration and was unconscious at presentation. He was seen by a third ER physician and after taking the history from the attenders and the fact that this was his third visit to ER with chest pain. He was admitted to the hospital. A brief workup showed a blood pressure of 80/60 mmHg, random blood glucose of 160 mg/dL, and rapid low volume pulse. Intravenous access was established, fluids were started, and a repeat ECG was advised. ECG was shared with a consultant who was quick to diagnose an ongoing acute inferior-posterior ST elevation myocardial infarction. Under the supervision of a cardiologist, the patient was admitted to the intensive care unit who shifted the patient to the cardiac catheterization lab; a quick coronary angiogram demonstrated 100% occlusion of the left circumflex artery. Patient attendees were explained the need for further intervention, and the left circumflex artery was opened. Following the treatment, the patient regained consciousness, blood pressure normalized, and chest pain had decreased considerably. The patient was moved to the intensive care unit where he was observed for further 24 h and after 3 days was discharged from the hospital. He made a good recovery and will follow up with his family physician.

Discussion

Description of chest pain was not evaluated appropriately. Patients have their way of expressing the pain and grading it over a scale. The patients should be encouraged to explain their pain, and every attempt should be made to refrain from jumping to a diagnosis [4]. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines on evaluation and diagnosis of chest pain recommend using the term noncardiac chest pain to describe pain in the region of the chest that is irrelevant to the heart [5]. The onset and duration of chest pain should never be missed as this can point toward the seriousness of the symptoms. Precipitating factors, location, radiation of pain, and associated symptoms should all be given equal importance and evaluated by guiding the patient's attention to these details [6]. Last but not least for non-native speakers of English, wherever and whenever possible, translator services with appropriate attention to cultural background should be practiced. Chest pain is usually not a reliable indicator of myocardial origin in smokers, women, diabetics, as well as elderly [7]. In this patient, the history of diabetes and smoking had masked the intensity of chest pain and could have been a reason for misdiagnosis.

ECG: This is a very important tool in the diagnosis of heart diseases in the hands of trained. ACC/AHA recommends an ECG in all patients presenting to ER with chest pain or any pain in the region of the chest within 10 min of arrival and repeats as and when required in suspected cases [8]. ECG should be read by comparing with a previous one whenever available, and if no such ECG is available, then repeat ECG taken at least an hour apart in all suspected cases should be followed carefully looking for any new ST-T changes. In patients with normal ECG but cardiac sounding chest pain, right-sided ECG [9] leads should be considered which can save many a heartburn later. In this patient, if a right precordial chest ECG was done, the diagnosis could have been made much earlier. In patients having left circumflex or right coronary artery occlusions or posterior wall ischemia, the ECG can be deceivingly normal like in this patient, and the right precordial lead ECG should have been advised. ECG whenever is normal in patients with chest pain should always be repeated at 1 h intervals and expert opinion sought if one is not very confident in interpreting the ECG.

Biomarkers: these can come to the rescue when in ambiguity about the diagnosis and should always be advised in all suspected cases of chest pain with normal ECG; ACC/AHA recommends cardiac Troponin I or T because of their high sensitivity and specificity [10]. Although certain other diseases of the heart muscle also cause an elevation in troponins, proper interpretation of the results of biomarkers should be done in correlation with all the clinical information. In our case biomarkers were not advised to begin with, and that led to a considerable delay in making the diagnosis, which could have been easily avoided. There are many other diagnostic tools that are available which will aid in the diagnosis of chest pain but are of limited clinical relevance.

Differential Diagnosis

1. Musculoskeletal chest pain – Pain usually in the region of the entire chest with or without extension to the back of chest. History of preceding course of events helps to differentiate.
2. Traumatic chest pain – Pain in the chest following any blunt injury to the chest wall following a fist fight or otherwise or may be due to an accidental fall. A good clinical history will almost always establish the diagnosis.
3. Chest pain secondary to dissection of the aorta – Excruciating pain in the region of chest, usually sudden in onset and mostly in the younger age group.
4. Acute gastritis – Unrelated to a specific age group, but history of alcohol abuse and or irregular diet should raise the suspicion, more common in certain ethnic groups.
5. Angina pectoris – More prevalent in the fairer sex, usually accompanied with prior history of similar chest pain that is precipitated on increased physical activity.
6. Herpetic infections – A history of fever or a skin rash over the chest should raise a suspicion.
7. Stress (loss of a close relative or financial loss) – A common but almost always neglected aspect of clinical medicine. Paying close attention to the physical appearance and habitus of the patient should help in exclusion.

Conclusion

It is of prime importance that all patients coming to ER with chest pain should be evaluated thoroughly, in the suspected few, additional evaluations should be considered, and wherever possible expert opinion should be sought to identify those requiring hospitalization and further management. Patients visiting the ER with cardiac sounding chest pain should undergo a triage so as to identify the potential from the confounding cases, and wherever possible patients should be offered ACC/AHA guidelines-based treatments, sex of the patient or ethnicity should not be a deterrent. The current guidelines recommend percutaneous coronary intervention or intravenous thrombolysis for all patients presenting within the golden hour unless otherwise contraindicated. All patients presenting within a reasonable period of time with evidence of acute myocardial infarction should be offered treatment according to the standard operating protocols of the treating hospital. Whenever the ER physician is presented with a challenging patient, the above algorithm should come in handy (Fig. 17.1).

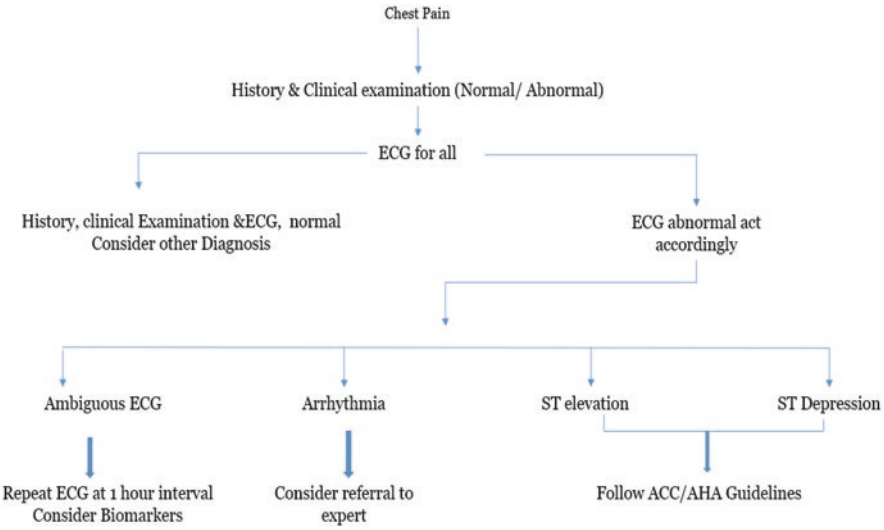

Fig. 17.1 Diagnostic algorithm for evaluation of chest pain

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Chapter 18
Diabetic Neuropathy Misdiagnosed as Right Lower Limb Injury

Alluri Vasu

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Discuss why diabetic neuropathy may be a complication of poorly controlled diabetes.
2. Discuss the significance of appropriately enquiring about the comorbidities that a patient might be having.
3. Enumerate the complications and refer patients for expert management.
4. Restate the importance of tight glycemic control to prevent the complications of diabetes.
5. Rationalize and select drug therapy that should be dictated by the blood glucose levels augmented by a diet as well as exercise regimen.

Introduction

In the modern world, there is an alarming desire to outwit each other, and that applies to the occurrences of disease as well. The current COVID-19 pandemic has forced the young as well as the old to stay indoors, which has greatly restricted outdoor activities and has almost resulted in no physical activity. Now, as the world slowly but steadily is moving toward the new normal, the medical fraternity is going to be overwhelmed with an increase in lifestyle/metabolic diseases. We are going to see an increase in the number of new as well as uncontrolled diabetic patients. Diabetes has since long been known as a lifestyle disease. Modern-day lifestyle as

A. Vasu (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: alluri.vasu@martinus.edu

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well as the increased availability of energy-dense foods has contributed significantly to diabetes. Stress, an often-overlooked factor is not given the importance it deserves. This pandemic that we are in now has increased the stress levels of one and all. The fear of diseases such as COVID-19 as well as loss of employment and a decrease in family time have worsened the incidence of several diseases, diabetes in particular. Diabetes is a multifactorial, multiorgan, and often accepted as a naïve disease when treated adequately with strict control of blood glucose to the normal therapeutic range. The glucose metabolism is hampered in all patients suffering from diabetes, and as the blood glucose increases, so do the complications that are associated with it. The degree of blood glucose, as well as the duration of diabetes [1], plays an important role in the prevalence of associated complications and are equally prevalent in all irrespective of gender and age. A recent review of literature has shown the presence of both microvascular and macrovascular complications of diabetes and the steady decline of macrovascular complications the world over due to improvement in approach to diabetes, but the microvascular complication remains a cause of concern, and peripheral neuropathy is more prevalent in these patients with type II diabetes [2]. It is now a known fact that by the time of diagnosis of diabetes, patients already have one or more complications of the disease. The reason for the high prevalence of complications of diabetes even before the diagnosis of the disease is attributed to the prevalence and degree of hyperglycemia apart from other coexisting comorbidities. Between the microvascular and macrovascular, microvascular complications develop early in the course of the disease. There has been a steady increase in the number of drugs that are better than the previous ones in managing blood glucose on one hand and greatly decreasing the complication on the other hand. With these modifications in treatment options, patients with diabetes are now able to slow not only the development but also the progression of both micro- and macrovascular complications. Patients are now being increasingly trained and encouraged for home monitoring of blood glucose. The practicing doctors have recognized the importance of patient education as well as participation in managing diabetes and often actively engage with patients in titrating their medication. Patients now monitor their blood glucose using point-of-care devices and update their doctor through various digital apps. This way adequate monitoring of out-of-hospital blood glucose in the real world has enabled the treatment of diabetes adequately with a visible difference in the quality of life of the affected patients. Despite this, diabetes happens to be the Achilles heel of medical science, and with our expanding knowledge, we learn more about this syndrome. There is no organ left untouched by diabetes if blood glucose is not under control. The practicing doctor should always remember to manage blood glucose not with medications but also with diet and exercise. All three (diet, drugs, and exercise) contribute equally and should always be emphasized on each visit to the clinic by a patient suffering from this disease. Despite the several advances in the diagnosis and management, diabetes happens to be a challenge, and frequently patients present with complications that affect the eyes, kidneys, and nervous tissue. If managed inadequately this syndrome can always end with unpleasant consequences.

Clinical Case Presentation

A 40-year-old male "Mr. X" was seen in the emergency room (ER) for a bleeding injury to his right great toe, which he sustained while getting off the bus. He was attended to immediately, the bleeding was arrested, the right greater toe was dressed adequately, and he was discharged home. Neither the patient "Mr. X" nor the doctor gave any thought to a follow-up visit or further evaluation. A week later the patient revisited the ER with pain and swelling of the right foot. "Mr. X" was quick to recognize the young and attractive doctor, who had attended to him and reminded her of his last visit. It came as a surprise to the doctor that "Mr. X" did not get his checkup or went to see any other doctor for his wound care. On further questioning "Mr. X" gave a history of diabetes of 10 years' duration and use of insulin for effective control of his blood sugars, although he did not remember the type of insulin and other medication he was on for his diabetes care. He confirmed that he has missed his last few appointments with his physician who was managing his diabetes as he was stressed out about meeting his targets for his sales job and did not remember when he last got tested for his blood sugars. On examination, the right greater toe was badly infected and foul-smelling as the dressing was opened. There was a considerable spread of the infection up to the lower third of the foot. He was referred to a surgeon for further management. Mr. X was seen by the surgeon the next day and was advised of a battery of investigations. The reports of which pointed toward uncontrolled blood sugars, peripheral diabetic neuropathy, and early signs of renal insufficiency. The wound on the right greater toe was severely infected and had spread considerably, and he was advised below-knee amputation of the right lower limb to prevent any further spread of infection and salvage the kidney. "Mr. X" was operated on and had undergone a right lower limb below-knee amputation. He was discharged the following week with strict advice to follow up with his physician for postoperative care as well as diabetes.

Differential Diagnosis

1. Diabetic neuropathy when suspected should be differentiated from peripheral neuropathy – Vascular causes of neuropathy should be excluded.
2. Sensorimotor polyneuropathy – Diabetic neuropathy usually develops a decade after the onset of symptoms in type I, but in those with type II may present at diagnosis. It is usually bilateral and diffuse.
3. Diabetic neuropathy when diagnosed is usually present along with the involvement of other organs gastrointestinal neuropathy, bladder dysfunction, and erectile dysfunction.
4. Mononeuropathy and focal neuropathy can occur with the involvement of either the ulnar, radial, or peroneal nerves.
5. Vitamin deficiencies (vitamin B1 and B12) should be excluded before confirming the diagnosis of diabetic neuropathy.

Discussion

The case in discussion is a good learning example of how important history is, a simple but very effective part of the management of patients and almost always prevents pitfalls. A few words with the patients during their visit prevent volumes of papers from defending oneself. During the initial visit of this patient, a very brief history irrespective of the cause of the injury could have saved his limb. The duration of diabetes greatly determines the degree and extent of diabetic neuropathy [3] patients often do not feel any pain when injured, and it's the bleeding from the injured site that brings them to medical attention. Apart from attending to the obvious, every attempt should be made to know more about other comorbid conditions [4] the patient might be having at the time of presentation. In all patients with diabetes, diabetic triopathy should be suspected and evaluated thoroughly whenever possible. Some simple tests like pinprick test, temperature test, and vibration tuning fork test [5] can be done at the point of care to detect diabetic neuropathy and require no additional training. These can be completed in a very short time. If only doctors could spend that additional few minutes of time with patients, many complications can be avoided and go a long way in restoring the confidence of our patients. Aggressive management of blood glucose prevents the onset and spread of neuropathy irrespective of the type of diabetes [6]. When recognized early and treated adequately, complications of diabetes can be prevented. Foot ulceration and loss of limbs are the disastrous complication of ineffective management of diabetes and are often associated with psychologically traumatic experiences and loss of productive years of life, in addition to healthcare costs [7].

Conclusion

The management of a patient should not be limited to attending to the primary complaint but also guiding the patient for follow-up visits to primary care physicians. All diabetic patients should be appropriately trained in foot care and ambulatory blood sugar monitoring. Patients should be encouraged to follow diet, exercise, and effective pharmacologic therapy to reach their target glycated hemoglobin (HbA_1C) goals to prevent complications of diabetes.

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Chapter 19
Multiple Sclerosis Is Misdiagnosed as Migraine

Alluri Vasu

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Discuss the progression of multiple sclerosis as relapsing-remitting, primary progressive, or secondary progressive.
2. Appreciate that women in the reproductive age group and overall women outnumber men for this disease.
3. List the symptoms along with supportive investigations (MRI brain) to help diagnose the diseases.
4. Enumerate the treatment regimen when the patient presents symptomatically and the disease-modifying immunomodulators for long-term benefit.

Introduction

Reaching the diagnosis within a short time frame is a challenge the doctors working in ER are constantly experiencing. The doctors in ER are trained to look for early signs and symptoms when attending to a patient, and they then come to a reasonable working diagnosis to treat the patient. Many times because of several reasons, diagnosis is missed, which gets amplified as the patients reach the wrong ward or get mistreated. Misdiagnosis is a costly mistake that often ends up with doctors being sued. Physicians who just joined medical practice should not hesitate in seeking help from seniors while dealing with unfamiliar cases. When faced with a

A. Vasu (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: alluri.vasu@martinus.edu

H. Tohid et al. (eds.), *The Misdiagnosis Casebook in Clinical Medicine*,
https://doi.org/10.1007/978-3-031-28296-6_19

challenging case, enough attention should be paid to all symptoms and signs however small and unrelated they might appear. Special attention should be paid while handling a certain group of patients, for example, the elderly, women, and pediatric group of patients. The elderly usually exaggerate their symptoms, whereas females are hesitant to express themselves to the opposite sex (male doctors), and children are the most difficult to handle; while attending to a pediatric patient, one should seek the company of the parents of the child which helps immensely in reaching a diagnosis. Certain barriers like religious beliefs, language, and the degree of education prevent reaching a diagnosis, depending on the familiarity with the language, patient's often present a similar complaint in multiple different ways. It is always a good practice to get acquainted with the frequent medical conditions endemic to the population visiting the ER of a particular hospital. Such an approach helps in saving precious time when patients present to the ER. One should not hesitate to ask for additional investigations to reach a final diagnosis. It is not necessary to reach a quick diagnosis, but a complete workup including appropriate history, paying adequate attention to all symptoms and signs, and finally correlating these with the test reports help save not only the patients but also the doctors from many unpleasant situations later. Multiple sclerosis is the most common nontraumatic cause of ER visits in the younger generation with a majority of them being young women in their reproductive age group. The present pandemic (COVID-19), work from home, as well as stress, increased incidence of smoking, obesity, sedentary lifestyle, lack of exercise, and vitamin D deficiency have contributed to an increased incidence in the recent past. Patients may present with relapsing and recurrence of symptoms and need to be evaluated adequately before confirming the diagnosis.

Clinical Case Presentation

A 40-year-old African American lady was brought to the ER with a history of severe headaches and vomiting for a couple of hours. She mentioned a progressive difficulty in reading and also about an episode of tripping while climbing stairs not so long ago apart from urinary incontinence on arrival at ER. She was briefly questioned, and a note was made that she had a history of multiple sclerosis but was asymptomatic for the last couple of months. She had a history of cigarette smoking but was willing to give up. She also gave a history of another elder sibling suffering from progressive multiple sclerosis. The mention of increasing pain in her legs and easy fatigue over the last couple of weeks was brushed aside, and she was admitted, and given IV fluids along with some pain relief medication. She was advised to continue the medication for a couple of more days and was discharged after a day with a diagnosis of acute migraine with dehydration. The doctor in ER did not feel it was necessary to investigate nor take opinions from other senior colleagues before starting her on symptomatic treatment. She revisited ER the following day finding no relief of symptoms and requested to see a specialist given her history. A specialist neurologist on call was more than happy to see her and was quick to diagnose

relapsing-remitting multiple sclerosis (RRMS). She was managed symptomatically and asked to follow up with a neurologist for a disease-modifying therapy and long-term relief of symptoms.

Differential Diagnosis

The ER physician must be aware of several pitfalls in the diagnosis of MS. Many inflammatory diseases of the CNS such as the following:

1. Neuromyelitis optica spectrum disorder (NMOSD) secondary to syphilis infection and Vitamin B_{12} deficiency.
2. Acute disseminated encephalomyelitis (ADEM) secondary to Lyme diseases and copper deficiency.
3. Sjogren's syndrome, secondary to HIV and leukodystrophies.
4. CNS lupus antiphospholipid antibody syndrome.
5. Sarcoidosis, CNS vasculitis, and migraine [1] can all mimic MS.

Discussion

The doctors working in ER should have good knowledge about the most frequently encountered problems endemic to the geographical location [2] and think of the most common diseases first. In the index case, the patient had a previous history of multiple sclerosis (MS); despite this, the symptoms were assigned to migraine. Although the symptomatology of both these diseases is similar, the experience of the doctors at the first point of contact almost always dictates further treatment to the patient. Patients suffering from MS usually relapse with gradual worsening of symptoms over several hours to days and then depending on accessibility to medical care recovery throughout time [3]. There is an increase in the incidence of MS in the post-pandemic world as a result of frequent lockdowns, limited outdoor activities with reduced exposure to sunlight, and the growing problem of vitamin D deficiency [4], which only seems to contribute increasingly. Women have an increased risk of MS than men and women who are current smokers have a higher risk [5]. MS is characterized by pathology of periventricular inflammatory lesions resulting in demyelinating plaques of oligodendrocytes [6]. Axonal damage is rare in the initial stages and gradually worsens as the disease progresses [7]. Although MS exists clinically in three different forms, the pathological changes are continuous, and there is no characteristic difference histologically between them as remyelination is seen in all disease stages [7]. Symptoms of MS are a combination of lesion size and location. Every relapse occurs following the development of many asymptomatic lesions. MS can best be described as a disease spectrum extending from relapsing to progressive, from inflammation leading to neurodegeneration indicating that

inflammation is present from the beginning which is later accompanied by neurodegeneration as the years pass [3]. This also presents a growing point of view that MS is a precursor for other neurodegenerative diseases like Alzheimer's and Parkinson's. Finally, there is no single confirmatory diagnostic test for MS. The diagnosis is based on the clinical findings supported by investigations. Magnetic resonance imaging (MRI) happens to be an important diagnostic tool for establishing MS. All suspected patients should have an MRI of the brain to help confirm the diagnosis [8]. The 2017 revision of McDonald's criteria for MS diagnosis was proposed by the European magnetic resonance imaging in MS (MAGNIMS) and is now accepted for early diagnosis as a criterion for starting disease-modifying treatment for MS. There is a strong voice of concern raising ethical questions about the division of MS into different subclasses by the pharma industry to begin interferon-beta treatment for MS [9]. Understanding the spectrum of MS is important for early diagnosis as effective disease-modifying treatment will benefit all patients.

Conclusion

Multiple sclerosis (MS) is usually a disease with prolonged periods of symptoms-free intervals; a diagnosis of MS should be suspected in all patients with optic neuritis unless proved otherwise. MS is a complex disease with no pathognomonic symptoms or signs, and clinical experience plays a significant role in diagnosis and treatment as no single confirmatory diagnostic test exists for MS. The diagnosis is based on the clinical findings supported by investigations. Magnetic resonance imaging (MRI) is used for establishing MS. With increasing access and using diagnostic tools like MRI, it is now possible to diagnose MS early. Patients often experience a relapse of the disease over hours to days, while each clinically relevant episode leaves a scar as evidenced in several clinical trials involving MRI, and each episode causes some percentage of neuronal loss which eventually reaches a stage where neurological deficits start to manifest. Irrespective of the subtype of MS (relapsing-remitting, primary progressive, or secondary progressive), adequate treatment with the possible use of immunomodulatory drugs can significantly improve patient quality of life.

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Part IV
Endocrinology

Chapter 20
Addison's Disease Along with Hyperkalemic Periodic Paralysis and Acute Renal Failure Misinterpreted as Peripheral Motor Neuropathy

Bilal Haider Malik and Momina Shahid Hameed

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Identify the causes of hyperkalemia.
2. Discuss the causes of generalized weakness.
3. Articulate the knowledge to link different symptoms and investigation results to develop a working diagnosis.
4. Discuss the role of multiple comorbidities in a complex presentation.
5. Identify presentations mimicking peripheral motor neuropathy.

Introduction

Primary adrenal insufficiency is an uncommon condition that can be hard to diagnose because of ambiguous signs and symptoms which patients present with such as exhaustion, weakness, anorexia, and skin hyperpigmentation. Hyponatremia and hyperkalemia are two electrolyte disorders that are frequently encountered. Hyperkalemia can be because of the acute kidney injury (AKI) in hyperkalemic periodic paralysis with ARF, which can plausibly be confused with presentation of Addison's disease. ARF has been documented to be a presenting symptom of primary adrenal insufficiency in a few cases in the literature [1–3]. Peripheral motor

B. H. Malik (✉)
Dermatology, Betsi Cadwaladr University Health Board, Mold, Wales

M. S. Hameed
Partner GP, Strathmore Medical Practice, Wrexham, Wales

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neuropathy can be a rare diagnosis to make which has a varied presentation and can be a challenge to diagnose so delayed diagnosis is a valid probability. On the same lines, hyperkalemic periodic paralysis is another rare diagnosis which has to be clinically and serologically correlated. This case also highlights how different systems of the body are physiologically dependent on each other to maintain homeostasis.

Clinical Case Presentation

A 37-year-old presented after waking up from a nap, with severe weakness of his limbs. He previously had comparable episodes of sensations of weakness after prolonged periods of rest, but none as severe as this episode. There was no history of trauma or any gastrointestinal symptoms. The patient didn't have any other noteworthy medical history. The patient had low blood pressure (BP) when he arrived at the accident and emergency department (A&E) of 88/60 mm of Hg and a pulse of 98/min. Physical examination revealed intact sensations along with motor weakness in all four limbs. The patient went into cardiac arrest while having labs done. Rhythm revealed sinus rhythm with QRS complex widening and prolonged PR interval. Patient was resuscitated and intubated, with spontaneous circulation returning with 10 min of CPR. Acute renal damage with serum creatinine of 2.2 mg/dL, hyponatremia of 117 mmol/L, and hyperkalemia of 7.9 mmol/L were found in his blood work. Patient received emergency hemodialysis for hyperkalemia and then transported to the ITU. MRI in cervical spine and brain was performed to rule out central nervous system causes of paralysis, but the results were normal. Nerve conduction studies were performed to rule out possible peripheral motor neuropathy, which were inconclusive. Viral causes were ruled out using swabs for respiratory viruses, which included enteroviruses, as well as CMV serology and HIV serology. Negative thyroid peroxidase antibodies and normal TSH ruled out thyroid abnormality as a reason for paralysis. The urine toxicology testing came back negative as well. Antibodies to ANA, ANCA, rheumatoid factor, double-stranded DNA, anti-SSB, anti-SCL-70, and anti-SSA turned out to be negative that ruled out vasculitis. A draining urinary catheter ruled out an obstructive uropathy as the source of the ARF and hyperkalemia, while imaging revealed no evidence of retention. Rhabdomyolysis was ruled out as myoglobin and creatine phosphokinase (CPK) levels were normal. Hypotension, hyperkalemia, and hyponatremia led to a possible diagnosis of adrenal insufficiency as a differential. Plasma renin activity, serum cortisol, aldosterone levels, and ACTH were all checked. It showed low aldosterone and increased renin and ACTH levels along with very low cortisol levels of 0.2 g/dL. Imaging revealed bilateral atrophic adrenal glands. Diagnosis of primary adrenal insufficiency was made. Additional testing showed adrenal antibodies, which

could indicate autoimmune cause. Patient had hemodialysis for another 72 h. On renal replacement therapy (RRT), his potassium levels gradually normalized. On the fifth day of his hospitalization, he was taken off the RRT and was extubated. His motor weakness had fully vanished by this point. The patient was eventually discharged on fludrocortisone and hydrocortisone.

Differential Diagnosis

1. Glomerulonephritides – Glomerulonephritides can have a varied presentation and causes culminating in acute or chronic renal failure leading to electrolyte disturbances.
2. Motor neuron disease – Motor neuron disease has multiple presentations with a host of causes. Can lead to paralysis.
3. Peripheral motor neuropathies – Peripheral motor neuropathies present with different signs and symptoms. Investigative results can compound the confusion related to diagnosis.
4. Vasculitides (systemic) – Systemic vasculitides can affect different organs of the body concurrently or spaced in time. Patients with multiple organ involvement must be investigated for these.
5. Autoimmune disease processes like systemic lupus erythematosus – Autoimmune diseases can be challenging to diagnose as they need a multidisciplinary team approach. They need clinical and serological correlation.

Alternative Diagnosis/Potential Misdiagnosis

1. Peripheral motor neuropathy
2. Motor neuron disease
3. Vasculitides

Note

Alternative diagnoses were considered, and the correct diagnosis was made in light of all available information.

Discussion and Action Plan

Addison's disease is an endocrine condition showing a prevalence of 35–140 cases per million and a mortality rate of 4 cases per million [4]. The most common cause of Addison's illness had been tuberculosis (TB). With the development of efficient TB medicine, autoimmune reasons are now thought to be the most common etiology [3]. Adrenal insufficiency doesn't show up on imaging until 90% of the gland has been damaged or atrophied. With such a wide range of symptoms, it's notoriously tough to diagnose. Weakness, weariness, skin pigmentation, and anorexia can navigate us toward Addison's disease, along with hyperkalemia, hypotension, and hyponatremia. Life-threatening form of Addison's illness is acute adrenal crisis that affects up to 25% of patients [3]. Acute renal failure as a presenting symptom of adrenal crisis is not very common, with a reported incidence of 6% in the literature [2]. Because renal failure can show hyperkalemia and hyponatremia, such a presentation can steer us to a delayed or missed diagnosis of adrenal insufficiency. Our patient had hyperkalemia, which could have been caused by acute renal failure. However, there was no discernible etiology of the kidney injury. Many pathophysiological pathways have been proposed to explain why people with adrenal insufficiency develop AKI. The likely etiology of AKI in our patient was mineralocorticoid deficiency-induced intravascular volume depletion, which led to decreased renal perfusion and a reduction in GFR [1]. Hyperkalemia can cause paralysis which is a rare and reversible complication. There are two types of paralysis: primary and secondary. A congenital abnormality in the SCN4A gene, which affects the sodium channel in muscles, causes primary hyperkalemic periodic paralysis [5]. Secondary hyperkalemic paralysis can be caused by adrenal insufficiency, rhabdomyolysis, acute or chronic renal failure, excessive potassium ingestion, and a variety of medications [6, 7]. Hyperkalemic paralysis caused by primary adrenal insufficiency is uncommon, but it can result in deadly arrhythmias. Even when the picture is confused by AKI, a strong suspicion should be maintained. In patients with acute adrenal crisis, resuscitative and steroid replacement therapy must be started as soon as possible. In such patients, life-threatening hyperkalemia is refractory to routine insulin dextrose therapy, as observed in our instance. Renal replacement therapy was given to the patient to lower his potassium levels and subsequently control his deadly arrhythmias. Mechanism of development of hyperkalemia and subsequent paralysis in adrenal crisis in patients with Addison's disease is shown in Fig. 20.1.

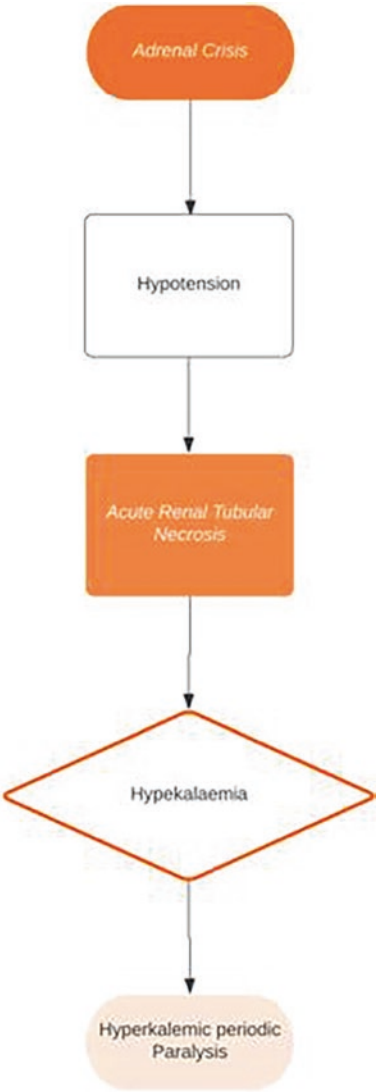

Fig. 20.1 Mechanism of Development of Hyperkalemic periodic paralysis in Addison's disease

Conclusion

Acute adrenal crisis caused by Addison's disease that manifests as acute renal failure with hyperkalemic paralysis is highly uncommon and can cause a misdiagnosis. In such circumstances, physicians should rule out adrenal insufficiency because in such cases hyperkalemia can be resistant to standard modes of therapy and can lead to arrhythmias if identification is delayed.

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Chapter 21
Hypopituitarism Secondary to Macroadenoma with Vomiting and Hyponatremia Misdiagnosed as Episodes of Gastritis/Esophagitis

Bilal Haider Malik and Momina Shahid Hameed

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Analyze common presentations with unusual rare diagnoses.
2. Identify central causes of common symptoms like nausea and vomiting.
3. Discuss pathophysiological processes behind space occupying lesions in the brain.
4. Enumerate metabolic changes arising secondary to macroadenoma.
5. Identify pathophysiology behind electrolyte imbalances due persistent nausea and vomiting secondary to central space occupying lesions.

Introduction

Recurrent vomiting is a debilitating condition that has a substantial negative influence on one's quality of life. Vomiting can be caused by a variety of factors, ranging from well-known to uncommon. Visual abnormalities, headaches, and signs of anterior pituitary hormone shortages are common symptoms of nonfunctioning pituitary macroadenomas. The patient came with recurrent vomiting and acute hyponatremia, which was an uncommon presentation of a nonfunctioning pituitary macroadenoma. In the sellar area, a common type of tumor is a clinically nonfunctioning pituitary adenoma [1]. Nonfunctioning pituitary adenomas have an incidence of 60–100 occurrences per million people [1, 2]. The incidence rate is 1.02–1.08 per

B. H. Malik (✉)
Dermatology, Betsi Cadwaladr University Health Board, Mold, Wales

M. S. Hameed
Partner GP, Strathmore Medical Practice, Wrexham, Wales

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100,000 [1, 2]. It has a bimodal peak incidence between the ages of 25–45 years and 60–70 years. Both men and women are affected equally [1, 2]. These lesions are typically discovered by chance (mostly microadenoma) or identified due to signs and symptoms of anterior pituitary hormone insufficiency, as well as compressive symptoms such headache and vision field abnormalities [1]. In our case patient had been suffering from cyclical vomiting for 2 years. There are a variety of reasons behind this vomiting. Vomiting frequently throws off the body's acid-base and electrolyte balance. Our example demonstrates that frequent clinical presentations and investigative abnormalities might be caused by rare etiologies. Identifying the correct etiology can save a person's life. Intractable nausea and vomiting are seen in patients with adrenal insufficiency, according to a few case reports [3]. Nonfunctioning pituitary macroadenoma can present atypically with cyclical vomiting. The case demonstrates that organic pathology should be investigated despite the presence of multiple psychosocial difficulties, instead of linking the symptoms to a psychiatric disorder. As a result, we chose to share our clinical expertise by reporting this case.

Clinical Case Presentation

A 35-year-old female presented to the emergency department (ED) after experiencing many episodes of vomiting for the last 4 days. She had 7–8 episodes of vomiting each day, which were accompanied by scorching chest discomfort and regurgitation. Vomiting was not a projectile, bilious, or fecal occurrence. Hematemesis was not present. Fever, stomach discomfort, dysuria, abdominal distention, or changed bowel habits were not seen. She did, however, complain of a loss of appetite and overall bodily weakness for the past 3 years, as well as symptoms of dizziness. She denied experiencing photophobia, headaches, vision problems, or weight loss as a result of the treatment. Further examination of her medical history revealed that she had repeated hospital trips in the previous 3 years owing to similar types of recurrent vomiting episodes. These episodes always started with a quick onset of nausea, followed by vomiting that lasted for 3 days. Every day, there were seven instances of nausea along with vomiting. She was treated by her general practitioner for these episodes of vomiting with prokinetics, antiemetics, and proton pump inhibitors without being thoroughly evaluated. She was otherwise leading a normal life. The first episode took place 3 years prior. Initially, these episodes of nausea and vomiting were less frequent, with only three occurrences every 4 months, but these symptoms had progressed to be more frequent recently. She rejected excessive exercise, as well as any medication intake to reduce weight, all of which can be seen in eating disorders. She had no preconceptions about body image distortion. She refused to drink a considerable amount of water. Polyuria, polydipsia, and nocturia were not present. She had reached menarche at the age of 12. She didn't have galactorrhea. She had been prescribed anxiolytics for a 5-year period following the end of her relationship. The anxiolytics were only used for a month. She revealed that her

mother died 7 years ago from an astrocytoma. Her stepmother, siblings, and father all lived with her. Her GCS was 15/15. Her BMI was only 16 kg/m^2. Her blood pressure was 85/55 mmHg and her heart rate was 94 beats per minute. There were no parotid enlargement, dental cavities, brittle hair, or erosions over the knuckles of the hands, which are all symptoms of eating disorder. The rest of her systems examination was normal. On admission, her blood glucose level was normal at 77 mg/dL. The hemoglobin, platelet count, white cell count, serum albumin, alkaline phosphatase, liver transaminases, total bilirubin level, and serum amylase level were all within acceptable limits. Her urine analysis, ECG, and X-ray all came out unremarkable. Her pregnancy test (ßHCG) was negative. CRP and ESR were also normal. Her serum electrolyte levels, on the other hand, were significantly out of whack. Her sodium level in her blood was 120 mmol/L. Serum potassium and chloride were 2.9 mmol/L and 69 mmol/L, respectively. Serum electrolyte levels were consistently low. Respiratory alkalosis was detected on arterial blood gas measurement. Her urea level in her blood was normal. The creatinine level in the blood was 44.9 mol/L. The osmolality of the blood was 221 mOsm/kg, while the osmolality of the urine was 264 mosm/kg. Daily urine production averaged 1230 ml. Urinary electrolyte tests revealed low potassium and sodium levels in the urine. The chloride level in urine was 22 mmol/L. The electrolyte abnormalities that were discovered were thoroughly investigated. Her random blood cortisol level was low when she was admitted. TSH was 0.26 IU/mL, free triiodothyronine (T3) was 1.44 pg/mL, and normal free tetraiodothyronine (T4). Her luteinizing hormone (LH) and follicular stimulating hormone (FSH) levels were also low. A hypoplastic uterus was discovered during an ultrasound abdomen check. The ultrasound scan of the abdomen revealed no additional abnormalities. Her prolactin level was revealed to be somewhat higher than normal. The level of serum prolactin was 73 ng/mL and 90.8 ng/mL following a 5:1 dilution. She had hypothyroidism, hypoadrenalism, mild hyperprolactinemia, and hypogonadotropic hypogonadism in her biochemistry. An MRI of the pituitary was performed to further investigate her hypothalamic-pituitary axis. MRI scan revealed a mass occupying the sellar and suprasellar areas, with mass influence on the optic tract and optic chiasma, optic tracts. Bitemporal hemianopia was seen on examination. Pituitary nonfunctioning macroadenoma with mass effect was diagnosed, resulting in hypothyroidism, hypoadrenalism, hyperprolactinemia, and hypogonadotropic hypogonadism. She was given antiemetics when she was admitted. Vomiting-induced volume loss was replenished with the same amount of fluid given via oral route. Because she seemed to tolerate low levels of serum sodium, we diagnosed her with chronic hyponatremia. As a result, aggressive care of hyponatremia was avoided. Suspecting hypoadrenalism, a 100 mg intravenous hydrocortisone was given, followed by 50 mg intravenous hydrocortisone every 6 h. Vomiting was assumed to be the cause of low serum chloride and potassium levels, which were rectified following oral hydration. Due to stress induced hyperventilation, she developed respiratory alkalosis. The patient was commenced on levothyroxine. Her serum sodium level stabilized around 134 mmol/L 4 days following hormone replacement. Her vomiting had subsided. Her appetite and widespread body weakness both improved significantly. After 21 days of treatment,

hydrocortisone was switched to oral route, and the patient's condition improved even more. Four weeks following the diagnosis, the pituitary tumor was removed via transsphenoidal resection. A pituitary adenoma was discovered in histology. She was discharged with a daily dose of hydrocortisone and levothyroxine.

Differential Diagnosis

1. Functional causes of vomiting – Self-induced vomiting can mimic such presentation and need a keen observing physician to decipher such a cause.
2. Psychiatric illness – Psychiatric causes are becoming more prevalent in the current medical landscape and must not be discounted.
3. Stress – Different lifestyle choices can have an impact on different psychosocial reactions manifested by the patients.
4. Multiple concomitant endocrinopathies – Endocrinopathies can be challenging to diagnose as one can mimic the other with similar signs and symptoms so need to be investigated thoroughly.

Alternative Diagnosis/Potential Misdiagnosis

1. Gastritis
2. Esophagitis

Note

Patient was initially treated for gastritis and functional causes were considered. Finally the right diagnosis was made after detailed evaluation. No legal proceedings.

Discussion and Action Plan

Pituitary tumors are responsible for 15.5% of all central nervous system (CNS) neoplasms [1, 4]. Pituitary adenomas are responsible for 30% of CNS malignancies in young adults (20–34 years) [1, 4]. Nonfunctioning pituitary adenomas make up around a third of all pituitary adenomas, which is less than prolactinomas, which make up about half of all pituitary adenomas [1, 5]. Pituitary adenomas that aren't working. Pituitary macroadenomas are the most prevalent type of pituitary tumor [1]. In 60–80% of instances, their symptoms and signs are caused by anterior

pituitary hormone insufficiency and mass influence on neighboring structures, particularly the optic chiasma [1, 2]. One or more anterior pituitary hormone deficits are found in the majority of patients with nonfunctioning pituitary adenomas [1, 6, 7]. Two or more hormone deficits affect more than 20% of patients with nonfunctioning pituitary adenoma [1, 6]. Hypogonadotropic hypogonadism affects 40–75% of individuals with a nonfunctioning pituitary adenoma, and central hypothyroidism and hypocortisolism affect 20–40% of cases [1, 6]. Due to the tumor compressing the pituitary stalk and disrupting the descending dopaminergic effects, moderate hyperprolactinemia (100 mg/mL) can occur [1]. Pituitary apoplexy can occur in 8–10% of pituitary adenomas [6]. The patient in this case had unusual symptoms of a nonfunctioning pituitary macroadenoma. She had recurrent episodic vomiting. The patient had generalized body weakness with loss of appetite, which could be generic hypoadrenergic symptoms. Our patient experienced a variety of psychological concerns, including the loss of her mother at a young age and the end of a relationship recently. The patient linked the onset of all of her symptoms to the dissolution of her relationship, which occurred shortly after she started university. Having a number of psychosocial issues may cause clinicians to deviate from the proper diagnosis path. Although there may have been coexisting psychological difficulties, it is necessary to rule out organic factors before making a psychological diagnosis. This case emphasizes the significance of ruling out organic factors before reaching a psychiatric conclusion. Another uncommon symptom of a nonfunctioning pituitary macroadenoma was severe hyponatremia, as seen in this patient. With a history of recurrent vomiting, it's easy to mistake vomiting for the source of the electrolyte imbalance. Because there can be several underlying etiologies for an electrolyte imbalance, this instance emphasizes the significance of thoroughly analyzing it. When examining chronic or persistent hyponatremia, a high index of suspicion is required [8]. Hyponatremia is defined as a sodium level in the blood that is less than 135 mmol/L. When serum sodium falls below 125 mmol/L, severe hyponatremia develops, which is linked to increased morbidity and death [8] and must be investigated thoroughly. Secondary hypoadrenalism rather than central hypothyroidism is the commonest cause of hyponatremia caused by hypopituitarism [9]. In the absence of normal cortisol action in the kidney, hyponatremia related to secondary hypoadrenalism is produced by reduced electrolyte-free water excretion [9]. Higher secretion of arginine vasopressin, a secondary adrenocorticotropic hormone (ACTH) secretagogue, results in increased urine concentration and can worsen hyponatremia [9]. Hypothyroidism causes changes in renal perfusion and a reduction in glomerular filtration. The inability to eliminate free water causes hyponatremia in hypothyroidism. The hormone arginine vasopressin has an effect on urine dilution. Hypothyroidism produces hyponatremia because a lower glomerular filtration rate reduces water supply to the tubules, lowering free water excretion [9].

Patients with secondary hypoadrenalism are less prone to develop hyperkalemia than those with primary hypoadrenalism since there is no mineralocorticoid deficit. Due to the persistent nature of our patient's hyponatremia, she experienced limited hyponatremic symptoms. However, the patient's hyponatremia was exacerbated by episodic vomiting and reduced salt intake, as seen by low serum chloride and

potassium levels, as well as low urinary potassium and sodium levels. Her urine production was normal, and she denied polydipsia and polyuria. Her plasma osmolality was low, but her urine osmolality was slightly higher. Her urea level in her blood was normal. This prompted an investigation into the cause of hidden euvolemic chronic hyponatremia. This led to the discovery of a pituitary macroadenoma beneath the surface. Vomiting and a reduced salt intake were blamed for the low serum potassium and chloride levels.

Conclusion

Although symptoms and signs of anterior pituitary hormone shortages and mass effect on neighboring structures are common in nonfunctioning pituitary macroadenomas, they can sometimes show in unique ways. Atypical symptoms of nonfunctioning pituitary macroadenomas include cyclical vomiting and severe hyponatremia. In a patient with recurrent vomiting and hyponatremia, numerous etiologies might be found. The precise etiology can save a person's life. When examining recurrent vomiting with hyponatremia, a high level of suspicion is required.

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Chapter 22
Hypothyroidism with Nephrotic Syndrome Misdiagnosed as Cardiac Failure

Bilal Haider Malik and Momina Shahid Hameed

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Understand the relationship between nephrotic syndrome and hypothyroidism.
2. Apply the knowledge gained from the case in a clinical setting where appropriate.
3. Understand the pathophysiology of cardiac failure.
4. Apply the knowledge to understand pathophysiology behind presentations mimicking cardiac failure.
5. Understand pathophysiological changes in the body secondary to nephrotic syndrome.

Introduction

The kidney and thyroid work together in a vital way to ensure that both organs operate properly. Thyroid is important for renal development and glomerular and tubular processes; the kidney also engages in metabolism of thyroid hormone and disposal [1, 2]. Thyroid function problems, particularly hypothyroidism, have long been linked to chronic kidney disease (CKD) [3–7]. Thyroid function test results in this clinical scenario are highly variable, based on renal disease's severity [4, 5], as well as the thyroid reserve and h/o thyroid disease previously [8], as well as other factors (such as furosemide, glucocorticoids, or other drugs) [9]. Edema, proteinuria (>3.5 g/24 h), hyperlipidemia, and hypoalbuminemia are all symptoms indicating

B. H. Malik (✉)
Dermatology, Betsi Cadwaladr University Health Board, Mold, Wales

M. S. Hameed
Partner GP, Strathmore Medical Practice, Wrexham, Wales

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nephrotic syndrome (NS). Excessive excretion of urinary proteins which is because of a significant increase in glomerular permeability leading to urinary losses of transthyretin, albumin, and thyroxine binding globulin (TBG) in addition to thyroxine (T4) and triiodothyronine (T3) [8, 10]. Furthermore, renal tubule damage can coexist with free thyroid hormone reabsorption and compromise it [11]. In the absence of thyroid disease previously, levels of free T4 and T3 (fT4 & fT3) remain within acceptable ranges in the early stages of the NS, and we see euthyroid state biochemically and clinically. In individuals with prolonged and severe proteinuria and inadequate thyroid reserve, urinary losses of free and protein-bound thyroid hormones are enough to cause subclinical hypothyroidism [2, 4, 5]. Regular changes to replacement therapy doses is necessitated in patients who have previously received hormone replacement therapy [2, 8, 11]. The use of immunosuppressive medications and steroids in addition to euthyroid sick syndrome [9, 12] should be considered while diagnosing and managing problematic NS patients. Several studies have been reported that relate hypothyroidism to NS patients, mainly in adolescents and patients with prior thyroid dysfunction [11, 13–16].

Clinical Case Presentation

A 41-year-old male had been checked by his primary care physician for mild shortness of breath and widespread edema with swelling of the face, belly, and legs. He was a regular smoker. He had antiphospholipid syndrome and Raynaud's phenomenon in the past. Except for the presence of excessive edema of the abdominal wall and lower limbs, the physical examination was normal. His weight had increased by 15% in just 3 months, to 92 kg. Cardiac failure was considered as a possible diagnosis by the junior member of the team. Proteinuria of 62 g/L was detected in urine and PCR (protein-to-creatinine ratio) of 17 g/g. eBlood tests revealed low serum protein levels of 3.5 g/dL, low albumin levels of 1.9 g/dL, and increased serum lipid levels. Renal function was retained with serum creatinine: 0.82 mg/dL, eGFR of 128 mL/min/1.73 m^2. TSH level was 2.9 UI/mL. Except for inadequate corticomedullary differentiation, renal ultrasonography (US) revealed maintained anatomy of the kidneys. The patient had a kidney biopsy, which revealed C3 glomerulonephritis. We initiated glucocorticoids in high doses and showed no response, so mycophenolate mofetil and cyclosporine were initiated. Over the next few days, severe hypoalbuminemia, worsening renal function, and recurrent episodes of cellulitis developed in the patient. Thyroid function tests revealed abnormalities 2 weeks after his admission TSH, 18 UI/mL; total T4, 2 g/dL; fT4, 0.24 g/dL; total T3, 0.5 ng/mL; and fT3, 0.70 pg/mL. There was no previous history of thyroid illness in the patient. There were no nodules and no enlargement of thyroid gland found during the examination. Thyroid US indicated a homogeneous, regular, and slightly enlarged, with no obvious nodular lesions. Serum anti-thyroglobulin and antithyroid peroxidase titers were also negative. Clinical hypothyroidism secondary to nephrotic syndrome came up as a differential for this case, and oral levothyroxine

treatment was commenced and was gradually increased. Patient's condition remained unresponsive to immunosuppressive medication after 6 weeks in the hospital. The patient was recommended for bilateral nephrectomy due to steroid side effects, recurring infections, and unresponsiveness to immunosuppression. The histology of the kidney showed focal segmental glomerulosclerosis. Thyroid function tests 7 days following surgery indicated TSH of 1.9 UI/mL, fT4 of 1.1 g/dL, and fT3 of 1.8 ng/dL (RR: 2.66–4.33), allowing the LT dose to be reduced. The patient was seen to be biochemically and clinically euthyroid after discharge, with gradually reduced LT dosage requirements. The patient has been on hemodialysis since bilateral nephrectomy, waiting for a kidney transplant.

Differential Diagnosis

1. Hypothyroidism – Hypothyroidism can present with lethargy, generalized edema, and shortness of breath. Causes of hypothyroidism must be deciphered to address the underlying pathology.
2. Cardiac Failure – Cardiac failure is a pertinent differential diagnosis with all the signs and symptoms present.
3. Hypoproteinemia (Various Causes) – Hypoproteinemia is more common than we think for these host of signs and symptoms seen in this case.
4. Glomerulonephritides/Nephrotic Syndrome – Renal failure chronic or acute can present with above signs and symptoms and need to be dealt with in a timely manner.
5. Vasculitides – Multisystem involvement can be a presentation of underlying autoimmune processes like vasculitides.

Alternative Diagnosis Considered/Potential Misdiagnosis

1. Heart failure
2. Liver failure

Alternative diagnoses were considered, but correct diagnosis was made in light of investigation results by the senior member of the team.

Discussion and Plan of Action

T4 and T3 both are poorly water-soluble, and more than 99.5% of them circulate in the blood attached to proteins: roughly 10% to prealbumin, 70% to TBG, and 20% to albumin. Only modest quantities of free hormones are metabolically active in the

tissues and are responsible for all thyroid activities [12, 17]. Urinary protein losses are negligible under normal circumstances. In NS, however, substantial urinary protein losses occur, including T4 and T3 along with their binding proteins, as well as the free fractions fT4 and fT3 to a lesser extent [2, 4, 5, 18, 19]. This explains why thyroid function abnormalities are so common in people with NS, which is a renal-endocrine illness [2]. Milder symptoms and normal levels of free hormones are seen early in the disease process [2, 4]. fT4 and fT3 are also dramatically lowered if the protein losing processes carry on for longer periods causing subclinical hypothyroid state [4, 19]. High urinary protein levels and increased serum creatinine were found to be independent risk factors for thyroid dysfunction in a study of individuals who had been officially diagnosed with NS, while a greater level of plasmatic albumin was found to be an independent protective factor [5]. In five children with congenital NS, lasting cure of hypothyroidism after bilateral nephrectomy had already been documented [14]. This finding demonstrates that hypothyroidism was not caused by an intrinsic abnormality in the thyroid gland. Corticosteroids may contribute to thyroid dysfunction by suppressing serum TSH levels, impairing peripheral T4 to T3 conversion, and lowering TBG synthesis (which might be the contributory factor in this case) [9]. In addition to NS, hypothyroidism has been linked to some glomerulonephritides (GN) [2, 20, 21].

Conclusion

Renal disease evaluation should be commenced when diagnosis of hypothyroidism is made. Severity of thyroid dysfunction and treatment response are determined jointly by clinical circumstances and proteinuria severity. The necessity of a clearer understanding of the relationships between thyroid and renal functions is highlighted in this case study. When nephrotic syndrome is first identified, it is fair to evaluate thyroid function and then perform serial testing.

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Chapter 23
Adrenal Insufficiency Misdiagnosed as Syndrome of Inappropriate ADH Secretion

Ivan Cancarevic

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Identify the clinical findings associated with adrenal insufficiency.
2. Discuss and enumerate the classification and common causes of hyponatremia.
3. Apply the aforementioned concepts in a clinical scenario.
4. Analyze the basics of hyponatremia management.
5. Discuss the potential for misdiagnosis of the cause of hyponatremia in the setting of adrenal insufficiency.

Introduction

Hyponatremia is generally defined as a sodium level below 136 mEq/L and can be seen in a variety of clinical settings. Pseudohyponatremia refers to a falsely low reading of serum sodium levels, usually due to the presence of very high amounts of protein or lipid in the blood, giving the appearance of a larger serum volume [1]. Real hyponatremia usually also indicates serum hyperosmolality. It is further divided based on the patient's volume status into hypovolemic hyponatremia, euvolemic hyponatremia, and hypervolemic hyponatremia [2]. Hypovolemic hyponatremia develops in the setting of a loss of both free water and sodium; however, the loss of sodium exceeds the loss of free water [2, 3]. Hypervolemic hyponatremia, on the other hand, develops in the setting of disproportionate retention of free water in comparison to sodium, leading to decreased concentration of serum sodium, typically in patients with underlying heart or liver disease [2, 4, 5]. Euvolemic

I. Cancarevic (✉)
Icahn School of Medicine at Mount Sinai, New York, NY, USA

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hyponatremia refers to the setting where the patient is euvolemic, but the serum concentration of sodium is low. The most common causes are the syndrome of inappropriate antidiuretic hormone (SIADH), primary polydipsia, and endocrinopathies, such as hypothyroidism and adrenal insufficiency [2, 6, 7].

Aldosterone, the end hormone of the renin-angiotensin-aldosterone system (RAAS), acts on the distal nephron stimulating potassium secretion and sodium reabsorption. Adrenal insufficiency, therefore, tends to present with impairment of both processes resulting in hyponatremia and hyperkalemia [8]. Patients are typically hypovolemic, although it can be difficult to assess since volume loss is not always significant [2].

Clinically, there are a number of ways to assess volume status, although it is not always easy to do. Vital signs, physical exam, and even findings on the point-of-care ultrasound testing all help get a sense of the patient's volume status, but unless the volume deficit is severe, it may go unnoticed [9]. Therefore, it is easy to understand why diagnosing the etiology of hyponatremia is challenging, and misdiagnosis is common.

Clinical Case Presentation

A 53-year-old female with a past medical history of hypothyroidism managed with a stable dose of levothyroxine was admitted to the hospital for a syncopal episode, which happened while walking to the bathroom in her apartment. The patient also reported a recent history of fatigue, nonspecific abdominal discomfort, and anorexia. Vitals signs on admission were significant for blood pressure of 100/64 mmHg and heart rate of 105/min. Initial laboratory tests revealed hemoglobin of 10.7 g/dL (the patient at the time still had regular periods), sodium of 126 mEq/L, and potassium of 5.1 mEq/L. Initial EKG showed sinus rhythm. A head CT was ordered, and it was unrevealing. The physical exam was unremarkable, and there was no evidence of volume depletion – skin turgor was normal, and the patient's mucosal surfaces were not appearing to be dry. Due to the patient's apparent euvolemic state and lack of clinical findings suggestive of acute hyponatremia, the admitting resident initially diagnosed the patient with SIADH-induced euvolemic hyponatremia, and water restriction was ordered. The resident feared that, in the setting of low hemoglobin levels, the patient might have an underlying malignancy that may have triggered the SIADH, and he recommended pursuing a malignancy workup in this patient. Additionally, in order to rule out a cardiogenic cause of syncope, the patient was placed on telemetry monitoring. The next day, the patient got dizzy when she attempted to go to the bathroom, and her morning sodium level was 124 mEq/L despite having less than 1200 mL of water the previous day. Thyroid-stimulating hormone (TSH) levels obtained on admission were found to be within normal range, effectively ruling out thyroid disease causing any of the patient's symptoms or findings. On the physical exam, her volume status was notably changing, and her mucosal surfaces appeared much drier than on admission. Telemetry revealed no abnormal

rhythms at any time, although sinus tachycardia was noted around the time when the patient went to the bathroom and became dizzy. Supine blood pressure remained stable. Orthostatic vital signs were obtained, and the patient became hypotensive to 74/52 mmHg, and a 1 L bolus of normal saline was administered, leading to mild symptomatic improvement and blood pressure elevation. Urine electrolytes were obtained and showed sodium of 45 mmol/L with markedly decreased urine potassium, indicating simultaneous sodium wasting and potassium retention. Those findings, combined with postural hypotension, generalized fatigue, and anorexia, were consistent with the diagnosis of adrenal insufficiency, and an endocrine workup was initiated. Aldosterone levels were found to be markedly decreased with elevated levels of renin, indicating primary adrenal disorder. The patient was subsequently started on fludrocortisone which led to the normalization of her electrolyte levels.

Differential Diagnosis

1. Adrenal insufficiency – it is frequently diagnosed late because the symptoms are highly nonspecific, and even the laboratory findings, other than decreased hormone levels, can be seen with a number of other conditions – notably, a combination of hyponatremia and hyperkalemia is characteristic.
2. Hyponatremia – rarely symptomatic unless acute and/or severe, in which case patients usually present with neurological symptoms. It can be caused by a number of factors and is classified according to the patient's volume status.
3. SIADH – a common cause of euvolemic hyponatremia, frequently in the setting of another disease or condition, such as malignancies or brain or lung disease, and is typically managed with water restriction.

Alternative Diagnoses

Initially, due to the lack of obvious signs of hypovolemia, an inexperienced clinician diagnosed the patient with SIADH and placed the patient on fluid restriction, which made her symptoms worse.

Discussion

As illustrated in this case, determining the etiology of hyponatremia is not always straightforward, and the consequences of inaccurate diagnosis and treatment can be life-threatening for the patient. The initial step in the assessment of hyponatremia is to ensure that it is not pseudohyponatremia by doing the appropriate corrections. Afterward, as previously stated, carefully assessing volume status is crucial in

patients with newly diagnosed hyponatremia. Moreover, analysis of osmolality and electrolyte levels both in the blood and in the urine is necessary to determine the exact etiology. For example, hypovolemic patients are likely to have very low levels of urinary sodium, whereas someone like the patient presented in this case, who has adrenal insufficiency, will have higher levels of urinary sodium, indicating sodium wasting. Serum potassium levels are important, in particular, to assess adrenal function since adrenal or aldosterone receptor diseases have the opposite effects on sodium and potassium. Treatment, importantly, also varies based on the etiology of hyponatremia. Volume repletion is generally needed in cases of hypovolemia, while water restriction is encouraged with euvolemic and hypervolemic hyponatremia [10]. In cases of euvolemic hyponatremia, psychogenic polydipsia needs to be ruled out – usually by assessing urine osmolality and, as needed, doing a water deprivation test which will result in a prompt increase in urine osmolality [11]. Frequently, in the hospital setting, SIADH becomes the "default" diagnosis even before the entire workup has been completed, which, like in this case, increases the probability that subtler presentations of other conditions may be missed. Another thing worth mentioning is that, in this case, the patient already had a history of hypothyroidism, which predisposes her to other autoimmune endocrine disorders, such as adrenal insufficiency. Moreover, hypothyroidism itself could be a cause of hyponatremia in some patients, although this patient's current TSH level is normal, so it is not a likely cause in her. Obtaining hormone levels if there is any suspicion of endocrine disease needs to be part of the workup since the condition can progress and become life-threatening [12]. For instance, had this patient not been diagnosed, it is feasible that in the near future, she could have developed an adrenal crisis. Treatment of adrenal insufficiency depends on the hormones that are affected (which depends on the zones of the adrenal gland that are affected) but typically involve glucocorticoids, such as hydrocortisone or prednisone, as well as fludrocortisone. Hormonal supplementation should lead to the normalization of electrolyte levels.

Conclusion

When a patient is found to be hyponatremic, it is extremely important not to assume the diagnosis without performing an adequate workup. Moreover, assessment of volume status is essential and should include vital orthostatic signs. Endocrine disorders, such as hypothyroidism or adrenal insufficiency, should not be overlooked as a possible cause of hyponatremia. Treatment depends on the underlying etiology, and misdiagnosing and incorrectly treating hyponatremia can have dire consequences.

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Chapter 24
Pheochromocytoma Misdiagnosed as COVID-19

Allison Foster

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Discuss the clinical findings associated with pheochromocytoma.
2. Enumerate the clinical findings associated with COVID-19.
3. Apply the aforementioned knowledge to clinical scenarios.
4. Analyze the risk of misdiagnosis of pheochromocytoma.
5. Discuss the initial management of said conditions.

Introduction

Pheochromocytoma is an uncommon tumor of the adrenal medulla that secretes catecholamines. It typically presents with hypertension, headaches, diaphoresis, and palpitations, which may be constant or intermittent [1]. Those symptoms, however, are not specific and can be suggestive of a variety of other cardiac or pulmonary diseases. Therefore, the condition is frequently diagnosed late or misdiagnosed [1, 2]. In those cases, it can become life-threatening [1, 2]. Symptoms are caused by catecholamine overproduction, and the best diagnostic test is to measure metanephrines or normetanephrine in the urine [3]. It is managed with alpha-blockers, as well as other appropriate treatments for hypertension and arrhythmias [3]. The definitive and often curative treatment is surgery [3]. Excess catecholamines or adrenergic agonists can lead to the development of cardiomyopathy [4, 5]. In fact, in many cases, an underlying pheochromocytoma has been discovered in patients with cardiomyopathies even without characteristic symptoms of catecholamine excess [5].

A. Foster (✉)
Icahn School of Medicine at Mount Sinai, New York, NY, USA

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COVID-19 is the most talked-about disease of 2020 and 2021 since it created a global pandemic, the likes of which have not been seen in decades. It is spread through the respiratory route, and it typically presents with a combination of upper and lower respiratory symptoms, such as cough, shortness of breath, and fever [6]. Importantly, a number of atypical presentations of COVID-19 involving almost any other organs and systems have been reported. Myocarditis is one of the most frequently reported ones [7, 8]. It typically presents with chest discomfort and dyspnea, although more dramatic presentations, including sudden cardiac death, can occur [9]. Precise diagnosis often requires either advanced imaging, such as cardiac MRI or even myocardial biopsy [8]. In patients suffering from COVID-19 who are short of breath at baseline, the diagnosis of myocarditis may be delayed even further. Therefore, for a patient with acute shortness of breath and chest discomfort, COVID-19 would likely be one of the first differential diagnoses a clinician would think about, while many will not even think about pheochromocytoma.

Clinical Case Presentation

A 42-year-old female presented to the emergency department with new-onset acute shortness of breath. She had also experienced intermittent chest discomfort that she could not describe any further, nausea, vomiting, and generalized malaise for several days prior to this presentation. On physical exam, she was mildly febrile with a temperature of 38.2 °C (equivalent to 100.8 °F), heart rate was 102 per minute, and blood pressure was normal, but the patient desaturated on room air and was placed on 12 L of oxygen via OxyMask in order to achieve saturation of 97%. Initial lab work was significant for a white blood cell (WBC) count of 25,000/uL with lymphopenia. Troponin and pro-BNP were markedly elevated. Chest CT was significant for diffuse ground-glass opacities with septal thickening, a finding frequently associated with COVID-19 pneumonia. EKG was significant for ST depression in leads II, III, and aVF. At the time, PCR testing for the SARS-CoV-2 virus took 48 h, and patients were typically treated for COVID-19 based on clinical findings alone, pending results of the nasal swab PCR. The patient was, therefore, diagnosed with COVID-19 pneumonia and COVID-19-related non-ST elevation myocardial infarction (NSTEMI) . She was initially treated with broad-spectrum antibiotics for possible secondary bacterial pneumonia and aspirin and heparin for NSTEMI. Corticosteroids were not given. She was provided symptomatic treatment for COVID-19. Interestingly, the PCR test for COVID-19 was negative. It was subsequently repeated and returned negative again, so COVID-19 was ruled out as a differential diagnosis, and another cause of pneumonia was suspected. In the meantime, pro-BNP continued trending up, tachycardia persisted, and the patient became hypotensive. An echocardiogram was performed, which showed an ejection fraction of 25% with segmental wall motion abnormalities. No previous echocardiograms were available, but the patient-reported unlimited exercise tolerance and no history of chest pain or dyspnea. A repeat CT scan was performed a week after the presentation, and

ground-glass opacities mostly resolved, which supported the idea that the patient had suffered from pneumonia that improved with treatment. At the time, the working diagnosis became idiopathic acute heart failure. The patient started developing worsening volume overload. Overnight, 10 days after the admission, the patient complained of worsening abdominal discomfort, and the covering physician ordered a CT scan of the abdomen which incidentally showed a mass in the left adrenal gland. Blood pressure was on the lower end of the reference range throughout the hospitalization. Renin and aldosterone levels were within normal range.

Urine metanephrines were minimally elevated. Left adrenalectomy was performed, and the tissue biopsy confirmed the diagnosis of pheochromocytoma. All symptoms resolved, and cardiac function returned to baseline 3 months after the surgery. The patient was subsequently followed for a year and remained symptom-free.

Differential Diagnosis

COVID-19 – it is nowadays one of the most common respiratory infections that can affect both upper and lower airways, with the most common symptoms being dyspnea, cough, and fever, although a number of nonspecific symptoms and atypical presentations have been reported.

Myocarditis – inflammation of the myocardium, frequently viral, presenting with symptoms which can be confused for COVID-19, including shortness of breath and cough.

Pheochromocytoma – tumor of the adrenal medulla that secretes catecholamines and presents with constant or intermittent hypertension, headache, and palpitations.

Alternative Diagnoses

Due to the similarity of the clinical presentation and high prevalence of COVID-19 in the general population, the patient had been initially diagnosed with COVID-19 based on the clinical picture and missed the actual diagnosis of pheochromocytoma-induced myocarditis.

Discussion

This case clearly illustrates many of the issues faced by providers in clinical practice. Initially, the patient presented with nonspecific symptoms, which could be explained by a number of different cardiovascular or pulmonary conditions. At the

time, COVID-19 testing was less widely available, and many patients were diagnosed and treated based on clinical findings alone. CT of the chest was consistent with the diagnosis of COVID-19 pneumonia. The patient had no typical signs or symptoms of pheochromocytoma. Importantly, the patient satisfied the criteria for acute heart failure with elevated pro-BNP and decreased ejection fraction in the setting of meeting criteria for NSTEMI (elevated troponin, ST deviation on ECG, and segmental wall motion abnormalities on the echocardiogram). COVID-19 has been reported as a potential trigger for myocardial infarction, which is in line with an already relatively well-established link between COVID-19 and thrombosis development [10, 11]. Under those assumptions, the patient was placed on the appropriate treatment at the time, including supportive management of COVID-19, broad-spectrum antibiotics due to leukocytosis, and aspirin and anticoagulation. Myocardial infarction can lead to acute heart failure, which can also lead to pulmonary edema. Once COVID-19 was ruled out by two consecutive negative PCR tests, the case became even more complicated. The patient's symptoms remained nonspecific and only consistent with heart failure without much clinical evidence of an underlying pheochromocytoma. Mild intermittent tachycardia (present on the initial physical exam but not on the EKG) could have been explained by sympathetic activation due to decreased ejection fraction. Improvement in lung imaging was attributed to pneumonia treatment, although it is questionable whether radiological findings of pneumonia would have disappeared over a period of 1 week, even with the resolution of the infection itself. Pheochromocytoma was diagnosed incidentally because the patient started complaining of abdominal discomfort, which could have been related either to the tumor itself or to worsening volume overload in the setting of heart failure with reduced ejection fraction.

Therefore, an abdominal CT scan was ordered. Even though, as previously explained, pheochromocytoma is a possible cause of heart failure, a pheochromocytoma workup is not typically undertaken when a patient presents with signs and symptoms of heart failure. That means that, in the absence of symptoms which would trigger an appropriate workup, cases of pheochromocytoma-induced heart failure with minimal obvious hyperadrenergic findings are likely to be diagnosed late. Once the adrenal tumor was found, endocrine studies were ordered to determine its etiology, and finally, a pathological diagnosis was made after surgical resection. The etiology of the tumor itself remains unclear, although, in the literature, there are reports of pheochromocytoma being triggered by COVID-19 [12].

Conclusion

Even if a disease is highly prevalent in the population at the time, it is important not to jump to conclusions and label patients with the diagnosis prematurely. Moreover, cases of acute heart failure of unknown etiology, especially in a younger patient, should prompt a more thorough workup. We believe that it is not unreasonable to obtain urine metanephrines in individuals with sudden onset acute heart failure even

without obvious signs of elevated catecholamines since the test is simple and relatively inexpensive and may detect cases that would otherwise remain undiagnosed until it is too late.

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Part V
Gastroenterology

Chapter 25
Initial Misdiagnosis of Celiac Disease with Life-Threatening Presentation

Anthony V. Baratta Jr.

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Discuss the variable presentations of celiac disease.
2. Recognize those at increased risk for celiac disease.
3. Create a differential diagnosis for celiac disease and celiac crisis.
4. Review the challenges in accurately diagnosing celiac disease.
5. Recognize the common and uncommon complications of celiac disease.

Introduction

Celiac disease is an immune-mediated illness precipitated by ingestion of gluten in genetically susceptible individuals [1, 2]. It is a disorder of the small intestine, characterized by villous atrophy and mucosal inflammation, with improvement following withdrawal of gluten from the diet. Note celiac disease differs from non-celiac gluten sensitivity, in which symptomatic improvement off gluten is not associated with histologic or serologic evidence of celiac disease.

Over 98% of individuals with celiac disease have the human leukocyte antigen (HLA) DR3-DQ2 and/or DR4-DQ8, compared with 30–40% of the general population of most developed nations [3, 4]. In patients with celiac disease, the immune response to gliadin promotes infiltration of chronic inflammatory cells in the lamina propria, progressing to villous atrophy. The inflammatory cascade triggers the release of tissue transglutaminase from endothelial cells and fibroblasts.

A. V. Baratta Jr. (✉)
Gastroenterology Associates of Rochester, Rochester, NY, USA

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Transglutaminase deamidation of gluten peptides potentiates stimulation of T cells [5, 6].

The estimated prevalence of celiac disease is approximately 1% in most countries, based primarily on serologic studies [7, 8]. The known cases of celiac disease may represent only the tip of the iceberg, as suggested by population-based studies. Those without symptoms may account for symptomatic individuals by a ratio of 7:1. Moreover, the prevalence of celiac disease has been gradually increasing over the past several decades [9–12]. High-risk groups for celiac disease include first- and second-degree relatives, along with Down syndrome and several autoimmune disorders (autoimmune thyroid disease, type 1 diabetes mellitus) [13, 14].

The clinical presentation of celiac disease is variable, ranging from asymptomatic patients to those with profound malabsorption [15]. Classic presenting features may include diarrhea with malodorous floating stools, from steatorrhea. Other symptoms may include abdominal pain, bloating, and even constipation. Consequences of malabsorption may include weight loss and iron deficiency anemia, along with deficiency of B vitamins. Extraintestinal manifestations may include elevated liver enzymes, recurrent headaches, fatigue, dermatitis herpetiformis, reduced fertility, peripheral neuropathy, dental enamel hypoplasia, osteoporosis, aphthous stomatitis, and cerebellar ataxia. Rarely, patients may initially present with "celiac crisis," characterized by acute large volume diarrhea, dehydration, and metabolic disturbances. Complications may include neuromuscular weakness, seizures, and potentially fatal arrhythmias [16].

It is important for clinicians to recognize both the typical and atypical presentations of celiac disease in order to arrive at a timely diagnosis. This is important both to improve quality of life as well as to minimize potentially serious complications of untreated celiac disease. Prior to availability of serologic testing and endoscopic biopsy, individuals with celiac disease often suffered consequences of misdiagnosis or lengthy delays in diagnosis. Testing for celiac disease is most accurate when patients are on a diet containing gluten. Those considered at low risk for celiac disease should first undergo serologic testing. The serum tissue transglutaminase test (tTG-IgA) is most commonly used, along with measurement of total IgA levels (as those with IgA deficiency require IgG celiac antibody serology testing). Those with positive transglutaminase serology should undergo upper endoscopy with biopsies of the proximal small intestine. Negative serology results often have a high negative predictive value in those at low risk for celiac disease, such that endoscopy in those individuals can be avoided.

Individuals with a high probability of celiac disease may include those with typical symptoms as outlined above, along with those having significant risk factors. Individuals with high probability should undergo both serologic testing and upper endoscopy with duodenal biopsies. Celiac disease is confirmed when positive serology is combined with abnormal duodenal biopsies, typically villous atrophy. Those with mucosal inflammation (increased intraepithelial lymphocytes) but normal-appearing villi may require close monitoring with consideration of repeat endoscopy months or several years later.

Testing for HLA DQ 2 and HLA DQ8 may be helpful in equivocal cases, especially those on a long-term gluten-free diet. Some individuals already avoiding gluten may be unwilling to undergo a gluten challenge. Negative testing for both HLA DQ 2 and HLA DQ8 helps to exclude celiac disease with at least 98% accuracy.

Multiple biopsies from the duodenum are recommended for confirming celiac disease. Histologic features may range from an increase in intraepithelial lymphocytes to severe villous atrophy with crypt hyperplasia. The Marsh classification is often used to grade histologic severity.

Clinical Case Presentation

Presenting to the emergency department is a 34-year-old female with over 2 weeks of severe diarrhea (7–10 stools per day) along with weakness of extremities, accompanied by weight loss of 22 pounds over 2 months. She reported taking oral iron supplementation. Physical examination revealed severe muscle weakness involving all extremities, along with a positive Trousseau's sign. The patient's vital signs were assessed and within normal range, and the abdominal exam was unremarkable. Electrocardiogram revealed sinus rhythm, flattened T waves along with U waves, type 1 atrioventricular block, and QTc prolongation. Laboratory testing revealed profound electrolyte disturbances, including severe hypokalemia (1.6 mmoL per L), severe hypocalcemia (0.9 mmoL/L ionized), hypomagnesemia (1.6 mmol/L), and hypophosphatemia (1.6 mg/dL). Complete blood count revealed hemoglobin of 8.5 g/dL and ferritin of 2 ng/mL, along with folate deficiency (2 ng/mL) and hypoalbuminemia (2.6 g/dL). She received adequate rehydration along with replacement of potassium and correction of other metabolic abnormalities. The initial differential included infectious gastroenteritis and acute onset Crohn's disease. Stool tests were unremarkable for culture and occult blood. Abdominal radiograph and ultrasound were unremarkable. Transaminases were slightly elevated, including aspartate transaminase (60 U/L) and alanine transaminase (47 U/L). Upper endoscopy eventually was performed to investigate the iron deficiency anemia and weight loss, revealing scalloping of duodenal folds with a mosaic pattern, and duodenal biopsies revealing severe villous atrophy. Tissue transglutaminase was mildly elevated at 23 U/mL, and IgA endomysial antibody was elevated (1:80). A diagnosis of celiac disease was made on the basis of the clinical presentation accompanied by severe villous atrophy and elevated celiac antibodies. Fortunately, the patient responded to gluten withdrawal, without the need for steroid therapy (steroids are often considered for celiac crisis). The diarrhea and muscle weakness improved significantly, and the patient was discharged 1 week after admission [17].

Differential Diagnosis

The differential diagnosis in this case includes the following.

1. Infectious enterocolitis—Always needs to be considered in patients presenting with acute or subacute diarrheal illness, as it is one of the leading causes with this presentation.
2. Acute onset inflammatory bowel disease—May also have a similar atypical presentation.
3. Celiac crisis—While rare, needs to be entertained given the significant diarrhea and weight loss along with laboratory features of malabsorption.
4. Microscopic colitis—Sometimes associated with celiac disease.
5. Ischemic colitis—May cause diarrhea and cramps, sometimes with bleeding, more often in older individuals. Ischemic colitis may occur in younger patients as well, related to coagulation disorders or medication-induced bowel ischemia.
6. Medication-induced diarrhea.
7. Carcinoid syndrome—While rare, may cause a subacute presentation of a secretory diarrhea, usually accompanied by flushing.
8. Intestinal tuberculosis—Rare but may sometimes mimic Crohn's, with diarrhea and abdominal pain accompanied by fever and other constitutional manifestations. Risk factors include impaired immunity and exposure to infectious persons.
9. Amebiasis—Affected individuals in developed nations often report recent travel to endemic areas.

What Was Misdiagnosed in This Case and Why?

The possibility of celiac crisis was not initially considered in this patient. Rather, infectious enteritis and inflammatory bowel disease were considered higher in the differential, as they are more commonly encountered than acute celiac crisis.

Discussion

It is important to consider the variable presentations of celiac disease in order to make a prompt diagnosis, with appropriate management. The classic presentation for celiac disease may include chronic diarrhea with bloating, malodorous stools, and modest weight loss. However, many individuals do not present with classic, typical features. Other important presentations may include iron deficiency anemia, constipation, recurrent headaches, and recurrent fetal loss.

Atypical and extraintestinal manifestations include unexplained elevation in serum transaminases, dermatitis herpetiformis, B12 deficiency, aphthous stomatitis,

premature osteoporosis, dental enamel hypoplasia, peripheral neuropathy, and cerebellar ataxia [18, 19].

Individuals at increased risk for celiac disease may include first and second-degree relatives, Down syndrome, autoimmune thyroiditis, and type 1 diabetes mellitus. Practitioners should consider testing for celiac disease in any of these clinical scenarios.

Clinicians are more likely to consider testing for symptomatic celiac disease in those with chronic diarrhea rather than acute diarrhea. In our case presentation, the acute/subacute presentation was not typical of celiac disease. However, clues in this patient suggesting celiac disease included persistent diarrhea with weight loss, iron deficiency anemia, transaminase elevation, and significant metabolic disturbances (as may occur with severe malabsorption).

Late diagnosis of celiac disease was not unusual many decades ago, prior to the availability of endoscopy (with duodenal biopsies) and prior to currently available serologic tests for celiac disease. Indeed, the two most important tests for diagnosing celiac disease include abnormal duodenal histology and serology. An assured diagnosis can be made in the presence of high titer transglutaminase levels combined with villous atrophy. However, it is important to appreciate a spectrum exists, such that a diagnosis is often challenging with minimally elevated celiac antibodies and/or with minimally abnormal histology. Relative to these cases, one must also consider the clinical presentation and the response to gluten withdrawal, along with family history, HLA testing, and consideration of follow-up testing (repeating endoscopy/biopsy and obtaining additional serology such as anti-endomysial antibodies and/or deamidated gliadin peptides). These measures may help improve the accuracy for diagnosing celiac disease [20].

While misdiagnosis of medical conditions often refers to delayed or incorrect diagnoses, the potential for "overdiagnosis" is often under-recognized and underappreciated. At a tertiary referral center in Italy, of 614 patients diagnosed with celiac disease at other institutions, only 70% were able to be confirmed. The remaining 30% did not have a combination of villous atrophy and abnormal serology and were determined not to have celiac disease [21]. Many had other diagnoses (Crohn's disease, irritable bowel syndrome, microscopic colitis) and were unnecessarily following a gluten-free diet without clinical benefit.

All patients with confirmed celiac disease should adhere to a gluten-free diet. There are several important components of managing celiac disease, including the following: education about celiac disease, consultation with a skilled dietitian, lifelong adherence to a gluten-free diet, identification and management of nutritional deficiencies, access to a celiac support group, and long-term follow-up by a multidisciplinary team.

Fortunately, online and other educational resources for celiac disease are much more extensive today than existed several decades ago. The biggest challenge for those with celiac disease is strict lifelong adherence to a gluten-free diet. Local and online support groups may be extremely helpful, both for dietary advice and emotional support.

Affected patients should also meet with a registered dietitian who is knowledgeable regarding celiac disease. The primary components of dietary gluten include wheat, rye, and barley. Dietitians can provide instructions for basic dietary modification, along with suggestions for minimizing inadvertent gluten ingestion.

The response to dietary gluten is extremely variable among patients. While some are asymptomatic, others are sensitive to minute amounts of gluten. Rare patients may be at risk for celiac crisis, as in our case presentation.

Risks of untreated celiac disease may include iron deficiency anemia, micronutrient deficiency, metabolic abnormalities, osteoporosis, other autoimmune disorders, and increased risk for malignancy (including lymphoma and gastrointestinal cancers).

Plan of Action

Recognize both the typical and atypical presentations of celiac disease. Appreciate how celiac crisis may present as a severe atypical infectious gastroenteritis, with potentially fatal outcome if misdiagnosed. Consider transglutaminase testing more often in these clinical settings, including the various presentations outlined above.

Conclusion

Celiac disease is a small bowel disorder with villous atrophy induced by exposure to gluten and improved with withdrawal of gluten from the diet. Testing should be performed for those with gastrointestinal or extraintestinal manifestations of celiac disease. While evaluation often begins with transglutaminase serology, upper endoscopy and small bowel biopsy usually are necessary for confirmation and accurate diagnosis. Clinicians should appreciate both the classic and atypical presentations of celiac disease.

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Chapter 26
Misdiagnosis of Colorectal Cancer with Emphysematous Epididymo-Orchitis as a Camouflage

Akshay K. Shetty

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Establish appropriate differential diagnosis in patients presenting with symptomatology suspect for colorectal cancer by investigating all relevant details of the patient's medical history along with physical examination of the patient.
2. Analyze the differences of investigative methods in determining patient possibility of presence of colorectal cancer.
3. Discuss the consequences of a misdiagnosis or delay in establishing colorectal cancer for individual patient prognosis.
4. Explain the difficulty of accurately diagnosing colorectal cancer.
5. Enumerate the features of emphysematous epididymo-orchitis.

Introduction

Colorectal cancer, excluding skin cancers, is the third most common cancer diagnosed in the United States [1]. When it comes to colorectal cancer, the symptoms themselves may not be present in an individual for quite some time. The severity of tumor growth and the symptoms that come with the growths vary from person to person giving only a general outline. It is up to the medical team/presiding physician to ensure that the complaints of the patient are met with utmost speculation as prolonging a diagnosis of colorectal cancer can greatly affect the prognosis of the patient. Another thing to note is that changes in bowel habits, which can suggest colorectal cancer, may not be as pronounced as other bowel disorders. In addition to

A. K. Shetty (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: akshay.shetty@martinus.edu

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this, colorectal cancer has been known for its ability to invade surrounding tissues as well via the formation of fistulas [2].

That ability of colorectal cancer, to form fistulas, is the highlight of the following case report. Due to this ability, the importance of anatomical awareness begins to rise as supporting structures and organs can be the possible locations for this cancer to route. Even though there is only one case discussed in this paper, it should be noted that the variability of colorectal cancer and its aggressiveness can produce a myriad of other symptoms. This case will highlight the importance of early screening as well as facilitate a discussion as to how colorectal cancer can be a suspicion among seemingly unrelated symptoms.

Clinical Case Presentation

A 69-year-old male came into the emergency department with acute scrotal pain found on the right side. At time of admittance, the patient mentioned that there was no history of trauma, sexual exposure, or any notable medical disease to be documented, with the exception of intermittent diarrhea in recent months. Vital signs were noted: blood pressure 76/54 mmHg, pulse rate of 72 beats per minute, body temperature of 38 °C, and a respiration rate of 19 breaths per minute. When performing the physical examination, it was revealed that the acute scrotal pain was located on the right-hand side and continued to the ipsilateral inguinal region without perineal involvement. The patient's labs revealed that hemoglobin level was 12.7 g/dL, white blood cell count 12.240/μL, and lastly C-reactive protein (CRP) was 14.55 mg/dL. Imaging showcased, utilizing scrotum sonography, bright spots and hypoechoic areas, giving the impression of acute epididymo-orchitis with abscess and gas formation. The patient was sent for right unilateral orchiectomy and debridement. Culture of the pus obtained revealed the presence of *Clostridium* spp. and *Bacteroides fragilis*. After which the patient was discharged following necessary antibiotics with ceftriaxone and metronidazole at stable wound condition. Unfortunately the associated scrotal pain was noted with purulent discharge from the initial surgical wound 1 month later, pathogen proved as mixed organisms including *Klebsiella pneumoniae*, *Clostridium* spp., and *Bacillus fragilis*. Examination through digital rectal exam demonstrated an indurated enlarged prostate without palpable rectal mass. With these features the patient was sent for computerized tomography (CT) of the scrotum and pelvis, which revealed heterogeneous density of the prostate with central low attenuation, rectum thickening of the whole wall, and lymph node enlargement. With these findings advanced-stage rectal cancer with prostatic abscess was assumed. Colonoscopy was performed and revealed a tumor lesion with annular type 5 cm above the anal verge, biopsy was performed, and the analysis confirmed adenocarcinoma of the rectum. Tumor markers showed carcinoembryonic antigen (CEA) of 9.40 ng/mL and carbohydrate antigen 19-9 (CA19-9) of 21.30 U/mL. Further investigation using positron emission tomography (PET) scan revealed no abnormal fluorodeoxyglucose (FDG) uptake

throughout the whole body region and presumed stage of the patients rectum adenocarcinoma was T4N1M0. Infection control was addressed via suprapubic cystostomy for urinary diversion and T-loop colostomy practices. Lastly the patient was sent for exploratory laparotomy with abdominoperineal resection and radical prostatectomy. Analysis later revealed an adenocarcinoma that was moderately differentiated from the colonic origin with direct invasion into the bilateral prostatic tissue. It should be noted the final stage was ypT4bN1bM0. Adjuvant chemotherapy with oral intake capecitabine was administered up until present time. Lastly, tumor marker results after performing the resection of the rectal tumor were CEA levels indicating 1.16 ng/mL and a CA19-9 level of 11.36 U/mL, further imaging revealed no evidence of tumor recurrence [2].

Differential Diagnosis

1. Colorectal cancer—While the patient arrived and was assessed for scrotal pain as observed during the medical interviewer, colorectal cancer was the root cause of the patients complaints. It was not until the patient followed up with additional scrotal pain and a digital rectal exam with features of an enlarged prostate and induration that a CT was performed. The CT, followed by a colonoscopy, led the way to a biopsy of a polyp to confirm cancer markers. Notably, the patient was positive for CEA and CA19-9 which also steer toward a diagnosis of colorectal cancers. The patient is 69 years old, and most patients suffering from colorectal cancer tend to be >50 years of age [1].
2. Emphysematous epididymo-orchitis—This is an uncommon diagnosis characterized as an acute inflammatory process of epididymis and testis with a presence of air [3]. The patient having come for a checkup due to right-sided acute scrotal pain steered the medical team toward a diagnosis within the realm of anterior pelvic region. This was greatly emphasized by the inclusion of the symptom of pain that extended from the right side of the scrotum ipsilateral to the inguinal region without perineum involvement. Lastly, the bacterial involvement found from the pus culture led the team to an initial diagnosis of emphysematous epididymo-orchitis.
3. Benign prostatic hyperplasia—The age of the patient, 65-years-old, is a determining factor in the inclusion of benign prostatic hyperplasia. Digital rectal examination demonstrated an enlarged prostate with induration.

What Was Misdiagnosed in This Case and Why?

Colorectal cancer was misdiagnosed as emphysematous epididymo-orchitis. The reality of their initial diagnosis is that the features found on the initial medical examination were caused by an underlying colorectal cancer that was camouflaged.

The original diagnosis was supported by the presence of acute scrotal pain with ipsilateral inguinal pain extension that did not involve the perineum. The patient also denied any history of trauma, sexual exposure, or major medical disease, the only exception being an admission of intermittent diarrhea. Following initial treatment of emphysematous epididymo-orchitis, it was revealed there was no reduction in pus formation after treatment with antibiotics. Following such it was revealed via CT and colonoscopy that the patient showed a tumor that was then biopsied to reveal markers in accordance with colorectal cancer.

Discussion

There are several things to consider when reaching a diagnosis of colorectal cancer and the fundamentals should not be dismissed. In order to make this diagnosis, the patient's medical history, physical examination, and presentation at time of admittance should be taken into consideration. While colorectal cancer may not always present the same way on admission, the signs and symptoms should be well-known among the clinicians present. Symptoms include change in bowel habits, such as diarrhea, constipation, or narrowing of the stool, that last for more than a few days, feeling that a bowel movement needs to occur that is not relieved by defecation, rectal bleeding with bright red blood, blood in the stool which may change the color, cramping or abdominal pain, weakness and fatigue, and lastly unintended weight loss [4]. Colorectal cancer may not cause all of the symptoms right away or may be unnoticed all together by the patient, and thus the burden of responsibility on asking questions similar to the symptoms is shouldered by the clinicians. In cases similar to the one presented here, the patient may be experiencing one symptom and think that the relation is to the reason of their admittance. Another factor to take into consideration when discussing colorectal cancer is the epidemiology and guidelines for patients that were created based on epidemiological factors. Colorectal cancer is known to affect patients that are >50 years old and tend to have a familial link to the cancer. Due to this, the American College of Gastroenterology screening recommendations have suggested that patients be screened for colorectal cancer, starting at age 50, every 10 years via a colonoscopy. In instances where the patient is not eligible or willing to undergo a colonoscopy, patients should be offered an alternative such as a flexible sigmoidoscopy or a computerized tomography. At the very least, there is a recommendation for a fecal immunochemical test to be performed [5]. At the time of admittance the patient in this report was 69 years old with no history of screening, let alone major medical diseases that were documented by the clinicians. With only the symptom of intermittent diarrhea, the medical team was focused on the symptoms of scrotal pain as well as ipsilateral inguinal pain that extended from the scrotum but did not include the perineum. The initial impression of acute epididymo-orchitis with abscess and gas formation was what the team had settled on. This is characterized as inflammation of the epididymis and testicles characterized by the presence of air within the tissue. While ultimately the diagnosis was

colorectal cancer, the presence of emphysematous epididymo-orchitis was a direct cause of the underlying cancer. With the anatomical location of these structures being fairly intimate, advanced colorectal cancer invading the urinary tract is not uncommon [6]. In the graphic provided (Fig. 26.1), a digital rectal exam (DRE) is shown, although a technique to check the quality of the prostate, it can be understood that this technique is utilized due to the intimacy of the respective organs. In order for this to occur as a result of the colorectal cancer, there inherently needs to be the formation of either direct invasion or fistula formation. There have been several cases in which a fistula being formed between the colon and the seminal vesicle has occured [8]. It is through these mechanisms and the presenting symptoms that aided the clinical team to make the initial diagnosis of emphysematous epididymo-orchitis for this patient. It was after the primary treatment for this issue that the symptoms did not subside which ultimately led to the medical team to utilize other means of investigation. Following an abnormal digital rectal examination and subsequent CT that the whole wall thickening of the rectum and tumor lesion that was biopsied was the colorectal diagnosis made. The biopsy revealed the presence of cancer markers found in the tumor lesion that helped in the diagnosis. The patient was positive for two markers, carcinoembryonic antigen and carbohydrate antigen. In some studies, high carcinoembryonic antigen concentrations in patients with stage II and stage III colorectal cancer were indicative of more aggressive types of cancer [9, 10]. The

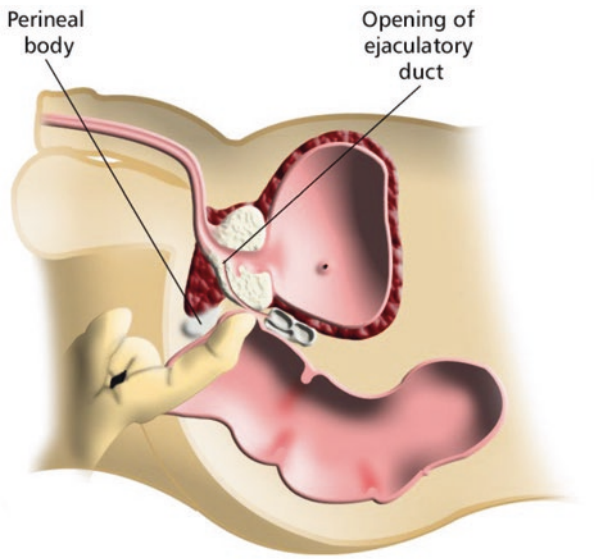

Fig. 26.1 Image of a digital rectal examination and the intimacy of the bowels and its surrounding structures [7].

presence of carbohydrate antigen 19-9 should also be of notoriety. It is a glycoprotein whose relevance in colorectal cancer diagnosis remains an issue. There is a conclusion among various researches that carbohydrate antigen 19-9 is much inferior to that of carcinoembryonic antigen, and elevated carbohydrate antigen 19-9 is a poor prognostic factor [11–14]. With that in mind, given the advanced nature of this patient's colorectal cancer, it's possible a better prognosis could have been achieved had the patient followed guidelines for routine screening with the idea that this diagnosis could have been achieved at an earlier time. As the presenting symptoms were found to be a consequence of the colorectal cancer, an earlier diagnosis could have potentially avoided this patient's emphysematous epididymo-orchitis.

Plan of Action

Appreciate both the typical and atypical presentations of colorectal cancer, as well as how fistula formation allows for a seemingly complex route of transmission to surrounding tissues, similarly to the case shown here. Consideration of early usage of computerized tomography could have easily shown early signs of the patients colorectal cancer as well as tissue thickening. Initial suspicion of the cancer would have prompted biopsy and tissue sampling at a much earlier time as well with intent to screen for carcinoembryonic antigen.

Conclusion

Colorectal cancer, excluding skin cancers, is the fourth most common cancer in the United States overall and represents the 3rd leading cause of cancer-related deaths in the United States. Although emphysematous epididymo-orchitis is very rare, especially in conjunction with locally advanced colorectal cancer, root causes should be accurately investigated. A major issue in investigation has to do with collection time of the samples when taken from the rectum, as seen in discrepancies associated with 3 and 6 min withdrawal times [15]. While cases like the one shown here may be rare, clinicians should appreciate classical as well as atypical presentations of colorectal cancer.

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Chapter 27
Misdiagnosis of Inflammatory Bowel Disease due to Features Similar to Granulomatosis with Polyangiitis

Akshay K. Shetty

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Analyze the differences of investigative methods in determining patient possibility of presence of inflammatory bowel disease.
2. Discuss the consequences of a misdiagnosis or delay in establishing inflammatory bowel disease for individual patient prognosis.
3. Review the difficulty of accurately diagnosing inflammatory bowel disease.
4. Establish appropriate differential diagnosis in patients presenting with symptoms suspect for inflammatory bowel disease by investigating all relevant details acquired from the patient's medical history along with physical examination of the patient.

Introduction

Inflammatory bowel disease is a seemingly straightforward diagnosis to make with symptoms that are multisystem in nature as well as directed at the bowel. Unfortunately due to the multisystem nature of this disease, it is possible that some symptoms may proceed others. Extraintestinal manifestations of symptoms can be reported with frequencies ranging from 6 to 47%; the extraintestinal manifestations are also known to occur at any time during the course of the disease be it before or after a diagnosis of inflammatory bowel disease has been made [1]. The following case report will illustrate that the course of inflammatory bowel disease does not necessarily take the same course that other patients may experience. Due to the

A. K. Shetty (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: akshay.shetty@martinus.edu

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possibility of variability in symptoms, be it extraintestinal or intestinal, this proves to be a challenge for physicians/medical teams when it comes to making a diagnosis. The aim of this paper is to help elucidate this variability, as well as show clinicians a specific instance of inflammatory bowel disease that did not follow the usual projected course.

Clinical Case Presentation

A 54-year-old African-American man presented to our resident clinic at Johns Hopkins Hospital for discharge follow-up after admission for wrist pain and suspected viral gastroenteritis. He did not have a primary care physician due to lack of health insurance and had been seen in our emergency department several times over the past year.

He had been well until 7 months earlier when he developed unilateral pain and redness of his right eye. An ophthalmologic evaluation in our emergency department revealed anterior uveitis, which was resolved with topical steroids. Five months later he sought care for right ear pain. Computed tomography (CT) imaging revealed inflammation of his pinna, consistent with auricular chondritis. This resolved spontaneously without treatment. Two months later, he again returned to our emergency department with pain and redness of his right wrist. He was diagnosed with cellulitis and empirically treated with oral clindamycin for 7 days with minimal improvement. Just 3 days later, he was admitted for sudden onset of fever and diarrhea. A viral etiology was suspected given the quick resolution of his symptoms and management with conservative therapy. He was discharged home within 48 h with follow-up in our internal medicine resident clinic. At his outpatient visit a few days after discharge, he had persistent swelling of his right wrist that limited his ability to operate motor vehicles at his job as a valet. Further questioning revealed a 27 kg (60 pounds) unintentional weight loss over the past 6 months. He denied epistaxis, cough, hemoptysis, chest pain, dyspnea, recurrent ocular symptoms, rash, low back pain, abdominal pain, frequent stools, melena, or hematochezia. He had no significant past medical or surgical history. His family history was unremarkable. He did not smoke tobacco, drink alcohol, or use illicit drugs. On examination, he was a well-developed, well-nourished black man who appeared comfortable. He was alert and fully oriented. His vital signs were within normal limits. He had no rash, oral ulcers, or cutaneous nodules. There was no lymphadenopathy. Sclerae were not injected. A comprehensive musculoskeletal examination revealed mild synovitis of his right wrist without overlying erythema but limited range of motion due to pain. Cardiac, pulmonary, abdominal, and neurologic examinations were unremarkable. A laboratory evaluation during admission revealed iron deficiency anemia with hemoglobin of 10.1 g/dL and a white blood cell count of 12,100 cells/mm^3 with a normal differential. His albumin was low at 2.9 g/dL, alkaline

phosphatase was elevated at 182 U/L, and there was mild transaminitis. There was microscopic hematuria: red blood cells (RBC) 55/high-power field (hpf); he had normal creatinine and no proteinuria. His inflammatory markers were elevated with C-reactive protein 11.1 mg/dL and erythrocyte sedimentation rate 124 mm/h. His fecal lactoferrin was positive. A chest radiograph showed a small ill-defined patchy infiltrate in the upper lobe of his right lung. An infectious workup included the following negative studies: bacterial stool and blood cultures, human immunodeficiency virus (HIV) viral load, cytomegalovirus (CMV) serum polymerase chain reaction (PCR), gonorrhea and chlamydia urine PCR, stool *Clostridium difficile* toxin, and stool ova and parasites. Antinuclear antibody, anti-mitochondrial antibody, anti-smooth muscle antibody, rheumatoid factor, and anti-cyclic citrullinated peptide were negative. His complements were normal. C-ANCA was positive at a titer of 1:40 with elevated proteinase 3 by enzyme-linked immunosorbent assay (ELISA; 102.6 units). Perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) and myeloperoxidase by ELISA were negative. With infection effectively ruled out, his clinical picture seemed most consistent with GPA. He was seen in consultation by rheumatology and started on prednisone 60 mg daily with marked improvement in symptoms and laboratory abnormalities. However, 8 weeks later he developed hematochezia, left lower quadrant pain, and a perirectal abscess and fistula. A colonoscopy was performed and multiple biopsies were taken. Histologic examination of the biopsy from his descending colon (Fig. 27.1) showed cryptitis and crypt abscesses. A biopsy from his rectum (Fig. 27.2) showed early crypt distortion and basal plasmacytosis. In the absence of an infectious etiology, these findings were suggestive of chronic colitis and/or IBD. There were no granulomas, vasculitis, or dysplasia.

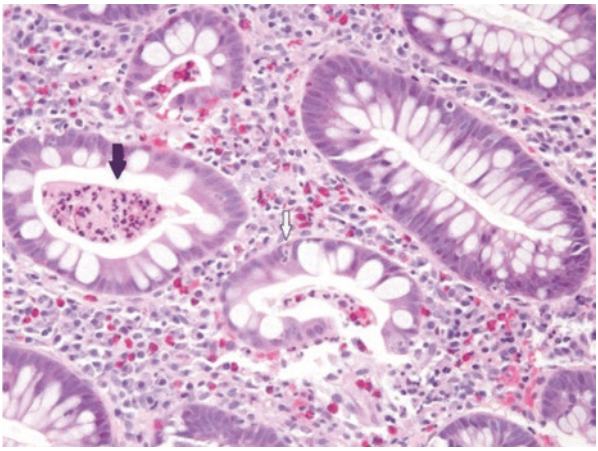

Fig. 27.1 Descending colon biopsy. This histologic section from the descending colon, taken 9 months after initial presentation, shows a crypt abscess (black arrow) and cryptitis (white arrow). Enlarged at 20× [2].

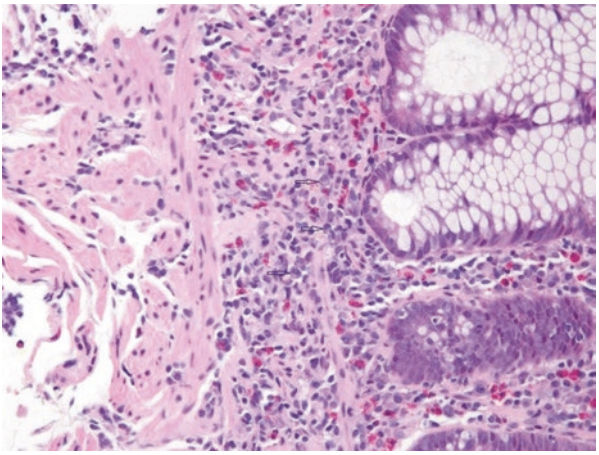

Fig. 27.2 Rectum biopsy. This histologic section from the rectum, taken 9 months after initial presentation, shows basal plasmacytosis (arrows). Enlarged at 20× [2].

Treatment for IBD was initiated with azathioprine and infliximab with healing of his fistula and continued clinical improvement. Therapy was well tolerated. For the past 1.5 years, he has been doing well on the same therapy with no further GI or extraintestinal manifestations of IBD [2].

Differential Diagnosis

1. Inflammatory bowel disease—Intestinal manifestation seen with this patient being the hematochezia as seen at 8 weeks post-initial GPA diagnosis. Although the patient denied a rash, the patient was seen to have anterior uveitis, auricular chondritis, monoarthritis, fever, and weight loss.
2. Granulomatosis with polyangiitis—The initial diagnosis made by the medical team was supported by symptoms such as fever, weight loss, auricular chondritis, anterior uveitis, microscopic hematuria, monoarthritis, and c-ANCA positivity. However, GPA is much more common in white individuals, and uveitis is also rarely reported in GPA with scleritis being more common. The patient also did not have proteinuria which would be more common in GPA given its renal involvement. Irritable bowel syndrome recurrent abdominal pain associated with defecation and/or change in stool frequency and/or change in form/consistency of the stools. This diagnosis however is better supported in patients that are female and are older in age. It also lacks multisystem symptoms that would be better explained by the diagnosis of GPA or IBD.

What Was Misdiagnosed in This Case and Why?

Inflammatory bowel disease was misdiagnosed as granulomatosis with polyangiitis (GPA) , since the clinical picture of the patient was in line with this diagnosis. This was due to the fact that the patient, while suffering from multisystem processes, was not established as a patient suffering from multisystem processes until care was started with an internist and rheumatologist. Once care was established, it was noted that this patient's clinical course was characterized by a myriad of inflammatory features ranging from c-ANCA positivity to auricular chondritis and even unilateral anterior uveitis. It was at this point that the diagnoses were boiled down to either inflammatory bowel disease or granulomatosis with polyangiitis. As the disease progressed, it was noted that the GI tract of the patient was the primary inflammatory target. IBD was subsequently confirmed following a colonoscopy.

Discussion

As with most diagnoses, in order to accurately and effectively come to a specific diagnosis, it is imperative that the medical team has followed the necessary steps in terms of the medical interview and physical examination. For instance, in the scenarios involving gastrointestinal disorders, such as this case, the medical interview becomes extremely essential especially when it comes to the timeline of symptoms appearing. In a study involving 1249 patients, there were a total of 366 patients that experienced extraintestinal manifestations; approximately one quarter of patients with inflammatory bowel disease had these manifestations appear before the time of diagnosis [1]. It is due to this fact that the past medical history of patients suspected of suffering from gastrointestinal disorders is not taken lightly. The patient in this case had appeared with a variety of symptoms that did not immediately raise the flag of inflammatory bowel disease. As described by the medical team, being a patient that did not have health care, his complaints were treated as individual, piecemeal, visits. Once he had been under the care of an internist and rheumatologist, his multisystem symptoms were considered as a whole to another diagnosis. At this point the medical team was between two diagnoses for this patient, being granulomatosis with polyangiitis and inflammatory bowel disease. This was due to the symptoms of c-ANCA positivity, auricular chondritis, fever, weight loss, microscopic hematuria, monoarthritis, and unilateral anterior uveitis. The initial misdiagnosis of granulomatosis with polyangiitis was chosen at first due to the clinical picture and c-ANCA positivity. Along with the negative enzyme-linked immunosorbent assay (ELISA), that would test for any antibody/antigen binding. With an approximated 80–90% of patients with granulomatosis with polyangiitis displaying ANCA positivity, this diagnosis was well supported [3]. This diagnosis was also scrutinized due to atypical features that did not immediately match with the purported clinical picture. The patient was suffering from anterior uveitis which does

not normally occur in these patients when scleritis is more often reported [4]. While renal manifestations occur in granulomatosis, this is usually in conjunction with proteinuria. The patient also lacked textbook manifestations of pulmonary issues, and this was confirmed in the medical interview [5]. After the initial treatment for granulomatosis, with prednisone, 8 weeks had passed before the patient also started to develop abdominal manifestations in the form of hematochezia, left lower quadrant pain, and a perirectal abscess and fistula. Under the care of the internist and rheumatologist, a colonoscopy was suggested, and histological specimens suggested inflammatory bowel disease. As reported earlier, while extraintestinal manifestations can occur before the diagnosis of inflammatory bowel disease is made, it is not the majority of cases. This particular case is also unusual due to the presence of c-ANCA. ANCA positivity is not unusual in the case of inflammatory bowel disease, but p-ANCA is more common than c-ANCA in this scenario [6]. With the suspicion of granulomatosis at first and subsequently inflammatory bowel disease, it is not entirely impossible that this patient may be suffering from both. Vasculitis and inflammatory bowel disease have been reported in patients at the same time before, where they occurred at the same time as well as one preceding the other [7]. When it comes to inflammatory bowel disease, the medical team should be prepared to see patients that may not present with the symptoms in a specific order. This should be evident through the case reported here, and due to this, clinicians should not rule out not to consider a diagnosis of inflammatory bowel disease even if the intestinal manifestations have not yet been seen. Investigative measures such as a colonoscopy and histological study can and should be implemented upon suspicion to rule in or out the diagnosis.

Plan of Action

1. As a basic rule of care, the presenting patient is entitled to a visit that entails a carefully sought out medical history.
2. The patient should be viewed holistically in terms of their previous medical history. All past medical history should be viewed as potential symptoms towards a possible reasoning to an alternate diagnosis.
3. Physicians should be trained and upgraded in order to have sufficient up to date knowledge of multisystem affecting disorders.
4. It is an important responsibility of the physician to seek meaningful and beneficial consults with physicians in other disciplines in order to accurately diagnose disorders.
5. In the event an investigation reveals information that may disprove an existing diagnosis, the medical team should not discredit the original diagnosis until the results prove without a doubt that it should be removed.

Conclusion

While this patient suffers from an unusual presentation of IBD: c-ANA positive, with prominent extraintestinal manifestations preceding GI complaints, failure to establish this unusual presentation may delay diagnosis [2].

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Chapter 28
Small Bowel Carcinoma Misdiagnosed as Ileal Crohn's Disease

Anthony V. Baratta Jr.

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Compare and contrast the variable presentations of Crohn's disease.
2. Discuss the challenges in diagnosing Crohn's and small bowel carcinoma.
3. Outline the regions of the gastrointestinal tract most commonly affected by Crohn's.
4. Create a differential diagnosis for a possible flare of Crohn's disease.
5. Discuss how to test for malignancy as a potential complication of Crohn's disease.

Introduction

Inflammatory bowel disease (IBD) involves two primary disorders, Crohn's disease (CD) and ulcerative colitis (UC). Crohn's disease may characteristically involve any portion of the gastrointestinal tract, from the oropharynx to the anal/perianal region. The intestinal inflammation in Crohn's is transmural, whereas inflammation in UC is confined to the mucosal layer. Almost 80% of Crohn's patients have small bowel involvement, often the distal/terminal ileum, whereas 20% have inflammation limited to the large bowel. Roughly half have inflammation involving both ileum and large bowel (ileocolitis) , and one third have inflammation only in the distal ileum. Approximately 10% have involvement of the upper gastrointestinal tract [1–3]. Most patients with Crohn's have one or more of the following symptoms: abdominal pain, diarrhea, weight loss, and fatigue. Rectal bleeding may occur with CD but is more

A. V. Baratta Jr. (✉)
Gastroenterology Associates of Rochester, Rochester, NY, USA
e-mail: Anthony.Baratta@RochesterRegional.org

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common in UC [2]. Those with disease restricted to the terminal ileum often present with right lower quadrant pain. Acute presentation of right lower quadrant pain is uncommon and may be misdiagnosed as appendicitis [4]. Fever may occur due to transmural inflammation, fistula complications, or abscess. Roughly one third have perianal involvement, typically fistulas [5]. Chronic inflammation and fibrosis may progress to strictures, resulting in small bowel obstruction (typically of distal/terminal ileum, less often large bowel). Weight loss may be due to partial obstruction and/or malabsorption [6]. Extra intestinal manifestations occur in roughly 30% of Crohn's patients and may include peripheral arthritis, ankylosing spondylitis, sacroiliitis, uveitis, erythema nodosum, pyoderma gangrenosum, and sclerosing cholangitis [7]. The diagnosis of Crohn's is based on clinical presentation combined with elevated blood and/or stool inflammatory markers, abnormal imaging (typically computerized tomography (CT) or small bowel series), and abnormal findings on colonoscopy and histology [8]. While most CD patients have some response to medical therapy, roughly half will eventually require surgical intervention [9, 10]. Uncommon yet life-threatening complications of Crohn's include carcinoma of large or small bowel, other malignancies, and severe infection. Colonic adenocarcinoma is associated with the duration and extent of colonic inflammation in both UC and Crohn's, and the long-term risk is threefold higher than in the general population. Small bowel carcinoma complicating Crohn's is much less common than colonic adenocarcinoma, yet the relative risk is much higher than in the general population [11].

Clinical Case Presentation

A 69-year-old female presented with 1 month of progressively worsening periumbilical pain. Her past history included hysterectomy (for uterine dysplasia), ovarian cysts, and lactose intolerance. She was a former smoker. Her father had colon cancer at age 68. Her abdominal pain was daily, intermittent, and variable in intensity. She ranged between 1 and 5 loose non-bloody stools per day. Appetite was reduced, with weight loss of 17 pounds over 2 months. She appeared in no distress and was hemodynamically stable and afebrile. The abdomen was nondistended and soft, with normal bowel sounds, minimal periumbilical tenderness, and no hepatosplenomegaly or palpable mass.

C-reactive protein was mildly elevated at 4.4 (normal less than 3). A complete blood count and the complete metabolic panel were unremarkable. The patient was seen at the emergency department for worsening abdominal pain, bloating, and early satiety. CT of the abdomen/pelvis revealed two areas of wall thickening and narrowing of the distal ileum along with proximal small bowel dilatation. The findings were suggestive of Crohn's.

Given these findings, along with her family history (Crohn's in a nephew) and a prior history for nonspecific ileitis over 15 years prior, she was started on oral prednisone for a presumed diagnosis of Crohn's ileitis. At discharge she was placed on a full liquid diet. Subsequent barium small bowel series revealed findings

"consistent with Crohn's disease" of the distal ileum. She had a modest response on prednisone and was referred for possible surgical resection given ongoing weight loss (up to 25 pounds over 4 months) and persistent albeit improved small bowel dilatation (from 8 cm on prior imaging down to 4.5 cm). The surgeon preferred she first attempt biologic therapy. Despite induction with adalimumab, she continued to have progressively worsening obstructive symptoms and ongoing weight loss. She was hospitalized for bowel obstruction and underwent ileocecectomy with ileostomy. Pathology revealed signet ring cell carcinoma of the terminal ileum, stage pT3N2, along with Crohn's enteritis. She received adjuvant FOLFOX but had rapid recurrence following completion. Despite additional chemotherapy regimens, she had progressive metastatic disease. She eventually expired roughly 3 years after the initial steroid treatment for the Crohn's.

Differential Diagnosis

The differential diagnosis for small bowel Crohn's includes the following:

1. Infectious enteritis—Always needs to be considered in the differential of patients presenting to the emergency department with abdominal pain and diarrhea, with or without weight loss. Stool studies for culture, parasites, and *C. difficile* are often included in the initial testing and evaluation.
2. Ischemia—May also cause a similar presentation, usually in older individuals, sometimes accompanied by blood in the stool.
3. Carcinoma—Must always be in the differential of any patients with unexplained weight loss accompanied by abdominal pain and change in bowel pattern.
4. Intestinal tuberculosis—While rare, may present in similar fashion as in patients with Crohn's disease, with abdominal pain and diarrhea accompanied by constitutional features. Many of these individuals have risk factors including immunosuppression and/or exposure to affected persons.
5. Small bowel diverticulitis—More often involves jejunum than ileum and may occur in scleroderma or other conditions causing intestinal neuropathy/myopathy.
6. Nonsteroidal anti-inflammatory (NSAID) enteropathy—Is often overlooked and may present as subclinical iron deficiency anemia, occult or overt intestinal blood loss, abdominal pain with or without partial intestinal obstruction, malabsorption, and/or hypoalbuminemia.

What Was Misdiagnosed in This Case and Why?

This patient had a delayed diagnosis of signet ring cell carcinoma of the terminal ileum. She was initially misdiagnosed as having Crohn's of the distal ileum, based on clinical presentation combined with CT and small bowel imaging studies.

Discussion

Crohn's disease is characterized by chronic transmural inflammation involving small or large intestines, or both. The prevalence of IBD has been increasing over several decades, with Crohn's now occurring in 250/100,000 individuals in the United States [12, 13]. Chronic inflammatory Crohn's may have a delayed diagnosis in individuals initially thought to have irritable bowel syndrome, lactose intolerance, celiac disease, and intestinal enterocolitis [14]. Fibrotic Crohn's involving the terminal ileum may present with abdominal pain and partial or complete bowel obstruction. Our patient presented with recurrent and progressive small bowel obstruction despite treatment with corticosteroids and subsequent biologic therapy. She had progressive weight loss and ultimately was diagnosed with signet ring cell adenocarcinoma of the terminal ileum. Her presentation and imaging studies were consistent with Crohn's ileitis, and colonoscopy confirmation was not attempted given presumed difficulty with a bowel prep (given chronic small bowel dilatation from obstruction). In retrospect, colonoscopy visualization and biopsy may have allowed for earlier diagnosis of the ileal carcinoma. She did not improve as anticipated on prednisone, and this should have prompted earlier endoscopic investigation. Signet ring cell carcinoma is a highly malignant, rare adenocarcinoma usually involving the stomach, uncommon in the ileum. This type of carcinoma is poorly differentiated and carries a poor prognosis. Long-standing small bowel inflammation from Crohn's may be a risk factor [15, 16].

Plan of Action

In patients with a flare of inflammatory bowel disease and suboptimal response to medical management, it is always important to consider other possibilities. In addition to excluding *C. difficile*, the rare possibility of coexistent carcinoma must also be considered.

Conclusion

The increased risk for colorectal cancer in the setting of chronic inflammation from Crohn's and ulcerative colitis is well recognized in the medical community. Small bowel adenocarcinoma is much less common but may develop in 1.5% of patients with long-standing Crohn's. It is rarely diagnosed preoperatively given similar clinical and imaging presentation as in those with active Crohn's ileitis. The possibility of small bowel carcinoma always needs to be considered especially in those with excessive weight loss and suboptimal steroid responsiveness. Direct and thorough colonoscopic imaging of the ileum may allow an earlier diagnosis.

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Chapter 29
Foreign Body Ingestion Misdiagnosed as Irritable Bowel Syndrome

Akshay K. Shetty and Danna Soria

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Analyze the differences of investigative methods in determining patients' possibility of the presence of irritable bowel syndrome and foreign body ingestion.
2. Analyze the consequences of a misdiagnosis or delay in establishing a foreign body ingestion patient.
3. Establish meaningful differential diagnosis in patients presenting with irritable bowel syndrome and foreign body ingestion.
4. Recognize that a patient presenting with a complete medical history and physical examination could be suffering from a foreign body ingestion and not irritable bowel syndrome.

Introduction

Foreign body ingestion can occur at any time, be it intentional or unintentional, and can prove to be an unexpectedly hard issue to diagnose. Because of the likelihood that most foreign bodies of all types will not cause complications, it is advisable to treat them expectantly [1]. Given the elusiveness of foreign body ingestion, it is particularly difficult to keep it as a diagnosis if the patient at hand is unaware of

A. K. Shetty (✉) D. Soria
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: akshay.shetty@martinus.edu; danna.soria@martinus.edu

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foreign body consumption. As symptoms begin to arise in the patient, it is important for the physician and patient to have a clear timeline in terms of these symptoms. Providing a timeline can help aid the medical team/physician in being able to determine if investigation in the matters of a potential foreign body would be deemed necessary. A major issue when considering a diagnosis of foreign body ingestion is the variety of symptoms that can change solely based on the location of the foreign body along the digestive tract. There have been instances where ingestion has been mistaken for other bowel disorders like Crohn's disease [2]. Even though symptoms can be characterized as several different disorders, it is imperative to the prognosis of the patient that a correct diagnosis is made. That is the case with the following case presentation listed in this report. Even though this report highlights one specific case of misdiagnosis in conjunction with a foreign body ingestion, this scenario is not rare. This case also highlights the personal consequences for the patient when it comes to a misdiagnosis when dealing with a foreign body ingestion. The case is meant to highlight this potential issue in medicine and help refresh the possibility of a foreign body ingestion when dealing with abdominal complaint patients.

Clinical Case Presentation

A 56-year-old Greek Caucasian woman presented to a primary care setting, in rural Crete, Greece, complaining of mild lower abdominal pain, cramping, and bloating, during the last 4 months. The pain was located primarily in the left upper quadrant and often affected the entire abdomen. Her symptoms gradually worsened over time, with only temporary relief with defecation. She reported that her bowel habits changed approximately 1 month after the onset of her abdominal symptoms. Alternating constipation and diarrhea was reported, with diarrhea being more predominant. She also reported a sensation of incomplete bowel emptying. A change in the frequency of bowel movements was also reported. She denied any bleeding,

fever, or weight loss. She also denied having any aggravating symptoms such as stress and certain foods over the last few months. Complete physical examination was within normal limits. Vital signs were also within normal limits. Our patient's medical history included hypertension (treated with an angiotensin II receptor antagonist, telmisartan), hypothyroidism (treated with L-thyroxine), and hypercholesterolemia (treated with atorvastatin), as well as some other minor bowel and gastric disorders that were chronic. There were no concerning associated signs or symptoms such as anemia or weight loss that would have led the family physician to initiate further studies. No abdominal or other surgical operations were reported. The family history for colorectal cancer was negative. The first impression was that the patient had IBS. General dietary advice according to the National Institute for Health and Clinical Excellence (NICE) guidelines for primary care management of IBS was given (regular meals, avoiding long gaps between eating, adequate and appropriate fluid intake). The patient also received mebeverine hydrochloride 135 mg three times daily for 3 weeks. The diagnostic approach included laboratory tests and an abdominal ultrasound control. Laboratory tests results revealed a normal complete blood count, normal erythrocyte sedimentation rate and C-reactive protein, and normal stool studies. Abdominal ultrasound revealed that her gallbladder, biliary tree, pancreas, spleen, and right kidney were all within normal limits. The lower portion of the left kidney was difficult to visualize secondary to the presence of a loop of bowel. Because her symptoms persisted despite treatment, a colonoscopy was ordered. The colonoscopy revealed the following: rectum with first-degree hemorrhoids, sigmoid and descending colon with increased spasticity and normal mucosa, and a normal ileum. In the ascending colon, a sharp piece of a birthday cake decoration was found and removed (Fig. 29.1). No necrosis of bowel mucosa or hemorrhage was observed. The increased bowel spasticity that was observed was interpreted by the gastroenterologist who performed the colonoscopy as possible IBS resulting as a consequence of the foreign body irritation (Fig. 29.2). The dimension of the foreign body is shown in comparison with a key in Fig. 29.3. One week after the removal of the foreign body, all symptoms resolved. Our patient was free of symptoms after 8 months of follow-up [3].

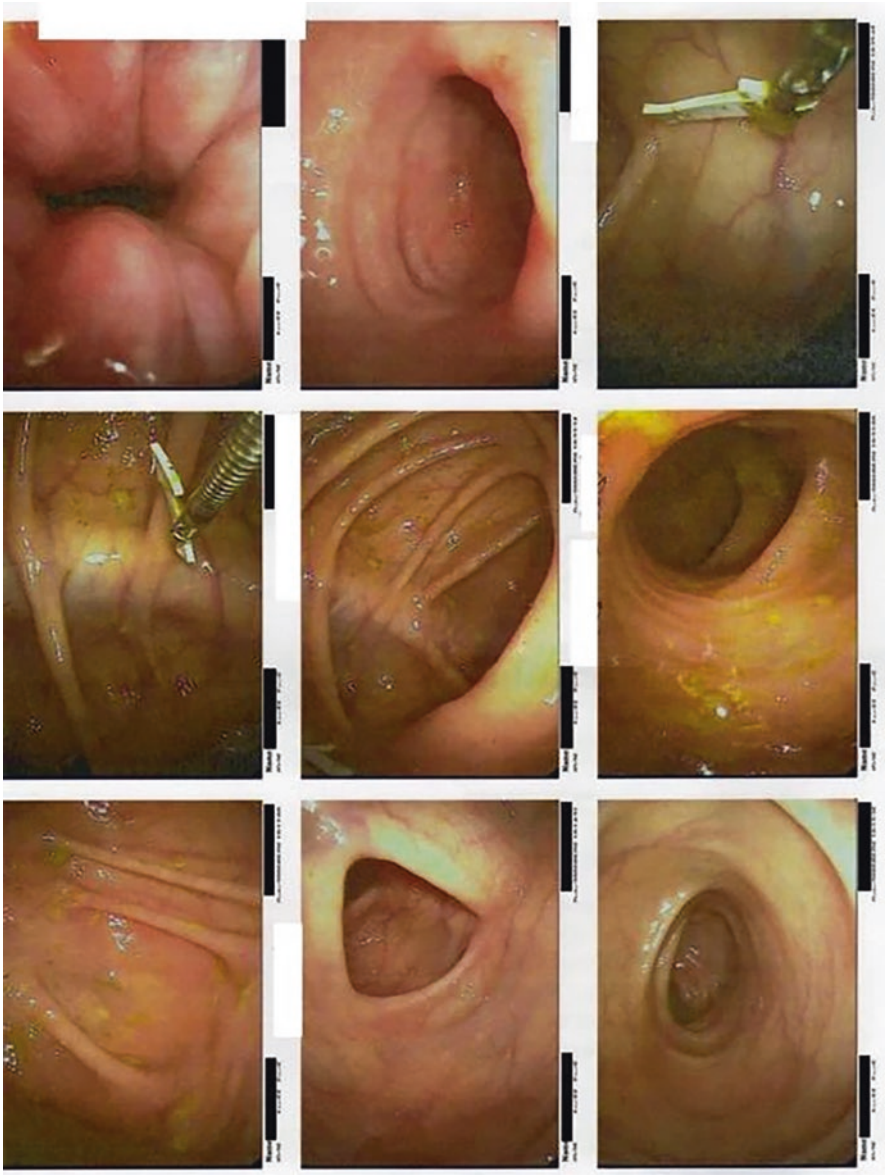

Fig. 29.1 Colonoscopy images showing the foreign body [3]

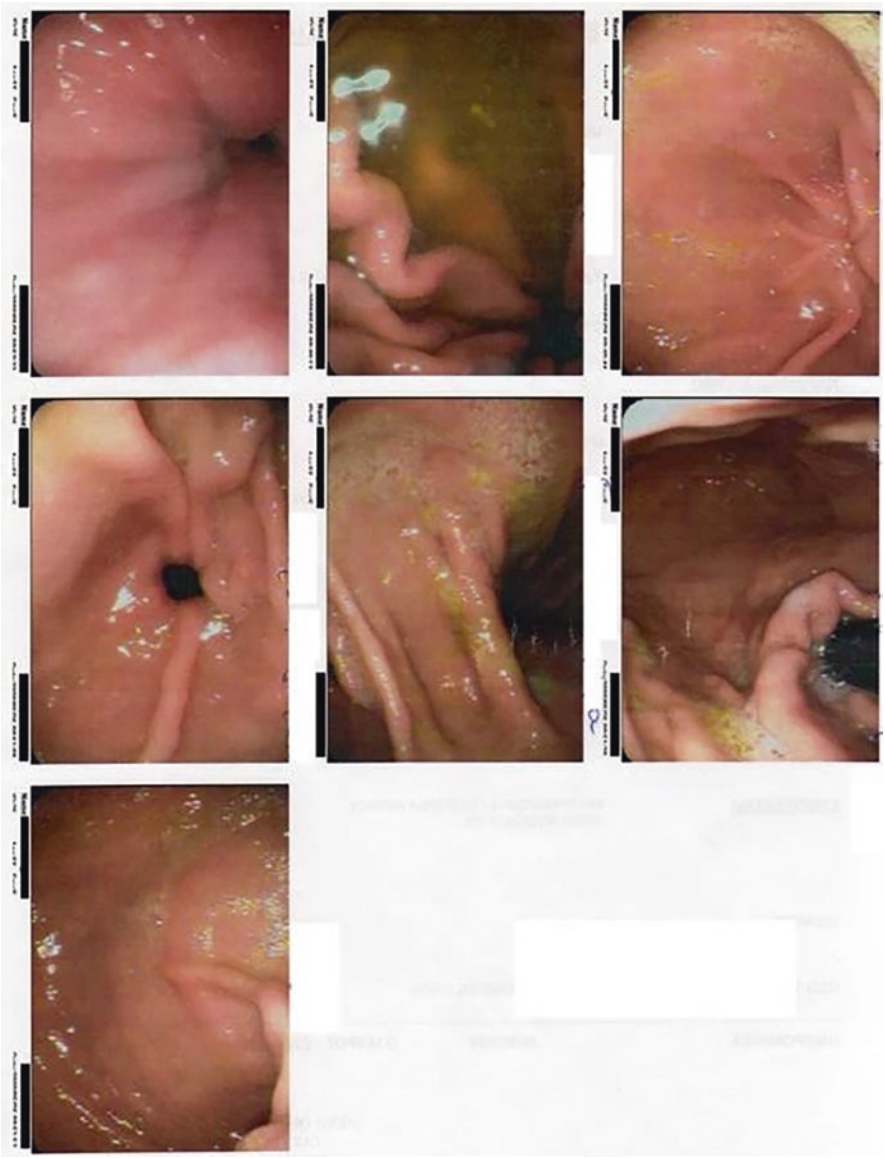

Fig. 29.2 Colonoscopy images showing increased bowel spasticity [3]

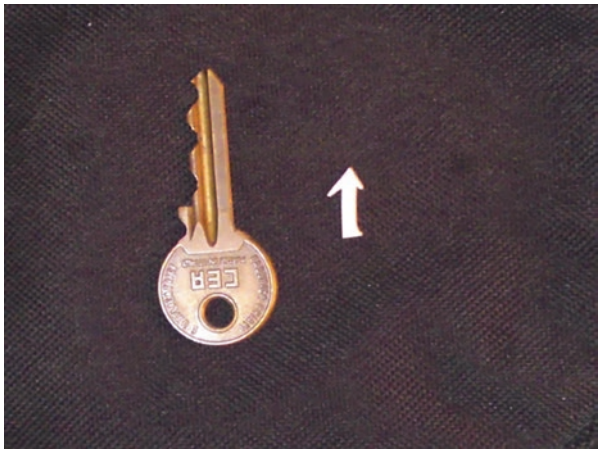

Fig. 29.3 Dimension of the foreign body in comparison with a key [3]

Differential Diagnosis

1. Irritable Bowel Syndrome (IBS)—The patient presentation as described earlier would lean heavily toward irritable bowel syndrome without the knowledge of the patient having ingested a foreign body. Irritable bowel syndrome is characterized as having symptoms such as abdominal pain and altered bowel habits (diarrhea and/or constipation) as seen in this patient. In addition to this, the patient was noted for meeting the Rome III criteria for IBS [4].
2. Inflammatory Bowel Disease (IBD)—Subsequently, once again going back to the patient presentation and history, given the alternating constipation and diarrhea, inflammatory bowel disease was another differential. The patient's gastrointestinal issues outside of the defecation also included abdominal pain which is a feature of IBD.
3. Foreign Body Ingestion—The patient presented with mild lower abdominal pain, cramping, and bloating, during the last 4 months. With pain located primarily in the left upper quadrant, affecting the entire abdomen at times. With relief only coming, temporarily, at times of defecation. The symptoms also were stated that she encountered alternating constipation and diarrhea. Due to denial of bleeding and not noticing that she had ingested foreign material, this was ultimately not considered until later. It wasn't until the recurrence of these symptoms after initial treatment for irritable bowel syndrome did the team go for further investigation. In a study, it was found that foreign bodies are encountered at endoscopy in almost half of the cases. Foreign body ingestion and food impaction are one of the most frequent emergencies in gastroenterology/flexible endoscopy [5].

What Was Misdiagnosed in This Case and Why?

Foreign body ingestion was misdiagnosed as irritable bowel syndrome in this patient. Given the immediate symptoms present at time of admission and subsequent medical history and a complete physical examination within normal limits, the physicians honed in on diseases that manifested alternating diarrhea and constipation. In viewing this patient and utilizing Rome III diagnostic criteria for IBS being symptoms lasting at least 3 months, preceded by at least 6 months of recurrent abdominal pain or discomfort associated with two or more of the following; improvement with defecation, onset associated with change in frequency of stool, or; onset associated with a change in form of stool [4, 5]. The physicians on hand noticed that their patient met the criteria laid out in the Rome III guidelines, and given that NICE guidelines for management of IBS does not indicate ultrasound or colonoscopy, there would normally not be a follow-up in terms of investigative nature. It was due to the team pushing for a colonoscopy after treatment did not affect the symptoms that the foreign body was found. In addition to this, it should be noted that the patient herself did not realize she had ingested a foreign body, which led to a significant delay.

Discussion

In order for a medical team to reach the diagnosis of foreign body ingestion, there are certain considerations that need to be taken by the team. While foreign body ingestion remains a common clinical issue, there are various techniques that will help elucidate a better understanding of the natural history of foreign body ingestion [1]. While it is entirely possible that the patient does not remember ingesting foreign material, it is the responsibility of the presiding medical team to fully explore the medical history in an attempt to uncover an ingestion. When the patient does not remember that they have ingested something out of the norm, this should not immediately rule out the possibility by the medical team. There should always be an individualized approach to patient care. While suspicion may vary, the most direct way to confirm the suspicion of foreign body ingestion is via investigative measures, be it computerized tomography (CT), endoscopy, or colonoscopy. In the case described in this report, these investigative measures did not occur until the preliminary diagnosis of IBS was made and treatment did not alleviate the symptoms. The medical team in this report utilized the Rome III criteria for functional GI disorders. Rome III criteria is an aid to help distinguish between functional GI disorders and offers a basic framework for physicians to work within in order to help make accurate and specific diagnosis for those suffering from GI issues. As described in the report, the patient was not aware of the consumption of foreign material, which led the medical team to a diagnosis that did not involve foreign body ingestion. Through

the use of the Rome III criteria, they were able to suspect the patient was suffering from irritable bowel syndrome. The criteria outlined in the Rome III that led them to this diagnosis involved improvement with defecation, onset associated with a change in frequency of stool, or onset related to a change in form (appearance) or stool [4]. Using the framework provided, they deduced that the patient at hand had met all of the criteria and thus the diagnosis was made in favor of irritable bowel syndrome. As described previously the patient did not have any alleviation of their symptoms after initial treatment which prompted the usage of ultrasound that revealed the obscurity of the left kidney due to the presence of a loop of bowel. With the persistence of the symptoms, this also prompted a colonoscopy to be ordered. The case report details the results of that colonoscopy which ultimately led to the removal of the foreign body, which was described as a birthday cake decoration. With the passage of this foreign body into the ascending colon where it was then lodged, this proves to be a deviation from the norm of most foreign body ingestions. In most patients with foreign bodies, they are passed simultaneously ($n - 410$, 75.6%) without complication, and only 4.87% ($n - 76$) required surgery for removal of the foreign material [6]. Impaction of a foreign body in the location of the colon is not a common occurrence, as most foreign bodies are either passed or are found in the upper gastrointestinal tract [7]. Due to the unusual nature of the foreign body as present in the patient described in the case, it helps others understand the thinking process of the presiding medical team. The patient could be seen as more of an irritable bowel patient as opposed to a foreign body suspicion. If not for the failure of the alleviation of the symptoms, it is entirely possible that the foreign body could have manifested other complications in the long run.

Plan of Action

1. When a patient is admitted for abdominal complaints, the presiding physician should obtain a detailed medical history. With an emphasis on normal eating behavior, ask about changes to diet as well as the possibility of eating something that could be considered foreign.
2. The presiding physician should be up to date with physical examination practices in consideration of abdominal complaints. Even if the medical history seems trivial, a proper workup should be executed
3. The suspicion of a foreign body should be elevated unless proven otherwise via further investigation.
4. Analyze the variety of diagnostic tools, and accurately determine what investigative method could rule in or rule out foreign body ingestion or other bowel related disorders.
5. In the event a diagnosis, not in line with foreign body ingestion, is made, take into account the possibility of a foreign body being present at time of follow-up visit with intention to review any changes in symptoms after initial treatment.

Conclusion

With IBS-like symptoms that were an unusual manifestation due to a foreign body, there would need to be an increase in suspicion from the primary care physicians when dealing in the treatment and diagnosis of abdominal complaints.

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Part VI
Gynecology

Chapter 30
Hydatidiform Mole Misdiagnosed as a Threatened Abortion

Pushpa Bhatt and Revathi Myneni

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Define the HM pregnancy with differential diagnosis in a patient presenting with symptoms of vaginal bleeding suspecting for vesicular mole with complete history with physical examination of the patient.
2. Evaluate the medical history and complete physical examination to exclude other clinical conditions and most appropriate course of investigation needed to a definitive diagnosis of HM.
3. Discuss the consequences of misdiagnosis of HM.
4. Apply if a hydatidiform mole is suspected on clinical grounds, ultrasonic scanning, and quantitative estimation of serum ß-HCG should be carried out to confirm the diagnosis.
5. Diagnose and treat HM will probably result in the decrease of complications with positive outcome as found in this study.

Introduction

A hydatidiform mole is also known as molar pregnancy. It is a rare complication of pregnancy characterized by the abnormal growth of trophoblasts, the cells that normally develop into the placenta. Due to the distinctive gross appearance, hydatidiform moles (molar pregnancies) have been described since ages. Hydatidiform mole (HM) was first described by Hippocrates around 400 BCE as "dropsy of the uterus" [1]. Molar pregnancy is common in Southeast Asia, African countries, and Central

P. Bhatt (✉) · R. Myneni
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: pushpa.bhatt@martinus.edu

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and Latin America. Molar pregnancy affects about 1–2 in every 1000 or 2000 pregnant women in North America [2]. The incidence of complete mole is more marked in adolescent and advanced maternal age [3]. In developed countries incidence of complete hydatidiform mole (CHM) is approximately 1–3 per 1000 pregnancies, and those of the partial hydatidiform mole (PHM) is about 3 per 1000 pregnancies [4]. Molar pregnancies are more marked in upper and lower extremes of maternal age. Among the younger group between 13 and18 years and among the older group between 45 and 50 years are more prevalent [5]. The ratio of complete mole to partial mole changes significantly with age, while the overall figure is 42% for those aged 13–18 years, 63% are complete mole; aged 18–40 years 39%; aged 41–49 years, 54% and aged 50, 93% [5]. The migrated Hispanic and Asian populations in the USA have increased incidence of molar pregnancy. Global disparity in the incidence is related to various genetic, demographic, environmental, and host-related factors [6]. Indonesia is reported to have the highest incidence rate which is 1 per 77 pregnancies and 1 per 57 deliveries [7, 8]. The incidence in India and the Middle East is 1 per 160 pregnancies [9]. Since the late 1970s, hydatidiform moles have been categorized as a complete or partial hydatidiform mole based on the genetic and histopathologic features [10]. According to the World Health Organization (WHO), hydatidiform mole is considered gestational trophoblastic disease (GTD). GTD is a group of rare diseases in which abnormal trophoblast cells grow inside the uterus after conception. It is usually due to two sperm fertilizing one normal ovum (that usually should not happen). It means plenty of genetic materials are present leading to excess trophoblastic tissue. The trophoblastic tissue grows and dominates the growth of fetal tissue; therefore the fetus residual tissue may or may not present. There are two types of benign molar pregnancy, complete molar pregnancy and partial molar pregnancy. In a complete hydatidiform mole, there are no fetal parts present; in partial hydatidiform moles, there are some fetal remaining tissues [11, 12].

Clinical Case Presentation

This is a case of 19-year-old, G0, P0, who presented to a Baitadi Hospital to establish care for an emergency visit, with the complaint of bleeding per vagina and worsening shortness of her breath. She stated that she never had a history of asthma ever since, and outdoor exercise activities seemed to exacerbate her symptoms, and she generally felt “normal” while sitting. She did not have any chest pain, and the review of systems was negative for fever, chills, diarrhea, musculoskeletal pain, and dysuria but was positive for headache, mild nausea and vomiting, and slight lower abdominal pain. Her family history was nonsignificant. She was currently sexually active with her husband, and they did not use any barrier contraceptive method. The patient had no known drug allergies, and she used to take contraceptives for painful menstrual cycles each month for 6 months but was told that she had stopped taking. Four months prior, her periods had stopped completely. Further questioning revealed that the patient was pregnant, it was confirmed pregnancy test, and she had not had

any antenatal care. At this stage, the patient also mentioned that she had off and on irregular bloody-brown vaginal discharge that occurred for the past 3 months. Pregnancy and vaginal bleeding immediately prompted to concentrate more on obstetric history and physical examination on that line. During her emergency visit, the routine tests were conducted, and in addition, a speculum exam was done as her complaint of the bloody-brown discharge, and an abdominal examination to assess the fetal well-being and speculum examination was conducted and was further supplemented with a urine pregnancy test to confirm the initial positive result from the home pregnancy test. On the physical exam, the patient had stable vitals. Lungs were mostly clear to auscultation bilaterally, with some wheezing noted on both inspiration and expiration, without any rhonchi. An abdominal exam showed fundal height is more than amenorrhea and mild suprapubic tenderness. The uterus was palpable and was smooth without irregularities and was consistent with a 28–30-week gestation (palpable above the umbilicus), though her last menstrual period was 16 weeks prior. The speculum exam showed a dilated nulliparous cervix with brown discharge with fresh bleeding present in the vaginal vault area. On auscultation there was no sign of fetal heart sound. The rest of the exam was insignificant. Her hemoglobin level was 7.4 g%. The serum ß-HCG levels were not available immediately; later it was found to be 172,000 mIU/m. Lipid profile and liver function test were normal. She was kept under observation as a case of threatened abortion. To exclude pulmonary edema and other respiratory illnesses, X-ray chest was performed. She was given complete bed rest, with intravenous (IV) fluid and intravaginal progesterone tablets inserted. Three hours later after the insertion of progesterone, she had profuse bleeding like some structures were expelled out with no fetal tissues. However, the expulsion of complete mole by itself, and IV fluids continued and central venous pressure (CVP) was monitored. Tissue was sent for histopathology in India and found to be a complete vesicular mole. After 7 days of symptomatic treatment with antibiotics and rest, she was discharged with following instructions. Oral contraceptives were initiated to ensure that any ß-HCG being monitored would be from remnant mole alone, and not a new intrauterine or ectopic pregnancy. The patient was advised to follow-up every 2 weeks, and she agreed to this plan of action. She was advised to abstain from pregnancy till her ß-HCG level is low, and she was given oral contraceptives for 5 months. After 2 years she conceived a male baby.

Discussion

Bleeding in the first trimester of pregnancy can be fatal. Patients often overlook vaginal spotting. Because timing matters, antenatal clinic providers should be well-versed in recognizing early signs and symptoms, as well as the repercussions of bleeding throughout early pregnancy. We will focus here on a case of molar pregnancy, where the patient was initially treated for threatened abortion vesicular mole in this discussion with differential diagnosis to threatened abortion. A threatened abortion happens when a little quantity of vaginal bleeding occurs before the

pregnancy reaches 28 weeks. Paroxysmal gastrointestinal pain or lower back pain is frequently associated with the hemorrhage [13]. However, if the vaginal bleeding or lower abdominal pain worsens, the pregnancy may end in an unavoidable abortion. A threatened pregnancy occurs in 25% of all pregnancies [14], and this rate has been rising in recent years. The majority of occurrences occur during the first 8–12 weeks of pregnancy, with only a handful after 12 weeks. Approximately 14.3–50% of women who have been threatened with abortion will have a full miscarriage [15]. As a case of hydatidiform mole, all patients present with amenorrhea, severe fundal enlargement, and bleeding. A hydatidiform mole (also known as a molar pregnancy) is a type of gestational trophoblastic disease (GTD) that begins in the placenta and can spread throughout the body. This tumor is derived from prenatal tissue rather than maternal tissue [16], to avert a potential miscarriage. Vaginal bleeding occurs during pregnancy, while the cervical os stays closed in threatening abortion. A threatened abortion, according to the World Health Organization (WHO) , is defined as pregnancy-related vaginal bleeding in the first half of pregnancy without cervical dilatation. A hydatidiform mole, also known as a GTD, is a nonviable pregnancy caused by the fertilization of a potentially empty ovum with one or more sperm in an atypical way. The resulting mole is a benign but quickly expanding cystic tumor, culminating in a characteristic pregnant image with no pregnancy outcome. Vaginal bleeding with lower abdomen pain and the discharge of grape-like vesicles are the most typical symptoms. This instance was unconcerned about bleeding and spotting. Anemia was caused by bleeding. Complete molar pregnancy is associated with anemia, bleeding, and respiratory problems [10, 17]. All of these issues were present in this case. Anemia is caused by continuous occult per vaginal bleeding and significant blood loss in molar pregnancy. Acute cardiac distress has been found in 27% of instances after molar pregnancy evacuation, particularly in individuals with a uterine size of over 16 weeks and above. The severity of the clinical indications varies, and several fatalities have been reported. Within 96 h, the patient is usually back to normal [18]. Our patient made a full recovery in 36 h with no severe complications. When a complete pregnancy diagnosis is suspected, the patient should be checked for medical problems such as anemia, hypertension, and hyperthyroidism. A baseline serum ß-HCG level, thyroid function tests, and a complete blood count with platelets should be performed on all patients. ß-HCG is produced by the hyperplastic syncytiotrophoblastic cells typical of molar pregnancy, and patients with full hydatidiform mole frequently have ß-HCG levels in excess of 100,000 mIU/ml. Ultrasound pregnancy assessment during the first trimester can confirm suspected cases of molar pregnancy. Whereas in full molar pregnancies, the snowstorm pattern is more prominent, with an echogenic intrauterine mass comprising many tiny cystic gaps (grape-like structures), as shown in Figs. 30.1 and 30.2. Complete moles are usually easier to detect with ultrasonography than incomplete moles.

There are two alternative ways in which the entire mole can appear [19]. Normal fertilization takes place right away, but the mother's genetic material is quickly absorbed. A sperm repeats itself at this point, with the chromosomal configuration giving rise to 46 XX to the entire mole. The remaining 5–10% two sperm can fertilize a normal oocyte that is originally devoid of maternal genetic material, resulting

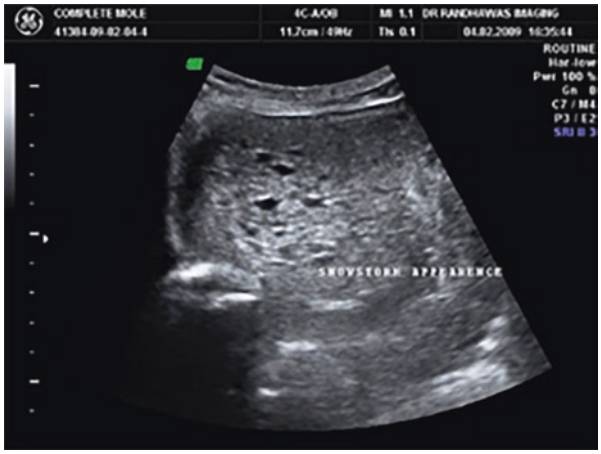

Fig. 30.1 Transabdominal complete mole USG showing snowstorm appearance

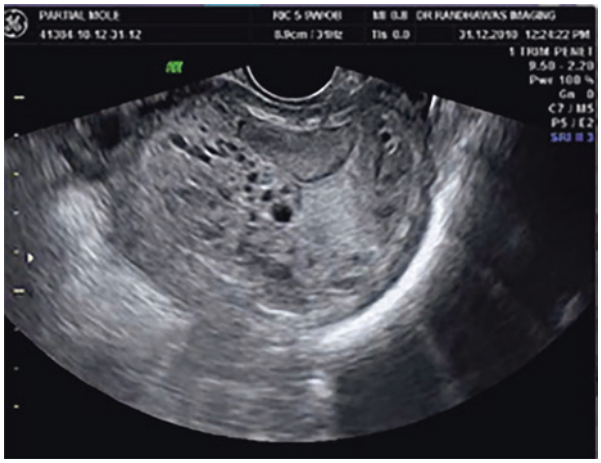

Fig. 30.2 Transvaginal incomplete mole with snow storm pattern

in 46 XY genotype manifestations across the entire mole [20]. Sperm multiply to prepare for fertilization, and syncytiotrophoblasts are generated by the proliferation process [21]. The ovum keeps its genetic material during fertilization to generate a zygote. Although maternal genes are deleted after fertilization and the fetus stops growing in the absence of fetal cells, trophoblasts proliferate to form a cystic formation in the uterus. There is a minimal dissociation of the placenta within the decidual lining in the case of threatened abortion, resulting in vaginal bleeding in the form of spotting or scanty bleed without discomfort in the abdomen or risk to the mother's life. However, there have been cases of poor pregnancy outcomes, notably intrauterine growth restriction (IUGR) [15]. In the first trimester, people with hydatidiform mole sparse vaginal hemorrhage experience extreme nausea and vomiting, as well

as occasional grape-like vesicles passing through per vagina. With anemia, the uterus may appear to be larger than the gestation term. Thyrotoxicosis manifests itself in a variety of ways [22].

Choriocarcinomas are malignant trophoblastic tumors that arise from villous GTD cells in the uterus. A complete molar gestation causes 50% of all choriocarcinomas, 25% after a normal pregnancy, and 25% after a spontaneous miscarriage or ectopic pregnancy. Choriocarcinomas release a lot of angiogenic growth factors and can alter the uterine vasculature, resulting in bleeding. Irregular vaginal bleeding, an enlarged uterus, cough, hemoptysis, headache, and vomiting are the most common clinical manifestations. Although choriocarcinoma in the vaginal canal can cause purple/blue nodules and asymmetrical uterine enlargement, not all women will have all of these symptoms. There's also intraperitoneal bleeding and elevated ß-HCG levels in the blood [23]. Chromosomal anomalies characterize hydatidiform moles, allowing for choriocarcinoma malignant transformation. Activation of oncogenes, inactivation of tumor suppressors, and changes in telomerase regulation are the most prevalent changes that contribute to malignant transformation [24].

According to a Nepalese study, irregular uterine bleeding was the most common complaint in vesicular moles (86.3%). Pain (33.8%) and hyperemesis (26.5%) were the other presenting symptoms, respectively [25]. Dilatation and curettage (D&C) are the first line of treatment for vesicular moles, followed by symptomatic treatment and follow-up. The majority of cases of threatening abortion respond effectively to early pregnancy therapy with bed rest, sedation, and progesterone suppositories. Progesterone 100 mg is taken twice daily in the form of a vaginal tablet up to 10–12 weeks of pregnancy [26]. Patients who have had a past molar pregnancy should utilize oral contraception to delay pregnancy until their ß-HCG level returns to normal [15]. When ß-HCG levelsl are zero for 6 months after treatment for a hydatidiform mole, the patient may become pregnant, even if pregnancy occurs before the 6 month follow-up period is completed. Termination of pregnancy should not be recommended until the ß-HCG levels are negative [26].

Conclusion

In conclusion, complete molar pregnancy can present with an enlarged fundal and then the actual gestational period. Bleeding can lead to severe anemia. Molar pregnancy with bleeding presents a challenges in diagnosis generally misdiagnosed as a case of threatened abortion. Molar pregnancy should be included in the differential diagnosis for first trimester vaginal bleeding. The distinction between complete hydatidiform mole and partial hydatidiform mole is important for determining the appropriate line of treatment. For complete hydatidiform mole, USG findings along with high ß-HCG are alone helpful in establishing the diagnosis with a typical snowstorm presentation in USG, but to confirm the diagnosis histopathological examination is must. Follow-up for treated cases of HM is important and required careful evaluation for serum ß-HCG level. If the ß-HCG level falls to normal within

56 days (8 weeks) of the evacuation, then the monitoring continues for a total of 6 months from the day of the evacuation. It is advised that a further pregnancy is post-pended with oral contraceptives until the end of the follow-up period, because early new pregnancy may relapse the condition.

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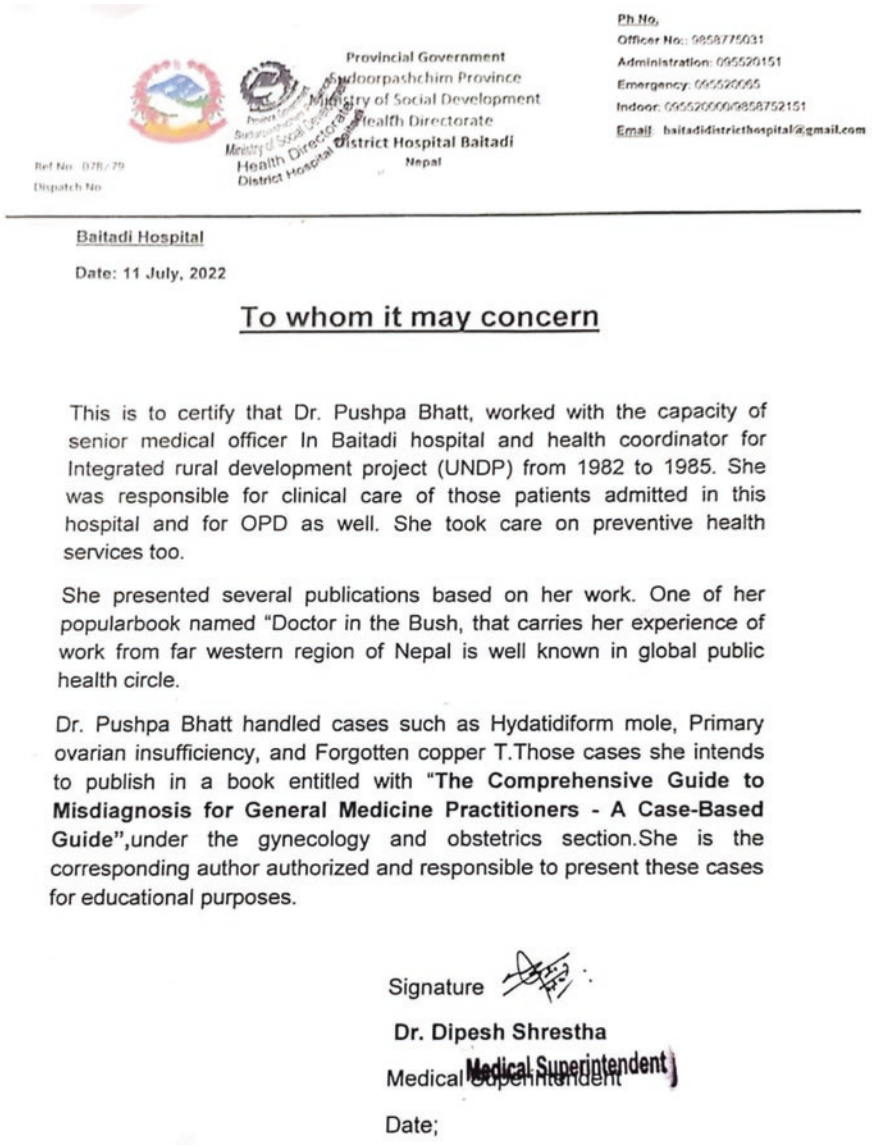

Provincial Government
Sudoorpashchim Province
Ministry of Social Development
Health Directorate
District Hospital Baitadi
Nepal

Ph No.
Officer No.: 9858775031
Administration: 095520151
Emergency: 095520065
Indoor: 095520000/9858752151
Email: baitadidistricthospital@gmail.com

Ref No: 078/79
Dispatch No:

Baitadi Hospital

Date: 11 July, 2022

To whom it may concern

This is to certify that Dr. Pushpa Bhatt, worked with the capacity of senior medical officer In Baitadi hospital and health coordinator for Integrated rural development project (UNDP) from 1982 to 1985. She was responsible for clinical care of those patients admitted in this hospital and for OPD as well. She took care on preventive health services too.

She presented several publications based on her work. One of her popularbook named "Doctor in the Bush, that carries her experience of work from far western region of Nepal is well known in global public health circle.

Dr. Pushpa Bhatt handled cases such as Hydatidiform mole, Primary ovarian insufficiency, and Forgotten copper T.Those cases she intends to publish in a book entitled with **"The Comprehensive Guide to Misdiagnosis for General Medicine Practitioners - A Case-Based Guide"**,under the gynecology and obstetrics section.She is the corresponding author authorized and responsible to present these cases for educational purposes.

Signature

Dr. Dipesh Shrestha

Medical Superintendent

Medical Superintendent

Date;

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Chapter 31
Gestational Choriocarcinoma Misdiagnosed as Ovarian Ectopic Pregnancy

Revathi Myneni

Learning Objectives
By the end of this presentation, the clinician will be able to:

- Analyze ways in which choriocarcinoma can be more accurately diagnosed to prevent misdiagnosis.
- Discuss why choriocarcinoma is often misdiagnosed or goes undiagnosed which can lead to metastasis.
- Analyze the similarities and differences between choriocarcinoma and ectopic pregnancy.
- Discuss as one of the misdiagnosed disorders (the case helps us understand the consequences of a misdiagnosis or delay in reaching a correct diagnosis for the individual patient's progress).
- Emphasize the need for follow-up to prevent recurrence and metastasis.

Introduction

Choriocarcinoma is an uncommon and aggressive trophoblast neoplasm. It is most likely to develop during pregnancy, indicating that it is of gestational origin. Hydatidiform mole can induce abortion, ectopic pregnancy, and preterm birth. Non-gestational choriocarcinoma is uncommonly reported since it is not linked to pregnancy [1]. In rare exceptional cases, it has metastasized to the lungs, brain, gastrointestinal system, liver, and dermal tissues [2]. It's hard to ascertain the distinction between these two types of tumors, and there are no significant immunohistochemical or microscopic changes between them [3]. To differentiate between the

R. Myneni (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao

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two entities, deoxyribonucleic acid (DNA) analysis and cytogenetic tests are used, but if this is not possible, a history of pregnancy would be used for differential diagnosis [4]. According to the research, the outcome of these two forms of cancers can be different. Choriocarcinoma occurs in 76% of cases and is associated with distant metastases and in ectopic locations. It can appear anywhere from 5 weeks to 5 years after conception, including after menopause [5]. At the time of diagnosis, almost 30% of choriocarcinoma patients have metastases [6]. The diagnosis of this disease is difficult due to the diversity of signs and symptoms. The extent of the illness and the location of metastases determine the clinical appearance of choriocarcinoma. The clinical appearance of gestational choriocarcinoma is frequently related to bleeding from the metastatic location [7]. After a full-term or preterm pregnancy, choriocarcinoma can cause amenorrhea and abnormal uterine bleeding due to uterine cancer progression or bleeding from a metastatic location. Abdominal discomfort, hemoptysis, and melena can develop from uterine perforation or metastatic lesions bleeding [8]. Patients with central nervous system (CNS) metastases frequently experience headaches, dizziness, seizures, or hemiplegia as a result of increased intracranial pressure caused by intracerebral bleeding [9, 10]. Dyspnea, cough, and chest pain are common symptoms in patients with widespread pulmonary metastases [11]. Because of its rapid growth, extensive distribution, and high proclivity for hemorrhage, choriocarcinoma constitutes a valid medical emergency, and early detection and treatment is a well-known driver of prognosis [12].

Clinical Case Presentation

A 35-year-old woman, gravida 6, para 4, and abortion 2, was admitted to the emergency room at Imam Hussein Hospital, Shahid Beheshti University of Medical Science, Iran, with severe pelvic pain, fatigue, and cough. The patient had been experiencing pelvic pain for a month, which had intensified at the time of referral, and she mentioned feeling sick and vomiting three times over a period of 12 hours. She also noted a cough that began a month prior to her referral. Her cough did not respond to any of the over-the-counter medications. The patient had a cesarean section and tubectomy 9 months prior and had been experiencing amenorrhea ever since. Her blood pressure was 104/65 mmHg at admission, her heart rate was 120 beats per minute (bpm), her respiration rate was 24 breaths per minute, and her body temperature was 36.8 °C. On physical examination, her abdomen was firm, with diffuse discomfort in the right lower quadrant. Ultrasound revealed a 50 × 58 mm (millimeter) hyperechoic tumor in the right adnexa with moderate free fluid in the pelvis. Hemoglobin was 5.7 g/dL (grams per deciliter), hematocrit was 18.4, mean corpuscular volume (MCV) was 81.8, and ß-hCG was positive. Ectopic pregnancy was diagnosed based on clinical symptoms and lab studies, and a gynecological appointment was requested [13]. The patient had laparotomy with the suspicion of a ruptured fallopian tube due to her unsteady symptoms. There was no blood in the intra-abdomen and 200 cc of serosal fluid in the abdomen was drained during

surgery. There was no abnormality in the fallopian tube and uterus, and a purple mass measuring 5–6 cm on the right ovary was suspected to be a pregnancy outcome. The patient's ß-hCG level was 33,827 mIU/mL after surgery. Due to continuous coughing, the patient had a chest X-ray, which revealed scattered patchy opacities in the lower lobes. She was diagnosed with choriocarcinoma and underwent further testing to rule out further metastatic sites. Multiple widespread pulmonary nodules, pleural effusion, and partial consolidation in the lower lobes were seen on lung CT (computed tomography) scan, indicating metastasis. Abdominopelvic CT scan with intravenous (IV) and oral contrast revealed a large increased tissue mass with necrotic components in the left pelvic cavity, measuring 101 × 96 mm, as well as deterioration of the surrounding left iliac bone spreading to the left paracolic gutter. Both the kidneys and the spleen revealed some metastatic lesions. A solitary occipital lobe metastasis was also discovered on a brain CT scan. All of this evidence pointed to choriocarcinoma in its fourth stage with many metastases, which was verified by pathology of the ovarian lesion and biopsies of the abdominal lesions. The data findings showed that she was suitable for chemotherapy, and she was admitted to the intensive care unit 3 days after her initial visit. After four cycles of EMA-EP (etoposide, methotrexate, and actinomycin D/etoposide and cisplatin) and five cycles of EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine), the patient responded to treatment, and ß-hCG was undetectable after 2 months of treatment. During her 3-month follow-up, the patient's ß-hCG level was elevated again, indicating relapse. Chemotherapy was restarted with three cycles of paclitaxel, cisplatin, and etoposide, followed by four cycles of liposomal doxorubicin and carboplatin and then five cycles of fluorouracil and dactinomycin, as well as brain radiotherapy. As a reaction to the chemotherapy, the patient developed a fever and neutropenia. The woman appeared with stomach pain, bloody ascites, and shock at our emergency department after 25 sessions of chemotherapy and 10 sessions of radiotherapy, 8 months after her initial diagnosis, and she died [13].

Differential Diagnosis

When considering the patient's history and physical exam findings, one should begin to build a differential diagnosis.

1. Acute appendicitis: Its symptoms prior to surgery include fever, abdominal pain, pelvic pain, nausea, and vomiting.
2. Adnexal torsion: This causes nausea, vomiting, and sudden, intense pelvic discomfort. Women may experience intermittent, colicky discomfort for days or even weeks prior to the abrupt pain, which is likely caused by intermittent torsion that gradually resolves.
3. Tubo-ovarian abscess: Lower abdomen pain that begins suddenly, chills, dyspareunia, fever, and vaginal discharge are some of the typical symptoms. There

have also been reports of nausea, vomiting, and unusual vaginal bleeding as additional symptoms.
4. Hemorrhagic corpus luteum: Small cysts typically don't exhibit symptoms unless they rupture and begin bleeding or torsion happens. These disorders result in excruciating pelvic pain, excruciating nausea and vomiting, or excruciating weakness.
5. Ovarian cyst rupture: The majority of cysts are harmless; however ruptured ovarian cysts can cause abrupt, severe abdominal discomfort, pain accompanied by fever or vomiting, feeling chilly with clammy skin, rapid breathing, lightheadedness, or weakness.
6. Miscarriage: Symptoms include light to heavy bleeding, intense cramps, back pain that gets worse or is unbearable, fatigue, fever, weight loss, white-pink mucus, contractions, and tissue that resembles blood clots flowing from your vagina.
7. Pelvic inflammatory disease: Symptoms include severe pain and discomfort in the pelvic area, fatigue, vomiting, fever, irregular menstruation, bleeding or spotting between periods, pain in the lower back pain, dyspareunia, and atypical vaginal discharge.

These are all important differential diagnoses to consider with ectopic pregnancies. The patient's history and hemodynamic status at the time of clinical presentation will determine the order of these differential diagnoses as well as the lab testing required to exclude such differentials.

Discussion

Gestational choriocarcinoma is a type of gestational trophoblastic illness that begins in the uterus. The ovaries, fallopian tubes, cervix, vagina, and other pelvic organs may also be affected. Choriocarcinoma most usually develops after a molar pregnancy; however, it can also develop after a term pregnancy, abortion, or ectopic pregnancy. A series of diagnostic tests is done to diagnose the gestational choriocarcinoma: urinalysis, cancer antigen 125 blood test (CA-125 blood test), ß-hCG blood test, and pelvic ultrasound. Additional tests may be done to see if the cancer has spread to other parts of the body; some of the tests are chest X-ray, abdominal and pelvic CT scans, magnetic resonance imaging (MRI), and lumbar puncture [13].

Cardiopulmonary problems brought the most patients to clinical attention, followed by gastrointestinal and central nervous system signs. In addition, several cases were discovered as a result of fetal-maternal hemorrhage, renal, and ophthalmic symptoms [14]. Figure 31.1 shows a quick review of the numerous clinical manifestations associated with choriocarcinoma.

Choriocarcinoma is distinguished by very high levels of human chorionic gonadotropin (ß-hCG), necessitating a careful distinction from pregnancy [15]. Because of increased ß-hCG, early-stage ovarian choriocarcinoma poses a considerable

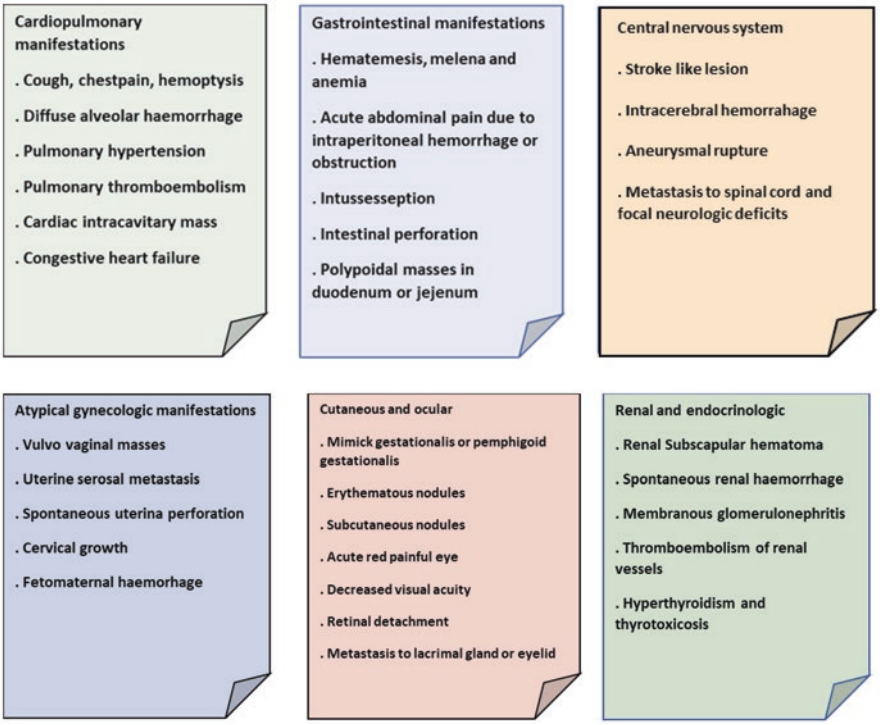

Fig. 31.1 Clinical manifestations associated with choriocarcinoma

diagnostic problem in the reproductive-aged patient [16]. While ectopic pregnancy and gestational trophoblastic illness are both possible diagnoses, non-gestational choriocarcinoma is rarely considered. Abnormal vaginal bleeding, abdominal pain, and the discovery of a pelvic mass are all common symptoms and indicators associated with high ß-hCG levels [17].

Gestational trophoblastic neoplasia (GTN) was classified as a neoplasm with a strong proclivity for hematogenous spread and dissemination. As a result, extra pelvic metastases should be recognized as a possible concern [14, 18, 19]. Outside of the pelvis, the most common locations of metastases were the lung, liver, and brain. Renal involvement was uncommon; however renal metastasis was frequently subsequent to lung metastasis in certain patients. Surgery in the treatment of patients with metastatic choriocarcinoma is debatable. Furthermore, it appears that a selective fraction of patients can be treated with local resection of metastatic illness. Control of hemorrhage, infection, blockage, and removal of chemotherapy-resistant residual illness have all been common surgical reasons in GTN. Remission has been achieved in some patients quickly after the removal of the uterus and cervical metastases [14]. Even in advanced disease, GTN is generally very sensitive to treatment. Single-agent chemotherapy (reduced side effects) has been used to treat this condition in patients with early stages of disease, and it has proven to be highly effective.

Multi-agent chemotherapy regimens, on the other hand, were accessible for advanced-stage management. However, it should be noted that despite its high effectiveness this regimen may be linked to an increased risk of recurrent cancers. In our research it is shown that all advanced-stage disease patients had received combination chemotherapy (EMA-CO) regimen, and the results were positive [14]. A review of case reports from the last 10 years gathered from the PubMed database on choriocarcinomas that were first diagnosed with ectopic pregnancy. A total of 24 women with ectopic pregnancy symptoms were assessed at the time of admission. The patients were between the ages of 12 and 46, with an average age of 28. Tubal ectopic pregnancy was the most prevalent symptom, which was often accompanied by ovarian ectopic pregnancy and inclusion of the serous and uterine myometrium. Only one instance had myometrial involvement, while most of the cases were ovarian and tubal ectopic pregnancy. The other 14 people developed choriocarcinoma, either secondary or prenatal. The majority of the gestational type ovarian involvement happened after a normal pregnancy. The time between the previous pregnancy and the onset of symptoms ranged from 23 days to 5 years. The majority of patients initially complained of stomach pain and irregular uterine hemorrhage. Amenorrhea, shock, a steady ß-hCG titer, a palpable mass, and fever were among the other symptoms. The average ß-hCG concentration was 308,634 IU/mL (international units per milliliter), with values ranging from 13 IU/mL to 4,000,000 IU/mL. During the surgery, ultrasounds of 13 patients revealed pelvic free fluid that was bloody. At the time of diagnosis, 14 patients had metastasis, with lung metastasis being the most prevalent. There was no evidence of brain metastases. Salpingo-oophorectomy and hysterectomy were the most common operations performed. Twenty patients received chemotherapy before or after surgery, 21 recovered completely, 2 patients' outcomes were unknown, and only 1 patient died from an uncontrolled intra-abdominal bleeding from the liver [20].

Conclusion

The recent growth of conservative care for ectopic pregnancy highlights the importance of pathological testing in conjunction with ß-hCG level monitoring, not only to diagnose recurrent ectopic pregnancy but also to avoid potential malignant trophoblastic disease. When a patient is being treated for an ectopic pregnancy, they should be informed of the likelihood of choriocarcinoma. The importance of pathologic examination in conjunction with serial ß-hCG concentration monitoring in the treatment of ectopic pregnancy will be critical not only to determine trophoblastic disease but also to avoid a surprise like choriocarcinoma. An early correct diagnosis of postpartum choriocarcinoma can improve the outcome greatly. Although the risk of postpartum choriocarcinoma is relatively low, it must be monitored on a frequent basis. Careful postpartum placental examination, histological investigation in patients with anomalies, and ß-hCG monitoring in high-risk pregnant women can all help with early identification and prognosis of postpartum choriocarcinoma.

The International Federation of Gynecology and Obstetrics staging and World Health Organization prognostic grading systems should be used to deliver stratified treatment. Furthermore, ß-hCG is a sensitive marker for assessing therapy success and monitoring postpartum choriocarcinoma remission. Following GTN treatment, ß-hCG monitoring every month for at least 12 months is required to monitor for relapse. During this time, reliable contraception must be used.

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Chapter 32
Misdiagnosis of Mullerian Agenesis in a Patient with 46, XX Gonadal Dysgenesis

Revathi Myneni

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Analyze the process of diagnosing a woman with primary amenorrhea.
2. Enumerate the blood tests that should be performed in a patient with primary amenorrhea.
3. Discuss how to assess appropriate hormone profiles and karyotype analysis in cases of suspected Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome or Mullerian agenesis.
4. List the early detection of disorders of sex development (DSD).
5. Discuss how to provide psychological support to the patient and limit the risk of associated complications.

Introduction

Gonadal dysgenesis with female morphology is characterized as a primary ovarian failure that results in early ovarian failure in some of the healthier 46, XX females as a result of gonadal failure or gonadotropin resistance. Depending on the degree of gonadal maturation, it induces primary amenorrhea with varying hypogonadism or impuberism [1]. The karyotype can be 46, XX; 45, X0; 46, XY or mosaicism 45, X/46, XX; 45, X/46, X,del(X) (p22.2); and 46,X,i(Xq) [1–3]. In phenotypically and karyotypically normal girls with functional ovaries, Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a type of Mullerian duct malformation defined by agenesis or hypoplasia of the uterus and upper two-thirds of the vagina. It is the

R. Myneni (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao

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second most prevalent cause of primary amenorrhea, following gonadal dysgenesis [4].

A correlation between these two disorders is extremely rare and appears to be unrelated to chromosomal abnormalities. When patients with the 46, XX karyotype present with primary amenorrhea, one of the differential diagnoses is MRKH syndrome or Mullerian agenesis. It is said to induce primary amenorrhea in up to 15% of women [5]. Patients with Mullerian agenesis lack all Mullerian duct derivatives (fallopian tubes, uterus, cervix, and upper vagina), but they do have ovaries and go through puberty with breast development and pubic hair growth. In all cases of a suspected diagnosis of this illness, hormone profiles and concomitant congenital defects should be thoroughly explored. A straightforward initial step in ensuring the existence of circulating estrogen is to determine the presence or absence of secondary sexual characteristics, particularly breast development [6]. Other differential diagnosis or the possibility of co-occurrence of other disorders is needed in teenage or adult patients without secondary sexual features [7]. In patients with significant estrogen deficit, the uterus may not be visible using several imaging modalities, including laparoscopy [8]. Therefore, the diagnosis of Mullerian agenesis should be re-evaluated after 6–12 months of exogenous estrogen treatment [9].

Clinical Case Presentation

A 23-year-old virgin female presented with primary amenorrhea and poor breast development. Her prenatal and neonatal phase went fine. There was no history of major congenital abnormalities in the patient's family. She was diagnosed with primary amenorrhea by a local gynecologist when she was 16 years old. There were no other tests other than karyotype and pelvic ultrasonography. The normal 46, XX karyotype was confirmed by chromosomal analysis. Although no information on the pelvic ultrasound was available, the patient had been told that her uterus was missing. The patient did not receive treatment at that time, and after a few office visits, she was lost to follow-up. After being diagnosed with MRKH, she never menstruated and had no breast growth. At our hospital, her initial height and weight were 157 cm and 49 kg. There were no signs or symptoms of Turner syndrome, and no skeletal deformities were observed. Breast Tanner stage I and pubic hair stage III were found in the secondary sexual characteristics examination. The gynecological exam revealed female external genitalia and a typical vagina that ended in a blind pouch. The remainder of the physical examination was normal [9]. The probable diagnosis of MRKH syndrome or Mullerian agenesis was questioned due to the lack of breast development. Hypergonadotropic hypogonadism (FSH 130 IU/L, LH 2 IU/L, serum estradiol 5 pg/mL) with verified 46, XX karyotype was discovered

during the initial laboratory study at our clinic. On pelvic magnetic resonance imaging (MRI), the internal genitalia (ovaries, uterus, and upper two-thirds of vagina) and streak gonad were not visible. Other laboratory evaluations, such as a complete blood count, renal function, liver function, prolactin hormone, and thyroid function test, all came back normal. A bone density examination, dual-energy X-ray absorptiometry (DEXA scan), revealed osteoporosis (T score 2.7) in the lumbar spine and osteopenia (T score 1.5) in the hip. Due to the absence of a uterus and ovaries, the diagnosis of 46, XX gonadal dysgenesis associated with MRKH syndrome was suggested. X-rays of the skeleton revealed no abnormalities in the spines. There were no pathogenic mutations found in the deoxyribonucleic acid (DNA) sequence analysis of putative genes (WNT4, WNT9, RSPO1, SOX9, NROB1, GATA4, STAR, WT1) related with 46, XX gonadal dysgenesis [9]. The patient began hormone replacement therapy with 0.625 mg of oral estrogen every day (Premarin). The patient had developed Tanner breast stage III 6 months following therapy, which progressed to a Tanner breast stage V 18 months later. To prevent additional bone loss, calcium and vitamin D were given orally. At the 18-month follow-up DEXA scan, the bone mineral density had improved, although there was still osteopenia at the lumbar spine (T score at the lumbar spine increased from 2.7 to 2.2, and T score at the hip increased from 1.5 to 1.3) [9]. At 18 months, an ultrasound of the pelvis was performed again. 1.3 × 3.8 cm rudimentary uterine buds were discovered with no evidence of the ovaries or upper section of the vaginal canal. Twenty-four months after starting estrogen treatment, a pelvic MRI was performed to confirm the presence of a developing uterus (uterine dimension 1.8 × 2.9 × 4.9 cm, endometrial thickness 1.3 cm). The reappearance of a normal uterus with the size of a normal 16-year-old girl confirmed the diagnosis of pure 46, XX gonadal dysgenesis without Mullerian agenesis. To prevent unopposed estrogen action on the uterus, the patient's medication was changed from estrogen only to cyclical oral estrogen/progesterone replacement therapy (10 mg of cyclic medroxyprogesterone acetate 10 days each cycle). No breakthrough menstruation has yet occurred. She has been advised about the possibility of having children through adoption or surrogacy in the future. The patient was capable of dealing with her definitive diagnosis and had a thorough understanding of her illness [9].

Differential Diagnosis

Any diagnosis of a woman with primary amenorrhea should start with a thorough physical examination and a thorough review of her medical history. A set of blood tests, including female sexual hormones (estrogen and progesterone), follicle-stimulating hormone (FSH), and luteinizing hormone (LH), should be included.

In order to investigate the reasons of amenorrhea, it is necessary to determine the existence or absence of secondary sexual features, particularly breast development. If secondary sexual characteristics are present, an imaging examination (pelvis ultrasonography or nuclear magnetic resonance) is recommended to confirm the presence of the uterus. Mullerian agenesis (congenital absence of vagina and aberrant uterus development, often rudimentary) accounts for 15% of all cases of primary amenorrhea. If the uterus is present, an obstruction in the outflow tract should be considered (e.g., an imperforate hymen). If the uterus is missing or malformed, the karyotype should be determined next.

A hormonal investigation should be undertaken in cases when breast growth is insufficient. FSH levels in the plasma greater than 40 UI/mL (hypergonadism) indicate ovarian failure due to a lack of active follicles in the gonadal tissue. In 2% in 50% of cases of primary amenorrhea, this is the most prevalent cause.

Gonadal failure is usually linked to X-linked chromosomal deletions, whether complete or partial. Thus, Turner syndrome (45 X0) accounts for 50% of gonadal dysgenesis cases, mosaics for 25%, and pure gonadal dysgenesis (46, XX) and Swyer syndrome (46 XY) for the other 25%. Our next diagnostic step is to determine the karyotype for hypergonadotropic hypogonadism (Fig. 32.1).

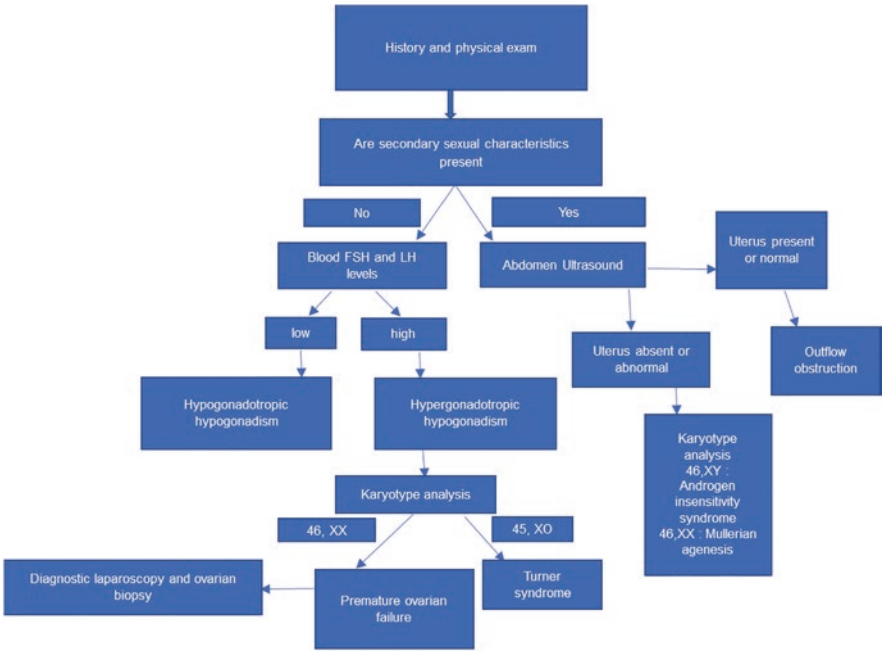

Fig. 32.1 The assessment of women with primary amenorrhea

Discussion

Genetic changes cause gonadal dysgenesis, which results in poor gonadal development. When the gonads do not develop normally, it causes difficulties with both internal and external genitalia growth. The hypothalamic-pituitary-gonadal axis is likely to be dysfunctional in all patients with gonadal dysgenesis. GnRH (gonadotropin-releasing hormone) is produced by the hypothalamus and acts on the pituitary to release LH and FSH. LH and FSH stimulate the gonads, which then create estrogen and testosterone as sex hormones. Because of the absence of gonadal growth found in gonadal dysgenesis, the gonads respond to LH and FSH stimulation in a minimum or nonresponsive manner, resulting in lower estrogen and testosterone levels, as well as fewer ovarian follicles and sperm [10].

Complete 46, XX gonadal dysgenesis is characterized by female internal and external genitalia, as well as streaked or hypoplastic ovaries. Female patients with gonadal dysgenesis will experience amenorrhea and will be sterile since their gonads are insensitive to FSH and LH. Males with gonadal dysgenesis are often sterile because their testes are underdeveloped or absent. Gonadal dysgenesis is clinically significant because of the problems it can bring for the patients' physical and emotional health. Hormone therapy will almost certainly be required for patients with gonadal dysgenesis to establish suitable secondary sexual characteristics. Even with hormone therapy, a considerable percentage of these patients may not develop normally and remain infertile, which can have serious consequences for their mental health. Adults and children with gonadal dysgenesis may be self-conscious about their appearance [10].

The cause of MRKH syndrome is unknown, but it is thought to be caused by a disruption in embryological development during the sixth or seventh week of pregnancy. Because the mesonephros (which develops to kidneys), the Mullerian ducts, and the skeleton all come from the mesoderm, it's thought that something bad happens at this stage of pregnancy, causing the MRKH syndrome's defects [11]. The significant gaps in misdiagnosis of MRKH syndrome or Mullerian agenesis in a patient with 46, XX gonadal dysgenesis were highlighted in this instance. A diagnosis like this has therapeutic and psychological implications. MRKH syndrome is thought to affect 1 out of every 5000 women and is usually discovered in late puberty when menstruation stops [5]. However, it is important to note that this disorder has normal ovarian function. Hormonal testing is required to verify the correct diagnosis. Another key indicator in this patient is a lack of breast development, which could indicate estrogen insufficiency. Premature diagnosis of MRKH syndrome in prepubertal patients should be avoided due to uterine underdevelopment, which can be missed in all imaging modalities due to the small size of the uterine bud. Due to the limited surgical field, even laparoscopy can miss a small uterus [12].

As a result, all patients with MRKH syndrome should have lab exams done (ultrasonography, magnetic resonance imaging, and urography) to rule out any anomalies. The laparoscopy is the last resort, and it usually confirms and classifies

the MRKH [13]. By bone study, pelvic ultrasound, and laparoscopic study, they ruled out concomitant renal and skeletal defects [2].

Previous MRKH syndrome and 46, XX gonadal dysgenesis case studies have been disputed since they did not include uterine imaging following adequate estrogen treatment. Following that, after at least 6–12 months of estrogen replacement, the uterus must be re-evaluated. Treatment with estrogen and progesterone is necessary to reduce the risk of endometrial hyperplasia and cancer, which will increase if estrogen is used without opposition for a long time. Pelvic ultrasonography revealed a rudimentary uterus in our patient 18 months after starting estrogen replacement, which was later verified by pelvic MRI. After several years of estrogen treatment, the uterus may continue to expand into adult size, and these patients may be able to have a healthy pregnancy utilizing donor oocytes in vitro fertilization [9].

Many genes involved in ovarian development are unknown, and the cause of 46, XX gonadal dysgenesis has yet to be found. Clinically, clinicians should concentrate on the long-term impact of estrogen insufficiency, which is a significant risk factor for neurological, metabolic, cardiovascular, and bone health issues. To prevent bone loss, estrogen medication should be started as soon as possible. To preserve bone health, an oral calcium and vitamin D supplement should be taken for the rest of one's life. Bisphosphonates should only be used in patients who have substantial bone loss and have failed to improve their condition with estrogen replacement treatment [14].

Conclusion

The female patient had primary amenorrhea with XX gonadal dysgenesis but was misdiagnosed as having MRKH syndrome. In the case of primary amenorrhea, a single pelvic ultrasound without further study can be misleading. Premature diagnosis of MRKH syndrome should be prevented in the presence of significant estrogen insufficiency. To identify MRKH syndrome from other sex development problems, focused physical tests and hormone profiles are required. The provision of effective long-term care and emotional support to the patient requires an early and precise diagnosis of 46, XX gonadal dysgenesis.

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Chapter 33
Premature Ovarian Insufficiency: Misdiagnosis as Pregnancy

Pushpa Bhatt and Revathi Myneni

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Explore the symptoms of premature ovarian insufficiency (POI) and the diagnoses and investigations to establish the causation of POI as described.
2. Define that premature ovarian insufficiency is a clinical syndrome presented by loss of ovarian activity before the age of 40. POI is characterized by menstrual disturbance (amenorrhea or oligomenorrhea) with raised gonadotropins and low estradiol.
3. Enquire about symptoms of estrogen deficiency in women presenting with oligomenorrhea or amenorrhea and to exclude women with amenorrhea/oligomenorrhea or estrogen deficiency symptoms below the age of 40 years.
4. Exclude causative factors such as diseases developed by thyroid and adrenal malfunctioning and to discuss surgical removal of ovary or radiation that could cause POI.
5. Discuss with the patients the possibility of POI being a consequence of a medical or surgical intervention to be discussed with women as part of the consenting process for that treatment.

Introduction

Primary ovarian insufficiency is a disorder when ovaries stop functioning prematurely and present menopausal-type symptoms. The ovary is a secretory structure within its graafian follicle developed from the primordial follicle each month.

P. Bhatt (✉) · R. Myneni
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: pushpa.bhatt@martinus.edu

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Menopause, a physiological condition characterized by permanent cessation of menses, results from the depletion of functional primordial follicles. The mean ± standard deviation (SD) age at the time of natural menopause is 50 ± 4 years [1]. Menopause before the age of 40 years is considered to be premature. When the ovaries no longer produce hormones including estrogen, women with low estrogen levels are at an increased risk of certain health issues. Premature ovarian insufficiency (POI) is previously referred to as "ovarian failure," because the ovaries can intermittently (occasionally) function, begin releasing eggs, and even result in successful pregnancy is the loss of normal ovarian physiology that occurs among women before the age of 40 years [2], and amenorrhea for four or more months with increase of follicle-stimulating hormones (FSH) but deficiency in estrogen hormones, a woman subfertile and estrogen-deficient long before to the normal age of menopause [3]. POI is most frequently idiopathic but may also occur due to genetic disorder, autoimmune diseases, infections or inflammatory conditions, or metabolic syndromes [4, 5]. Premature ovarian insufficiency is a medical condition in which ovarian follicles are depleted and cease to function normally both as reproductive organs and endocrine organs in women under 40 years old [6]. It is characterized by deficient ovarian sex hormones and decreased ovarian follicles that accelerate the onset of menopause [7]. This condition often results in infertility, as it is associated with hypoestrogenism, which causes menstrual irregularities and pregnancy failures [8]. The decrease in estrogen secretion level also causes a classical menopausal symptoms, such as hot flashes, night sweats, and insomnia. In addition, long-term consequences of premature loss of ovarian function increase the lifetime risk of skeletal fragility and cardiovascular and neurocognitive disorders [7]. POI affects approximately 1% of women below the age of 40 years [9], and spontaneous early menopause is reported approximately to 5% of women between ages 40 and 45 years [10]. Delay in clinical presentation and low awareness toward these diseases lead to a delay in diagnosis and subsequent treatment. Ovarian dysfunction in POI may be spontaneous or induced depending upon the underlying causes. The end result in both cases is the same, ova reserve is low diagnosis for spontaneous delay due to clinical presentation and in iatrogenic POI intervention is early to manage health outcomes risk due to hypoestrogenism. The prevalence of POI was higher in countries with medium and low human development indexes [6]. The frequency is roughly 4–8% in women experiencing secondary amenorrhea and 10–28% in cases of primary amenorrhea [11]. The estimated incidence rate ratio varies with age; the ratio is 1:100 cases by the age of 40 years, 1:250 cases at the age of 35 years, 1:1000 cases by 30 years, and 1:10,000 cases during the age of 18–25 years. Epidemiological studies have shown that POI incidence also depends on ethnicity [12]. In many occasions the cause of primary ovarian insufficiency is not known.

Other causes include:

- Autoimmune disorders
- Cancer treatments such as chemotherapy and radiation treatments
- Genetic disorders including Turner syndromes (genetic disorder involving an abnormality in one of a female's two X chromosomes) or fragile X syndrome

- Surgical causes that include hysterectomy and oophorectomy (surgical removal of uterus and ovaries, respectively)
- Viral infections

Clinical Case Presentation

The clinical presentation in women with POI varies. They include having difficulty in conceiving, irregular menstruation after pregnancy or after stopping the use of oral contraceptives, or complete absence of menstruation due to surgery, chemotherapy, or radiation. Premature ovarian insufficiency is suspected when a healthy woman before the age of 40 years presents with amenorrhea for 3 consecutive months [3]. They may exhibit premenopausal and estrogen-deficient symptoms, such as hot flashes, painful intercourse, night sweats, dry eyes, and diminished sexual drive. Sometimes in primary amenorrhea, they may not present with any signs and symptoms of hypoestrogenism. They may also present with various syndromes. Turner syndrome is the most frequent hereditary cause of POI, with symptoms manifesting before menarche [3]. Some women with POI present with signs and symptoms of Turner syndrome, for example, a short stature, shield-like chest, wide carrying angle elbow, low-set ears, and low hairline. Occasionally family history of dwarf built, hearing loss, and eyelid tumors also presents with POI [3].

Disorders with autoimmune diseases linked with thyroid and adrenal gland have also been reported with women in POI [13]. Such cases present with associated adrenal and thyroid disorders. Some women may exclusively present with menstrual disorder leading to amenorrhea. Others may have skin manifestations, while some patients present with autoimmune diseases.

Various symptoms for POI are presented under the following category [3]:

1. Menstrual abnormalities

   Missed cycles leading to amenorrhea
   Sudden onset of secondary amenorrhea
   Primary amenorrhea
   Subfertility/infertility
   Menopausal symptoms (hot flashes, vaginal dryness, and sleep disturbances)

2. Skin-related symptoms

   Hyperpigmentation
   Hypopigmentation
   Vitiligo
   Alopecia

3. Autoimmune

   Vitiligo (autoimmune)
   Hyperpigmentation-adrenal insufficiency (autoimmune)

Hair loss/alopecia (autoimmune)
Goiter (autoimmune)
Fatigue
Anxiety/depression

Although most women show minimal symptoms of primary ovarian insufficiency, the condition should be suspected if the patient has irregular periods or is having difficulty conceiving. For diagnosis, a detailed menstrual cycle history, usage of oral contraceptives, susceptibility to poisons such as chemotherapy or radiation therapy, and prior ovarian surgery are all required. Ultrasound is employed to analyze the function of ovaries and no follicle production is key in finding the POI. The majority of cases of secondary amenorrhea fall under four major conditions: the polycystic ovary syndrome, hypothalamic amenorrhea, hyperprolactinemia, and primary ovarian insufficiency [14]. Diagnosis usually involves a physical exam that includes a pelvic exam and blood investigation for hormone level, β-human chorionic gonadotropin (β-hCG), follicle-stimulating hormone (FSH), prolactin (PRL), and thyroid-stimulating hormone (TSH). The differential diagnosis is based on the results of initial tests that include pregnancy test, an FSH level, and assessment of hyperandrogenism. Generally accepted diagnostic criterion for POI is 4 months of amenorrhea with menopausal level of FSH [15]. Premature ovarian insufficiency is diagnosed when a woman presents with amenorrhea (no menstruation) before 40 years of age [3] with an elevated serum level of pituitary gonadotropin follicle-stimulating hormone (FSH) with low levels of estradiol (E2). Serum levels of FSH and E2 are measured on at least two separate occasions with more than 4 weeks of interval, and patients that present with continuously elevated FSH levels (greater than 25 IU/L) are diagnosed with POI [7].

Differential Diagnosis

The differential diagnosis is based on the exclusion of other causes of amenorrhea (absence of menstruation for more than 6 months) with parameters for the exclusion of each of the following conditions presented:

- Pregnancy: signs and symptoms of pregnancy with high chorionic gonadotropin levels. Fetal part visible through ultrasonography (USG)
- Iatrogenic causes (surgery, antineoplastic treatments, radiations, antidopaminergic drugs): history and complete anamnestic investigation
- Hypothalamic-pituitary disease (pituitary tumors, hyperprolactinemia, Kallmann syndrome): visual disturbance with history of headache, high prolactin (PRL) and low/normal gonadotropin levels, alterations at imaging of brain/sellar region
- Hypothalamic amenorrhea (induced by stress, intensive exercise, anorexia, weight loss, fasting, severe diseases): low/normal gonadotropin levels, normal thyroid-stimulating hormone (TSH), and normal prolactin

- Polycystic ovaries: alterations at ovarian ultrasound, normal gonadotropin and high androgen levels; obesity, acne, hirsutism, oily skin, irregular menstrual period; negative serum β-hCG, normal range of follicle-stimulating hormone (FSH); normal level of thyroid-stimulating hormone, normal prolactin levels, and normal to elevated estradiol
- Enzymatic defects of steroidogenesis (e.g., 21-hydroxylase deficiency): alterations at physical and adrenal ultrasound, normal gonadotropin, high androgen and adrenocorticotropic hormone (ACTH) levels
- Endocrine disorders, such as hyperthyroidism, hypothyroidism, and Cushing's syndrome: complete clinical/biochemical evaluations, normal gonadotropin levels with different signs and symptoms
- Only in patients with primary amenorrhea:
  - Vaginal/uterus anatomical abnormalities, such as Mayer-Rokitansky-Küster-Hauser syndrome or Asherman's syndrome: alterations at physical examination/pelvic ultrasound, normal gonadotropin levels
  - Disorders of sexual differentiation (e.g., resistance to androgens): alterations at secondary sex and physical appearance/ultrasound examination, evaluation of karyotype, measurement of androgen/anti-Müllerian hormone levels

Discussion

A diagnosis of POI has a strong impact on the physical and emotional health of affected women. Patients may develop depression, anxiety, and other disorders largely related to the uncertain reproductive prognosis. Therefore, suspected cases must be identified and management should be individualized according to the specific needs of each case. Some patients show absence of menses after a pregnancy or after they have stopped taking hormonal contraceptives. They are categorized as dysfunctional uterine bleeding; such patients should be evaluated for their general health for underlying conditions such as diabetes and celiac disease [16]. A patient is to be ruled out if she has undergone reproductive surgery such as oophorectomy or has gone for any radiation treatment. Patients with POI can achieve spontaneous pregnancy in 5–10% of cases [17]. In one of the French cohort studies published in 2011 [17], 358 POI patients were followed from 1997 to 2010, and 4.4% had spontaneous pregnancies. Women to whom fertility is a priority should be counseled to seek assisted conception through in vitro fertilization (IVF) with egg or embryo donors. An observational study showed a cumulative delivery rate of 86.1% after four cycles of oocyte donation in women with ovarian failure due to POI, oophorectomy, menopause, or chemotherapy [18]. However, concerns exist regarding ethical and legal issues according to different countries that may limit the practicality of this procedure. Another option currently at the research stage involves cryopreservation and IVF for ovarian tissue in women at risk. In the study in Japan of ovarian tissue cryopreservation followed by infertility treatment by in vitro activation of

dormant follicles and ovarian autotransplantation among 37 patients with POI, 20 patients had residual follicles. With this technique three patients had successful pregnancies. After the POI diagnosis and treatment, an increased anti-Müllerian hormone levels were predictive of fertility success [7]. Etiologic diagnosis of POI remains challenging; almost 65% of cases are deemed idiopathic [5], and there is an association with autoimmune diseases [10]. In light of this evidence, it is recommended that women with POI of unknown etiology, and particularly those with a family history of POI, should undergo screening. Another concern highlighted is for young women with POI commonly seen with lower bone l density [11]. One literature also discusses whether testosterone deprivation in POI is associated with impaired bone mass. A clinical trial assessed the effect of testosterone treatment (150 μg/day via transdermal patch) in addition to estrogen (100 μg/day) and progestin therapy (medroxyprogesterone 10 mg/day for 12 days per month) on bone density in patients with POI [12]. Usually calcium if taken 1200 mg per day can maintain the adequate level of vitamin D status (serum 25-hydroxyvitamin D level $\geq$ 30 ng/mL). Adults with inadequate sun exposure may take 800–1000 IU of vitamin D3 per day [12].

Conclusion

In POI ovaries spontaneously stop functioning normally in people who are younger than 40 years. It is also a type of premature menopause. In people with POI, the ovaries either stop releasing eggs or release them only intermittently. Ovaries stop producing the hormones estrogen, progesterone, and testosterone or produce them only intermittently. Therefore, POI makes pregnancy unlikely.

The diagnosis is more than infertility and can affect both physical and emotional well-being. Management of the condition must be addressed to both partners. Before deciding about your plans for a family, there are multiple choices available.

Estrogen replacement, in primary ovarian insufficiency (POI) treatment, is replacing the estrogen that the ovaries have stopped producing. That's important because estrogen is vital to certain normal processes. The bones, for example, need estrogen stimulation to stay strong and resistant to fracture. Without estrogen, people with POI are at risk of developing osteoporosis (a disease in which the bones are weaker than normal). Estrogen therapy aims to prevent or relieve all of these consequences of estrogen deficiency. However, most people cannot take estrogen alone; they must combine it with a progestin (a form of progesterone) to prevent a condition that could lead to cancer of the uterus. People who do not have a uterus (i.e., have had a hysterectomy) can take estrogen alone.

Types of estrogen therapy: The main form of estrogen that the ovaries normally produce is called estradiol. People who choose estradiol can get it in pill form, in a patch that is worn on the skin, or in a ring that is inserted into the vagina. The estradiol patch and vaginal ring may offer advantages over the pill form, including the following:

- They secrete the same hormone that the ovaries make.
- The estrogen directly passes through the bloodstream without passing through the liver.
- The estrogen absorbs slowly and gets into the body.
- The estrogen can be measured easily in the bloodstream.

Infertility management: Around 5–10% of people with POI are able to conceive and give birth normally without any special treatment.

One treatment that is successful is in vitro fertilization (IVF) with donor eggs. Embryo donation, in which frozen embryos are donated to the couple, is also often successful and in general less expensive.

If a patient wants to get pregnant, care providers need to identify the cause of the condition before the patient starts trying treatment. Some underlying causes of POI can cause problems with a pregnancy or a fetus, if a pregnancy is successful. In such situations, adoption is a good option.

A diagnosis of POI can be emotionally devastating to many people, especially if they were planning to become pregnant in the future. If that is the case, there are limited choices that include adoption, pregnancy with donor eggs, seeking a gestational carrier (surrogacy), and remaining childless. In conclusion, diagnosis and management still pose a challenge in clinical practice. Some mechanisms of this disease remain unexplained. Evaluation of fertility prognosis and the bone mineral density which is generally impaired by estrogen deficiency is an essential aspect of management.

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Chapter 34
Forgotten Copper T: An Intrauterine Contraceptive Device Misdiagnosed as Secondary Sterility

Pushpa Bhatt and Revathi Myneni

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Create a diagnosis based on history and clinical presentation confirmed by X-ray.
2. Discuss and summarize a case with forgotten copper IUD which can be misdiagnosed as secondary sterility.
3. Discuss the clinical case presentation of the patient and what were the features that resulted in the misdiagnosis.
4. Enumerate the differential diagnosis of secondary sterility.
5. Emphasize the need for consent and proper communication with the patient.
6. Apply the knowledge gained from the case in a clinical setting.

Introduction

The abbreviation "IUD" stands for intrauterine device. It offers long-term contraception. It is a "T"-shaped device inserted into the uterine cavity. The T-shaped plastic frame with copper wire around stops sperm from fertilizing with the egg, thus preventing pregnancy. This device is also called copper T. An intrauterine device (IUD) is a highly effective and reversible long-term method of family planning used in Asia; 27% of women use reversible IUD globally; the IUD is the most widely used reversible contraceptive. In Scandinavia, 20–40% of contraceptive users have IUD, while about 60 million Chinese women use this type of contraceptive [1]. IUD use varies by nation, reflecting differences in culture, contraceptive

P. Bhatt (✉) · R. Myneni
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: puhshpa.bhatt@martinus.edu

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availability and choice, provider views and training, and women's fertility objectives. IUD for women wishing to practice long-term contraception is highly effective birth control without having to resort to hormonal methods [2]. Copper T can be inserted anytime during a normal menstrual cycle. For breastfeeding mothers they are recommended 8 weeks after delivery before inserting copper T. Before inserting, healthcare providers evaluate overall health and do a pelvic exam to exclude pregnancy and evaluate the status of the uterus. The patient is also screened for sexually transmitted infections (STI) . Common complications after insertion include vaginal discharge, failed insertion, pain, infection, menstrual disorders, and perforation [3, 4]. Sometimes it remains inside the uterus for more than 10 years. Many times patients are unaware of its existence inside. We are reporting such a case where we found copper T placement as an accidental finding during secondary sterility management. In this case copper T was inserted at one of the hospitals of India. She was seeking treatment for secondary sterility. The case was managed with different modality.

Clinical Case Presentation

A 35-year-old married woman, gravida 1 and para 1, was referred to Baitadi hospital of Far Western Region of Nepal with the complaints of vaginal discharge off and on and being unable to conceive for the past 14 years. Her past history revealed that 5 years after the birth of her first baby, she was unsuccessful to conceive further. She went to several health facilities where they offered different treatments such as dilation and curettage (D&C), oral contraceptive for menstrual regulation for few months, treatment for sexually transmitted diseases, etc. This continued off and on for 12 years in India and in Nepal as well. She was under treatment from the primary health care of Patan village development committee, where she was referred to Baitadi hospital. In Baitadi hospital, her thorough history revealed that, for the last few months, her vaginal discharge has increased. She was given vaginal tablets for 7 days and both husband and wife were treated for chlamydia and referred to our hospital for secondary sterility. Her history revealed that she lived in Guwahati in India with her husband. There she had delivered a female baby. Patient had a follow-up visit for immunization of the baby after 6 weeks of delivery. She was offered some counseling on family planning and asked to visit after 6 months.

This patient revealed, 6 months after the birth of her baby after the first menses, she visited a family planning clinic to seek advice in Gohati hospital. She was examined and asked to lie down on a table. The patient was told to watch for the thread that should hang down into the vagina. She never felt it. The patient did not realize that it was placed. However, she was given a bunch of papers to keep them safely for her record. She was unaware of having any consent. There was confusion because the patient was unable to remember if at all the IUD insertion took place or not. And she did not notice any thread as well. A thorough history of her menstrual cycle was taken, and cross-questioning for Depo injection (people's choice in Nepal

for long-term family planning) was asked and IUD insertion (once it was a very popular family planning program in India) as well. Among the migrant and mobile couples, copper T is the choice for family planning in India. On speculum examination she had moderate vaginal discharge and on per vaginal examination showed an anteverted normal size and non-tender uterus. The semen analysis result of her husband was normal. Her blood test was all in a normal range. Venereal disease research laboratory (VDRL) tests for both were negative. We wanted to exclude all possibilities for sec sterility. Pelvic X-ray was done, and it showed IUD is in the pelvic cavity based on her history of presence of copper T, so it was easy to anticipate that due to the copper T, she was unable to conceive. The patient's history was taken into consideration and she was referred to a referral hospital in Pithoragarh district, located at the border between India and Nepal, for surgical removal of copper T. After 7 days the patient came back to Baitadi hospital with the copper T in her hand that was removed under general anesthesia. Her report shows that "through cervical dilatation copper T was removed, lying in the cavity of a normal size uterus, and the size of the thread was too small." She was given antibiotics for 5 days and asked to plan further to conceive. In 1 year she conceived and visited Baitadi hospital for antenatal care.

Discussion

Globally, it is estimated that more than 60 million women use IUD, and the forgotten IUD are not documented [5]. There are several reasons for this phenomenon: the IUD may fragment at removal, the absence of threads may be misinterpreted, or the patient may simply have forgotten that she had an IUD inserted. Presently various types of IUD are available. Long-acting reversible contraceptive (LARC) methods, including IUD, the levonorgestrel-releasing intrauterine system (LNG-IUS), depot-medroxyprogesterone acetate (DMPA) injections, and implants, are highly cost-effective than the oral contraceptive pill. Furthermore, IUD, intrauterine suppositories, and implants are more cost-effective than injectable contraceptives [6]. IUD are good choice for breastfeeding women and those who had abortion, have some diseases such as diabetes, or have chronic migraines with or without aura. The effectiveness, safety, long duration of action, and reversibility of IUD made it a popular choice among women in the global population. Intrauterine contraceptive devices are used by over 50% of the women in some Asian countries and between 6 and 27% in Europe [7]. Woman who aspire to use an IUD device, whatever the type should get detailed information in the form of oral as well as written format that will alert them on what family planning method to choose [6]. Most importantly they should get routine follow-up after the insertion of the IUD. This follow-up is required to confirm the presence of IUD in its place and also to exclude if any unwanted symptoms appear after the insertion such as bleeding, pain, and discharge [8]. Women should be advised that menstrual bleeding and cramping may initially increase with the use of the copper T. Some investigators have already

reported on gynecologic symptoms caused by such forgotten IUD, such as actinomycotic pyometra [9] and dysfunctional uterine bleeding and perforations [10]. The patient was not given relevant information on follow-up. So she lost the follow-up contacts. When she aspired to have a second baby, she was not investigated for IUD. She unnecessarily had to go to different institutions where she received irrelevant investigation and treatment. Studies indicate that the copper IUD exerts its contraceptive effects primarily by preventing fertilization through inhibition of sperm motility and viability [11]. The copper ions cause an intrauterine inflammatory response that is cytotoxic to sperm and phagocytizes them; 18 h after natural insemination, no viable spermatozoa remain in the endometrial cavity. Copper has a direct negative impact on sperm motility and the capacity of sperm to enter cervical mucus. Copper ions also cause inflammatory changes around the egg during ovulation, which is similar to what women with endometriosis experience. The US Food and Drug Administration (FDA) has approved the use of the copper IUD for up to 10 continuous years, during which it remains highly effective. It has a reported failure rate at 1 year of 0.8 per 100 women [12]. The most common side effects reported are heavy menstrual bleeding and pain [13]. If our patient had received X-ray, the IUD would have been visualized early enough to avoid all time-consuming follow-up for secondary sterility. The patient was not a case of secondary sterility but misdiagnosed as such because of the copper T, making her unable to conceive, that was forgotten by a patient and not identified by healthcare providers [13].

Conclusion

There is not much data on forgotten IUDs, but we believe issues and problems should be reported more. Counseling is the central issue to be addressed effectively. To avoid unintended pregnancy, healthcare providers at all levels should incorporate effective counseling for using IUCD during the postpartum period. The most effective long-term, safe, and reversible method is IUCD. Counseling should be clear and be offered with informed consent. Follow-up is required with IUCD to see if copper T strings are in the right place. Our patient needed to be counseled more, and she could not locate the strings; thus, she was lost for follow-up. The healthcare providers may have offered to counsel, she was not able to understand well enough to report at the healthcare facility, or she ignored the consequences. Healthcare providers are therefore required to be sure that all information is well understood. The family planning services should aim to improve quality through proper counseling and follow-up services which help to support women if they choose to use IUCD in the postpartum period effectively. It is essential to consider unexplained secondary sterility resulting from a forgotten IUD.

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Part VII
Hematology

Chapter 35
Congenital Methemoglobinemia Misdiagnosed as Polycythemia Vera

Mohammed Mohammed

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Define methemoglobinemia.
2. Consider the diagnosis of congenital methemoglobinemia in patients presenting with cyanosis and dyspnea when cardiopulmonary causes are excluded.
3. Evaluate a patient suspected to have methemoglobinemia.
4. Avoid unnecessary procedures and treatments in patients suspected to have congenital methemoglobinemia.
5. Formulate an appropriate management plan for patients with congenital methemoglobinemia.

Introduction

Methemoglobinemia is a rare hematologic disorder that causes cyanosis and dyspnea unrelated to cardiac and pulmonary causes. Methemoglobinemia is usually asymptomatic, even when methemoglobin levels are as elevated as 40% of the total Hb levels [1]. Hereditary congenital methemoglobinemia due to deficiency of nicotinamide adenine dinucleotide (NADH) cytochrome b5 reductase enzyme is a remarkably rare recessive inherited disorder which is not well reported in medical literature. In this clinical case of congenital methemoglobinemia, the patient presented with persistent cyanosis and polycythemia in the absence of cardiopulmonary causes which led to a misdiagnosis of polycythemia vera for which the patient unnecessarily underwent bone marrow biopsy and was treated with imatinib.

M. Mohammed (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: mohammed.mohammed@martinus.edu

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Clinical Case Presentation

A 29-year-old man from India had generalized fatigue and discoloration of hands for 6 months. His CBC revealed high red blood cell (RBC) count (6.7×10^6/uL), increased Hb (20 g/dL) with normal leukocyte and platelet counts, and unremarkable peripheral blood smear. The patient was evaluated in another medical center based on his persistent polycythemia, and he was diagnosed with polycythemia vera. Bone marrow examination showed erythroid hyperplasia but without panmyelosis. Despite the fact that molecular studies were negative for JAK2 mutation, the patient was treated with imatinib based on the assumed diagnosis of polycythemia vera.

In a different institute, the patient was reevaluated, and he was found to have cyanosis of the face and both upper limbs since the age of 13 years old, but it became more evident in the last 1 year following treatment with imatinib after the assumed diagnosis of polycythemia vera. There was no history of chest pain, syncope, or palpitations. There was no history of medication intake or exposure to oxidants. He had no history of growth or developmental retardation or neurologic manifestations and no hepatosplenomegaly. Pulse oximetry revealed oxygen saturation of 92%, however the patient didn't show any evidence of respiratory distress, and his clinical examination was unremarkable. The diagnosis of polycythemia vera was challenged and ruled out because of negative *JAK2* gene mutation, normal erythropoietin level, and absence of panmyelosis features in the bone marrow examination, which was repeated 4 months after stopping treatment with imatinib. A different diagnosis of hemoglobin M disease is considered because of the cyanosis and no evidence of cardiopulmonary disease; however, hemoglobinopathies screening by high-performance liquid chromatography and manual hemoglobin electrophoresis showed normal hemoglobin pattern. Arterial blood gas showed the following results: pH, 7.380 (normal range: 7.35–7.45); PCO_2, 38 mmHg (normal range: 35–45 mmHg); PO_2, 96–101 mmHg (normal range: 83–108 mmHg); arterial O2 saturation, 100% (normal range: 95–99.0%); low HCO_3 at 21.8 mmol/L (normal range: 23–29 mmol/L); and low oxygen saturation (O_2 Hb) at 62.4% (normal range: 94–98%).

The finding of cyanosis and low oxygen saturation despite the normal arterial oxygen tension was strongly suggestive of methemoglobinemia.

Arterial blood gas showed a methemoglobin level of 38% (normal range: 0–1.5%). Cytochrome b5 reductase (methemoglobin reductase B) was found to be deficient at level of <2.6 U/g Hb (normal range: 6.6–13.3), and therefore the diagnosis of congenital methemoglobinemia was confirmed. Karyotyping was done and showed no chromosomal abnormalities. Other family members had no family history of hemoglobin disorders or cyanosis, and they were asymptomatic. He was managed with vitamin C 500 mg once daily because of the lack of methylene blue tablets. After 1 month of treatment, the cyanosis improved significantly and methemoglobin levels were reduced remarkably from 38 to 19.2%.

Differential Diagnosis

1. Polycythemia vera
2. Hemoglobin M disease
3. Acquired methemoglobinemia

What Was Misdiagnosed in This Case and Why?

Congenital methemoglobinemia was misdiagnosed because of the following reasons:

1. Cyanosis was overlooked.
2. Not taking into account the bone marrow findings (absence of features of panmyelosis) and the negative JAK2 mutation.
3. Lack of systematic epidemiological studies about congenital methemoglobinemia.

Discussion

Methemoglobin results when ferrous iron is oxidized to ferric iron within the heme component of hemoglobin [1]. Normally, less than 1% of hemoglobin is present in the oxidized form (methemoglobin), which has decreased the ability to carry oxygen, but with increased oxygen affinity at the remaining binding sites [2]. This leads to decrease of oxygen delivery to tissue causing hypoxemia and lactic acidosis. Acquired methemoglobinemia due to oxidizing agents is not uncommon; on the other hand, congenital deficiency of the methemoglobin reductase B enzyme is extremely rare, and only very few cases are reported in medical literature worldwide; therefore the clinical characteristics and the incidence of congenital methemoglobinemia are almost unknown because of the underreporting of these cases. The patient had a *saturation gap* which occurs when there is a difference between the sulfur dioxide (SO_2) measured by pulse oximetry (the lower value) and the SO_2 on arterial blood-gas analysis. This was the hint for the diagnosis of methemoglobinemia. Patients with methemoglobinemia typically have a saturation gap of greater than 5% [3]. The failure of very high oxygen saturation to correct cyanosis is highly suggestive of methemoglobinemia. Patients with congenital methemoglobinemia develop physiological compensatory mechanisms and can remain asymptomatic even with high levels of methemoglobin (up to 40%). These compensatory mechanisms include changes in the concentration of 2,3-diphosphoglycerate and pH, synthesis of globin chains, and secondary polycythemia [4, 5].

If levels of methemoglobin exceed 70%, that is usually fatal [1].

As a result of the methemoglobinemia induced left shift in the oxyhemoglobin dissociation curve, compensatory increase in hemoglobin concentration is observed in patients with recessive hereditary methemoglobinemia [6]. Congenital methemoglobinemia is classified into two main types: one due to deficiency of methemoglobin reductase enzyme (cytochrome b5 reductase) and the other due to hemoglobin M (abnormal oxygen affinity hemoglobin) [7]. Methemoglobin reductase enzyme deficiency is further classified into type I and type II; type I, cytochrome b5 reductase deficiency, affects only RBCs, and patients most commonly present with fatigue and dyspnea due to methemoglobinemia, and they have normal life expectancy.

Type II methemoglobinemia, which constitutes about 10% of all cases of congenital methemoglobinemia, affects both RBCs and WBCs. It manifests with severe neurologic dysfunction and reduced life expectancy with death occurring in the first few years of life. Cytochrome b5 reductase activity is less than 20% of normal [8, 9]. Patients with type I hereditary methemoglobinemia remain asymptomatic throughout infancy and childhood and develop symptoms later in life. For this reason physicians tend to overlook congenital methemoglobinemia and rather think of acquired methemoglobinemia, investigating exposure to exogenous oxidative stress as the most likely cause of the manifestations. There is only one reported case wherein the onset of manifestations in the patient started at the age of 8 years [10]. When congenital methemoglobinemia is considered, methemoglobin reductase enzyme activity should be checked in all immediate family members. Because of the autosomal recessive transmission, in heterozygous deficiency, methemoglobin reductase activity is low, and therefore heterozygotes will have a lower threshold for development of acquired methemoglobinemia in response to oxidative stress exposure. However, under normal circumstances the level of enzyme activity is not too low to cause clinical disease [11].

This rare hemoglobin disease is underreported and often overlooked and misdiagnosed. The first description of familial idiopathic methemoglobinemia in the United Kingdom was reported in two members of one family in 1943 [12].

In the English medical literature, there are only 23 cases diagnosed as congenital methemoglobinemia due to deficiency of cytochrome b5 reductase—17 cases of type I and 6 cases of type II. Seventy-three percent of the cases are males and 26% are females. About half of reported cases (12 cases) are Indian, 3 are English, 2 are Japanese, 2 are Arabic, 1 case is Spanish, and 1 case is Italian.

The median calculated age for type I is 31 years with cyanosis and shortness of breath being the most common clinical manifestation. For type II, all cases are in the pediatric age group. The median calculated age at presentation is 6 years with neurologic manifestations and mental retardation being the most common clinical features in type II.

There are different treatment modalities: methylene blue alone, methylene blue with vitamin C, or vitamin C alone. Vitamin C either alone or in combination with methylene blue was used in seven cases within this category with no response in one case [5], while the other six cases (including the case described here) responded well.

Plan of Action, the Points Clinician Should Consider, Pitfalls to Avoid, and Pearls of Knowledge to Consider

Clinical cyanosis can be diagnostically challenging since causes are multiple, especially in the absence of cardiopulmonary causes. In this case, the cyanosis was basically overlooked and hematology workup was misdirected toward investigating polycythemia. The finding of cyanosis and low oxygen saturation despite the normal arterial oxygen tension should strongly suggest methemoglobinemia. In heterozygous cytochrome b5 reductase deficiency, methemoglobin reductase activity is low, and the patient will have a lower threshold for acquired methemoglobinemia in response to exogenous oxidative stress.

Conclusion

Because of the lack of systematic epidemiological studies, congenital methemoglobinemia is misdiagnosed since it is under-investigated and usually overlooked, especially when patients develop symptoms in adulthood and in the absence of obvious acquired agents. In this clinical case, which is misdiagnosed as polycythemia vera, we highlighted the challenges in diagnosis of congenital methemoglobinemia and pointed out the important points to consider as a physician to be able to suspect this rare disease so that the proper treatment is administered and unnecessary treatment with imatinib and exposure to invasive bone marrow procedures are avoided.

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Chapter 36
Thrombotic Thrombocytopenic Purpura Misdiagnosed as Autoimmune Cytopenia

Adedamola Bello

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Create an appropriate differential diagnosis of thrombotic thrombocytopenic purpura in the presence of microangiopathic hemolytic anemia and acute peripheral thrombocytopenia.
2. Evaluate the different components of the medical history and physical examination, which indicate the most appropriate order within the differential diagnosis and hence a correct course of further diagnostic procedures needed to reach a definitive diagnosis.
3. Review the diagnostic importance of peripheral blood smears for TTP.
4. Discuss the diagnostic role of genetic testing for ADAMTS13 in TTP.
5. Analyze the impact of the delayed diagnosis on prognosis, sequelae, and quality of life for patients.

Introduction

TTP (thrombotic thrombocytopenic purpura) is a kind of thrombotic microangiopathy (TMA) characterized by severe cytopenia (thrombocytopenia and hemolytic anemia). Additionally, extensive microvascular thrombi in TTP cause multi-organ failure of varying severity with a 20% death rate [1]. A significant deficiency of the von Willebrand factor-cleaving protease ADAMTS13

A. Bello (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: adedamola.bello1@martinus.edu

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(A Disintegrin And Metalloproteinase with ThromboSpondin-1 motifs, 13th member) causes the accumulation of large multimers of von Willebrand factor (ULVWF) in plasma. The presence of a significant ADAMTS13 deficiency is currently considered part of a positive diagnosis [1, 2]. TTP is a deadly disease that necessitates prompt diagnosis and treatment in the event of an emergency. TTP, on the other hand, might be difficult to diagnose in an emergency environment because of its rarity (4 instances per 106 people per year) [3]. Furthermore, because TTP is characterized by peripheral cytopenias, it can be confused with other conditions, particularly autoimmune cytopenias (AIC) , such as autoimmune thrombocytopenia associated or not with autoimmune hemolytic anemia (Evans syndrome) , which adds to the difficulty of obtaining a positive diagnosis [4]. In this context, determining the activity of ADAMTS13 is particularly useful in determining the diagnosis of TTP in patients with peripheral cytopenias [5]. However, in cases of diagnosis ambiguity, a quick ADAMTS13 activity evaluation is not routinely accessible in all centers, resulting in diagnostic inconclusiveness with potentially severe repercussions on prognosis by delaying therapeutic plasma exchange (TPE). As a result, it is critical to pinpoint the factors that lead to TTP misdiagnosis using AIC, as well as the implications for prognosis. A retrospective multicenter study was conducted, allowing for the retrograde analysis of the outcomes of these misdiagnoses and understanding the causes or missed events that led to a misdiagnosis in these cases.

Clinical Case Presentation

A retrospective study was conducted. Based on these studies, it was found that the clinical cases that were misdiagnosed as autoimmune cytopenias included females with less profound anemia, lack of schistocyte observation on the first blood smear, more frequent history of autoimmune disorder, and less severe disease. In these presentations, a positive DAT was commonly observed, including with immunoglobulin G (IgG) alone or in association with C3a, a complement protein. Some misdiagnosed patients had both positive DAT and low or absent schistocytes.

Patients were primarily misdiagnosed with Evans syndrome (51% of cases) and autoimmune thrombocytopenia (37% of cases). Other diagnoses included heparin-induced thrombocytopenia, HELLP syndrome, lymphoid neoplasm, medication toxicity (two instances each), myelodysplastic syndrome, and catastrophic antiphospholipid syndrome (one case each). As an initial treatment, none of these individuals underwent TPE or plasma infusion. Intravenous immunoglobulins were given to 29 (34%) of the patients. Steroids were given to 45 patients (54%). Before TTP diagnosis, rituximab, splenectomy, and danazol were also employed as initial treatment (in one instance each). The prior diagnosis was amended in the majority of cases, and the TTP diagnosis was finally considered due to the fact that early treatment was ineffective (49%) and/or organ failure occurred (34%).

Differential Diagnoses

1. Evans syndrome
   Due to a history of autoimmune disorders in most cases, a less severe presenting anemia, lack of schistocytes initially, as well as positive direct antiglobulin test and IgG. Evans syndrome was considered in most cases.
2. Autoimmune thrombocytopenia
   Due to a history of autoimmune disorder in most cases, a less severe presenting anemia, lack of schistocytes initially, as well as positive direct antiglobulin test and IgG. Autoimmune thrombocytopenia was considered in cases in which the most significant presenting symptom was thrombocytopenia.
3. Heparin-induced thrombocytopenia
   In cases where the clinical picture may have included heparin use, the etiology of thrombocytopenia was attributed to heparin-induced thrombocytopenia (HIT) rather than TTP.
4. HELLP
   Hemolysis, elevated liver enzymes, and low platelet count syndrome. Some cases showed the presence of this constellation of symptoms without classic schistocytes and HELLP was the primary working diagnosis in these cases.

What Was Misdiagnosed in This Case and Why?

Thrombotic thrombocytopenic purpura was misdiagnosed based on the following observations:

1. Female gender
2. Less profound anemia than expected
3. Lack of/low amount of schistocytes on initial peripheral blood smear
4. Positive direct antiglobulin test
5. History of autoimmune disorder

Discussion

TTP is a potentially devastating illness whose prognosis has been dramatically improved by intense TPE-based therapy [6–8]. As a result, a quick diagnosis is a significant priority, and reasons for misdiagnosis must be addressed in order to minimize diagnostic straying and delayed tailored therapy, which may result in higher morbidity and death. In this national study, an unusually significant proportion (20%) of TTP patients were at first misdiagnosed with an AIC, resulting in a 5-day delay in appropriate management, a longer time to platelet count recovery, and more salvage therapies that could have been avoided, despite the fact that overall mortality

remained comparable between the two groups. Importantly, misdiagnosed patients are de facto selected patients who survived misdiagnosis's consequences, and it cannot be ignored that some patients with an AIC misdiagnosis succumbed to the illness before TTP was diagnosed and thus were not disclosed in the registry, potentially underestimating the death rate and incidence of misdiagnosed patients. There are various factors responsible for TTP misdiagnosed with AIC. The higher frequency of AIC, which is three to eight times that of TTP [9], and the relatively recent availability of ADAMTS13 as a viable technique for distinguishing TTP from other disorders both contribute to diagnostic inaccuracies. Furthermore, identifying a microangiopathic hemolytic anemia can prove to be complicated, especially in an emergency situation; indeed, in a large group of patients, schistocytes were found to be low or nonexistent in more than one-third of cases at first presentation, but positive in the days following. In 10% of all patients, a positive, low titer DAT that implies the diagnosis of autoimmune hemolytic anemia might be found, which adds to the difficulty of diagnosing microangiopathic hemolytic anemia. Positive DAT was noted anecdotally in the correctly identified group (5% of cases), which is consistent with prior reports from other groups [6]. Almost 20% of patients in the misdiagnosed group had a positive DAT. Further research is needed to examine the characteristics of antibodies directed against erythrocytes in these individuals, notably their specificity via elution, in order to truly comprehend their pathogenic implications. This unanticipated outcome might be attributed in part to improved knowledge of TTP diagnosis, enabling the detection of occurrences of TTP that were previously undetected prior to the availability of ADAMTS13. These two confounding factors thus characterize a subpopulation of patients with traditional AIC symptoms (low/absent schistocytes and a positive DAT at first presentation; 10% of the overall TTP population) for whom TTP diagnosis is incredibly complex. Findings from this study suggest that a positive DAT should not be used to rule out TTP diagnosis. Furthermore, in patients with peripheral cytopenias, a repeated and more comprehensive search for schistocytes should be performed to reduce the chance of misdiagnosis, particularly in patients with organ failure, when the diagnosis of TTP should be clearly favored until ADAMTS13 activity is known. As per this statement, despite organ involvement that should have suggested TTP, a disproportionately high number of TTP patients previously diagnosed with an AIC were detected. Interestingly, nearly half of misdiagnosed patients had a cerebral involvement, while neurologic events in AIC are extremely rare (1–4% of cases) [10, 11] and are mostly precipitated by intracranial hemorrhage. The emergence of cerebral sequelae following an initial diagnosis of AIC was the primary cause for diagnosis revision, which led to the definitive diagnosis of TTP in the current investigation. Although the number of misdiagnosed patients has declined with time, indicating that TTP has become much more well-recognized than in the past, there are still a substantial number of misdiagnoses. These findings suggest that vigorous awareness campaigns for practitioners who may be involved in the diagnosis of TTP, such as intensivists and urgent care physicians, hematologists, internists, and nephrologists, as well as general practitioners, should be undertaken. National policies should support awareness efforts focused on enhancing TTP diagnosis and early management in order to improve a broad understanding of these uncommon illnesses [10, 12] and provide practitioners with a resource activity [13].

Conclusion

TTP is commonly misdiagnosed with AIC, and characteristic biological markers such as schistocytes may be lacking at first, despite the presence of DAT. Low or undetectable schistocytes upon immediate presentation should not rule out TTP in the context of thrombocytopenia associated with hemolysis, especially when coupled with organ failure. Until ADAMTS13 testing is available, practitioners should preferentially choose the diagnosis of TTP over that of AIC because of the catastrophic prognosis of an untreated TTP.

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Chapter 37
Hemoglobin H Disease and Vitamin B12 Deficiency Misdiagnosed as Thrombotic Thrombocytopenic Purpura

Adedamola Bello

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Create an appropriate differential diagnosis in patients presenting with signs and symptoms of hemoglobin H disease.
2. Evaluate the different components of the medical history and physical examination, which indicate the most appropriate order within the differential diagnosis and hence a correct course of further diagnostic procedures needed to reach a definitive diagnosis.
3. Discuss the presence of hemoglobin H disease in high endemic locations where nutritional deprivation might complicate the disease progression.
4. Discuss the impact of the delayed diagnosis on prognosis, inappropriate management, and quality of life for patients.
5. Discuss and enumerate the diagnostic approach to fatigue and weakness and the appropriate investigations to elucidate the etiology of the illness.

Introduction

TTP (thrombotic thrombocytopenic purpura) is a rare life-threatening blood disorder marked by several clinical signs and symptoms, including microangiopathic hemolytic anemia (MAHA), thrombocytopenia, fever, renal dysfunction, and neurologic abnormalities [1, 2]. The majority of the time, clinical

A. Bello (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: adedamola.bello1@martinus.edu

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practitioners consider TTP when patients have thrombocytopenia, increased lactic dehydrogenase (LDH), and schistocytes in a peripheral blood smear test, albeit schistocytes may be nonexistent at the onset of the disease. If TTP is suspected, treatment should commence with exchange plasma transfusion [3], which necessitates the installation of a central venous catheter (CVC) [4]. Clinically, thrombotic microangiopathies (TMAs) are usually challenging to distinguish, and measuring ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) is still crucial for the diagnosis of TTP. In areas of Asia and the Mediterranean region, as well as in nations where people migrate from these regions, hemoglobin H illness is common [1]. Compound heterozygosity for both α^{+} -thalassemia (resulting from the deletion of one α-globin gene), which is common and has carrier rates as high as 70% in some regions of the world [2], and α^{0} -thalassemia (resulting from the deletion of two globin genes in cis), which was previously only seen in populations from specific regions [2] but is now being seen in other ethnic groups, is present in patients with this disease [1]. Rarely can point mutations in the gene that codes for α^{+} -globin cause α^{+} -thalassemia [2]. Among these mutations is the variant that results in hemoglobin Constant Spring, which is named after the Jamaican neighborhood where it was first discovered. This hemoglobinopathy is primarily found in people with Southeast Asian ancestry and is brought on by a mutation in the stop codon of the 2-globin gene, which is characterized by 31 extra amino acid residues at the C-terminus of the chain [3, 4]. Hemoglobin H illness, also known as deletional hemoglobin H disease, is often caused by the interaction of α^{0} -thalassemia and deletional α^{+} - thalassemia (HbH). Although less frequent than HbH, non-deletional hemoglobin H illness, such as hemoglobin H Constant Spring (HCS), has a more severe clinical course.

Clinical Case Presentation

An 8-year-old male presented to the emergency department with a 5-day history of worsening fatigue and deteriorating weakness and an unremarkable medical history [5]. On examination the patient seemed in good relative condition, conjunctival pallor was noted, and vitals were within normal limits. Physical examination was pertinent for hepatomegaly and splenomegaly (both noted at 5 cm under the costal arch). Diagnostic blood tests were obtained which revealed severe normocytic normochromic anemia with a hematocrit of 11% and hemoglobin of 3.8 gr/dL, mean corpuscular volume of 83.5 fL, and increased red blood cell distribution width of 20% [5]. The patient had a platelet count of 130,000/mL, a normal WBC count, and a reticulocyte count of 0.1% [5]. The chemistry panel showed an extreme elevation of LDH above 3700 IU/L [5]. Clotting assay resulted in a slight INR elevation at 1.12 and borderline fibrinogen of 155 mg/dL [5]. The patient was admitted at this time and transfused with four units of red blood cells [5]. Despite

the transfusion, a drop in platelet count was observed to be 55,000/mL [5]. A peripheral blood smear performed showed no schistocytes [5]. Due to the fact that TTP was on the differential, the patient underwent surgical placement of a central venous catheter in the subclavian vein, but minutes after cannulation the patient presented with perspiration, tachycardia, and pallor and then loss of consciousness [5]. When consciousness was regained, the patient complained of pain in the right hemithorax, and no respiratory sounds were auscultated. Consequently, O2 saturation dropped rapidly and the patient was intubated due to respiratory failure and hemodynamic instability. Moments later the patient was in cardiopulmonary arrest. Resuscitative measures were initiated and the patient was successfully resuscitated and transferred to ICU [5]. While admitted to the ICU, a thoracostomy tube and Bullau tube were placed and a blood output of 2400 mL was obtained. Chest X-ray revealed a large mediastinal hematoma in right hemithorax and thoracoscopy further exhibited multiple bleeding sites within the thorax [5]. The pt was administered units of RBCs and fresh frozen plasma and stabilized [5]. Subsequently, the peripheral blood smear was re-evaluated and a bone marrow aspiration was ordered to further evaluate. Bone marrow aspiration exhibited an 80% erythroblast reaction (erythroid hyperplasia) and few megakaryocytes which indicated a diagnosis of megaloblastic anemia. After arriving at the correct diagnosis, the patient received oral folic acid and intramuscular cobalamin [5]. There was a marked improvement in the patient's condition, and after stabilization, the patient was discharged on oral folic acid supplement and intramuscular cobalamin once a week for a month [5]. Reexamination as an outpatient at the hematology clinic was recommended and on follow-up the patient was doing well and had achieved baseline condition [5].

Differential Diagnosis

1. Thrombotic thrombocytopenic purpura (TTP)

   The initial presentation of the patient along with the marked drop in platelet count following transfusion led the physicians to believe that this could be a presentation of TTP in the setting of a pre-existing hemoglobinopathy, hemoglobin H disease.
2. Disseminated intravascular coagulation (DIC)

   Low hematocrit, hemoglobin, and eventually platelet count coupled with the presenting symptoms lead physicians to believe this was an atypical presentation of DIC.
3. Intermediate thalassemia

   The patient's lack of need for transfusions up until this point may have suggested a milder diagnosis of thalassemia such as thalassemia intermedia, coupled with the chronic hemolysis and the splenomegaly is likely intermediate thalassemia was on the list of differentials for the case above.

What Was Misdiagnosed in This Case and Why?

In the case presented above, a vitamin B12 deficiency was misdiagnosed as TTP in the setting of a pre-existing hemoglobinopathy, hemoglobin H disease. The initial presentation of the patient along with the marked drop in platelet count following transfusion led the physicians to believe that this could be a presentation of TTP. However, reevaluation of the patient's peripheral blood smear at a later time by a specialized hematologist revealed hypersegmented neutrophils, basophilic stippling, anisocytosis and poikilocytosis, reticulocytopenia, and complete absence of schistocytes. This led the physician-led care team to further investigate bone marrow aspiration which revealed erythroid hyperplasia coupled with a few megakaryocytes. At this point, B12 deficiency was suspected and confirmed with B12 serum levels and treated accordingly.

Discussion

TTP is a rare blood illness that develops from abnormal clot formation in narrow blood vessels inducing microangiopathic hemolytic anemia (MAHA) and thrombocytopenia. TTP is also typified by purpura, neurologic deficits, fever, and renal failure. TTP has been labeled as thrombotic microangiopathy (TMA) along with other clinical entities such as hemolytic uremic syndrome (HUS), disseminated intravascular coagulation (DIC) , and antiphospholipid syndrome (APS), but it can also occur in cases of malignant hypertension, systemic lupus erythematosus, preeclampsia, and others [4]. TTP has been linked to infections, autoimmune disorders, and idiopathic ADAMTS13 protein deficiency. A clinical scenario that includes thrombocytopenia, anemia, elevated LDH, and indirect bilirubin with a negative Coombs test should suggest the possibility of TTP. Despite the fact that schistocytes are a common observation in MAHA patients, they may be undetectable at the onset of the illness. There have also been reports of TTP being suspected in the absence of schistocytes and treated effectively with plasmapheresis [6, 7]. Differential diagnosis necessitates classifying probable diagnoses based on severity and likelihood. TTP is potentially fatal, and if clinical suspicion exists, therapeutic procedures, in this case, plasma exchange (PEX) transfusion, should be implemented. Prior to PEX, the rate of mortality was approximately 90%. Furthermore, plasma transfusion and PEX boosted survival rates to 58 and 71%, respectively [8]. Despite research on the utilization of peripheral venous access in PEX [9, 10], the insertion of a central venous catheter (CVC) is highly recommended and frequently employed in practice [11]. Patients must provide written consent and be educated about the procedure and its particular necessity along with potential consequences, which include pneumothorax, bleeding, deep vein thrombosis, central line-related infections, and arrhythmias [11, 12]. CVC implantation can be executed with ultrasound guidance or the "blind" anatomical landmark approach. Meta-analyses have

illustrated that real-time 2D ultrasound-guided CVC installation outperforms the anatomical landmark technique [13].

Megaloblastic anemia is attributed to improper DNA synthesis and relatively normal RNA and cytoplasmic component generation. The latter two circumstances cause a delay in cellular proliferation as well as the production of "trademark" big RBCs, as well as a halt in nuclear maturation. Large erythroblasts (megaloblasts) and hypercellularity are common bone marrow findings [14]. The main morphological characteristic is macrocytosis, which leads to categorization in macrocytic anemias and is associated with higher MCV in laboratory data. Nutritional deficiencies such as vitamin B12 (e.g., pernicious anemia) and folic acid are the most common causes, although other factors such as medications, hypothyroidism, liver disease, alcohol addiction, hemolytic anemia, and myelodysplastic syndromes may also be possible etiologies [15]. The disease is mostly related to disorders of RBCs; in advanced stages, it can affect all cell lines (WBCs, PLTs) and eventually leads to pancytopenia. Hemoglobin H disease is a variant of the thalassemia syndrome spectrum of disease that is most common in the Middle Eastern region, the Mediterranean, and the tribal belt of India. The syndrome is defined by various degrees of globin chain deficiency due to mutations-deletions affecting globin genes [16]. Due to a significant lack of globin chain production, globin chains precipitate and form tetramers (4), known as hemoglobin H (Hb H). Patients are typically asymptomatic and require no blood transfusions. The diagnosis may not be made until the first occurrence of acute hemolytic crises [16, 17]. Jaundice, indirect hyperbilirubinemia, elevated LDH, and a high reticulocyte count are all typical findings. A peripheral blood smear can exhibit target cells, microcytosis, hypochromia, and anisopoikilocytosis. Hepatosplenomegaly is a rather frequent complication.

Plan of Action, the Points Clinician Should Consider, Pitfalls to Avoid, and Pearls of Knowledge to Consider

Patients may report to the ED in an urgent situation, despite the fact that nutritional deficiency is typically considered a clinical entity that requires outpatient therapy and follow-up. Noteworthily, it is important to note the possibility that Hb H illness and other thalassemias may be an underlying/undiagnosed cause of anemia.

Conclusion

Although there have been a few cases of early vitamin B12 deficiency misdiagnosed as TTP in the literature, this clinical presentation is unique because no previous reports of pseudo-TMAs in patients with combined B12 deficiency and hemoglobin H disease have been published and because early resuscitation measures such as

CVC insertion, in this case, resulted in severe complications requiring ICU hospitalization/intubation. This adverse event could have been avoided if the correct diagnosis was achieved prior to intervention and stresses the importance of recognizing and considering thalassemia and other hemoglobinopathies in endemic regions coupled with possible nutritional deficiencies if they apply.

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Chapter 38
Hepatoerythropoietic Porphyria Misdiagnosed as Child Abuse

Mohammed Mohammed

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Define and understand the etiology of hepatoerythropoietic porphyria (HEP).
2. Emphasize the importance of considering HEP in children who present with skin fragility and scarring in sun-exposed areas, even in the absence of acute photosensitivity.
3. Emphasize the importance of recognizing anemia as a feature of HEP.
4. Compare the clinical manifestations of hepatoerythropoietic porphyria (HEP), familial porphyria cutanea tarda (PCT), and congenital erythropoietic porphyria (CEP).
5. Differentiate child abuse from hepatoerythropoietic porphyria and to avoid unnecessary stress to families of children with this condition.

Introduction

Hepatoerythropoietic porphyria (HEP) , a rare autosomal recessive heme biosynthesis disorder, results from severe deficiency of uroporphyrinogen decarboxylase (UROD) due to mutations in the *UROD* gene [1–5]. HEP is the recessive form of familial porphyria cutanea tarda (PCT), an autosomal dominant condition in which heterozygous *UROD* mutations predispose carriers to clinical manifestations [1, 2]. Since the initial description of HEP in 1969 [6], there have been approximately

M. Mohammed (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: mohammed.mohammed@martinus.edu

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40 reported cases [2, 7–34]. Clinical manifestations usually develop during infancy or early childhood and include extreme photosensitivity, skin fragility (bullae, erosions, and scarring) in sun-exposed areas, erythrodontia, hypertrichosis, and pink to red urine. Sclerodermoid skin changes often manifest over time. Compared to PCT, the cutaneous features of HEP typically have earlier onset, increased severity leading to disfigurement, and closer resemblance to those in congenital erythropoietic porphyria (CEP; Günther disease) [4, 5]. However, extracutaneous findings including hemolytic anemia are more frequent and severe in CEP than HEP [4, 5, 30]. In this case a 7-year-old girl had a 2-month history of erosions, blistering, and scarring on the dorsal aspect of the hands and forearms and shedding of her fingernails. These lesions manifested after intense sun exposure during summer. However, the presence of some of these lesions, namely, the multiple linear, round, and geometric scars, in all three affected siblings had led to the misdiagnosis of child abuse.

Clinical Case Presentation

The patient, a 7-year-old girl who was the third child of a Puerto Rican mother and a Dominican father, had a 2-month history of erosions, blistering, and scarring on the dorsal aspect of the hands and forearms and shedding of her fingernails. These manifestations developed after intense sun exposure during summer. She didn't receive medications and had not previously developed photosensitivity, although facial scarring had appeared after minor trauma. The patient had a history of severe neonatal thrombocytopenia for which she received a platelet transfusion. She also had chronic hemolytic anemia and chronic reddish-brown urine. Her growth was normal, but she was developmentally delayed, including a receptive and expressive speech disorder and poor coordination resulting in an abnormal gait; she had been evaluated by a neurologist and received speech, physical, and occupational therapy since infancy. Physical examination results revealed linear-to-polygonal scars and mottled hyperpigmentation on the face, dorsal aspect of the hands, and extensor forearms. She had mild facial hypertrichosis, brownish teeth, and no evidence of hepatosplenomegaly. Two of the patient's four siblings had similar cutaneous and extracutaneous findings, including chronic anemia and developmental delay. Affected siblings were older (a brother aged 11 years and a sister aged 10 years), and neither had exhibited photosensitivity. However, the presence of multiple linear, round, and geometric scars in all three affected siblings had led to a year-long child abuse investigation by state authorities, which was initiated by school nurses, teachers, and emergency department physicians. The unaffected siblings (a 5-year-old brother and a 3-year-old sister) had no history of photosensitivity, other skin findings, anemia, or developmental delay. Except for photosensitivity, these features had manifested in the affected siblings during the first years of life. The parents were nonconsanguineous and unaffected, although the mother had a history of sunburn. Biochemical studies in the affected siblings confirmed the diagnosis of

HEP. These included markedly elevated urine porphyrin levels, a plasma porphyrin fluorescence peak at 620 nm, increased erythrocyte zinc protoporphyrin levels, and decreased erythrocyte UROD activities. Sequencing of the UROD gene in the affected siblings revealed compound heterozygosity for two UROD mutant alleles. Analysis of the hemochromatosis (HFE) gene showed heterozygosity for the H63D mutation (a histidine-to-aspartic acid substitution at amino acid position 63) in the proband and her affected sister, both of whom had elevated serum ferritin levels and relatively pronounced skin fragility. Levels of folate and vitamin B12 and liver chemistry results were normal, and results of viral hepatitis screens were negative in all family members. Magnetic resonance imaging studies of the brain in the affected children were normal. A year after diagnosis, the proband and her older affected sister simultaneously developed pain, swelling, and limited range of motion in the interphalangeal and metacarpophalangeal joints and wrists of both hands; magnetic resonance imaging confirmed the presence of synovitis. Mild cutaneous sclerosis and tapering of the fingertips were noted. Results of a study for rheumatoid factor were negative in both girls, and the older sister had antinuclear antibodies (titer, 1:320) with a speckled pattern.

Differential Diagnosis

1. Child abuse
2. Familial porphyria cutanea tarda
3. Congenital erythropoietic porphyria

What Was Misdiagnosed in This Case and Why/How Was It Realized That It Was Misdiagnosed?

The conditions of the patient and her two siblings were misdiagnosed as child abuse because of the cutaneous lesions. Round erosions and scars suggested cigarette burns, while linear lesions suggested forceful use of other instruments. So the presence of multiple lesions in different stages of healing led to the suspicion of child abuse and the long-term investigation by the authorities which caused considerable stress to the parents.

Discussion

Most patients with HEP develop photosensitive eruptions during infancy or early childhood. Sun-induced erythema and blistering occurred by 2 years of age in 75% of reported cases [2, 6–9, 11–16, 19–24, 26–34]. Spontaneous improvement of

acute photosensitivity during later childhood, but persistent skin fragility, has been described [8, 11, 29, 33]. Other patients have presented in the second or third decade of life with mild skin fragility or photodistributed annular plaques [26, 28, 30, 33]. Photo-mutilation can result in considerable morbidity in patients with HEP via the impaired function of the hands and facial disfigurement, making photoprotection essential [4, 5]. Although helpful in PCT, phlebotomy and antimalarials are generally ineffective in HEP [5, 35].

The primary cutaneous manifestations in this patient were scarring, fragility, and hyperpigmentation during childhood rather than acute photosensitivity. Round erosions and scars resembled cigarette burns, whereas linear and geometric lesions suggested forceful use of other instruments. The presence of multiple wounds in different stages of healing, the lack of an explanation for the injuries, and their occurrence in several siblings were additional features suggestive of child abuse [36]. These skin findings had initially led to a long investigation by child protective services that resulted in considerable distress to the family.

More than 40 UROD mutations have been described, some occurring in both HEP and familial PCT [32, 34]. To date, 15 missense mutations, 2 deletions, and 1 nonsense mutation have been reported in HEP [3, 5, 17, 18, 21, 25, 26, 29, 30, 32–34]. Homozygosity for the F46L missense mutation causes relatively mild HEP [29, 30], as may be true of the novel V166A mutation in our family. In contrast, mutations that abolish UROD activity, like the 645del1053ins10 lesion in our family, are only compatible with life when the individual's other UROD allele encodes residual enzymatic activity [5]. The 645del1053ins10 was previously described in an Argentinean kindred with PCT [37]. The three siblings of our patient had the same UROD mutations, but the severity of their clinical manifestations varied, underscoring the role of environmental and genetic modifiers. Our proband and her most severely affected sibling were heterozygous for the HFE H63D mutation and had increased serum ferritin levels, which may have contributed to their clinical presentations. Severe cutaneous findings, an HFE H63D mutation, and elevated ferritin levels were recently described in a 2-year-old boy with HEP [32]. Sclerodactyly, osteolysis, and shortening of the phalanges and progressive joint deformities can occur as components of acral photo-mutilation in patients with HEP, CEP, and homozygous variegate porphyria [4, 5, 10, 13, 19, 35, 38]. To our knowledge, arthritis has not been previously reported in patients with HEP. Whether our two sisters' painful polyarticular arthritis represents a typical (but heretofore unrecognized) inflammatory precedent of joint deformity in HEP or an idiosyncratic inflammatory process, perhaps triggered by porphyrin deposition together with exposure to UV light or another environmental insult, remains to be determined.

Anemia was present in more than 50% of patients with HEP for whom hematologic status was reported (15 of 27) [2, 6–16, 19–22, 26, 28, 30, 32, 33], but severe anemia requiring transfusions or administration of epoetin alfa has been observed in only a few individuals [28]. The affected children in our family all had chronic

anemia and were followed by a hematologist for years before the diagnosis of HEP, emphasizing the importance of recognizing anemia as a feature of HEP. Thrombocytopenia, often due to secondary hypersplenism, has been described in patients with CEP (including neonates) but not in those with HEP [39–41]. In contrast to the autosomal recessive form of variegate porphyria, which is characterized by developmental delay and seizures [38], neurological abnormalities are not typically associated with HEP or CEP [4, 5, 39]. Nevertheless, developmental delay and seizures have been previously reported in HEP [22, 27]. A 4-year-old boy had delayed speech and language skills and subsequently had focal seizures and acute left hemiparesis [22]. Two young adults with severe HEP, aged 21 and 23 years, developed generalized seizures and had neuroimaging evidence of cerebral cortical atrophy and punctate calcifications in the frontal lobes, presumably related to hypoxic injury as in other porphyrias [27]. These observations, together with our affected siblings' developmental delay, support the neurological assessment of HEP patients to better define this possible manifestation. In summary, this report expands the clinical features of HEP to potentially include arthritis, neonatal thrombocytopenia, and developmental delay. The mutations identified in our kindred add to the UROD alleles that can cause HEP. We emphasize the importance of considering HEP in children who have skin fragility and scarring in sun-exposed sites, even in the absence of acute photosensitivity. Increased awareness of the clinical manifestations of HEP will allow recognition of more affected individuals, delineation of the phenotypic spectrum, and evaluation of future therapies [42].

Pearls of Knowledge to Consider. If Misdiagnosed, Was It Realized Later? How Was It Rectified?

Hepatoerythropoietic porphyria (HEP), a rare autosomal recessive heme biosynthesis disorder, results from severe deficiency of uroporphyrinogen decarboxylase (UROD) due to mutations in the *UROD* gene. Typically it manifests during infancy or early childhood with extreme photosensitivity, skin fragility in sun-exposed areas, hypertrichosis, erythrodontia, and pink urine. But in this case we can see that HEP can present without obvious photosensitivity; therefore the findings of multiple erosions and scars can lead to the misdiagnosis as child abuse.

Conclusion

This case expands the phenotypic and genotypic spectrum of HEP, highlighting mild cutaneous presentations that can occur without obvious photosensitivity; therefore it could be mistaken as child abuse.

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Chapter 39
Hereditary Spherocytosis Misdiagnosed as Glucose-6-Phosphate Dehydrogenase Deficiency

Adedamola Bello

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Create an appropriate differential diagnosis in patients presenting with signs and symptoms of hereditary spherocytosis.
2. Evaluate the different components of the medical history and physical examination, which indicate the most appropriate order within the differential diagnosis and hence a correct course of further diagnostic procedures needed to reach a definitive diagnosis.
3. Discuss the impact of the delayed diagnosis on prognosis, sequelae, and quality of life for patients.
4. Analyze and implement the importance of a holistic approach to patient care with an emphasis on obtaining a complete history and clinical picture and its influence on arriving at an appropriate diagnosis.
5. Discuss and enumerate the diagnostic approach to anemia and jaundice and the appropriate investigations to elucidate the etiology of the illness.

Introduction

Hereditary spherocytosis (HS) is hemolytic anemia that is caused by a gene mutation-induced aberration. Either a deficiency or dysfunction of one or more of band 3, protein 4.2, ankyrin, and α- and β-spectrin protein defects caused erythrocytes to change from standard biconcave disc shape into a spherical shape, and the

A. Bello (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: adedamola.bello1@martinus.edu

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number of peripheral blood spherocytes increased [1, 2]. Spherocytes are susceptible to damage in the spleen with a manifestation of anemia, jaundice, and splenomegaly. Osmotic resistance, hypertonic cryohemolysis test, eosin-5-maleimide (EMA) binding in flow cytometry, sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and ektacytometry are used in the diagnosis of HS. However, all tests have specific limitations [3]. Without appropriate laboratory evidence, HS might be easily misdiagnosed as glucose-6-phosphate dehydrogenase deficiency (G6PD) , pyruvate kinase deficiency [4], autoimmune hemolytic anemia (AIHA) , thalassemia, or diseases of the hepatobiliary system. For this reason, therefore when presented with the constellation of symptoms above, it is pertinent to investigate the possibility of a diagnosis of hereditary spherocytosis. This case also illustrates the pitfall of anchoring biases and how they affect physicians' abilities to make accurate diagnoses. Provided the clinical picture and negative testing results, further investigation into other possible etiologies needs to be considered in all cases till a definitive diagnosis is made.

Clinical Case Presentation

The first case was that of a 7-month-old boy who had been diagnosed with anemia and presented with jaundice early on in life. At the age of 5 months, he was transported to a local hospital exhibiting pallor and jaundice. Hemoglobin of 82.00 g/l, reticulocyte ratio of 16%, total bilirubin of 56.60 mol/l, negative direct antiglobulin test, regular G6PD activity, and no anomalies in hemoglobin peptide chain analysis were found in laboratory studies performed [5]. The local hospital did not conduct specific tests for HS at this time [5]. The local physician diagnosed this patient with autoimmune hemolytic anemia since the direct antiglobulin test is negative in certain individuals with warm-antibody-type autoimmune hemolytic anemia [5]. Prednisolone was therefore administered as a treatment for 2 months, but his condition failed to improve. In December 2013, he was referred to Guangxi Medical University's First Affiliated Hospital in China [5]. The patient was anemic and had scleral and skin jaundice, and his spleen was markedly enlarged, palpable 4 cm below the left costal edge upon physical examination at this institution [5]. Laboratory examination reported a red cell count of 2.90×10^{12}/l, the hemoglobin (Hb) was 81.40 g/l, the mean corpuscular volume (MCV) was 82.88 fl, the red blood cell volume distribution width was 24%, the mean corpuscular hemoglobin was 28.09 pg, the mean corpuscular hemoglobin concentration (MCHC) was 339.00 g/l, the reticulocyte ratio was 19%, and the mean sphered corpuscular volume (MSCV) was 71.66 fl [5]. Total bilirubin of 57.60 mol/l, direct bilirubin 19.10 mol/l, indirect bilirubin 38.50 mol/l, and alanine aminotransferase (ALT) 35 U/l were the findings of liver function testing [5]. Hemoglobin peptide chain analysis revealed no abnormalities. G6PD activity was within normal limits. IgG antiglobulin tests were negative both directly and indirectly. The bone marrow morphology revealed substantial,

active hyperplasia with no aberrant cells, indicating hypoplastic anemia. The size of the peripheral red blood cells varied, and mature and spherocytes were identified. As a result, a diagnosis of HS was obtained [5]. The second case study was the father of Case 1 discussed above. He was 29 years old at this time. Patient 2 was 18 years old at the point where he went to a local hospital for cutaneous and scleral jaundice. Hb was reported to be 133.30 g/l, total bilirubin 60.50 mol/l, and ALT 40 U/l, and hepatitis B surface antigen and antibody, hepatitis B e antibody, hepatitis C antigen and antibody, anti-hepatitis A virus, and anti-hepatitis C virus tests were all negative at the time. He was reported to have autoimmune hepatitis as a final diagnosis at this time [5]. Consequently, his jaundice failed to resolve with symptomatic therapy. In this hospital on physical examination, he was observed to have scleral and cutaneous jaundice, but no enlargement of the liver or spleen [5]. Further investigations were performed, and laboratory testing revealed that the red cell count was 3.84 x 10^12/l, Hb was 133.10 g/l, MCV was 96.75 fl, red blood cell volume distribution width was 18%, mean corpuscular hemoglobin was 34.69 pg, MCHC was 358.60 g/l, reticulocyte ratio was 17%, and MSCV was 77.78 fl. Total bilirubin of 62.5 mol/l, direct bilirubin 19.30 mol/l, indirect bilirubin 43.20 mol/l, and ALT 48 U/l were the findings of the liver function tests [5]. The hemoglobin peptide chain analysis revealed no abnormalities. G6PD activity was normal. IgG antiglobulin tests, both direct and indirect, were negative [5]. The smear of peripheral blood demonstrated an increased number of spherocytes [5]. Considering the pathognomonic finding, he was accurately diagnosed with HS [5].

Differential Diagnosis

1. Glucose-6-phosphate dehydrogenase deficiency (G6PD)
   The patient initially presented with anemia, jaundice, and splenomegaly. This constellation of symptoms is seen in G6PD which is the most common enzyme deficiency worldwide. The presence of neonatal jaundice along with other symptoms may have prompted G6PD to be listed on the differential; however it was quickly ruled out due to testing that showed normal enzyme activity.
2. Pyruvate kinase deficiency
   The initial presenting symptoms including neonatal jaundice, splenomegaly, hyperbilirubinemia, and normocytic anemia may also suggest pyruvate kinase deficiency which is commonly diagnosed in children. Enzyme studies would be needed to determine specific etiology.
3. Autoimmune hemolytic anemia (AIHA)
   The absence of an antiglobulin on a direct antiglobulin test does not exclude AIHA as the direct antiglobulin test is negative in certain individuals with warm-antibody-type autoimmune hemolytic anemia. This contributed to anchoring bias in the physician; therefore this was the working diagnosis in the patient until further studies were performed.

4. Thalassemia

   In a newborn or child, thalassemia is to be considered when confronted with the constellation of symptoms presented above, elucidating the pertinent history of similar problems in the family along with testing through hemoglobin electrophoresis which would help determine the diagnosis. In this case, there were other findings such as spherocytes to suggest another reasonable diagnosis.

5. Diseases of the hepatobiliary system

   Diseases of the hepatobiliary system may also cause neonatal jaundice and splenomegaly and can be suggestive of a plethora of diseases that may or may not cause anemia. These can easily be misdiagnosed in a child depending on age and circumstance of presentation. Elevated liver enzymes may also contribute to informing this classification of etiology such as seen in the second case.

What Was Misdiagnosed in This Case and Why/How Was It Realized That It Was Misdiagnosed?

Hereditary spherocytosis was misdiagnosed as autoimmune hemolytic anemia in this case due to nonspecific presenting symptoms and prevalent anchoring biases.

The 7-month-old boy had been diagnosed with anemia and presented with jaundice early on in life. At the age of 5 months, he was transported to a local hospital exhibiting pallor and jaundice. Although the patient had a negative direct antiglobulin test and regular G6PD activity and no anomalies in hemoglobin peptide chain analysis were found in laboratory studies, the local hospital did not conduct specific tests for HS at this time. The local physician diagnosed this patient with autoimmune hemolytic anemia based on the fact that the direct antiglobulin test is negative in certain individuals with warm-antibody-type autoimmune hemolytic anemia. After initiating the treatment regimen for AIHA with no resolution of symptoms, further testing including a peripheral blood smear was performed revealing pathognomonic findings for hereditary spherocytosis.

Discussion

Typical clinical manifestations of HS include anemia, jaundice, and splenomegaly. Complications of HS include pigment gallstones; aplastic, hemolytic, and megaloblastic crisis; poor growth; skeletal deformities; and, less commonly, skin ulceration and chronic dermatitis. The only curative therapy is splenectomy. Children or young adults who present with mild hereditary spherocytosis and also have gallstones are likely to benefit from combined splenectomy and cholecystectomy in terms of life expectancy [6]. A timely and correct diagnosis of HS directly affects the patient's

options for treatment and prognosis. The diagnosis of HS is usually based on a combination of clinical and family histories, physical examination (for splenomegaly or jaundice), and laboratory data. The variability of clinical manifestation is a primary factor in HS misdiagnosis. In individuals with HS, virus B19 infection can cause aplastic crises, with fever and abdominal discomfort as the presenting signs [7]. Liver dysfunction and skin outbreaks however are infrequent [7]. Patients with moderate HS may not develop anemia and thus be undiagnosed for an extended period of time. Sheikh et al. described a female patient who had scleral jaundice at the age of 14 but was only confirmed with an HS diagnosis when she reported to the hospital with 2 weeks of fatigue at the age of 35. She had no family history suggestive of the disease [8]. Considering the fact that G6PD, thalassemia, and AIHA all present with anemia, jaundice, and splenomegaly, HS must be differentiated from these pathologies. In the case that a patient is suspected of having hemolytic anemia, red cell indices, a peripheral blood smear, Hb electrophoresis, and DNA analysis, as well as the detection of G6PD enzyme activity and a direct antiglobulin test, should be ordered to distinguish G6PD, thalassemia, and AIHA from HS. Hb electrophoresis and DNA analysis have historically been used to diagnose thalassemia [9]. G6PD enzyme activity is normally evaluated by quantitative spectrophotometric measurement of the rate of NADPH generation to confirm the diagnosis of G6PD. AIHA is a simple diagnosis based on a patient who has a positive direct antiglobulin test. After excluding thalassemia, G6PD, and AIHA, red cell indices, peripheral blood smear examination, and other evidence suggesting a hemolytic process and/or a membrane defect should be conducted to diagnose HS [9]. Once the patient discussed in Case 1 initially appeared with anemia, jaundice, and raised reticulocytes, the local hospital conducted various tests to rule out other conditions. A direct antiglobulin test was negative, G6PD activity was predicted within normal limits, and hemoglobin peptide chain analysis revealed no abnormalities. Unfortunately, due to the assumption that patients with warm-antibody-type autoimmune hemolytic anemia had negative direct antiglobulin testing, the local hospital did not initiate a further investigation with HS-related studies. As a result, Case 1 was diagnosed with autoimmune hemolytic anemia and was treated for 2 months with a corticosteroid regimen. His hemoglobin, however, did not correct and this therapy was ineffective. Warm-antibody-type autoimmune hemolytic anemia responds to corticosteroid treatment, which would have resulted in a rise in hemoglobin in 1–2 months if an accurate diagnosis was made [10, 11]. As a result, Case 1 was misdiagnosed by the local hospital. When a patient is suspected of having AIHA but has a negative direct antiglobulin test, an immunoradiometric assay or analysis of the RBC eluate may be instrumental in finding an autoantibody directed toward one or more RBC antigens before contemplating corticosteroid therapy [9]. The predominant sign of HS in Case 2 was jaundice; the patient did not manifest any symptoms of anemia or splenomegaly. Hemolytic anemia in this patient class is frequently overlooked: they are readily misdiagnosed as having autoimmune hepatitis or cholelithiasis (the main complication of HS is cholelithiasis). Total, direct, and indirect bilirubin levels can be used to classify jaundice. In addition, patients

with hepatobiliary diseases frequently present with elevated total bilirubin levels, which are primarily due to an increase in direct bilirubin. An investigation into family history is an important factor in diagnosing HS. Mild HS, for instance, may not manifest as hemolytic anemia and can be detected only after a proband has been discovered with HS. Kataoka et al. cite an example where a 38-year-old male patient with HS was swiftly diagnosed as a result of his daughter [12] being diagnosed. The patient was only noted to have splenomegaly at the point of diagnosis. Case 2 was diagnosed in a similar manner. Nonetheless, not all HS subjects have a family history. Stefan et al. studied 107 instances with HS and concluded that autosomal dominant inheritance accounted for 54%, autosomal recessive inheritance for 36%, and spontaneous mutations for 5% and the causes were unknown in roughly 5%. Another study revealed autosomal recessive inheritance in 24/26 instances of moderate HS, whereas the reasons remain unknown in the remaining 2 cases [13]. Subjects with autosomal recessive inheritance and spontaneous mutations have no family history, making them vulnerable to long-term misdiagnosis. Bolton-Maggs et al. advocate the use of an eosin-5-maleimide (EMA) binding test, cryohemolysis test, and SDS-PAGE to reach a definitive diagnosis when a patient has laboratory findings that are highly indicative of HS with the absence of a family history of the disorder and unusual clinical signs [1]. Bianchi et al. reported that the EMA binding test for band 3-defect-HS had a sensitivity of 93% for HS, a sensitivity of 100% for combined spectrin/ankyrin defects, and a sensitivity of 88% for membrane protein defects [14]. When the percentage of surviving erythrocytes in a cryohemolysis test was 23.59%, Warang et al. found that the sensitivity and specificity for diagnosing HS were both 100% [15]. The EMA binding test, cryohemolysis test, and SDS-PAGE are all difficult to execute in a typical lab. Therefore another proposed method of diagnosing HS utilizes variables linked to reticulocytes. These variables can be employed to differentiate the type of anemia and offer strong evidence of HS. The sensitivity and specificity for diagnosing HS are 93.3 and 83.6%, respectively, when the reticulocyte count is >103.5 10^9/l. The sensitivity and specificity for diagnosing HS are 96.7 and 89.6%, respectively, when the ratio of reticulocyte count (10^9/l) to immature reticulocyte index is >7.7 [3]. MSCV is a reticulocyte-specific metric. The combination of MSCV and MCV is particularly efficient in diagnosing HS. According to Chiron et al., the sensitivity and specificity for diagnosing HS when MSCV < MCV are 100 and 93.3%, respectively [16]. Broséus et al. found that when MCV-MSCV >9.6 fl is used to diagnose HS, the sensitivity and specificity are 100 and 90.57%, respectively [17]. In previous studies, MCV and MSCV in 57 cases of HS and 109 cases of thalassemia and discovered MSCV < MCV in 56 cases of HS, MSCV > MCV in 1 case of HS combined with thalassemia, and MSCV > MCV in thalassemia patients, implying that when MSCV is <MCV, the sensitivity and specificity for diagnosing HS are 98.25 and 99.10 [18]. These metrics can therefore be utilized in ruling in a diagnosis of HS where family history is unknown or absent and can further decrease the rates of misdiagnosis of HS.

Conclusion

Mild and moderate HS can be easily misdiagnosed. HS has clinical manifestations similar to AIHA, G6PD, thalassemia, and autoimmune hepatitis. Measurement of the total, direct, and indirect bilirubin, as well as assessment of erythrocyte morphology and relevant cell variables (especially MCV and MSCV), can accurately distinguish HS from these diseases.

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Chapter 40
Inherited Thrombocytopenia Misdiagnosed as Myelodysplastic Syndrome

Mohammed Mohammed

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Describe thrombocytopenia 2.
2. Differentiate between acquired thrombocytopenia and inherited thrombocytopenia.
3. Consider the diagnosis of thrombocytopenia 2 in patients with isolated thrombocytopenia and dysmegakaryopoiesis.
4. Evaluate patients with thrombocytopenia before treating them with unnecessary chemotherapy and steroids.
5. Plan proper treatment for patients with thrombocytopenia 2.

Introduction

Thrombocytopenia 2 is an autosomal dominant disorder caused by point substitutions in the 5′UTR region of the *ANKRD26* gene [1]. Patients have congenital thrombocytopenia; normal platelet morphology and function with mild or no bleeding tendency; and dysmegakaryopoiesis [2]. Patients with THC2 have an increased risk of myeloid neoplasms, which occur in approximately 8% of patients [3]. Dysmegakaryopoiesis is a constant finding as it is present in all patients with THC2 independent of the development of myeloid neoplasms [2, 4, 5].

M. Mohammed (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: mohammed.mohammed@martinus.edu

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It's difficult and challenging to recognize patients affected with THC2. Since thrombocytopenia is usually asymptomatic, the low platelet count is frequently discovered only in adulthood. For this reason, physicians often do not suspect the genetic origin of thrombocytopenia in patients with THC2. It has been previously reported that this disorder may be misdiagnosed as immune thrombocytopenia (ITP) and treated unnecessarily with immunosuppression or splenectomy [2, 4]. Here, we describe two unrelated cases of THC2 who were misdiagnosed with MDS and treated with several courses of 5-azacytidine.

Clinical Case Presentation

Case 1

A 61-year-old man was referred in March 2016 for investigation of MDS presenting with isolated thrombocytopenia. He had unremarkable medical history until the age of 56 (March 2011) when thrombocytopenia came to attention upon blood examination performed for superficial phlebitis of the left leg. His platelet count was $25 \times 10^9\ L^{-1}$ at that time, whereas his white blood cell (WBC) count and hemoglobin levels were normal.

At another medical center, the patient was diagnosed with ITP and treated with prednisone and afterward with prednisone plus danazol for approximately 1 year, without any improvement of his platelet count. In June 2013, the patient underwent hematologic re-evaluation, and his platelet count was even lower at 20×10^9/L, his hemoglobin was normal, and his WBC count was at the upper limit of normal. On account of the poor response to treatment, bone marrow aspirate and biopsy were performed and showed an increased number of megakaryocytes with prominent dysmegakaryopoiesis (plenty of small, underdeveloped, hypolobulated megakaryocytes with typical micro-megakaryocytes) with no other relevant changes. Cytomorphological analysis of bone marrow aspirate showed that blast cells were 4%, and immunohistochemistry on bone marrow biopsy identified 2% CD34+ blast cells. Bone marrow cytogenetics was unremarkable. Based on these findings, a diagnosis of MDS, type refractory cytopenia with unilineage dysplasia (refractory thrombocytopenia), according to the WHO 2008 classification of myeloid neoplasms [6], was made. Consequently, the patient was treated with 12 courses of 5-azacytidine without any improvement. In December 2015, a follow-up bone marrow examination showed no changes with respect to baseline.

In 2016, the patient's platelet count was $20 \times 10^9\ L^{-1}$ with no other abnormalities of blood cell counts. He reported no symptoms and his physical examination was unremarkable. Analysis of peripheral blood smears revealed no cytomorphological abnormalities, except for a moderate reduction of platelet azurophilic granules.

Bone marrow examination confirmed dysmegakaryopoiesis without other significant abnormalities. The family history revealed that both the patient's brother and father had chronic thrombocytopenia that had never come to medical attention because it was asymptomatic. Therefore, a diagnostic workup for inherited thrombocytopenia (IT) was started [7]. Considering the picture of autosomal dominant, non-syndromic thrombocytopenia with normal platelet size, the disorders caused by mutations in *ANKRD26*, *ETV6*, *RUNX1*, or *CYCS* are considered[7]. A screening for *ANKRD26* was done first because of the highest incidence of THC2 among these conditions. Mutational analysis identified heterozygous substitution in the 5′UTR of *ANKRD26* [1], which segregated within the family, leading to the diagnosis of THC2 in the three affected individuals. All of them have stable isolated and asymptomatic thrombocytopenia and no peripheral cytomorphological abnormalities after a 15-month follow-up.

Case 2

A 65-year-old man was admitted for acute pneumonia and hemoptysis in November 2016. Blood cell count revealed low platelet count at $14 \times 10^9\ L^{-1}$, mild leukocytosis (WBCs $13.3 \times 10^9\ L^{-1}$) with neutrophilia, and normal hemoglobin level. Blood smears showed normal platelet size, mildly reduced content in platelet granules, and normal morphology of erythrocytes and leukocytes. Past medical history was significant for lung emphysema, and thrombocytopenia was discovered when he was in his 50s. In 2010 and at another institution, a hematologic workup including bone marrow aspirate and biopsy showed an increased number of megakaryocytes and dysmegakaryopoiesis (small, hypolobulated megakaryocytes and micro-megakaryocytes) without other relevant changes. Blast cells were 3%. On this basis, a diagnosis of MDS was made and therefore chemotherapy treatment was started. After eight courses of azacytidine, re-evaluation showed no hematological response, and chemotherapy was discontinued. The patient didn't develop any bleeding symptoms before or after chemotherapy treatment. In 2014, a follow-up bone marrow aspirate and biopsy were performed and demonstrated the same changes. Upon admission for pneumonia in 2016, the patient was first considered as having ITP and hence treated with intravenous immunoglobulins and prednisolone, in addition to antibiotic and antifungal treatment, without any increase in platelet count. But shortly after that, family history revealed that three of his six children and two of his six siblings had thrombocytopenia. Consequently, a diagnostic workup for inherited thrombocytopenia (IT) was started. The non-syndromic thrombocytopenia with normal platelet size and the dominant inheritance strongly suggested mutation of the *ANKRD26 gene*. Screening for the 5′UTR of *ANKRD26* identified a heterozygous substitution. This variant is segregated with thrombocytopenia

within the patient's family. After the pneumonia is resolved, the patient is asymptomatic with platelet count at 30–40 $\times 10^9$/L with no other blood count or cytomorphological abnormalities.

Differential Diagnosis

1. Myelodysplastic syndrome
2. Immune thrombocytopenic purpura

What Was Misdiagnosed in This Case and Why?

Myelodysplastic Syndrome

In both cases, patients developed thrombocytopenia and a prominent picture of dysmegakaryopoiesis (small, hypolobulated megakaryocytes and micro-megakaryocytes) upon bone marrow examination without further alterations. Consequently, a diagnosis of MDS was made and the patients received needless chemotherapy treatment.

Discussion

Although thrombocytopenia 2 is rare, it's one of the most prevalent forms of IT: in a series of 274 consecutive pedigrees with familial thrombocytopenia, THC2 accounts for 17% of the cases with a definite molecular diagnosis [8]. This disorder is underdiagnosed like other forms of IT. Low platelet count frequently comes to attention only in adulthood since patients with THC2 have no or mild bleeding tendency in addition to the normal size of platelets [9]. These features often lead to overlooking the genetic origin of the disorder. Therefore, patients with THC2 (including these two cases described here) are often misdiagnosed as having ITP and receive unnecessary immunosuppressive treatments, including splenectomy [1]. Misdiagnosis as ITP is rather frequent also in other forms of inherited thrombocytopenia with mild bleeding tendency [10]. The two cases described here demonstrate that THC2 patients can be misdiagnosed with MDS as well and hence can be subjected to undue myelosuppressive treatments. In both cases, the feature leading to misdiagnosis was the finding of prominent dysmegakaryopoiesis upon bone marrow examination, which is a constant finding in all THC2 patients and appears to be very similar to that present in MDS. Moreover, dysmegakaryopoiesis with similar features has been reported also in other forms of inherited thrombocytopenia, including those caused by mutations in *ETV6*, *RUNX1*, and *FLI1* [11–14]. Therefore, patients with these disorders also are at risk of being misdiagnosed as having MDS.

Plan of Action, the Points Clinician Should Consider, Pitfalls to Avoid, and Pearls of Knowledge to Consider

Inherited thrombocytopenias are rare disorders. However, recent observations revealed that MDS presenting with isolated thrombocytopenia and bone marrow dysplasia limited to the megakaryocyte lineage (refractory thrombocytopenia according to the WHO 2008 classification) is very rare too. For example, a multicenter study of 1145 patients with MDS and unilineage cytopenias found only 1 patient presenting the criteria for refractory thrombocytopenia [15], and Marinier et al. identified 6 cases of refractory thrombocytopenia in a single-center series of 293 consecutive MDS patients [16]. Therefore, when dysmegakaryopoiesis is demonstrated in a patient with isolated thrombocytopenia, MDS should not be considered the most likely diagnosis. In contrast, inherited thrombocytopenia should be regarded as the most likely diagnosis.

If Misdiagnosed, Was It Realized Later? How Was It Rectified? Were There Any Legal Ramifications?

Yes, it was realized later because of two factors:

1. Failure of treatment:

   The first patient was misdiagnosed as having MDS and received 12 courses of 5-azacytidine with no improvement.

   The second patient was misdiagnosed first as having MDS and hence also received chemotherapy treatment (azacytidine) without any improvement. Subsequently, he was diagnosed with ITP and treated with intravenous immunoglobulins and prednisolone, but no hematological response was detected.
2. Family history:

   In both cases, collection of family history revealed that family members had thrombocytopenia. Following that, a diagnostic workup for IT was started and mutation of *ANKRD26 gene* was identified.

Conclusion

The clinical picture of thrombocytopenia 2 in addition to other forms of ITs can be very similar to that of MDS. Whenever a patient presents with isolated thrombocytopenia and bone marrow examination shows only dysmegakaryopoiesis, inherited thrombocytopenia should always be thought of regardless of the patient's age at presentation. Systematic collection of family history is very important and is a cost-effective tool to avoid misdiagnosis with MDS, ITP, or other causes of

thrombocytopenia. The correct diagnosis of patients with inherited thrombocytopenia is crucial to avoid undue treatment with steroids and potentially harmful chemotherapy and also essential for them to receive the proper management and counseling.

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Part VIII
Infectious Diseases

Chapter 41
Hematogenous Disseminated Tuberculosis Misdiagnosed as Metastatic Lung Cancer

Akhil Ansary

Learning Objectives

By the end of this case report and discussion, the clinician will be able to:

1. Create an appropriate differential diagnosis in patients presenting with the symptomatology suspect for hematogenous disseminated tuberculosis by considering all relevant details of the medical history together with the physical examination of the patient.
2. Evaluate the different components of medical history and physical examination needed to reach a definitive diagnosis.
3. Analyze the characteristics of hematogenous disseminated tuberculosis and differentiate it from metastatic lung cancer.
4. Apply the correct initial diagnostic and confirmatory test to prevent misdiagnosis of hematogenous disseminated tuberculosis and also to emphasize the value of biopsy and 18F-FDG-PET in distinguishing TB and cancer.
5. Discuss and analyze the consequences of a misdiagnosis or delay in reaching a correct diagnosis for the individual patient prognosis, tuberculosis transmission, and public health.
6. Recognize a probable hematogenous disseminated tuberculosis the moment the patient presents through a complete medical history and appropriate physical examination, choose the correct tuberculosis diagnostic tools, and interpret the tests correctly, especially in the light of true or false test results.

A. Ansary (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: akhil.ansary@martinus.edu

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Introduction

Tuberculosis (TB) is recognized as a diagnostic chameleon that can mimic cancer. TB can cause pulmonary infiltrates and mediastinal lymphadenopathy in the thorax [1]. Every year, over ten million people get tuberculosis worldwide. According to the World Health Organization (WHO), *Mycobacterium tuberculosis* is present in around a quarter of the world's population [2, 3]. Despite well-documented and widely publicized techniques of prevention and cure, tuberculosis remains a global problem [4, 5]. Lung cancer is the leading cause of death among males worldwide [6]. The challenge of proper tuberculosis and malignancy diagnosis has been exacerbated by a constant increase in admissions to tuberculosis hospitals of malignant diseases associated with or imitating tuberculosis. Both disorders share the same symptoms and characteristics. This complicates the diagnosis. Lung cancer patients who wait longer to be diagnosed and treated have a worse prognosis and survival rate [7].

Clinical Case Presentation

A 73-year-old man was admitted to the hospital after suffering 2 months of chest pain, low-grade fever, asthenia, anorexia, and weight loss. The patient has a medical history of type 2 diabetes, for which he is being treated with gliclazide regularly. The body temperature was 36.7° C, the pulse rate was 96 beats per minute, the blood pressure was 133/83 mmHg, the respiratory rate was 20 breaths per minute, the oxygen saturation was 96%, and the skin and sclera were yellow. The respiratory, cardiovascular, neurological, and abdominal systems were all normal. Anemia (hemoglobin 114 g/L), abnormal liver function (alanine aminotransferase 57 U/L, aspartate aminotransferase 48 U/L, glutamyl transpeptidase 818 U/L, alkaline phosphatase 671 U/L, total bilirubin 44 mol/L), and elevated cancer antigen 19-9 (CA19-9, 165 U/ml) were discovered during the examination. The interferon release assay resulted in a negative result. Lacunar infarction in the bilateral basal ganglia was found on computed tomography (CT) skull scan. On a thorax CT scan, multiple rounds or round-like nodules of varying sizes were found across both lungs, indicating metastatic lung disease. The pancreatic head had a tumor. The pancreatic duct and intrahepatic bile duct showed dilation on abdominal enhanced CT. The testing results strongly suggested lung metastases originating from the pancreatic head or the intestine. However, TB infection could not be completely ruled out. The patient declined a second biopsy and instead elected to try rifampin and isoniazid as an experimental anti-TB treatment. A month later, a chest CT revealed that the lung lesions had not been absorbed. CA19-9 levels in the blood grew dramatically, reaching 1167 U/ml in a lab test. A sputum smear showed negative acid-fast bacilli (AFB). The doctor ruled out tuberculosis and suggested gastrointestinal malignant tumors with lung metastasis. After 3 months, his daughter convinced the patient to have a second opinion. Hyperbilirubinemia (total bilirubin 70 mol/L) and CA19-9

of 832 U/ml, cancer antigen 125 141 U/ml, neuron-specific enolase 22.98 ng/ml, angiotensin-converting enzyme 178 U/L, and serum (1,3)—D-glucan 235 pg/ml were all discovered in the laboratory. The lung, liver, pancreas, spleen, and gallbladder neck showed a high uptake on 18F-fluorodeoxyglucose positron-emission tomography (18F-FDG-PET) scans, indicating benign illness. The patient agreed to undergo endoscopic retrograde cholangiopancreatography to treat hyperbilirubinemia induced by bile duct obstruction. A biopsy of a brushed biliary cell revealed no malignant growth. The lump in the left upper lobe was biopsied using a CT scan-guided transthoracic needle biopsy, and the histology revealed coagulative necrosis with granulomatous inflammation. Periodic acid-Schiff staining was negative, whereas AFB staining was positive. Meanwhile, qPCR for MTB DNA in the sputum revealed 4900 copies per milliliter. As a result, the diagnosis of tuberculosis infection was confirmed. The patient then agreed to a 3-month course of isoniazid (300 mg/QD), rifampicin (450 mg/QD), ethambutol (750 mg/QD), pyrazinamide (1500 mg/QD), and levofloxacin (600 mg/QD), followed by 9 months of isoniazid (300 mg/QD) and rifampicin (450 mg/QD). The thorax CT 4 months following admission to our hospital demonstrated that the lung lesions were significantly absorbed. After a year of treatment, the patient discontinued the medications due to continued clinical and radiological improvement. At the 6-month follow-up after discontinuation, the patient was symptom-free.

Differential Diagnosis

1. Pulmonary tuberculosis

   Mycobacterium tuberculosis is the infectious species that causes pulmonary tuberculosis (TB) . *M. tuberculosis* frequently goes dormant in people before becoming active TB. Although TB most frequently affects the lungs and is contagious in this form, it can also affect nearly any organ system, including the lymph nodes, central nervous system, liver, bones, genitourinary tract, and gastrointestinal tract.
2. Gastrointestinal cancer metastasis to the lung

   The greatest cause of death for both men and women globally is lung cancer. The majority of lung cancer cases are discovered late in the disease. It could be challenging to differentiate between intrapulmonary metastases and pulmonary tuberculosis (especially when the tumor histologies are similar). The common clinical appearance of lung cancer makes it possible to mistake it for tuberculosis.
3. Miliary tuberculosis

   Miliary tuberculosis (TB) is characterized by microscopic tubercles visible on gross pathology that resemble millet seeds in size and shape. Miliary TB results from a large lymphohematogenous spread of *Mycobacterium tuberculosis* bacilli. Miliary TB can present with a wide range of nonspecific clinical symptoms. The diagnosis is frequently delayed by an unusual clinical presentation. Miliary TB is frequently misdiagnosed as widespread metastasizing cancer.

Discussion

Tuberculosis of the lungs is prevalent worldwide, especially in developing countries. Disseminated tuberculosis (TB) is an infection in two or more noncontiguous locations caused by *Mycobacterium tuberculosis* hematogenous dissemination due to primary infection or reactivation of a latent infection. Miliary tuberculosis also refers to TB that is progressing and widespread. Even if the conventional pathologic or radiologic signs are lacking, it implies a hematogenous spread to numerous organs [8, 9]. Tuberculosis is caused by the small aerobic non-motile bacillus *Mycobacterium tuberculosis* infecting the lungs (MTB). When patients with an active MTB infection cough, sneeze, or otherwise transmit their saliva, it spreads. Lung cancer is an etiologically complicated disease in which several genes play a role in the pathogenesis of the disease through various routes. Individuals may develop lung cancer when these genes interact with environmental conditions [7]. Tuberculosis must be distinguished from lung cancer to receive proper and timely treatment [10]. According to reports, delaying the identification and treatment of lung cancer often results in a poor outcome and survival rate [7]. However, because lung cancer and tuberculosis are often confused, an invasive biopsy separates the two diseases. Even radiologists with decades of expertise may misdiagnose tuberculosis and lung cancer utilizing CT imaging data in clinical practice or even miss the diagnosis entirely [11]. Pulmonary nodules are spherical intrapulmonary lesions less than 3 cm [12]. In both lung metastases and HDTB, several tiny pulmonary nodules are common. Because the imaging manifestations are so similar, it's challenging to make a definitive diagnosis [13]. Lung cancer nodules have defined edges and may contain cavities or ground-glass opacity. In hematogenous disseminated tuberculosis, the margins of nodules are not apparent and may show hollow or ground-glass opacity. The CT scan of the patient's lungs revealed several spherical nodules of various sizes with distinct borders and partial fusion. The intrahepatic bile duct and pancreas were dilated, the pancreatic head was enlarged, and the spleen had several low-density foci. CA19-9 is regarded as a pancreatic cancer marker. Pancreatic and biliary ductal cells and stomach, colon, endometrial, and salivary epithelia produce CA19-9 [14]. CA19-9 is only seen in trace amounts in serum. On the other hand, this signal has low specificity [15]. CA19-9 overexpression has been seen in various benign gastrointestinal illnesses and pancreatic tuberculosis [16, 17]. CA19-9 levels were dramatically elevated in our patient, who also played a role in the misdiagnosis of the disease. Disseminated tuberculosis, once almost exclusively diagnosed in children or people with immunosuppression, is increasingly detected in adults with no apparent immunological deficiency [18, 19]. The majority of these patients come from countries where tuberculosis is prevalent. Patients' access to the healthcare system is hampered by several circumstances, including a language barrier and frequent relocation, which can lead to a delay in diagnosis and, as a result, disease progression [19, 20].

Patients with disseminated TB and unusual radiographic findings might undergo various diagnostic tests. Sputum that has been expectorated or induced should be sent for testing to confirm the diagnosis in these patients. The samples must be subjected to smear, PCR, and mycobacterial culture tests and these must be performed on two sputum samples for a definitive diagnosis. At least 5000–10,000 bacilli/mm specimens are required for a positive AFB sputum test, while *M. tuberculosis* culture requires 10–100 microorganisms/mm [21, 22]. Endotracheal secretions and gastric lavage can also be utilized to establish the diagnosis if the patient cannot cough, as is often the case with comatose patients or children [23]. Fiberoptic bronchoscopy can provide alternative respiratory specimens for diagnosis in patients with suspected disseminated TB who have smear-negative or PCR-negative sputum or nonproductive cough or who are unable to expectorate through procedures such as bronchoalveolar lavage, bronchoscopic aspirate (BA), brushings, washings, and transbronchial biopsy (TBB) [24–26]. Specimens should be collected from as many locations as feasible to increase the chances of confirming the diagnosis. Furthermore, the utility of PET-CT in assessing the efficacy of TB treatment, particularly extrapulmonary TB, has long been acknowledged [27]. Unfortunately, due to its exorbitant cost, it is unavailable in China. For this reason, the patient also refused a PET-CT re-examination. Finally, a lung puncture biopsy revealed pulmonary tuberculosis. The "four-drug regimen," consisting of two phases of rifampicin, isoniazid (INH), pyrazinamide, and ethambutol/streptomycin administered daily for the first 2 months, is used to treat disseminated TB. Rifampicin and isoniazid are subsequently given for another 4 months, possibly being prolonged to 7 months [28]. The anti-TB regimen cured our patient completely.

Conclusion

A greater understanding of hematogenous disseminated tuberculosis and its accompanying characteristics could help a clinician's index of suspicion and lead to a more accurate diagnosis. Patients with immunosuppression and in endemic areas present with persistent pyrexia of unexplained origin, weight loss, lassitude, hepatomegaly, splenomegaly, liver function abnormalities, and abnormal hematological signs; hematogenous disseminated tuberculosis should be suspected and targeted for quick diagnosis and treatment [27]. It can be challenging to distinguish lung TB from neoplasm based on clinical and radiographic symptoms. On 18-FDG-PET scans, both disorders show parenchymal infiltrates with high metabolic activity and often have comparable symptoms. Considering tuberculosis as a differential diagnosis for PET-positive lung infiltrates might help prevent unnecessary diagnostic procedures, reducing diagnostic workup problems and expenses [1].

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Chapter 42
Severe Abdominal Sepsis Misdiagnosed as Pelvic Inflammatory Disease

Srushti Shahi

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Describe the pathophysiology of pelvic inflammatory disease.
2. Enumerate the signs and symptoms of pelvic inflammatory disease.
3. Recognize the diagnostic criteria used to diagnose pelvic inflammatory disease.
4. List the CDC-recommended pelvic inflammatory disease treatment regimens.
5. Consider all essential information of the medical history and the physical examination of patients who present with symptomatology suspecting pelvic inflammatory disease to make an appropriate differential diagnosis.
6. Describe ways for enhancing care coordination and outcomes in patients with pelvic inflammatory disease using an interprofessional team.
7. Explain why asymptomatic women should be screened and treated.

Introduction

> Sexually transmitted diseases (STDs) continue to take a heavy toll on our nation's health.
> ~Ronald Valdiserri

Pelvic inflammatory disease is an infection most commonly caused by *Neisseria gonorrhoeae* and *Chlamydia trachomatis.* It is an upper genital tract polymicrobial infection [1]. PID affects the uterus, ovaries, fallopian tubes, and cervix, which are all organs of the female reproductive system [2, 3]. There are 750,000 cases of PID

S. Shahi (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: srushti.shahi@martinus.edu

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each year in the United States, mainly in women 15 to 29 years of age. The sort key recommendation from the AAFP states that screening for lower genital tract chlamydial infection in younger and high-risk populations is recommended to reduce PID incidence [4–6]. Asymptomatic disease should be treated. PID can be fatal if not treated at the appropriate time or left untreated or undiagnosed. Fertility may be impacted by PID. According to studies, one in eight PID patients experienced trouble getting pregnant. Recurring infections made it more difficult for people to become pregnant. A fertilized egg must go from your ovary down your fallopian tube and into your uterus (womb). It can then be fertilized by the sperm. However, PID-related bacteria might leave your fallopian tubes scarred. The egg has a greater difficulty traveling where it needs to go because of the scar tissue [7–9]. In women, sexually transmitted diseases (STDs) that go untreated can lead to pelvic inflammatory disease (PID), a dangerous disorder. One in every eight women with a history of PID has trouble conceiving [4–6, 10, 11]. Its diagnosis is made clinically with a history of present illness and past medical history, most likely presented as lower abdominal pain, cervical motion tenderness, abnormal bleeding, dyspareunia, menorrhagia, metrorrhagia, fever, nausea, and vomiting, and is one of the most common causes of infertility after uterine fibroids and polyps [10, 12]. Salpingitis can be diagnosed more accurately with laparoscopy, as well a more complete bacteriologic diagnosis. However, this diagnostic tool is frequently unavailable, and its usage is difficult to justify when symptoms are minor or ambiguous. Furthermore, laparoscopy will not detect endometritis and may miss minor fallopian tube irritation. Whether or not the woman fits any of the following factors will determine whether or not hospitalization is necessary: [13, 14].

- One cannot exclude surgical emergencies (like appendicitis).
- Obstructive ovarian cyst.
- Pregnancy.
- Severe illness, nausea, or a temperature of more than 38.5 °C (101 °F).
- Incapable of adhering to or sustaining an outpatient oral regimen.
- No clinical benefit from oral antibiotic treatment.

As a result, a PID diagnosis is frequently based on ambiguous clinical findings [7, 14–16]. When compared to laparoscopy, data show that a clinical diagnosis of symptomatic PID has a positive predictive value of 65–90% for salpingitis [8, 9, 14, 17–23]. The positive predictive value of a clinical diagnosis of acute PID is determined by the epidemiologic characteristics of the population, with higher positive predictive values among sexually active young women (especially adolescents), women who visit STD clinics, and those who live in areas where gonorrhea or chlamydia is common [24]. A single historical, physical, or laboratory finding is neither sensitive nor specific for the diagnosis of acute PID, regardless of its positive predictive value. Endometrial biopsy with histopathologic evidence of endometritis; transvaginal sonography or magnetic resonance imaging techniques showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex, or Doppler studies indicating pelvic infection (e.g., tubal hyperemia); and laparoscopic findings consistent with PID are more specific criteria for diagnosing PID [7, 12,

25]. In some circumstances, a diagnostic evaluation that involves some of these more elaborate procedures may be necessary. The clinical response to outpatient treatment is comparable in younger and older women, and there is no evidence to suggest that adolescents have better outcomes from hospitalization for PID treatment [22]; because endometritis is the only symptom of PID in some women, endometrial biopsy is recommended for women having laparoscopy who do not have visual evidence of salpingitis [2]. It may also be confused with symptoms of appendicitis and ectopic pregnancy. Empiric, broad-spectrum coverage of probable infections should be included in PID therapy regimens. In randomized clinical trials with short-term follow-up, multiple parenteral and oral antibiotic regimens were effective in attaining clinical and microbiologic cures. Because early administration of prescribed antimicrobials is required to prevent long-term effects, treatment should begin as soon as the presumptive diagnosis is made [5, 8, 9]. Parenteral and oral regimens appear to be equally effective for women with mild-to-moderate clinical severity of PID. Doxycycline should, whenever possible, be given orally due to the discomfort associated with IV infusion. The bioavailability of metronidazole and doxycycline following oral and intravenous treatment is equivalent. When possible, ladies without a serious sickness or tubo-ovarian abscess should try taking metronidazole orally rather than intravenously because it is well absorbed. It is advised to switch to oral medication with doxycycline 100 mg twice daily and metronidazole 500 mg twice daily to finish the necessary 14 days of antimicrobial therapy after treatment response with parenteral therapy [2, 4–6, 10–12, 15, 26]. Women with mild-to-moderate acute PID may be candidates for IM or oral therapy because the clinical results of these regimens are comparable to those of IV therapy [12, 15, 24]. Within 72 h, women who do not react to IM or oral medication should be reevaluated to confirm the diagnosis and given IV therapy. First-generation cephalosporins carry the greatest risk of penicillin cross-reactivity, although the risk is minimal for most second-generation (like cefoxitin) and all third-generation (like ceftriaxone) cephalosporins. To prevent disease transmission, women should be told to refrain from sexual activity until their treatment is finished, their symptoms have subsided, and their sex partners have been treated (*Chlamydial Infections; Gonococcal Infections*) [3, 17, 26, 27]. All women diagnosed with PID should have *gonorrhea*, *chlamydia*, *HIV*, *and syphilis* tested. The utility of testing for *M. genitalium* in women with PID is uncertain (*Mycoplasma genitalium*) [21, 24, 28]. During therapy, all forms of contraception can be used. Maternal morbidity and premature birth are serious risks for pregnant women suspected of having PID. With the advice of an expert in infectious diseases, these ladies should be admitted to the hospital and given IV antibiotics [19, 22, 29]. Additional advice on taking care of yourself is as follows:

- To avoid transferring bacteria from your vagina into your uterus and fallopian tubes, avoid douching.
- After taking the medication for a few days, visit your doctor again to determine how well it is working.
- As directed, take all of your medications.

- To avoid infections, use dental dams or condoms each time you have sex.
- Wait a week after finishing your medication—and your partner's—before starting up again with your sexual relationship.

Below is a case misdiagnosed as PID due to elevated markers, imaging, and history [20, 29].

Clinical Case Presentation

A 41-year-old Caucasian woman was hospitalized in the hospital's intensive care unit with severe diabetic ketoacidosis. The patient had been sick and vomiting the day before admission and was eventually found unconscious and admitted to the hospital. Wild type 1 diabetes on insulin, diabetic retinopathy, depression, anxiety, and latent *hepatitis C* were all present in the patient's medical history. She had been an intravenous drug user in the past, was on buprenorphine treatment with occasional benzodiazepine and opioid addiction, and smoked cigarettes. Her surgical procedures were laparoscopic bilateral tubal ligation and a large loop excision of the transformation zone (LLETZ) conization for a CIN 2 cervical lesion. Her temperature was 29.4 °C, her respiration rate was 28, her pulse was 75, her blood pressure was 135/87 mmHg, and her Glasgow Coma Scale (GCS) was 10 when she was admitted. Severe metabolic acidosis, acute renal failure, and inflammation were discovered in laboratory tests. Given her highly elevated inflammatory markers and an unknown infection focus, the patient was started on therapy according to hospital diabetic ketoacidosis (DKA) protocol and intravenous meropenem. When the patient's condition had stabilized, she was discharged to the medical ward. She felt feverish a few days later and began complaining of lower abdomen pain, nausea, and vaginal bleeding during her period. Inflammatory markers were found to be increasing. The surgical team examined her and discovered she was constipated, so she was given laxatives. To pinpoint the infection's source, a pelvic scan was scheduled. Figure 42.1 shows the complex fluid within the pouch of Douglas. According to this research, pelvic infection is the most likely cause. The gynecology team evaluated the patient, and oral co-amoxicillin was prescribed.

On this medication, inflammatory indicators that had begun to decline on meropenem began to climb. As a result, the antibiotics were changed to oral ciprofloxacin and metronidazole. The woman complained of nausea, a metronidazole adverse effect throughout her hospital stay. When the patient was afebrile and feeling better, she was sent home with oral antibiotics. The patient returned to our hospital's emergency department 3 weeks later, complaining primarily of right iliac fossa pain, nausea, and anorexia. A hyperechogenic mass was observed in the pouch of Douglas on a transvaginal bedside ultrasound scan (Fig. 42.2) which was interpreted as an adnexal mass given the previous diagnosis of pelvic inflammatory disease (PID). Due to the patient's pain, the scan had to be stopped. An

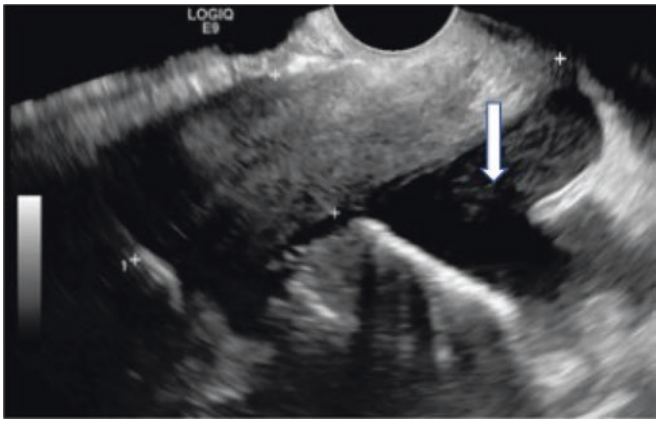

Fig. 42.1 Complex free fluid. Source: www.hindawi.com/journals/cris/2018/9561798/

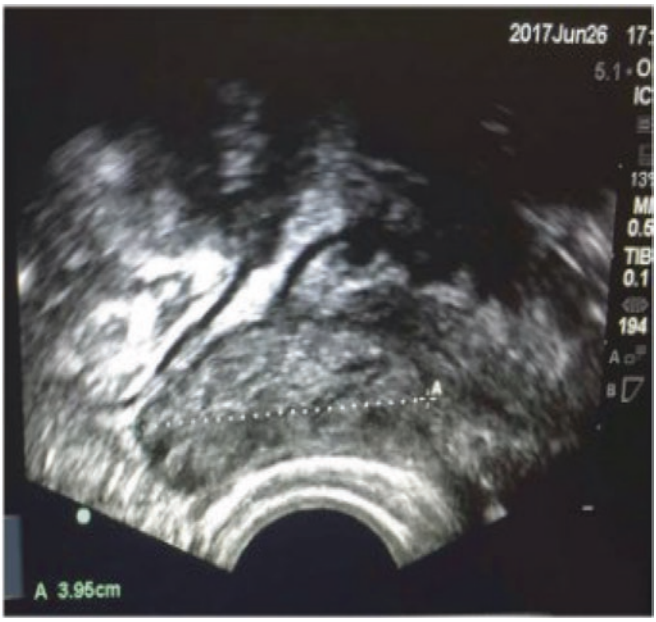

Fig. 42.2 Mass in the pouch of Douglas. Source: www.hindawi.com/journals/cris/2018/9561798/

abdominal (CT) computed tomography scan was scheduled to analyze the tumor further.

The transvaginal images were discussed with radiological colleagues but could not be linked to the CT findings (Fig. 42.3), which described the pelvic appearances as generic. Some pockets of fluid and enlarged loops of the small bowel

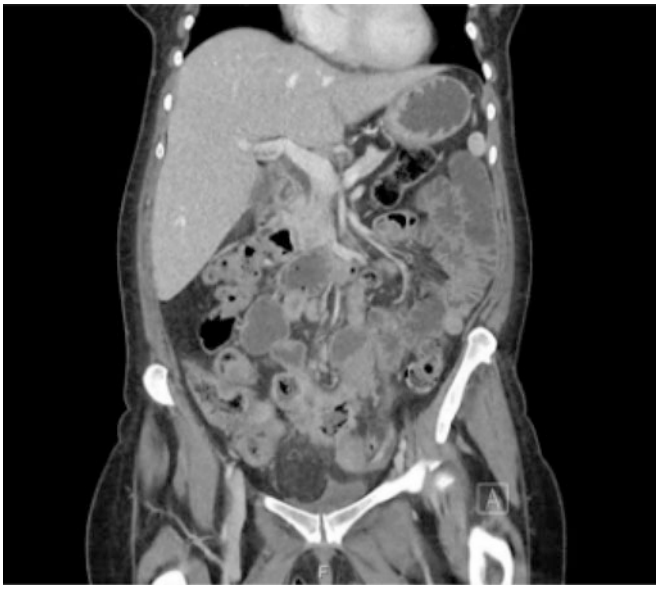

Fig. 42.3 CT scan with nonspecific inflammatory changes. Source: www.hindawi.com/journals/cris/2018/9561798/

indicate that the small bowel was involved in a secondary inflammatory process in the pelvis. The surgical team re-examined the patient, who advised that a surgical etiology for the patient's symptoms was doubtful. The gynecological group planned a diagnostic laparoscopy with the surgical team on standby. The patient began vomiting heavily while awaiting the procedure, necessitating the insertion of a nasogastric tube. Internal genitalia were found to be expected after diagnostic laparoscopy. The operation was changed to a midline laparotomy after the surgical team identified adherent intestinal tissue. In the upper region of the pelvis, there was a complicated, inflammatory mass with an abscess cavity. The ileum was fully gangrenous and necrotic but structurally intact in a 10 to 15 cm length. Surprisingly, there was no small bowel blockage, and the contents of the small bowel appeared to be moving through the gangrenous ileum's lumen. The presence of an expanded node in the ileal mesentery, along with significant fibrosis, raised the possibility of a neuroendocrine tumor (NET) nodal metastasis causing a mesenteric vascular blockage. A double-barrelled stoma was made after the inflammatory mass was excised, and an ileocolic resection was performed. The patient fully recovered following the surgery and was sent home a week later. The histology report revealed the presence of a well-differentiated ileal neuroendocrine primary tumor, which was not visible on laparotomy. One of the 20 mesenteric lymph nodes in the resected material was metastatic. When the CT imaging was reviewed after surgery, neither the primary tumor nor the nodal mass could be distinguished from the inflammatory tissue. A multidisciplinary tumor meeting was held for the patient,

and a staging CT chest-abdomen-pelvis was conducted. Thankfully, there were no signs of local recurrence or metastasis. The patient is doing well now after undergoing stoma reversal surgery.

Differential Diagnosis

Given the medical history of the patient, the most probable differential diagnosis could be:

1. Pelvic inflammatory disease (PID): When young sexually active women experience lower abdomen pain and atypical bleeding, PID should be suspected. The risk factors are multiple sexual partners, unprotected sex, a history of sexually transmitted diseases (STDs), and intrauterine devices. She presented with abdominal pain associated with fever, raised inflammatory markers, intermenstrual bleeding, and free fluid seen in her pouch of Douglas, which made the diagnosis of PID much more likely [4, 5, 16]. In addition to the presentation, the imaging was suggestive but not conclusive for PID. It can be misdiagnosed with appendicitis, ectopic pregnancy, kidney stones, ovarian cyst rupture, ovarian torsion, and pelvic cellulitis [14].
2. Tubo-ovarian abscess: The patient presented with abdominal pain, increased inflammatory markers, and intermenstrual vaginal bleeding; seeing her age and gynecology history with LLETZ conization, rupture of the abscess was considered [12]. Evaluating a female patient in the emergency department frequently results in a diagnostic difficulty, which has been emphasized in the literature numerous times [6]. Tubo-ovarian abscesses are a late complication of pelvic inflammatory disease (PID), and if the abscess ruptures and causes sepsis, they can be fatal. Retrospectively on CT, it was recognized as an abscess part of the inflammatory mass.
3. Ovarian cyst rupture: The patient presented with abdominal pain, intermenstrual bleeding, and tenderness in the pelvic area. Looking at the low socioeconomic status of the patient, it is assumed that she wasn't able to do a regular screening or well-woman exam; hence this can be considered a differential as it is one of the common causes of gynecology emergencies in young females [15]. The patient's history, clinical progress, and inability to respond to the routine antibiotic treatment were unusual for PID. Furthermore, the imaging was suggestive of PID but not conclusive. An early laparoscopy could have been avoided if a more comprehensive differential diagnosis had been considered [12].
4. Acute abdominal infection: Lower abdomen pain can also be caused by infections that are not always transmitted sexually. The most prevalent kinds are pelvic inflammatory disease (PID) and urinary tract infections (UTIs). PID is an upper genital tract infection that is most frequent in sexually active women. In our situation, an ultrasound scan performed during the patient's initial presenta-

tion revealed what was termed as "complex fluid," but no tumors were visible [29]. Despite the previous conversation, the transvaginal ultrasound images could not be connected with the CT scan, which revealed only nonspecific intestinal alterations and thus did not aid in the proper diagnosis, leading to the differential of abdominal infection [16, 24].

5. Acute hepatitis: The patient has a low socioeconomic status and an active *hepatitis C* infection; she has a history of drug abuse and LLETZ conization for cervical intraepithelial neoplasia (CIN 2), making this patient highly prone to sexually transmitted diseases [30]. According to the American College of Obstetricians and Gynecologists (ACOG), transmission from sharing needles is higher than sexual activity [31].

What Was Misdiagnosed in this Case and why?

Severe abdominal sepsis was misdiagnosed as PID. Evaluating a young female patient in the emergency room commonly leads to diagnostic difficulty, which has been highlighted in the literature multiple times [16]. The patient presented with very distinct features of PID, leading to the suspicion of it. Still, the imaging was inconclusive for the same as it showed an adnexal mass, creating another differential of tubo-ovarian abscess. The patient reported right iliac fossa tenderness, persistent nausea, and anorexia, increasing abdominal infection suspicion.

Discussion

PID frequently causes lower abdomen pain in women. Age under 25, age at first sexual intercourse under 15, lower socioeconomic level, being single, a self-reported history of a sexually transmitted disease, and *C. trachomatis* exposure are all risk factors [6].

The woman in our case had been a prior drug user and had a low socioeconomic background, an inactive *hepatitis C* infection, and a history of LLETZ conization for CIN 2, making her a high-risk patient for sexually transmitted disease [6]. Furthermore, because her abdominal pain was accompanied by fever, elevated inflammatory markers, intermenstrual bleeding, and "complex," free fluid in the Douglas pouch, PID was quickly diagnosed. She was in a stable relationship. Risk-lowering factors included having bilateral tubal ligation; nonetheless, this was inadequate to rule out the diagnosis. On reflection, the patient's medical history and clinical course and the failure to respond to the routine antibiotic treatment were not wholly typical of PID. Furthermore, the imaging was suggestive of PID but not conclusive. An early laparoscopy could have been avoided if a more comprehensive differential diagnosis had been considered. NETs are made up of neuroendocrine cells dispersed throughout the

gastrointestinal tract's mucosa. The ability to express proteins usually associated with neural cells, such as neuron-specific enolase and synaptophysin, and the ability to produce hormones like somatostatin, substance P, and vasoactive intestinal peptide, gives these cells their name. Sixty-four percent of all NETs are thought to start in the gastrointestinal system, whereas 28% begin in the lungs and bronchi. The small intestine (29%), rectum (14%), stomach (5%), and appendix (5%) are the most often afflicted areas within the gastrointestinal system [10, 12]. Irritable bowel syndrome [11] is a rare tumor form, and 60% of individuals with NETs are asymptomatic and discover their tumors by chance during medical workup for something else [10]. Lesions are typically >2 cm in diameter at diagnosis, with the invasion of the muscularis propria and metastases to regional lymph nodes if they are not an accidental observation. Even in the absence of a visible abdominal mass, midgut NETs are associated with mesenteric fibrosis, which can compress mesenteric arteries and produce bowel ischemia and malabsorption [26]. Multiple lesions are discovered in up to 40% of patients [15]. The annual incidence of NETs has risen from 40 to 50 cases per million in recent years, owing to improved diagnostic tools that have become increasingly available [29]. This is likely not due to an actual increase in incidence but rather to better diagnostic tools increasingly available. The evaluation of a female patient in the emergency department frequently results in a diagnostic difficulty, as evidenced by numerous studies [1, 16–19, 24, 25, 32], to name a few instances. CT or ultrasound imaging, on the other hand, proved helpful in all of those cases in determining an accurate diagnosis. In our situation, an ultrasound scan performed during the patient's initial presentation revealed what was termed as "complex fluid," but no tumors were visible. A transvaginal scan revealed a mass in the pouch of Douglas on her second presentation, which was misinterpreted as an adnexal mass given her previous diagnosis of PID. It was later discovered that the abscess, not the tumor, was the source of the inflammatory mass seen intraoperatively. Despite the prior discussion, the transvaginal ultrasound images could not be connected to the CT scan, which only revealed nonspecific intestinal alterations and hence could not aid in the accurate diagnosis. Our case shows that, despite advances in diagnostic tool development, rigorous history taking and clinical examination remain essential and cannot be replaced solely by imaging.

Plan of Action, the Points Clinician Should Consider. Pitfalls to Avoid and Pearls of Knowledge to Think about

The fundamentals must not be overlooked:

1. When a patient comes, a thorough and complete medical history should be collected and pathognomonic and crucial facts. The most common risk factors should be considered keeping the patient's condition in mind.

2. A comprehensive physical examination is also required in primary health care, even or especially when the medical history appears to be minor. An annual well-woman exam effectively minimizes the severity of diseases like PID by diagnosing them early.
3. Alternative diagnoses were not regarded enough when the patient continued to complain of gastrointestinal issues and did not respond well to antibiotic treatment.
4. It is important to look into all the aspects related to each sign and symptom presented by the patient.
5. It's crucial to rethink your diagnosis, especially if a patient's symptoms linger despite receiving proper treatment for the initial diagnosis. Prevalent things are common; nevertheless, if the patient continues to be unresponsive to therapy, a rarer differential diagnosis must be investigated.

Conclusion

Regardless of sex partner therapy, all women diagnosed with *chlamydial* or *gonococcal* PID, including pregnant patients, must repeat *chlamydial* and *gonorrhea* testing in 3 months [15, 28]. Rescreening after 3 months is different from a cure test, which takes place sooner. Patients should be seen within 48 to 72 h of being discharged from the hospital or starting outpatient treatment to assess clinical progress and treatment tolerance. All sexually transmitted infections (STIs), including HIV and syphilis, should be tested. The need for more diligent screening for asymptomatic STIs in suitable female patients has been recognized in this review of the literature. This is to prevent PID through early treatment of STIs with the goal of preventing damage to the reproductive tract that predisposes patients to infertility and ectopic pregnancy [23]. Importantly, behavioral interventions that enhance provider and patient adherence to Centers for Disease Control and Prevention (CDC) treatment guidelines work, but they must be widely implemented for population outcomes to improve [11, 13]. Three days after starting medication, women should show clinical improvement (e.g., defervescence; reduction in direct or rebound stomach soreness; and reduction in uterine, adnexal, and cervical motion tenderness). If there has been no clinical improvement after 72 h of outpatient IM or oral medication, hospitalization, evaluation of the antibiotic regimen, and additional diagnostics, including diagnostic laparoscopy for alternative diagnoses, are advised. Regardless of whether their sex partners have been treated, all women who have been diagnosed with *chlamydia* or *gonococcal* PID should be retested 3 months after therapy [2, 28, 33]. If retesting at 3 months is not practicable, these women should be retested 12 months following treatment when they next seek medical care.

> To reverse the STD epidemic, we should all learn to talk more openly about STDs- with our parents, partners and providers.
>
> ~Dr. Gail Bolan, Director of CDC's Division of STD Prevention

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Chapter 43
Syphilitic Uveitis Misdiagnosed as Viral Retinitis

Akhil Ansary

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Create an appropriate differential diagnosis in patients presenting with the symptomatology suspect of ocular syphilis by considering all relevant details of the medical history together with the physical examination of the patient.
2. Evaluate the different components of medical history and physical examination needed to reach a definitive diagnosis.
3. Analyze the characteristics of ocular syphilis, its subtypes, and the different stages of syphilis infection.
4. Apply the correct initial diagnostic and confirmatory test to prevent misdiagnosis of syphilis.
5. Discuss the consequences of a misdiagnosis or delay in reaching a correct diagnosis for the individual patient prognosis, the transmission of syphilis, and the public health.
6. Recognize probable ocular syphilis the moment the patient presents through a complete medical history and appropriate physical examination, choose the correct syphilitic diagnostic tools, and interpret the result of the tests correctly, especially in the light of true or false test results.

A. Ansary (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: akhil.ansary@martinus.edu

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Introduction

Syphilis, a sexually transmitted infectious disease caused by *Treponema pallidum*, is emerging as a global health issue despite the availability of sensitive tests and treatment. Syphilis presents with copious manifestations and affects different organs, therefore also known as the "great mimicker" [1]. Ocular manifestations of syphilis are seen in secondary syphilis in the form of keratitis, iris nodules, iridocyclitis, episcleritis, scleritis, uveitis, chorioretinitis, and papillitis [2, 3]. Ocular syphilis is overrepresented in patients with HIV and men who have sex with men (MSM) [4]. This case exemplifies a case report of a patient with syphilitic uveitis misdiagnosed as viral retinitis leading to loss of vision in one eye.

Clinical Case Presentation

A 38-year-old female patient presented with pain, redness, and blurred vision in the left eye for the last 5 days. Her past medical history includes hypothyroidism and gastroesophageal reflux disease (GERD). She is currently being treated for them. She denied the history of any sexual experience in the past. A visual acuity test and an anterior segment examination of the right eye showed normal vision, and the left eye showed visual acuity of 6/36. Examination of the anterior segment of the left eye showed keratic precipitates, anterior chamber cells 2+ with flare, and iris pigments on the anterior lens capsule. A hyperemic disc with posterior placoid retinochoroiditis was found on fundus examination of the right eye. In contrast, thick vitritis with hyperemic disc and punctate yellowish lesions indicative of superficial retinal precipitates were found on fundus examination of the left eye. Intraocular pressure was normal in both eyes. Investigations were recommended, but she went missing for a month and was diagnosed with viral retinitis elsewhere. The tests revealed a lower white blood cell (WBC) count of 3980 mm3 and a higher erythrocyte sedimentation rate (ESR) of 35 mm/h. After 72 h, the Mantoux test yielded an induration of 0 mm. Treatment consisted of oral valacyclovir 1 g thrice daily, topical prednisolone acetate 1%, and oral corticosteroids 1 mg/kg weight, which she had been on for 2 weeks. She appeared with blurred vision in the right eye for the past week and ocular pain in both eyes after missing for a month. The visual acuity test in the right eye was 6/36 and the hand motion (HM) <36 in the left eye. Anterior chamber cells 2+ with flare were seen in both eyes and keratic precipitates and iris pigments on the anterior lens capsule in the left eye. A hyperemic disc with ground glass retinochoroiditis and superficial retinal precipitates along the inferotemporal arcade was seen on fundus examination in the right eye. In contrast, dense vitritis with a hyperemic disc, intraretinal hemorrhage superonasal to the disc, and superficial retinal precipitates were seen in the left eye. A hot disc with a hyperfluorescent edge of the posterior placoid retinochoroiditis lesion was seen on fundus fluorescein angiography (FFA) in the right eye, and perivascular leakage was seen in the left

eye, indicating active vasculitis. The treponema pallidum hemagglutination (TPHA) test and the venereal disease research laboratory (VDRL) test (1:128) were both positive. The CD4 count dropped to 198 cells per microliter. Hepatitis A, B, and C were all negative, but she was positive for the human immunodeficiency virus (HIV). She was started on antiretroviral therapy (HAART—highly active antiretroviral therapy) and treated with an injection of benzathine penicillin 2.4 million international units (IU) intramuscularly (IM) weekly for 3 weeks while being closely monitored. The use of oral valacyclovir and corticosteroids was discontinued. VDRL was detected in the cerebrospinal fluid (CSF). For 2 weeks, ceftriaxone 1 g intravenous twice daily was introduced. After 3 weeks of treatment, a repeat CSF tap for VDRL was negative, and the CD4 count had improved to 319 cells/microliter. As a result of this therapy, her vision was restored in the right eye. Later anti-treponemal therapy was stopped, and the antiretroviral therapy was continued. At 6 weeks, the right eye's visual acuity was 6/18, N6, and the left eye's finger counting (FC) at 1 m was N36. The right eye's fundus examination revealed pigmentary changes along the inferotemporal arcade, while the left eye's fundus examination revealed disc pallor, sclerosed vessels, pigmentary changes, and ERM at the macula. At 6 months, the right eye's visual acuity was 6/12, N6, while the left eye's FC was 3 m, N24. There was no sign of recurring active inflammation on inspection.

Differential Diagnosis

1. Viral retinitis

   Retinal inflammation, or retinalitis, can result in irreversible visual loss. Retinitis can be brought on by a variety of microbes, such as toxoplasma, cytomegalovirus, herpesvirus (causing herpes zoster and herpes simplex), and candida. Retinitis can also be the primary ocular manifestation of noninfectious conditions like Behçet syndrome. Depending on the primary site of involvement, retinitis can present as retinochoroiditis or chorioretinitis, or it can show with variable degrees of choroidal involvement.
2. Sarcoidosis

   Sarcoidosis is characterized by immune-mediated, widespread noncaseating granulomas. Female African Americans between the ages of 30 and 50 are more likely to experience it. Ninety percent of patients with symmetrical bilateral hilar adenopathy and diffuse lung micronodules experience intrathoracic involvement. Skin lesions, *uveitis*, liver or splenic involvement, peripheral and abdominal lymphadenopathy, and peripheral arthritis are the most prevalent extrapulmonary symptoms, with a prevalence of 25–50% each.
3. Behçet syndrome

   Behçet syndrome (BS) is a rare form of systemic vasculitis that manifests clinically in a variety of ways. It is typically identified by a triad of symptoms, including recurrent outbreaks of vaginal ulcers, uveitis, and mouth ulcers (aphthous ulcers, canker sores).

4. Infectious uveitis

   Uveitis is the uvea's inflammation. The iris, choroid, and ciliary body make up the uvea. Depending on where the predominant anatomical location of the inflammation in the eye is, uveitis can be further categorized into anterior, middle, posterior, and panuveitis.

What Was Misdiagnosed in This Case and Why?

Syphilitic uveitis was misdiagnosed as viral retinitis in this case. Syphilitic uveitis, a common manifestation of ocular syphilis, is seen in HIV-positive individuals, especially in men who have sex with other men. Our patient does not fit into this description. She also denied any past sexual exposure. This misrepresentation of patient history leads to the misdiagnosis.

Discussion

Syphilis has varied presentations depending upon the time course and stage of infection. Initial infection presents as primary syphilis, a painless, solitary, non-tender genital chancre. Chancers can also present in extragenital areas like the cervix or anus/rectum, which can go unnoticed. Untreated primary disease can progress to secondary syphilis, which commonly presents as maculopapular/papulosquamous exanthem that involves the trunk, face, and extremities. Ocular syphilis has been reported in almost all stages of syphilis but is commonly reported in secondary and tertiary syphilis [5–7]. Because of its ubiquitous nature and lack of distinguishing clinical features, ocular syphilis is often misdiagnosed [5]. The most common presentation of ocular syphilis is non-granulomatous anterior uveitis. Uveitis is the inflammation of the uvea, which is the eye's middle layer, which includes the iris, ciliary body, and choroid. Uvea is in between the retina and sclera. Syphilis can also present as vitritis, papillitis, scleritis, interstitial keratitis, granulomatous uveitis, vasculitis, and chorioretinitis [8]. Posterior ocular uveitis is common in patients with syphilis and HIV co-infection. The most common finding is focal or multifocal chorioretinitis, which is usually associated with varying degrees of vitritis, and placoid chorioretinitis in the macula is the pathognomonic feature in syphilitic uveitis [6]. The most common manifestation is retinochoroiditis (a subtype of uveitis), in which inflammatory cells from the choroidal capillaries infiltrate the Bruch's membrane and retinal pigment epithelium in disease development [9]. The patient was misdiagnosed with viral retinitis and started on antiviral medication and corticosteroids elsewhere, which led to deterioration, bilateral involvement, and lifelong impairment to the left eye with no vision return. This is pathognomonic of syphilitic uveitis; however, syphilitic uveitis is more common in males, and the patient was a non-married female who denied any previous sexual exposure. This was a

significant misrepresentation of the patient's history, resulting in erroneous studies and delayed diagnosis confirmation. The diagnosis of ocular syphilis leads to the diagnosis of underlying HIV in the patient. According to the CDC, there are an increased risk of all primary and secondary syphilis cases in males who have sex with men and an increase in the number of ocular syphilis patients who are HIV co-infected [10, 11]. Immunocompromised status is the major risk factor for posterior uveitis, especially in HIV infection and AIDS patients. Multiple sexual partners and being between 18 and 30 are also risk factors. Our patient did not fit any of the significant risk categories and also denied any sexual exposures, resulting in a delay in diagnosis. Cytomegalovirus (CMV) retinitis, an opportunistic ocular infection, is most common among AIDS patients. Unlike CMV retinitis, which dropped as highly active antiretroviral therapy (HAART) became more widely available, the incidence of ocular syphilis has not reduced [12]. The drug of choice for treating all phases of syphilis is parenteral penicillin G. Syphilis is treated following CDC recommendations. Even if the CSF study is normal, ocular syphilis, according to the CDC, requires treatment similar to neurosyphilis. Intravenous (IV) penicillin is the standard treatment method [13]. Ocular syphilis has a good prognosis when treated with IV penicillin. The patient had restored vision in one eye and she was also started on antiretroviral therapy to treat the underlying HIV.

Conclusion

Syphilis can be presented initially as ocular uveitis without obvious systemic manifestation [14]. Because of its capacity to disguise all forms of uveitis, ocular syphilis should be evaluated as a differential diagnosis in all cases of uveitis, and ocular syphilis testing should be performed in all cases of uveitis. Despite the introduction of HAART, ocular syphilis remains a significant clinical problem among HIV patients. It can happen in patients with a negative serum RPR or VDRL test. Thus, clinicians should order serum treponemal testing if they have a high suspicion of ocular syphilis [12]. Treponemal tests, such as TPHA, have a higher sensitivity and specificity for ocular syphilis and should be used to screen for the disease. Ocular syphilis should be treated similarly to neurosyphilis, with a 14-day course of aqueous crystalline penicillin G with a dosage of 18–24 million units per day, administered as 3–4 million units intravenously every 4 h [15].

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Chapter 44
Human Immunodeficiency Virus (HIV) Misdiagnosed as Pharyngitis

Sirving Keli

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Create an appropriate differential diagnosis in patients presenting with symptomatology suspect for acute retroviral syndrome by considering all relevant details of the medical history together with the physical examination of the patient.
2. Evaluate the different components of the medical history and physical examination which indicate the most appropriate order within the differential diagnosis and hence the most correct course of further diagnostic procedures needed to reach a definitive diagnosis.
3. Analyze the characteristics of different available HIV-1 tests of different generations and the meaning thereof for the appropriate choice given the phase of HIV-1 infection the patient is presenting.
4. Apply the correct generation of HIV-1 tests and/or laboratory tests in relation to the estimated time since HIV-1 infection, to minimize the probability of misdiagnosis of HIV-1 in patients presenting with ARS.
5. Understand the consequences of a misdiagnosis or delay in reaching a correct diagnosis for the individual patient prognosis, for the transmission of HIV-1, and for the public health.
6. Recognize probable ARS the moment that the patient presents with a complete medical history and appropriate physical examination, to choose the correct HIV-1 diagnostic tools, and to interpret the result of HIV-1 tests correctly, especially in the light of true or false test results.

S. Keli (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: sirving.keli@martinus.edu

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Introduction

HIV-1 infections can occur asymptomatic but also symptomatic in a more or less severe form. The symptomatic presentation in the first months after the infection may often be mistaken for other diseases, especially mononucleosis infectiosa (*Morbus. Pfeiffer*), viral or bacterial pharyngitis. COVID-19 may be also considered due to the present pandemic; however possible co-infection is a real possibility. Although the presentation may be very similar, the treatments differ widely. Also, the prognosis is totally different. Therefore, a correct diagnosis is of pivotal importance. Furthermore, any delay in getting the correct diagnosis may affect the short-term and long-term prognosis for the patient. The delay may be prevented or even come to exist if the clues in the initial assessment of the patient are overlooked. Especially thorough medical history taking may point in the correct direction, since risk factors directing the differential diagnosis are most prominent in the medical history, especially the personal behavior of the patient. However, even when the correct direction toward the correct diagnosis is taken, using the appropriate statistical considerations and properties of the diagnostic tools involved may make the difference between the ultimate correct diagnosis and a misdiagnosis. That is the case with the following case report. Although one case report is discussed, the misdiagnosis of HIV-1 as especially mononucleosis infectiosa or acute pharyngitis is not rare. Furthermore, it illustrates that besides the personal consequences for the patient, also the public health consequences may be far reaching if the probability of a misdiagnosis is partially based on a testing tool that is widely used although inappropriate for the acute phase of the disease.

Clinical Case Presentation

This case report concerns the initial presentation of a 29-year-old man, initially diagnosed, by his general practitioner and also a second general practitioner he visited 1 day later, with pharyngitis, based on his presentation with sore throat, weakness, chills, a temperature of 38.5° C, and pain in the left arm and leg [1]. Despite prescribed antibiotics and paracetamol by the first general practitioner and confirmation by the second, the symptoms persisted. Because of fears emerging from his recent unprotected sexual activities, the patient sought HIV testing after 7 days, with a first fourth-generation test being reactive (positive), followed by four consecutive negative tests, all being third-generation HIV tests in, respectively, two primary care settings, one Public AIDS Counseling Center and one AIDS-NGO facility. Subsequently the patient underwent again a fifth HIV test, this time again using the fourth-generation test at the original laboratory of the first positive fourth-generation test result, and also this time the fourth-generation test was positive. However, confirmation by a third-generation Western blot test, in a reference laboratory, again was negative. Based on the long testing history and the history of the

patient, a thorough physical examination and a fourth-generation further testing eventually led to the correct diagnosis of acute retroviral syndrome, undergoing seroconversion, with HIV-1 RNA viral load of more than 3,000,000 copies/mL.

Differential Diagnosis

Given the medical history of the patient, the most probable differential diagnosis could be:

1. Acute retroviral syndrome: The patient presentation with pharyngitis, chills, myalgia, and lymphadenopathy, together with a history of recent risky unprotected sexual behavior, is the typical presentation of the acute retroviral syndrome as consequence of an acute HIV infection [2]. In a study done by Crowell and coworkers in which they reported the signs and symptoms in patients with acute human immunodeficiency virus infection, 335 of 430 study participants had ARS. In the 335 ARS subjects, 93% presented with fever, 79% with fatigue, 67% with pharyngitis, 64% with headache, and 57% with myalgia, while 18% presented with adenopathy [2].
2. Mononucleosis infectiosa: The presentation with adenopathy, and the other symptoms, raises a high suggestion of mononucleosis infectiosa, especially in young patients. However, given the history of multiple unprotected sexual contacts with males, this is to be considered in conjunction with acute HIV, which should be excluded. Furthermore, specific laboratory tests should manifest the presence of the typical mononuclear lymphocytes.
3. COVID-19: The pandemic of COVID-19 causes a high prevalence of COVID-19 and therefore increases the probability that patients presenting with fever, chills, myalgia, and weakness may have COVID-19. However, despite the wide range of symptoms and signs COVID-19 presents itself with, Struyf and coworkers reported in a review of 44 studies involving a total of 26,884 patients a sensitivity of 0.00% for adenopathy, which means that 0.00% of the COVID-19 cases presented with adenopathy [3]. Also, a review done by Rahman and coworkers in 2021 made no mention of adenopathy as part of COVID-19's first presentation [4]. Therefore, the presence of adenopathy takes COVID-19 lower down the differential diagnosis list, although it may not be excluded as a co-infection with HIV [5].
4. Acute bacterial pharyngitis: Based on the symptoms and the pharyngitis, combined with fever, and cervical adenopathy, a pharyngitis seems at first hand probable. However, the overall picture of myalgia and general weakness and especially the rare presentation of isolated bacterial pharyngitis in adults should push the diagnosis and treatment of the pharyngitis to a "per exclusionem" category, i.e., after exclusion of other causes. Furthermore, in adults, pharyngitis seldom presents as an isolated illness but rather as a part of a wider spectrum of diseases or syndromes. Also, when assuming an isolated pharyngitis, treatment

with antibiotics, if done, is to be preceded by a culture, in order to evaluate the choice. Here, the absence of any effect within 48–72 hours and, surely after 1 week, worsening of the symptoms should raise suspicion on the diagnosis, the treatment, or both.

What Was Misdiagnosed in This Case and Why?

HIV was misdiagnosed as pharyngitis, since the initial rapid antigen detection test 2 months before symptoms, as well as the four third-generation HIV tests performed 7 days after the onset of his symptoms, which resulted negative after one fourth-generation HIV test was reactive. Afterward, the fourth-generation was reactive again, but again the Western blot confirmation test used after the second fourth-generation rapid test resulted negative. The misdiagnosis resulted from the use of third-generation HIV antibody tests as either rapid tests or as confirmation tests, since they are not able to detect HIV in the early acute phase, disregarding the probability of false negatives in the acute phase of HIV. Also, important details in the medical history of the patient were disregarded, and adequately performed physical examination was missing or incomplete.

Discussion

The procedure to reach eventually a diagnosis consists of different fundamental steps, which all should be considered integrally to yield eventually the correct diagnosis. One of the fundamental conditions is that the natural history of the diseases that is contemplated must be completely understood, especially the different potentially misleading presentations it may carry along. However this is not sufficient, since the eventual detection and confirmation of the disease depend on the diagnostic tools used, their appropriateness, and their ability to predict a disease reliably in the phase the disease is actually presenting itself. The characteristic of especially the positive predictive value and negative predictive value of the diagnostic tools used and their interpretation by the physician will in the end play a pivotal role in preventing a misdiagnosis. When it concerns the different steps leading to a diagnosis, the first starting points are found in the medical history, and every detail must be weighed by the physician, in search of pathognomonic symptoms and signs, relevant patient behavior, and observations of the patient by others. Furthermore, the applicability and especially the limitations of all diagnostic tools involved must be well known. It must always be clear which diagnostic tool is able to detect disease, and in which phases of the disease. Furthermore results must be evaluated keeping in mind the possibility of false positive but especially also false-negative test results. In the subsequent case, the consequences of overlooking important information in the medical history, the absence of an optimal physical examination, and

application of a diagnostic tool that is not reliable in the early stage of HIV led to a misdiagnosis by two general physicians and a doctor's delay of 11 days. It was only when the clear indications in the medical history and an adequate physical examination were taken into account, also in combination of the correct laboratory diagnostic tools, that the correct diagnosis was reached.

Natural History of Acute HIV-1 Infections

The acute HIV-1 infection may occur asymptomatic in a percentage of cases that is variable per different population, ranging from 8% to 77% [2]. Especially in specific subgroups, this percentage shows great variation. The most important subgroups considered are men having sex with men (MSM), pregnant women, intravenous drug users, transgender individuals, and sex workers. The prevalence also shows a great variation across different parts of the globe [6–8].

The typical symptomatic presentation may consist of one or more symptoms: fever, myalgia, general weakness, lymph node enlargement, pharyngitis, fatigue, anorexia, weight loss, oral ulcer, diarrhea, and a great variety of other symptoms; see Table 44.1. The diagnosis of ARS is made by the presence of three or more of the symptoms and/or signs, together with a true-positive HIV-1 test result. While the symptoms and signs themselves are not typical for HIV-1 and especially mononucleosis infectiosa may also present with lymph node enlargement, the presence of risk factors should be assessed thoroughly, since these provide additional information directing the clinical picture presented.

Table 44.1 A comparison of the most frequent signs and symptoms in individuals with acute HIV infection

Sign/symptom	No acute retroviral syndrome (n = 95)	Acute retroviral syndrome (n = 335)
Fever	++	+++
Fatigue	+	+++
Pharyngitis	+	+++
Headache	+	+++
Myalgia	+	+++
Anorexia	+	+++
Weight loss	+	+++
Diarrhea	++	+++
Skin rash	+	+++
Arthralgia	+	+

Legend (range)
+ 1–9
++ 10–99
+++ 100+
Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5930255/

For acute infections, a fourth-generation HIV test is required. Also, the confirmation test must be a fourth-generation HIV-1 test. Thus, the patient in the case report displayed most of the symptoms and signs that point in the direction of ARS, while his risky behavior pushes the differential diagnosis into the direction of ARS until proven otherwise. Special attention is drawn to the fact that the specific reason the patient sought medical attention came from his sexual behavior, which he himself considered as risky, with high probability of having led to an acute HIV-1 infection. So, actually there was no patient's delay.

The natural history of the HIV infection is characterized by the acute retroviral syndrome [2]. The most frequent symptomatology of acute HIV-1 infections is shown in the following table.

The Importance of the Presence of ARS in the Progression of HIV-1 Infection and Patient Prognosis

Not all patients with an acute HIV-1 infection present with ARS. Colby and coworkers estimated 78% of patients (335 out of 430; 97% were men) that tested positive during voluntary HIV screening at the Thai Red Cross AIDS Research Centre in Bangkok [2]. However, once the ARS is diagnosed as the presenting form of acute HIV-1 infection, CD4+ cell depletion, a high CD4+ viral burden, and multiple body compartment immune activation were observed. Presence of ARS also predisposed to increased morbidity when inflammation persisted despite antiretroviral therapy (ART).

The importance of the early diagnosis from the individual patient perspective is the relationship between ARS, associated HIV RNA viral loads, and associated accelerated progression of HIV and worse prognosis. From the individual patient perspective, the most important aim is to give the patient, once diagnosed as having HIV-1, the best therapy available, with the best timing, in order to obtain the best treatment results. Antiretroviral therapy should be started as soon as the HIV-1 infection is confirmed [2, 7, 9, 10].

Early ARS Diagnosis from Public Health and Epidemiological Perspective

An early diagnosis of ARS is fundamental in epidemiological and public health perspective for limiting the transmission of HIV-1 to other persons, since it permits an early administration of ART in HIV-1 patients. Cohen and coworkers performed a clinical trial, comparing the early administration of antiretroviral therapy in early versus delayed ARS, and reported a 93% reduction of HIV-1 transmission in partners of the patients [2]. The corresponding hazard ratio for early treatment versus delayed treatment was 0.07 (95% confidence interval 0.02–0.022), and the study

was done with 1763 patients, divided in 886 receiving therapy at a CD4+ count of 350 to 550 cells per cubic millimeter, and 877 patients starting therapy at a CD4+ cell count below 250 cells per cubic millimeter. These clinical trial results are in accordance with previous observations of Le and coworkers in a prospective cohort study, involving 384 participants receiving late ART and 213 participants who had received early ART [6]. They concluded that initiation of ART during the 4-month period after HIV-1 infection was associated with an increased recovery of CD4+ cell counts. However, where Le and coworkers did not demonstrate the clinical benefit according to Walker and Hirsch [7], Cohen and coworkers showed the benefit, especially the public health importance and the importance of partners involved [9].

The Importance of HIV Test Generation and Detection of HIV Infection

In order to avoid misdiagnosis of HIV-1, it is fundamental to take into consideration the different stages of the HIV-1 infection. In the CDC guidelines for HIV-1 testing of 2014, updated in 2018, Branson and coworkers analyzed and summarized the different testing availability and expected results, based on the classification according to different laboratory stages of HIV-1 infection [11]. These laboratory stages include the eclipse period, the seroconversion window period, acute HIV infection, and established HIV infection (Table 44.2).

Figure 44.1 illustrates a graphical representation of the different stages and the corresponding sensitivity of the test generations. In the case report described here [1], the patient displayed symptoms, with a positive fourth-generation test, thus detecting the p24 antigen. However, due to the patient being in the seroconversion period, and not having entered the acute HIV infection period, the third-generation tests as well as the third-generation Western blot confirmation tests, as could be

Table 44.2 Based on the CDC guidelines for HIV testing, [11, 12] providing further explanation of the laboratory stages and the corresponding detectability for the different generations of HIV-1 tests

Stage	Description	Period	Indicated testing
Eclipse period	Immediately after HIV infection	0–10 days after initial infection	None. Viral markers undetectable
Seroconversion window period	HIV infection to detectability of HIV; p24 antigen appears	p24 detection, 14–20 days after initial infection	4th-generation immunoassay
Acute HIV infection	From detectable viral RNA to detectable antibodies	3 to 5 days after p24 antigen detection, 17 to 25 days after initial infection	3rd-generation and 2nd-generation immunoassay
Established HIV infection	IgG antibody response is complete	28 to 48 days after initial infection	1st-generation immunoassay

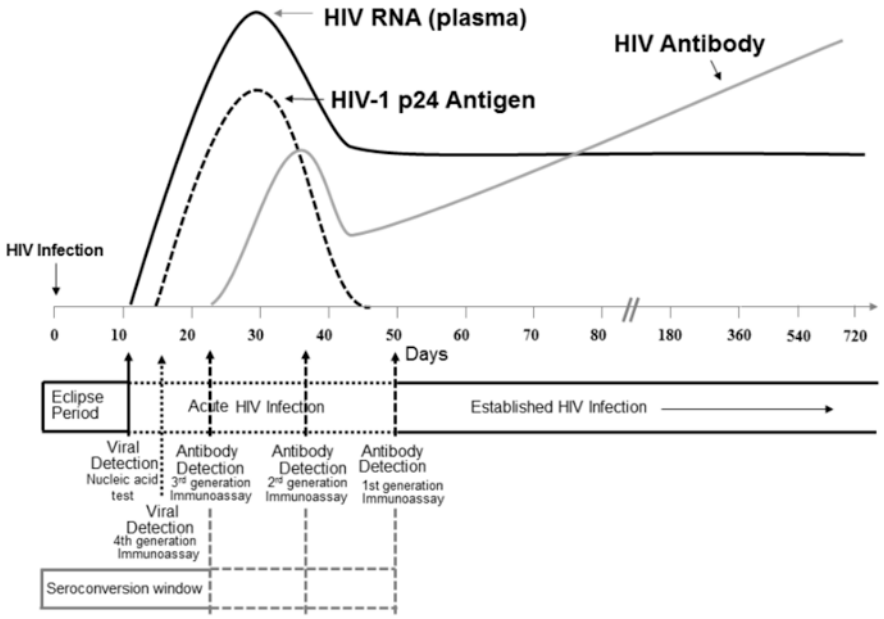

Fig. 44.1 The different HIV infection stages in relation to detectability and the choice of diagnostic tests [10]

expected, gave negative results. The fourth-generation confirmation test eventually resulted positive. It is of utmost importance to take into account the actual stage the patient might be in. Here, the medical history regarding the sexual behavior and history of the patient provide information about the potential or probable moments of the initial HIV infection. The development of clinical symptoms does not necessarily coincide with the development of IgM antibodies. In this aspect, HIV-1 does not differ from other infectious diseases, where in the first week of the symptomatic stage of disease the presence of IgM antibodies may not be detected, while PCR testing yields positive results. This also explains why, in the first differential diagnosis, HIV-1 often is misdiagnosed as mononucleosis infectiosa. However, in the case of mononucleosis infectiosa, the blood analysis from the laboratory is expected to yield the abundance of mononuclear cells, which should make the difference.

Causes of Delayed HIV-1 Other than Misdiagnosis

Besides misdiagnosis or near-misdiagnosis, other causes of delays in diagnosis of ART, the underlying HIV-1 diagnosis, have the same negative effect on both the individual patient and the public health. In a systematic review, Tan and coworkers identified factors at organizational level as well as on physician knowledge level that caused delay in HIV-1 diagnosis [13], and MacCarthy and coworkers identified several risk factors with their corresponding adjusted odds ratios for a delay in a

cross-sectional study in an urban area in Brazil [8]. The most important risk factors reported were male gender (adjusted odds ratio 3.02, 95% CI 2.0–4.6), provider-initiated testing (3.0, 95% CI 2.1–4.4), and age of 45+ years (1.67, 95 %CI 1.1–2.5). These factors may vary per country: in the United States, Chin and coworkers found men to be three times more likely than women to be diagnosed with HIV-1 on their first physician consultation [14].

Psychological Aspects of HIV and in Patients Contemplating the Possibility that They Might Have HIV

- Discuss the psychological effect of misdiagnosis of HIV.
- WBC count and others would have been considered directly and the effect on the probability of misdiagnosis of HIV.

Plan of Action, the Points Clinician Should Consider, Pitfalls to Avoid, and Pearls of Knowledge to Consider

The basics should not be overlooked:

1. When a patient presents, a careful and detailed medical history should be taken, and pathognomonic and important details should be considered. Risky sexual behavior points in the direction of HIV or other sexually transmitted disease, until proven otherwise.
2. Also in the primary healthcare practice, a thorough physical examination is a must, even or especially when the medical history seems trivial.
3. Physicians should be trained and upgraded in order to have sufficient up-to-date STD knowledge [13, 15].
4. Evaluate carefully the characteristics of each diagnostic tool: in the case of a laboratory, evaluate carefully which test to be used in which stage of a disease. In the case of HIV, the gold standard for the early phase is a PCR test, which is sensitive from the early phases and also has a high percentage of true-negative results.
5. In case a laboratory test is not in concert with the medical history and the physical examination, do not drop the diagnosis, but take into account possible false-negative results of the laboratory tests.

Conclusion

Third-generation HIV antigen tests should be avoided in the acute phase of HIV infections, due to the high rate of false-negative test results. A fourth-generation test or, preferably, PCR testing should be used.

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Chapter 45
Early Lyme Disease Misdiagnosed as Influenza

Sirving Keli

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Create an appropriate differential diagnosis in patients presenting with symptomatology that seems flu-like, but may carry signs of early Lyme disease, in the consciousness that seemingly trivial symptoms and signs can only be put in the right context where the patient is observed and carefully examined combined with an extensive medical history taking including possible travel, occupational, and recreational and/or weather- and disaster-related exposures.
2. Evaluate the different components of the medical history, especially occupational, recreational, and weather- and disaster-related information, and in-person physical examination which indicate the most appropriate order within the differential diagnosis and hence the most correct course of further diagnostic procedures needed to reach a definitive diagnosis.
3. Analyze the clinical presentation of the symptoms and signs, including those pointing clearly to Lyme disease, in order to choose the most appropriate diagnostic tools, including radiographic and laboratory testing.
4. Apply the appropriate panel of diagnostic instruments when Lyme disease is part of the differential diagnosis, given the potential serious clinical evolution and long-term sequelae of Lyme disease.

S. Keli (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: sirving.keli@martinus.edu

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5. Discuss the potentially serious consequences of a misdiagnosis or delay in reaching a correct diagnosis when the patient is handled only by phone, and not seen, observed, and examined in person.
6. Recognize the different faces and disguises Lyme disease may present itself with, especially in the early stage.

Introduction

Lyme disease may be easily missed, but nonetheless consequences remain serious. Caused by infected ticks carrying *Borrelia burgdorferi*, the typical appearance with the bite marks is the most immediate visible sign, if present. The presence of erythema migrans is an important sign, but might not always be visible. In contrast to North America where *Borrelia burgdorferi* is responsible for the majority of the infections, *Borrelia afzelii* and *Borrelia garinii* are causing the most infections in Europe [1]. However, especially in the Midwest of the United States of America, also *Borrelia mayonii* has been identified [2]. The infection of humans occurs by tick bites from ticks belonging to the *Ixodes ricinus* complex [1].

The treatment of Lyme disease consists of doxycycline and is in the majority of cases successful [1, 3]. However, in some cases, patients may show persistent clinical symptoms and signs despite treatment without evidence of treatment failure, relapse, or reinfection [3–6]. Klempner and coworkers determined that re-treatment of this group of patients was not only lacking benefit, but even carried significant risks [5]. Although at first hand the disease seems innocent, the infection becomes disseminated quickly with the patient. Acute neuroborreliosis may follow within weeks. It is estimated that this happens in one sixth of patients in the United States [6–8]. A serious clinical picture may subsequently evolve, with neck stiffness and meningitis, encephalitis, neuropathy, and other neurologic manifestations [7, 8]. In approximately 5% of patients, cardiac manifestations may be expressed by atrioventricular block, myocarditis, or fatal pancarditis [8]. Arthritis expresses itself through intermittent pain and joint swelling in large joints, with a predilection for knees [8], in approximately 60% of patients, starting months after the start of the disease, with 10% of all patients experiencing chronic persistent arthritis [8], is a late manifestation of Lyme disease [8, 9]. The extensive damage is the result of inflammatory reactions in the patient, which require only a small amount of bacteria in the tissues [9]. Also, *Borrelia burgdorferi* has a more extensive migration to different tissues than the other subtypes. This explains the difference between the mostly mild evolution of Lyme disease in Europe, where the agent most of the time is *Borrelia afzelii*, compared to North America, where *Borrelia burgdorferi* is the most prevalent agent [7–9].

In contrast to these serious symptoms and signs during the evolution of Lyme disease in a patient, before the multiplication and quick spread of the bacteria in the infected patient [9], the first presentation may be a very mild, influenza-like set of symptoms and signs, which may be misleading, as was the case in the clinical presentation [10]. It takes 2–3 weeks before the first humoral antibodies are formed and become detectable as IgM through ELISA in laboratory testing [11–13]. If present,

the erythema migrans, resulting from inflammation of the skin by *Borrelia*, is a key finding, together with the exposure history of the patient. The case series discussed here [10] shows the important role both the exposure history, as obtained from the medical history, and the presence of the erythema migrans play, in preventing a misdiagnosis in early Lyme disease.

Clinical Case Presentation

Aucott and Seifter described in 2011 a case of a 58-year-old woman, otherwise healthy, who had a phone consultation with the physician based on "flu-like" symptoms, including headache, generalized achiness, and a subfebrile temperature of 101.2° F (38.44° C), without cough [10]. Based on the phone consultation, the most probable working diagnosis adopted was acute influenza. Tamiflu twice per day 75 mg brought no improvement; that treatment was continued and after 2 days a sore throat resulted as the only symptom in the clinical spectrum. Also, the subfebrile temperature remained unchanged. Besides, the remainder of the clinical picture, regarding the generalized achiness and sore throat, also persisted without any improvement or worsening. Given this (lack of) development in the clinical picture, the Tamiflu twice 75 mg per day was maintained for the following days. However, after a welt on her stomach and generalized joint pain were reported on the 4th day, and also the patient remembered being bitten by something behind her knee with subsequent local irritation, she was invited for a physical consultation with her physician. The bite was estimated to have taken place 3 weeks before the flu-like symptoms started. On the subsequent physical examination, two lesions consistent with erythema migrans were observed behind her knee, as well as a second and third lesion in the abdominal lateral region. No other abnormal observations were done during the physical examination. Laboratory analysis revealed elevated AST and ALT liver enzymes with a value of 413 and 704, respectively, with alkaline phosphatase being 202. Subsequent serological analysis on the presence of Lyme antibodies with ELISA was performed. The results indicated a positive IgM and IgG [10]. Based on the results of the medical history during the live consultation, the results of the physical examination, and the laboratory results, the diagnosis of early Lyme disease was confirmed. Administering doxycycline made the patient recover from the rashes in 1 week, and remaining symptoms as well as the elevated liver enzymes quickly subsided during the next 2 weeks [10].

Differential Diagnosis

1. Lyme disease: In presence of the typical erythema skin lesion which is recognizable by the typical bull's-eye appearance with a center lesion and a centrifugal ring formation of inflamed skin (rash), the primary diagnosis to be considered is Lyme disease, especially when there is a medical history of tick bite or soaring locations

of the skin. In early stages, even in absence of the erythema migrans, ticks might still be present at the site(s) of the bite(s). Although the other symptoms might resemble flu (general weakness, fever, etc.), the erythema migrans is highly predictive for Lyme disease. In absence of the erythema, a history of tick bites and/or ticks still present at the site must lead to the consideration of Lyme disease, since it will typically take 7 to 14 days for the erythema to develop, but this is the case in only 70–80% of the patients. Preventive treatment might be given in this case.

2. Influenza: The initial presentation of influenza, with several symptoms such as general weakness, fever, runny nose, conjunctivitis, and myalgia, may resemble Lyme disease during the first days; however, the medical history typically does not include insect bites, but absence of runny nose, conjunctivitis, and frequent cough and sore throat may plead against influenza, especially during summer/tick bite season. Also, initial treatment with doxycycline 100 mg per day during 10 days will have no effect on the clinical picture, in contrast to Lyme disease, which will disappear in most cases. Also the laboratory presentation of especially white blood cells differs from Lyme disease.
3. HIV acute retroviral syndrome: The acute retroviral syndrome may also resemble flu in its early presentation; however a key finding in the medical history is the presence of recent sexual behaviors carrying the risk of HIV infection, combined with generalized lymphadenopathy. Key laboratory findings indicating HIV infection are the lowered CD4+ cell count and the positive fourth-generation screening HIV tests confirmed by fourth-generation PCR testing.

What Was Misdiagnosed in This Case and Why?

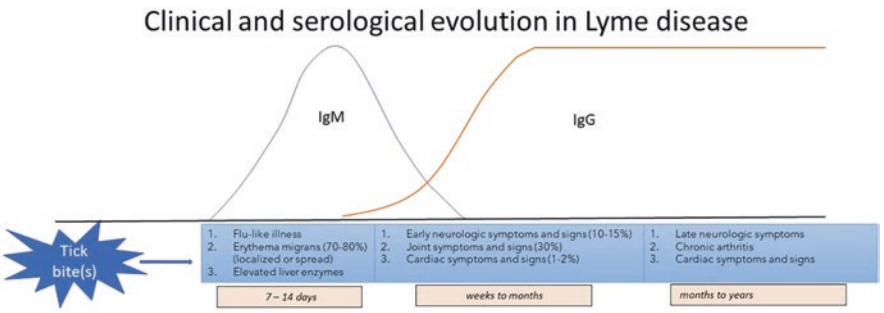
Lyme disease was misdiagnosed as summer influenza A, as a result from a diagnosis made by a phone consultation, without taking into account the patient's exposure history and also without seeing the patient and without performing a physical examination on the patient. No laboratory testing was performed either. The misdiagnosis could have been avoided if the patient was seen personally, and a complete medical history, physical examination and laboratory evaluation would have been done.

Discussion

A physician's consultation through the phone is extremely sensitive to misdiagnosis, especially in case of a first presentation of a health condition by a patient. The consultation is then limited to a listen and ask conversation, and important details captured by vision and interaction with the patient are lost. The medical history is to be taken extensively, despite any busy physician's office. It is the medical history that is able to reveal occupational, recreational, travel, and other exposure details that from a patient's perspective may be trivial but for the physician's differential

diagnosis may be holding the key. As in many cases of misdiagnosis, with the initial presentation of the patient with flu-*like* symptoms and signs, it is the medical history about possible exposures that will hint in the correct direction. Furthermore, only if the physician takes this into account and the concerning questions are asked to the patient will the key information come to light. In the current case, it was when the symptoms and signs persisted and extended that the direction was found. An important condition is that the physician should be well aware of the related exposures and exposure conditions in relation to the clinical picture presented. In the case report described above [10], it was not possible for the physician to have a physical examination of the patient during the telephone consultation; however, if physical inspection would have been done, either the rash or the previously present typical tick bites, with or without one or more ticks still present, would have been observed. Especially when patients do not consider physical locations to be relevant to their symptoms and signs or when patients cannot look at their body areas properly, the actual presence at the doctor's office and the physical examination make the difference. The presence of erythema migrans, recognizable by the annular rash spreading centrifugally, and which develops in the first 7 to 14 days after infection [7–9], is a key finding and results from several alterations of the skin with development of several inflammatory markers in the skin, which is where the first immune response process against *Borrelia burgdorferi* takes place. Furthermore, Marques and coworkers have shown that during the skin inflammation, a local immunosuppression process evolves, which permits and mediates the quick spread of *Borrelia* to elsewhere in tissues and organs of an infected patient [14]. It is therefore fundamental to diagnose Lyme disease in a patient as early as possible and start treatment immediately, since delays in treatment with subsequent hematogenous dissemination may lead to a more serious clinical picture including neurological, cardiac, and long-term arthritis complications [3, 7, 8]. Steere documented the erythema migrans skin lesion to be the earliest manifestation of Lyme disease, present in 70–80% of patients within 7 to 14 days after a tick bite [7]. Since both neurologic (10–15%) and cardiac symptoms (1–2%) may develop already from within weeks up to months after a tick bite [15], any delay in diagnosis must be avoided. The typical Lyme disease arthritis, which affects isolated large joints and has a pattern of migration in time, may affect up to 30% of patients and occurs mostly around 6 months or longer after a tick bite.

The clinical and serological evolution of Lyme disease is summarized in the following illustration.



Diagnosis of Lyme Disease

Diagnostic criteria of Lyme disease are based on the erythema migrans and/or the finding of *Borrelia* antibodies by laboratory testing of serum of suspected patients [12, 15]. In case Lyme disease is considered in the absence of the erythema migrans, the serologic tests will confirm the diagnosis. The procedure of laboratory testing is a two-step procedure, in which first an EIA (enzyme immunoassay) is performed, which if positive may be followed by the second step which consists of IgM testing of the serum. IgG becomes positive typically later during the disease.

Plan of Action, the Points Clinician Should Consider, Pitfalls to Avoid, and Pearls of Knowledge to Consider

1. Telephone consultations of the first presentation of disease in patients, even when it seems innocent, are a pitfall that must be avoided.
2. Body and organ descriptions by patients themselves carry substantial risks and may only be used as a part of medical history but may never substitute the physical examination of the patient, which should be done with the patient in person.
3. Always be extremely careful with patients who express a presentation of a flu-like disease, since a broad spectrum of infectious diseases present themselves as a flu-like set of symptoms and signs during the first days, sometimes even in the first 2 weeks. The physician must always check for exposure to specific diseases, and especially insect bites or soaring local irritations must be asked for and evaluated carefully.
4. Early diagnosis and treatment of Lyme disease may prevent more serious presentations and evolution in the patient with Lyme disease.

Conclusion

Since many infectious diseases present themselves in the early stages immediately after the end of their incubation period initially with flu-like symptoms, the recognition of the true underlying disease poses a considerable challenge. Especially during influenza season as well as epidemics of other infectious diseases that start likewise, the physician's task is not easy. As was shown in this case of Lyme disease, but also in other cases like leptospirosis, acute retroviral syndrome in HIV, and other diseases, what appears innocent in the early presentation may spell a potentially serious and in some cases even life-threatening evolution, unless recognized early and treated in a timely manner. While flu-like symptoms tend to prompt a non-etiological treatment but only symptomatic treatment, serious conditions that start in the same way need a specific treatment, aimed at the underlying cause. Even in case of antibiotics, generic or acquired antimicrobial resistance of the offending agent requires a specific approach.

The difference between the innocent versus serious underlying condition requires two fundamental elements. First is not only the specific knowledge but also the specific attention of the physician for details in the medical history that point to or may even be pathognomonic for serious underlying conditions. It cannot be assumed that the patient may be aware of these details and would mention them spontaneously or even by answering on an "anything else" basis. Second is the specific knowledge and attention of the physician regarding what to include or exclude at physical examination, as well as in the following diagnostic procedures as laboratory testing, etc.

Lyme disease belongs to the serious diseases and must be recognized, diagnosed, and treated as soon as possible. It is a diagnosis that cannot be made by telephone consultation; otherwise it will be missed easily. Since early treatment is simple but extremely important, it must be specifically considered when flu-like symptoms and signs are presented by patients, and the patient should be seen, spoken to, and examined in person by the physician.

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Part IX
Nephrology

Chapter 46
Apolipoprotein C-II Amyloidosis Misdiagnosed as Light Chain Amyloidosis

Shashwat Shrivastava

Learning Objectives
By the end of this presentation, the physician will be able to:

1. Distinguish between several amyloidogenic proteins through the use of microdissection and gene sequencing techniques and rule out potential differentials before making a definitive conclusion.
2. Understand the necessity of withholding empiric chemotherapeutic agents as it may react adversely to the confirmatory subtype of amyloidosis.
3. Reinforce the importance of having high suspicion to rare causes of systemic hereditary amyloidosis which reduces the propensity of mistreatment and propagates further evaluation.
4. Consider the presence of light chains as benign findings and differentiate from light chain amyloidosis through further testing.
5. Recognize serum protein electrophoresis (SPEP) and flow cytometry as poorly specific tools and understand that the use of therapeutic agents must be restricted before making a definitive diagnosis.

Introduction

Amyloidosis is a term used for multiple diseases caused by the extracellular deposition of insoluble proteins resulting in organ failure. This proteinaceous element forms misfolded aggregates resulting in a characteristic β-pleated sheet. Congo red dye binds to the extracellular aggregates producing apple-green birefringence under

S. Shrivastava (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao

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polarized light [1]. Amyloidosis is an autosomal dominant disease [2] that happens due to mutation in the proteins with amyloidogenic potential [1–3]. Systemic amyloidosis is a relatively uncommon disease and not many populations-based studies have been conducted. Some of the studies showed amyloidosis to be apparent in 6 (0.2%) of 3141 autopsies between 1937 and 1946 at the Royal Victoria Hospital in Belfast, Ireland. When the study was repeated at the same institution, 43 (0.4%) of 11,586 autopsies revealed systemic amyloidosis [3]. Another study in the United Kingdom mentions systemic amyloidosis as the cause of death in more than 1 in 1500 people [4]. Though reports have shown high penetrance of hereditary amyloidosis, amyloidogenic mutations have been occasionally witnessed in asymptomatic elderly individuals [4].

Substantial challenges are always incurred while diagnosing hereditary amyloidosis, leading to misdiagnosis and inappropriate treatment [4]. Proteins commonly associated with hereditary amyloidosis include transthyretin (TTR), lysozyme, gelsolin, cystatin C, fibrinogen Aα, and apolipoprotein A-1 or A-2. The most frequently detected protein associated with amyloidosis is the familial transthyretin-associated amyloidosis (ATTR) [1, 4–7].

The kidneys are the most common site for amyloid deposition in systemic amyloidosis. Kidneys provide an advantageous extracellular environment that potentiates amyloid formation and stabilization. The most common presentation of renal amyloidosis comprises nephrotic-range proteinuria and acute kidney injury [1]. Apolipoprotein C-II is found to have amyloidogenic potential in several in vitro studies [8]. Human apolipoprotein C-II is a lipid-binding protein that self-aggregates in a favorable environment forming fibrils and amyloid deposits [6].

This case describes a rare occurrence where the patient having apolipoprotein C-II was misdiagnosed as light chain amyloidosis. The report lays emphasis on the understanding of sensitivity and specificity of various diagnostic modalities. Though serum protein electrophoresis (SPEP) and flow cytometry are highly sensitive modalities, it should not be used for making a definitive diagnosis. Mistreatment could be detrimental to the patient's health due to their adverse effects such as in this case [7]. Chemotherapy has no role in treating hereditary amyloidosis and may expose the patient to unnecessary harm [4–6].

Through this case report, we hope to raise awareness regarding apolipoprotein C-II amyloidosis. We would also like the physicians to avoid pitfalls from valuable learnings of this case report and encourage a more strategic approach to diagnose the type of amyloidosis and amyloidogenic proteins involved. Recent advancements in diagnostic modality to identify the polypeptides must be included as routine workup in patients presenting with systemic amyloidosis.

Clinical Case Presentation

A 61-year-old presented with severe hypertension (160/90 mmHg) and worsening bilateral leg edema for the past year. Periorbital edema, dyspnea on exertion, fatigue, and 20-pound weight loss within 6 months were seen on examination. Hypertension

has been managed with multiple antihypertensive medications for the past year. She was prescribed furosemide 20 mg once daily and hydralazine 25 mg thrice a day. Previously, she was on lisinopril, losartan-hydrochlorothiazide, and amlodipine which were then discontinued due to their side effects. The patient's past medical history consisted of hypertension for the last 3 years, hypothyroidism, depression, colonic polyps, mitral valve prolapse, anxiety, and hyperlipidemia. Her family history included coronary artery disease, hypertension in her father, and uterine and breast cancer in her sister. The patient also admits to 18-pack-year smoking history but quitted 29 years ago. She claims to be a social drinker and has no history of drug abuse. Her other medications consisted of levothyroxine, alprazolam, escitalopram, and atorvastatin. All systems were unremarkable. The only concerning finding was the presence of bilateral pitting edema along with elevated blood pressure of 190/100. Laboratory tests revealed creatinine of 2.3 mg/dl, which was elevated from her baseline creatinine of 1.3 mg/dl. Complete blood count, electrolytes, and liver function tests were within normal limits. Urine dipstick came back positive for >3+ proteinuria, which was consistent with her last 3 years of proteinuria levels. Eleven to 24 red blood cells were visible in a high-power field (HPF). The urine protein to creatinine ratio was increased to 6.3 mg/g. Hypoalbuminemia was witnessed on complete blood count. Several tests and imaging were ordered to identify the underlying cause of patient symptoms. Chest X-ray indicated bilateral pleural effusions. Stress myocardial perfusion imaging showed normal ventricular thickness and normal ejection fraction. Serum electrophoresis with immunofixation revealed immunoglobulin A (IgA) kappa monoclonal protein which was identified as two bands in the beta globulin region. Free kappa light chain level was noted to be 2.45 (0.35–2.49 mg/dl), and free lambda level was 0.93 (0.5–2.71 mg/dl), with their ratio elevated at 3.91 (0.27–1.8). To keep the blood pressure under control, the patient was started on losartan, spironolactone and the dosage of hydralazine and furosemide were subsequently increased [15–19]. After controlling her blood pressure, the patient was scheduled for a renal biopsy after 1 month. The histopathological examination of the biopsy exposed amorphous, pale, eosinophilic, acellular material in the mesangium, tubular wall, and walls of the arterioles. The eosinophilic material displayed a positive reaction to Congo red staining on polarized microscopy, giving an apple-green birefringence. These findings led to the diagnosis of amyloidosis. Electron microscopy exhibited randomly arranged fibrils within the mesangium. The presenting features were characteristic of amyloid fibrils. Immunofluorescence reactions within the glomeruli to the antibodies targeted against IgG, IgM, IgM, and kappa and lambda light chains returned negative. Antibodies against C3 deposits reacted positively. Bone marrow biopsy exhibited 6% plasmacytosis and minimal amyloidosis. The flow cytometry showed kappa plasma cells within the bone marrow. The patient was devoid of any lytic lesions, and a positron emission tomography (PET) scan did not show any elevated uptake or other signs of malignancy. Bone marrow biopsy findings and renal biopsy results allowed for a presumptive diagnosis of kappa light chain amyloidosis (AL amyloidosis). The patient was started on combination chemotherapy with bortezomib, dexamethasone, and cyclophosphamide for presumed AL amyloidosis. At the same time, the peptides in kidney tissue were evaluated through laser microdissection

(LMD) and liquid chromatography-mass spectrometry (LCMS), which were extracted from positively staining areas from Congo red stain. High levels of apolipoprotein C-II were detected on LCMS. Surprisingly, the reports were negative for kappa and lambda light chains, transthyretin, and serum amyloid A. These new findings gave an affirmative diagnosis of apolipoprotein C-II-associated amyloidosis involving the mesangium, and the previous diagnosis was disregarded. Chemotherapy was discontinued post-LCMS results. By that time, two short courses of chemotherapy were already delivered to the patient. Genetic testing of the apolipoprotein C-II confirmed a mutation at codon 69 with glutamate to valine substitution. This missense mutation was also apparent in the patient's son but not the daughter [7].

Differential Diagnosis

1. Light chain amyloidosis: Serum electrophoresis revealed kappa and lambda light chain ratio. Flow cytometry showed kappa plasma chains within the bone marrow. These tests provided an inclination toward amyloidosis but failed to reveal the true nature of the amyloidogenic proteins. LMD and LCMS must be utilized to identify and evaluate the polypeptides.

Discussion

Amyloids are proteins misfolded and aggregated through various mechanisms, losing their normal functionality [1, 5–10]. Identifying the type of protein involved in the formation of amyloid is important while differentiating amyloid diseases and helps determine their diagnosis and management [1–9]. There are more than 20 polypeptides that are known to cause amyloidosis in vivo [11]. In the absence of family history, hereditary amyloidosis is usually neglected when considering differentials of systemic amyloidosis [4, 5]. Sometimes hereditary amyloidosis can present sporadically despite having a negative family history like this case. The kidneys are one of the most affected organs in apolipoprotein-associated amyloidosis [5]. Renal amyloidosis often manifests as nephrotic-range proteinuria [12]. Signs of proteinuria include edema, anasarca, hypoalbuminemia, and hypercholesterolemia [5]. The clinical presentation of hereditary amyloidoses like apolipoprotein C-II-associated amyloidosis and light chain amyloidosis (AL amyloidosis) is very similar. This leads to patients being misdiagnosed initially as having acquired amyloidosis and managed incorrectly with chemotherapy [4–6]. Amyloidosis is diagnosed by the presence of amyloid in the abdominal fat pad or the biopsy of the affected tissue. Apple-green birefringence under the polarized light and fibrillar aggregates on electronic microscopy are classical signs of amyloidosis. However, the management of amyloidosis vastly depends on the type of protein involved in the formation of amyloid [9]. Detection of the structure of the polypeptide is

achieved by laser microdissection and mass spectrometry (LMD/MS) which is a highly sensitive and specific diagnostic tool [9]. Serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) with immunofixation were ordered; however, both tests are neither sensitive nor specific for amyloidosis [1–13]. SPEP revealed kappa monoclonal gammopathy and kappa monotypic plasma cells in the bone marrow giving an inclination toward AL amyloidosis. Renal biopsy confirmed the presence of amyloidosis by giving the characteristic apple-green birefringence. Electron microscopy reaffirmed amyloidosis by reporting aggregation of amyloid fibrils. Because all types of amyloid fibrils demonstrate morphological resemblance, they cannot be differentiated on electron microscopy [14]. Immunofluorescence was done to identify the proteinaceous element. Various antibodies are targeted against proteins commonly affected in amyloid diseases [4]. Despite the immunofluorescence showing no signs of kappa and lambda light chains, a presumptive diagnosis of AL amyloidosis was still considered by acknowledging the SPEP findings. Chemotherapy was given for the treatment of wrongly diagnosed AL amyloidosis. Chemotherapy has no role in treating hereditary amyloidosis, including apolipoprotein C-II disease, and could be harmful to the patient [4–6]. At the same time, LMD/LCMS was performed to identify the involved protein's structural component, and surprisingly the protein affected came out to be apolipoprotein C-II. The new diagnosis of apolipoprotein C-II-associated renal amyloidosis was made, and the chemotherapy was discontinued immediately. Apolipoprotein C-II is an essential cofactor for lipoprotein lipase and plays a significant role in cholesterol transport [8]. In the presence of polar lipids (e.g., phospholipids), the apolipoprotein adopts an α-helical structure [15–18]. However, in the extracellular lipid-free surroundings, the apolipoprotein assumes a β-pleated configuration which then self-aggregates into amyloid fibrils [6, 15–19]. It is thought that the tendency to form amyloid fibrils is due to the genetic mutation associated with apolipoprotein C-II [19].

Conclusion

Apolipoprotein C-II-associated renal amyloidosis is a rare type of systemic amyloidosis. Due to a significant increase in the number of proteins associated with amyloid formation, the chance of misdiagnosis is always a possibility. Identifying the etiology and the amyloidogenic protein involved in the early stages helps avoid mistreatment and protect the patient from unnecessary harm. More studies on the epidemiological aspect of the rare causes of systemic hereditary amyloidosis should be done. Emerging techniques like LMD/MS have established their usefulness in determining the polypeptide's structural configuration leading to a more accurate diagnosis. This highly specific diagnostic tool should be more frequently used in patients presenting with systemic amyloidosis. More clinical trials must be conducted in the future to develop an effective treatment modality for the currently incurable.

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Chapter 47
Phyllodes Tumor Misdiagnosed as Benign Prostatic Hypertrophy and a Cyst

Shashwat Shrivastava

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Discuss rare differential diagnoses like the phyllodes tumor, especially in young patients presenting with dysuria and urgency.
2. Appreciate the imaging findings specifically in this case where the pelvic magnetic resonance imaging revealed a hyperplastic nodule with clear boundaries. This nodule could have given an inclination toward an obstructing tumor.
3. Raise awareness due to the rarity of the phyllodes tumor of the verumontanum wherein it has potential to cause obstructive symptoms like dysuria.
4. Discuss the long-term follow-up which becomes mandatory in order to detect possible recurrence, especially when there is academic scarcity regarding the phyllodes tumor within the verumontanum.
5. Acknowledge that a phyllodes tumor may be misdiagnosed as benign prostatic hyperplasia (BPH) and a cyst.

Introduction

To our knowledge, there have been no reports of phyllodes tumors of the verumontanum. The case report discussed below might be the first case of verumontanum phyllodes tumor [1]. Phyllodes tumor is termed as a neoplasm with a foliated structure composed of cellular stroma and benign epithelial elements. There are published articles for phyllodes tumors of the prostate and seminal vesicles. However, the presence of this tumor in the verumontanum has not been reported anywhere.

S. Shrivastava (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao

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The clinical outcomes and management protocols of phyllodes tumors of the prostate are not very well established. Poorly defined clinical courses are largely a product of little to no follow-up [2]. This neoplasm, though rare, is generally observed in female breasts and shares morphological resemblance to prostatic phyllodes tumor [3].

A high index of suspicion should be maintained for a possibility of phyllodes tumor of the verumontanum, especially in young patients presenting with bladder neck obstruction. Prostatic phyllodes tumor very commonly presents with symptoms of urinary tract obstruction and microscopic or macroscopic hematuria [4]. This study depicts a young male patient presenting with a urinary tract infection and difficulty in micturition. His diagnosis was misinterpreted as benign prostatic hyperplasia, and he was scheduled for prostatectomy. The cytopathology and histochemical examinations of the excised lump revealed a phyllodes tumor of verumontanum [1].

We would like to spread awareness about the phyllodes tumor and its presentation. Due to the rarity of this tumor, especially the verumontanum, the probability of misdiagnosis is very high. Young individuals with salient symptoms of bladder neck obstruction must raise a suspicion for posterior urethral tumors [1]. We understand the academic scarcity regarding the clinical course, etiology, and management of phyllodes tumor of the verumontanum. We would like physicians to be mindful of rare tumors and tabulate them as potential differentials. More research involving a phyllodes tumor of the posterior urethra is due. Effort must be put on to recognize effective treatment options which demand optimal clinical trials, continuous follow-ups, and close monitoring of the patient. This will deem beneficial for the patient and improve clinical outcomes with minimal adversity. We encourage physicians to take home important points facilitating early diagnosis and hope to learn from the shortcomings. Below is an interesting case of a patient presenting with a phyllodes tumor of the verumontanum misdiagnosed as benign prostatic hyperplasia.

Clinical Case Presentation

A 42-year-old gentleman presented to the urology department with a 6-month history of pain during micturition and urinary urgency. He denied any frequency or hematuria. A general physical examination revealed nothing significant and was within normal limits. A hard nodule was palpable on the right side of the prostate on a digital rectal examination. A cystic structure and hyperplasia of the prostate were feared possibilities on transrectal ultrasound. The patient was subjected to urodynamic flow studies, revealing bladder outlet obstruction. The maximum urine flow rate identified was 6 ml/sec. His serum prostate-specific antigen (PSA) level came to 21 ng/ml, and the histopathology reports of transrectal ultrasound-guided prostate biopsy confirmed benign prostatic hyperplasia. Magnetic resonance imaging of the transverse section displayed long T2 signals of multiple lobulations on the right side of the prostate. The sagittal section showed a bump of the posterior urethra

extruding into the bladder. Plasmakinetic resection of the prostate was carried out after informed consent. Surprisingly, a lobulated lump with an intact external surface was discovered within the verumontanum, to which a pedicle connected it. This lump behaved as a valve for the posterior urethra, which contributed to the outflow tract obstruction. Visually, prostatic hyperplasia was not apparent. The postoperative course was uneventful, and the urine flow rate improved to 23 ml/sec. The lump was excised and sent for histopathological examination. Upon assessment, the lump was delineated as a phyllodes tumor of the verumontanum. The microscopic slides showed scattered myxoid degeneration, mesenchymal fibroblasts, hyperplastic fibers, and transitional epithelium on the surface. The cells of stroma were pleomorphic and giant with multiple nuclei. Immunochemical studies revealed expression of Ki-67 and 12% Ki-67 proliferation index. For the evaluation of Ki-67 positivity, 500 cells were counted altogether [1].

Differential Diagnosis

1. Benign prostatic hyperplasia: Histopathology reports of transrectal ultrasound-guided prostate biopsy revealed the likelihood of benign prostatic hyperplasia. Age of the patient along with elevated prostate-specific antigen levels should have raised the possibility of an alternate pathology.

What Was Misdiagnosed in This Case and Why?

The primary reason for the tumor being misdiagnosed as benign prostatic hyperplasia lies in the rarity of the phyllodes tumor of the verumontanum. Though phyllodes tumors are common in breasts, this was the first case reported of the tumor being present on the verumontanum in 2015.

Discussion

In January 2020, Ali et al, published a case report of a phyllodes tumor of the prostate in a 35-year-old man. Phyllodes tumor of the prostate is poorly understood in management, clinical importance, and outcome. The criteria for benign and malignant differentiation are also obscure [2]. Phyllodes tumor of the prostate was first reported by Cox and Dawson, which is a rare occurrence [3]. Phyllodes tumor is commonly seen in breast tissue. Histopathological examination shows multiple lobes with epithelial hyperplasia and variable cellularity of secretory and basal layers [4].

Ferrari et al., in 2014, described a phyllodes tumor of the prostate in a healthy young man presenting with symptoms of urinary tract infection [5]. Bostwick and colleagues presented a three-stage grading system for phyllodes prostate tumors by classifying the histological findings as low, intermediate, and high grades. They reported 50% recurrence rates even in low-grade tumors. There is an elevated risk of malignant occurrence with multiple recurrences of this tumor, leading to decreased survival rates [6]. There is a remarkable resemblance between the phyllodes neoplasm of mammary glands and the prostate. Typically, leaf-like stromal protrusions and cystically dilated ducts are seen in both neoplasms. They display variable features such as stromal necrosis, mitotic activity, multicellularity, and atypia [4]. Immunohistochemical staining with various markers like Ki-67, proliferative nuclear antigens, and protein 53 (p53) expression is used for assessment [7].

The verumontanum is a vital structure of the prostatic urethra due to the presence of ejaculatory ducts, which play an essential role in reproduction. Polyps or cysts of the verumontanum can present with the symptoms of urinary tract infection and dysuria [8]. Phyllodes tumors typically occur in the breast tissue of females [9]. However, it is rare in verumontanum, and therefore this patient presenting with atypical symptoms, was diagnosed with prostatic hyperplasia. Diagnostic investigations include per-rectal ultrasound, urodynamic flow studies, magnetic resonance imaging, prostate-specific antigen (PSA) levels, and histopathological evaluation of prostatic biopsy. Phyllodes tumors exhibit distinctive features of epithelial and stromal tissues, which are essential for diagnostic confirmation [9]. They are classified on the basis of histological appearances such as infiltration of lump margins, necrotic debris, overgrowth, atypical proliferation, or count of mitotic cells per high-power field [9]. The findings of multicellularity and mitotic activity signify malignancy and metastatic possibility in the breast. In this case report, the tumor was identified as low grade with the Ki-67 proliferation index of 12% and minimal tumor proliferation. The prognosis and dependable outcomes of phyllodes tumors are still ill-defined. The phyllodes tumors of seminal vesicles are usually regarded as high-grade tumors due to high mitotic activity, stromal proliferation, and pleomorphism.

For breast phyllodes tumors, wide excision with clear margins is indicated to prevent recurrences and improve survival [10]. In this case, complete resection of the tumor was performed by plasmakinetic intervention expecting better long-term outcomes. The patient fared well with quick postoperative recovery.

Conclusion

Phyllodes tumor of verumontanum is hardly reported, and this is the only case reported to date. This neoplasm is rare, known to occur in female breast tissue, and behaves similarly to the histological pattern in the prostatic tumor. Patients with phyllodes growth in the prostate present with prostatic hyperplasia symptoms and are often misdiagnosed before surgery. Young patients presenting with bladder

outflow obstruction and detected to have a posterior urethral mass should be suspected of a probable phyllodes tumor. Cystoscopy should always be considered to confirm the location and nature of the tumor. Complete surgical excision with intact margins is always advised. This patient behaved well postoperatively with excellent recovery and improved urodynamics. However, long-term follow-up is mandatory to look for recurrences and timely intervention. The nature of this neoplasm in terms of management, survival, and neoplastic behavior is still debatable.

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Chapter 48
Large Calcified Renal Artery Aneurysm Misdiagnosed as Intrapelvic Calculus

Shashwat Shrivastava

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Discuss and consult with the radiology department on the slightest of doubtful images which are not in consensus with the patient's clinical and physical examination.
2. Express the importance of practicing a guided surgical approach which could help prevent operative complications especially under adverse surgical findings.
3. Evaluate elderly female patients presenting in the sixth decade of life with hypertension and low-density lesions in the renal pelvis for a possibility of renal artery aneurysm and deem further tests.
4. Infer patients having a lesion occupying the course of renal artery branches as an underlying case of vascular pathology.

Introduction

The incidence of renal artery aneurysm (RAA) is remarkably low, approximating to 0.09% in the general population. However, in the hypertensive subgroup, the incidence rates can reach up to 2.5% [1]. Previously, most of the information on RAA came from autopsy studies, and the incidence was claimed to be extremely rare (<0.01%–0.09%) [2, 3]. The angiographic records improved the diagnosis accuracy, but the RAA incidence rates barely managed to rise to 0.3%–0.7% [3]. RAA is shown to have a slow growth rate with no difference in the rates to changes

S. Shrivastava (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao

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in aneurysm morphology or calcification [2]. We still have limited information on their occurrence, natural history, and prognosis with or without treatment [4]. The incidence rates are slowly on the rise due to frequent use of cross-sectional imaging [4].

Below is a rare occurrence of RAA, which was incidentally found during the operation [1]. The patient was mistakenly diagnosed with a large right renal calculus during ultrasound and was scheduled for percutaneous nephrolithotomy (PCNL) as a mandatory therapeutic intervention. In this case, the patient had concomitant calcifications within the renal artery aneurysm, which skewed the diagnosis toward a renal calculus upon imaging [1]. Laying emphasis on the images produced by the computed tomography (CT) scan and ultrasound becomes vital to differentiate between a calcified RAA and renal calculus. Important markers like acoustic shadow and low-density regions must raise concern for an underlying vascularity and facilitate radiologist consultation [1].

Also, paying close attention to these findings can avoid mistreatment and invasive therapeutic procedures which may potentiate harm especially under an alternate diagnosis. PCNL intervention around RAA territory can elevate the risk of aneurysmal rupture. This case was managed heroically by carefully abiding by the basics of PCNL procedure and maneuvering the operation route to escape the risk of aneurysmal rupture. More elaborate picture of this has been presented in the discussion section below.

This case report highlights the clinical markers which should raise suspicion for the likelihood of renal artery aneurysm and details on how the clinical adversity was rectified. It also signifies the importance of deducing the image findings accurately and going for second consultation amid uncertainty. We hope to educate physicians on a rare case of a patient having RAA being misdiagnosed as renal calculus and reduce further rates of misdiagnosis through learnings from this case report.

Clinical Case Presentation

A 69-year-old woman was admitted to the hospital after finding a large right renal calculus on ultrasound examination. She has a past medical history of renal calculi and diabetes mellitus. The ultrasound revealed the presence of a large calculus in the right renal pelvis, multiple calculi in the left kidney, and hydronephrosis in both the kidneys. The shadows in the right renal pelvis were described as a “hyperechoic focus with an acoustic shadow.” The ultrasound findings were reinforced after doing the kidney-ureter-bladder (KUB) radiograph. However, the core of the calculus was noticed to be radiolucent on plain X-ray. The patient was devoid of any discomfort, and signs and symptoms were unremarkable. The computed tomography urography (CTU) also yielded similar outcomes. A large calculus and hydrops in the upper calyx were seen on the right kidney, and the left kidney showed multiple left renal calculi with hydronephrosis. However, upon reassessing CTU results, a low-density lesion was seen within the calculus on a

non-contrast-enhanced CTU sequence. The density of the right renal calculus was noted to be 508 HU with a size of 3 × 2.3 cm. This low-density lesion was hypothesized as an underlying infection or presence of a foreign body. In the light of new findings, empirical antibiotics were initiated. Percutaneous nephrolithotomy (PCNL) was decided on the right renal pelvis calculus. Posterior lower renal calyces were chosen as the puncture site to establish an operation route. No calculus was witnessed in the renal pelvis during the operation; however, a calcified lesion was felt with the forceps under the mucosa of the renal pelvis. The doctors decided to remove the mucosa using a holmium laser until the calculus was visible. To their surprise, while cutting the surface of the calculus, a fluctuating unruptured aneurysm was observed. This led to a new diagnosis of an unruptured renal artery aneurysm (RAA), and the previous diagnosis was dismissed. The operation was ceased immediately, and the patient was transferred to the endovascular unit. Computed tomography (CT) angiography was performed after checking hemoglobin levels post-PCNL. CT angiography exposed multiple aneurysms in both the kidneys. The right RAA was the largest one, located on the first bifurcation of the renal artery. On a contrast-enhanced CT scan, a branch of the right renal artery exhibited connectivity with the aneurysm. The endovascular unit later performed an RAA embolization after the ninth day of PCNL [1].

Differential Diagnosis

1. Intrapelvic calculus: Hyperechoic lesion on the imaging test skewed the diagnosis toward an intrapelvic calculus.
2. Foreign body: Absence of typical signs of urolithiasis along with a high-density lesion must raise suspicion for a foreign body.
3. Infectious etiology: Strong echo on ultrasound and radiolucency on X-ray could have raised a possibility for air-fluid levels which is a predominant marker for underlying infection. Absence of fever pointed against an infectious source.

Discussion

A renal artery aneurysm is defined as the dilation of a segment of a renal artery that is twice the diameter of a normal renal artery [4]. The American College of Cardiology (ACC) and the American Heart Association (AHA) elucidate renal artery aneurysm as size >1.5 times the diameter of the adjacent disease-free proximal arterial segment [5]. The general incidence of RAA in the general population is estimated to be 1% [3]. RAA is typically witnessed in the sixth decade of life. Women being more prone to fibromuscular dysplasia have higher incidence rates of renal artery aneurysm [6]. A study done by Lumsden et al., on 28 reported RAA cases, brought similar results, with 18 women and 10 men being afflicted with

RAA. The etiology of RAAs was essentially atherosclerosis (75%), fibromuscular disease (21%), and Ehlers-Danlos syndrome (4%) [7]. The majority of RAA patients are asymptomatic with unremarkable signs [3]. A few patients present with hematuria, abdominal pain, and flank pain. Hypertension seems to be the most common clinical finding in patients having RAA. Calcifications are observed in 56% of the cases [8], making it crucial to distinguish between renal calculi and the presenting aneurysm. Computed tomography is the most prevalent contemporary diagnostic modality, followed by magnetic resonance imaging (MRI), ultrasonography, and catheter-based arteriography [8]. If the RAA has concomitant calcifications, its propensity to get misdiagnosed as a renal calculus escalates dramatically, especially if the calcified vessel traverses through the sinus [9]. The ultrasound and CT scan showed a 3 × 2.3 cm-sized calculus on the right renal pelvis in the presenting case. The CT scan noted a low central density of 508 HU which should have given an inclination toward RAA, especially when considering the patient's gender and her sixth decade of life. Ultrasound gave similar remarks of the presence of a hyperechoic lesion and plain films revealed the core as radiolucent. The two differentials to explain these findings were a foreign body and an underlying infection. Calcified RAA did not occur as a potential differential at the time, which mistakenly led to PCNL surgery [1]. The paper goes on to say how following two principles of PCNL surgery prevented the risk of complications. First is by following the direction of renal papillae and creating an operation route instead of directly targeting the renal calculus. Secondly, the surface was manipulated first during lithotripsy instead of focusing on the calculus's core [1]. Currently accepted indications for RAA intervention include the size of >2 cm, female gender within childbearing age, and symptoms like pain, hematuria, and medically refractory hypertension (HTN) [3]. Open repair and endovascular repair have been the two primary strategic interventions for RAA for a long time. Recent advancements in endovascular repair have given the procedure an equal footing with open repair, especially considering its minimally invasive attributes. Upon comparison, no differences are reported in mortality, perioperative morbidity, length of hospital stays, and freedom from re-intervention [3, 8]. However, Cochennec F et al. state that despite endovascular repair being a good alternative, it remarkably raises the propensity of aneurysmal reperfusion. The authors treat endovascular repair as the primary choice of intervention in elderly patients and patients with ruptured aneurysms [10]. For this patient, the endovascular repair was chosen because the calcified wall was destroyed by the PCNL procedure. Chen et al. thought of the possibility of the aneurysmal wall being corroded by urine, which might increase the risk of rupture [1].

Conclusion

The primary reason for the unnecessary invasive procedure was the wrong diagnosis that was made before the operation. Poor attention was paid to the anomalies noted on imaging. The radiolucent core was given a differential of an underlying

infection, which failed to respond to the antibiotic therapy. More awareness should be maintained while deciphering KUB, CT scan, and ultrasound statuses, and physicians should be mindful of rare causes in the setting of clinical adversity. Ring-like calcification in the kidney region and strong echo lesions around the renal sinus firmly hint at a possibility of RAA. The patient's age, female gender, history of hypertension, and low-density core surrounded by calcifications must have raised suspicion of an underlying renal artery aneurysm. Chen et al. admit that the absence of classical signs and symptoms of urolithiasis should have paved the way for an alternate diagnosis.

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Chapter 49
Anastomosing Hemangioma Misdiagnosed as Renal Cell Cancer

Rupanshu

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Differentiate the findings from imaging techniques of anastomosing hemangioma from that of renal cell carcinoma.
2. Compare and contrast the relationship between end-stage renal disease (ESRD) and renal cell carcinoma.
3. Discuss the differential diagnosis of anastomosing hemangioma.
4. Analyze anastomosing hemangioma and why it can be misdiagnosed as renal cell carcinoma.
5. Discuss the findings from imaging techniques of anastomosing hemangioma.

Introduction

Renal adenocarcinoma, or renal cell carcinoma or hypernephroma, is one of the most common subtypes of cancer seen in patients with end-stage kidney disease [1]. On the other hand, anastomosing hemangioma (AH) is a rare and benign vascular neoplastic vascular lesion. It is mainly composed of irregularly anastomosing sinusoidal-like spaces lined by endothelial cells. They are also more frequently seen in end-stage renal disease (ESRD) [2]. It is primarily asymptomatic, often discovered incidentally, as was found in this case by imaging studies, owing to previously existing benign or malignant tumors. The findings of anastomosing hemangioma

Rupanshu (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: rupanshu.rupanshu@martinus.edu

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from radiology are similar to those of renal cell carcinoma [3, 4]. Previous studies have also reported the incidental detection of anastomosing hemangiomas in the kidneys or the adrenal glands [3].

Ever since its original description in the genitourinary system, an increasing number of anastomosing hemangiomas have been reported, deep in the body in various organs, with the same histologic features. In 2009, Montgomery and Epstein described a series of vascular tumors—named "anastomosing hemangioma"—with a complex architecture characterized by anastomosing vessels, rare hobnailing, and benign behavior [5]. Anastomosing hemangiomas have been reported to occur most commonly in the kidney. However, they can occur in other sites as well, such as the testes, thigh, abdominal wall, ovaries, adrenal gland, liver, and even gastrointestinal tract. Patients suffering from ESRD with an anastomosing hemangioma can be listed for living-donor kidney or deceased-donor kidney transplantation. The difficulty comes in because the imaging findings for anastomosing hemangiomas are similar to those for renal cell carcinomas [6]. The mean age of presentation of an anastomosing hemangioma is 50 years (range, 15–83 years), and the male sex accounted for 68.8% of the cases reported in the literature. The patients were mostly asymptomatic, with 62% of the cases documented as incidental findings [7]. Microscopically, the typical pathological image is sinusoidal anastomosing capillary-sized vessels with biological features of infiltration. Herein, a case is described in which an anastomosing hemangioma was misdiagnosed as a renal cell carcinoma before kidney transplantation took place.

Clinical Case Presentation

A 35-year-old woman suffering from lupus nephritis was admitted to the emergency department for the suspected uremic symptoms of nausea and general malaise. She had received hemodialysis due to ESRD, and living-donor kidney transplantation from her father was planned. On preoperative contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI), a 1.7 cm renal cell carcinoma was found in the right kidney. After staining was done that took place after the radical nephrectomy, irregularly shaped vascular spaces of different sizes were observed, with these spaces having an anastomosing pattern. With these findings of the anastomosing hemangioma similar to those of a renal cell carcinoma on imaging, histology examination was important to confirm the diagnosis of anastomosing hemangioma and prevent misdiagnosis and delay in listing for kidney transplantation.

During the pretransplantation medical workup, an enhanced CT of the abdomen was done which revealed a heterogeneous mass of 1.7 cm in diameter, located in the upper pole of the right kidney. On MRI, it was revealed that this mass was presented with high signal intensity on T2-weighted images, with heterogeneous enhancement done in the right kidney. Based on these findings, a diagnosis of renal cell carcinoma, stage T1aN0, was made. Because the right renal mass was small, with

no associated symptoms, a simultaneous right radical nephrectomy and kidney transplant were planned by the surgeon and urologist.

Open radical nephrectomy was performed through an incision in the subcostal area; the patient was then positioned for the kidney transplant. Hematoxylin and eosin staining was performed after nephrectomy revealed irregularly shaped vascular spaces of various sizes with an anastomosing pattern. After immunostaining, the sample was positive for cluster of differentiation (CD)34 and CD31 and negative for podoplanin, human herpesvirus-8, and glucose transporter-1. Based on these findings, a definitive diagnosis of the anastomosing hemangioma was made.

Her laboratory values indicated levels of blood urea nitrogen and serum creatinine had increased manyfold, with her serum inorganic phosphate level also higher than normal.

The treatment was planned with emergent hemodialysis and living-donor kidney transplantation from her father. After the kidney transplantation, good renal function was achieved, with no tumor recurrence [8].

Differential Diagnosis

1. Angiosarcoma: Hemangiomas are rare and benign as they don't metastasize to other tissues. Angiosarcoma has diffusely infiltrative growth patterns also seen in anastomosing hemangioma with multilayering of endothelial cells and mitotic activity.
2. Kaposi sarcoma: Kaposi sarcoma generally affects immunocompromised populations.

Discussion

When Montgomery and Epstein first described an anastomosing hemangioma of the genitourinary tract, it was concluded that such types of hemangiomas were rare and benign in contrast to an angiosarcoma which is cancer that afflicts the inner lining of blood vessels and lymph [5]. Hence, nephrectomy was not required clinically for this benign vascular neoplasm. Moreover, patients having ESRD who have an anastomosing hemangioma can be listed for living-donor kidney transplantation or registered for deceased-donor kidney transplantation. The patient was scheduled for a liver transplant; therefore the quick surgical removal of the heterogeneously enhancing kidney tumor took place immediately to prevent a delay in the transplant. The difficulty comes in that the imaging findings for anastomosing hemangiomas are similar to those for renal cell carcinomas, including heterogeneous enhancement of lesions on a CT scan and hyperintensity on T2-weighted MRI images [6]. As subcutaneous biopsy of vascular lesions does pose a considerable challenge because of the risk of profound bleeding [3], anastomosing hemangiomas have been diagnosed by nephrectomy in the majority of reported cases.

During the management of kidney cancer during medical workup for kidney transplantation, there's some controversy [9–15]. It results in the delay of the procedure, which is very alarming and daunting for the patient. Hence a concurrent radical nephrectomy and kidney transplant are recommended for these patients. Moreover, partial nephrectomy is also recommended for small solitary renal cell carcinomas because of the positive nephron-sparing effect [16].

The average size of anastomosing kidney hemangiomas is 1.5 cm (range, 0.1–8.0), with the hemangioma being <4 cm in the majority of cases [17]. Other than the radical nephrectomy, which is recommended for diagnosis and treatment of these patients, partial nephrectomy can also be suitable to preserve the residual renal function. The goal of a partial nephrectomy which is also called kidney-sparing surgery is to preserve as much healthy kidney tissue as possible by simply removing the malignant tumor or center of the infestation. But it was seen that the residual renal function was decreased for the patient because the patient was diagnosed with ESRD. Hence radical nephrectomy was the best option to secure adequate surgical safety margins. The right radical nephrectomy and kidney transplant were performed at the same time because the right renal tumor was minor and had no related symptoms. When hematoxylin and eosin staining was performed after radical nephrectomy, it revealed irregularly shaped vascular spaces of various sizes, with an anastomosing pattern. These results led to the final diagnosis of anastomosing hemangioma. Good renal function was attained following kidney transplantation, and there was no return of the malignancy.

Conclusion

In conclusion, it was found that in this case, an anastomosing hemangioma was misdiagnosed as renal cell carcinoma from the findings of MRI and CT scan. The residual renal function of the patient was also decreased due to the ESRD the patient had, which prompted radical nephrectomy instead of the partial nephrectomy to be the best course of treatment with hopes to secure appropriate surgical safety margins. In order to avoid delay in the transplantation, which can take place due to these findings in the pretransplantation medical workup, the prompt surgical resection of the heterogeneous enhancing renal mass must be proceeded.

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Chapter 50
Urethritis Associated Hematuria Misdiagnosed as C1q Nephropathy

Shashwat Shrivastava

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Demonstrate the emphasis of adhering to the basics of careful urine analysis in order to distinguish between glomerular and non-glomerular hematuria.
2. Appreciate the importance of clinical and histological correlation, discussion with the pathologists, and morphology of urine sediments in having a better understanding of the clinical scenario.
3. Establish the use of cystourethroscopy in the light of uncertainty. This can help to further explore undiscovered causes of isolated macrohematuria.
4. Illustrate the significance of differentiating between isomorphic and dysmorphic erythrocyturia in making a confirmatory diagnosis.

Introduction

One of the most common causes of isolated macrohematuria in a young adult is immunoglobulin A (IgA) nephropathy. Other common causes include thin basement membrane disease and Alport syndrome, given the hematuria of glomerular origin [1, 2]. Despite low sensitivity, phase-contrast microscopy could be deemed essential in differentiating the hematuria between glomerular and non-glomerular causes [3]. C1q nephropathy is a rare glomerulopathy that commonly affects pediatric patients and young adults. Due to the rarity of the disease, the prevalence rates range from 0.2 to 2.5% [4, 5]. C1q nephropathy is defined by the presence of C1q

S. Shrivastava (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao

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dense deposits within the mesangium. The prevalence rates are more significant in the pediatric age group, ranging from 2.1 to 9.2% [6].

Below is an interesting case of misdiagnosis, reported by Mandal et al., of a 19-year-old patient having persistent painless macroscopic hematuria for 3 months. The initial diagnosis was made as C1q nephropathy after noticing C1q dense deposits on immunofluorescence. Having no signs of improvement while being on immunosuppressants raised a possibility for a potential misdiagnosis. Further testing revealed prostatic urethritis, which was then treated with doxycycline. The patient responded to the medical treatment and improved dramatically [7]. The most common cause of nongonococcal urethritis is *Chlamydia trachomatis*, accounting for 20–50% of the cases [8]. All patients having urethritis must undergo a nucleic acid amplification test (NAAT) to look for *Chlamydia trachomatis* [9].

This case reveals the importance of being mindful of the results of fundamental tests like urine light microscopy. Inability to differentiate between glomerular and non-glomerular hematuria during the early stages can potentially facilitate invasive testing. Subjecting patients to invasive tests like renal biopsies can expose the patient to unnecessary harm. Providing medications to a wrongly diagnosed condition can elevate the risk of adverse effects from the given drug.

This case was chosen recognizing the rarity of C1q nephropathy. Though this disease was first explained more than three decades ago, we still lack the comprehensive details on its development and etiology [5]. Sometimes C1q deposits could be indicative of an underlying pathology, and sometimes it could be found incidentally without nephrotic syndrome such as this case [7]. Our goal is to raise awareness of such variations and discrepancies before concluding the diagnosis with C1q nephropathy and consider other differentials leading to isolated macrohematuria. Prostatic urethritis should also be noted while evaluating differentials for non-nephronal hematuria. Choosing tests like cystourethroscopy can help to detect other causes of isolated macrohematuria. Cystourethroscopy should be considered especially if no RBC casts are seen on urine light microscopy which then allows time to hold off invasive tests like renal biopsy. We hope to educate physicians and facilitate learning from this case of isolated macrohematuria due to prostatic urethritis which was misdiagnosed as C1q nephropathy.

Clinical Case Presentation

A 19-year-old male came with persistent painless macroscopic hematuria for 3 months. His past medical history was not suggestive of lower urinary tract infections, nephritic/nephrotic syndromes, and trauma. His family had no history of any renal disease. The patient had normal visual acuity and hearing. The patient did not have any recent sexually transmitted infections. The physical examinations were within normal limits, and no pallor and edema were observed. Laboratory tests revealed Hb of 15.8 gm/dl, total leukocyte count (TLC) 12,800/cmm, red blood cell

(RBC) 4.5 million/cmm, platelet 2 lakh/cmm, prothrombin time (PT) 29.6 seconds, activated partial thromboplastin time (APTT) 35 seconds, blood urea nitrogen (BUN) 7 mg/dl, serum sodium 138 meq/l, serum creatinine 0.93 mg/dl, total protein 6.5 gm/dl, and albumin 4.1 gm/dl. The blood pressure was 120/80. Urine light microscopy showed numerous RBC/hpf without any casts. Mild proteinuria was also observed upon urine spot protein/creatinine ratio on two separate occasions (0.4 and 0.9). Lupus serology, antinuclear antibody, and double-stranded DNA were negative. C3/C4 complement levels were within normal limits. The abdominal ultrasound showed a normal-sized kidney, normal echogenicity, and visible corticomedullary differentiation. Initially, IgA nephropathy was considered a potential diagnosis due to the presence of persistent gross hematuria, and a renal biopsy was scheduled which later reported C1q nephropathy. The light microscopy revealed normal renal histology, and C1q deposits were witnessed on immunofluorescence. Despite giving deflazacort (60 mg/day) for 4 weeks, the hematuria persisted with no signs of improvement. A change in medication regimen was considered. Mycophenolate mofetil (2 mg/day) was added along with prednisolone (60 mg), and deflazacort was discontinued. Upon reassessment after 1 month, the macrohematuria persisted despite having good medication compliance.

The patient's persistent presentation of macrohematuria was considered atypical, and a second renal biopsy was ordered to identify the underlying cause of hematuria. The results were within normal limits with no increase in cellularity. The basement membrane was thin, and no segmental sclerosis was seen. The overall report was unremarkable. Immunofluorescence revealed C1q mesangial deposits and minimal IgG and IgM deposition. On electron microscopy, several electron-dense deposits were seen in the mesangium giving an inclination toward C1q nephropathy. The patient also admitted to passing blood clots upon repeat questioning. The urine culture of midstream was negative. Upon having cystourethroscopy, the prostatic urethra showed significant congestion indicating prostatic urethritis. The patient was given an empiric dose of doxycycline for 2 weeks leading to dramatically improved symptoms. Repeat examination after 2 weeks showed clear urine without any hematuria or proteinuria for the first time in 5 months [7].

Differential Diagnosis

1. C1q nephropathy: The patient was diagnosed with C1q nephropathy after the immunofluorescence revealed C1q deposits. To much surprise, these deposits were a benign happening and the cause of isolated hematuria was a non-glomerular etiology.
2. Thin basement membrane disease: Thin basement membrane disease must always be an important differential for patients experiencing hematuria.
3. IgA nephropathy: Considering the patient's age, the most common cause of isolated macrohematuria is IgA nephropathy.

What Was Misdiagnosed in This Case and Why?

The patient's isolated macrohematuria was misdiagnosed as C1q nephropathy. The diagnosis was misled due to the renal biopsy, which demonstrated C1q deposits on the renal mesangium. C1q deposits were a benign finding proven by lack of improvement in hematuria despite being on medication regimen.

Discussion

This is a fascinating case, witnessed by Mandal et al., of a patient complaining of isolated gross hematuria with unremarkable clinical signs and symptoms. It is essential to differentiate between glomerular and non-glomerular hematuria for making appropriate clinical decisions. Glomerular hematuria is identified by the presence of red blood cell casts, dysmorphic red cells, and albuminuria (500 mg/24 h). Acanthocytes, also called spur cells, are irregularly shaped red cells with vesicle-like protrusions. Acanthocytes become a highly specific (98%) indicator for glomerular disease if their numbers exceed 5% on phase-contrast microscopy [10]. Though this criterion is relevant clinically, its absence does not entirely rule out the possibility of glomerular disease. IgA nephropathy, Alport syndrome, and thin basement membrane disease are the three significant disorders in patients who present with isolated macrohematuria [2]. Upon examination, this patient denied any recent history of infections and had normal visual acuity and hearing. The diagnosis gravitated toward C1q nephropathy due to the presence of C1q deposits within the mesangium and a few of them in the subendothelial region. C1q nephropathy was first chronicled in the year 1985 by Jennette and Hipp. The definition is histological, with characteristic C1q deposits in the renal mesangium in a dominant or codominant fashion and the absence of clinical features indicative of systemic lupus erythematosus (SLE) and membranoproliferative glomerulonephritis (MPGN) [4, 7]. The serological markers show negative antinuclear antibodies and normal complement levels [11]. One of the studies done by Vizjak et al. clearly emphasized the rarity of C1q nephropathy among healthy individuals. C1q immune deposits were commonly seen in patients having tubulointerstitial nephritis, proven hypertensive nephrosclerosis, thin basement membrane nephropathy, and hantavirus nephropathy. Markowitz et al. described C1q deposits as a nonspecific marker of increased mesangial trafficking in the setting of glomerular proteinuria [6, 12]. The pathogenesis of C1q nephropathy lacks clarity, and due to the avid use of C1q staining, the benign positive rates are escalating. This portrays a particular bias leaving potential differentials under the shadow [7]. This patient had a slight exception where C1q deposits were observed in a healthy individual with no history of preexisting renal condition and no family history of renal abnormalities. One of the key tests that pointed against the glomerular cause of hematuria was urine light microscopy, where the erythrocytes were normal appearing without any casts or dysmorphic features.

Plan of Action, the Points Clinician Should Consider. Pearls of Knowledge to Consider and Pitfalls to Avoid

It is essential to understand how careful interpretation of urine light microscopy can avoid invasive tests. This patient had normal-appearing red blood cells without casts which is indicative of a non-glomerular pathology. This understanding could have shifted the focus on exploring non-glomerular etiology, facilitating the probability of early detection.

If Misdiagnosed, Was It Realized Later? How Was It Rectified?

The medications given for C1q nephropathy were discontinued immediately. Doxycycline was given for 2 weeks after revelation of prostatic urethritis on cystourethroscopy, which led to complete resolution of the hematuria.

Conclusion

The patient was incidentally diagnosed with C1q nephropathy due to the presence of deposits on immunofluorescence. He was scheduled for cystourethroscopy since hematuria persisted even after being on immunosuppressive agents. Congestion of the prostatic urethra was observed, which responded quickly to doxycycline, and hematuria resolved. Due to the absence of any renal condition, these C1q deposits could be benign lesions or represent the initial stages of C1q nephropathy. Also, falling back to the fundamentals and carefully interpreting urine light microscopy could have avoided unnecessary renal biopsies and harmful invasive tests. More emphasis should be made on the urological aspect while tabulating differentials of isolated macrohematuria, especially when commonly occurring pathologies like IgA nephropathy and thin basement membrane disease are ruled out.

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Chapter 51
Primary Mucinous Adenocarcinoma of Renal Pelvis Misdiagnosed as Calculus Pyonephrosis

Maria Mohammed Javed Shaikh

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Evaluate and create a differential diagnosis in patients presenting with hematuria, pyuria, and flank pain.
2. Discuss the clinical and histological evidence in order to reach a definitive diagnosis.
3. Enumerate the treatment plan for primary mucinous adenocarcinoma.

Introduction

There are different subtypes of renal cancer. Transitional carcinoma accounts for over 90% of all cases. The other includes squamous cell carcinoma, adenocarcinoma, and clear cell carcinoma. All of the above present similarly with flank pain, hematuria, abdominal discomfort, and weight loss [1]. Primary mucinous adenocarcinoma of the renal pelvis is a rare malignant disease. Mucinous adenocarcinoma is likely ovarian and colorectal in origin. It consists of abundant mucinous secretion consisting of 50% of the total tumor volume [2, 3]. Primary mucinous adenocarcinoma of the renal pelvis is often diagnosed accidentally by nephrectomy and is associated with an increase in CEA levels—CEA 19-9 [4]. It is poorly identified and, therefore, misdiagnosed as calculus pyonephrosis. It has three different subtypes with tubulovillous being the most common, followed by

M. M. J. Shaikh (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: maria.shaikh@martinus.edu

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mucinous, which is 21.5%, and papillary type is least expected, accounting for only 7%. Thus far, the total number of cases that have been reported is 100; the first case of primary mucinous adenocarcinoma of the renal pelvis was reported in 1960 [5]. It is attributed to be caused by chronic irritation of the endothelium due to urolithiasis, chronic inflammation, and infection. Hydronephrosis can contribute to glandular metaplasia of the urothelium, dysplasia, and adenocarcinoma [2]. It is derived from metaplastic endothelium. There is difficulty in diagnosing this condition before the operation because it is rare and lacks characteristic symptoms and distinctive radiological features [6]. Overall only 100 cases have been reported worldwide. It has been studied that these cases are more commonly found in Asian countries which account for about 83.3%; most cases have been reported in India (33.3%). More cases accounted for in males (63.3%) as compared to females (33.3%), likely because incidence of smoking is higher in males. In ovarian cancer, mucinous type, tobacco smoking is the only clinical risk factor [3]. It most likely clinically presents as flank pain and discomfort, abdominal mass, and hematuria. These symptoms resemble a triad of renal malignancy suggesting long-standing or late-stage disease. It has a poor prognosis, and no standard treatment has been established because of the rarity of the tumor. However, it has been studied that focused history and physical examination can aid in the preoperative diagnosis of the tumor. It is speculated that serum tumor markers along with computed tomography (CT) scans can improve the likelihood of diagnostic accuracy rates. Calculus pyonephrosis is characterized by infectious hydronephrosis and accumulation of pus and calculi associated with pyogenic destruction of renal parenchyma, with complete or almost complete loss of renal function, seen in patients with kidney failure, also called nephropyosis. It can also cause urosepsis. It is crucial for the surgeons to bear in mind the possibility of malignancy while conducting percutaneous nephrostomy (PCN) on patients with pyonephrosis mainly in those who also viewed that radiotherapy, chemotherapy, and chemoradiotherapy should be proposed for colorectal and ovarian carcinoma, mucinous type [2, 3]. For this tumor, it is recommended that after nephroureterectomy adjuvant therapy with chemotherapy can improve the prognosis. Herein, we discuss the case with primary mucinous adenocarcinoma of the renal pelvis, initially misdiagnosed as calculus pyonephrosis.

Clinical Case Presentation

A 66-year-old man presented to the hospital complaining of a 2-month history of fever and right waist pain. He was devoid of nausea, vomiting, hematuria, and pyuria. The past medical history was consistent with a hepatitis B infection. After admitting the patient, a computed tomography scan showed multiple renal pelvic calculi, stenosis of the ureter, and severe hydronephrosis with cortical thinning. He was diagnosed with Calculus pyonephrosis and underwent percutaneous

nephrostomy (PCN). A considerable amount of gelatinous material was drained via a PCN catheter without urine. The catheter was blocked the second day, and PCN was performed again. However, these methods failed to curb the patient's fever, and he was transferred to the hospital. Physical examination was generally normal except for percussion tenderness in the right kidney region. Laboratory tests demonstrated elevated red (20/μL) and white blood cells (200/μL) in the urinalysis, a decreased red blood cell count (4.29 × 1012/L) and hemoglobin concentration (118 g/L), and elevated CEA (7.89 ng/mL) and CA19-9 (5.79 ng/mL). HBsAg was positive. Liver function, renal function, coagulation function, and stool routine examination were generally normal. Chest computed tomography scan showed an old tuberculosis scar on the right lung. The doctors suspected that he had gastrointestinal cancer and performed an upper gastrointestinal endoscopy and a colonoscopy. However, nothing abnormal was found on the gastric or colonic mucosa, and the gelatinous material collected from the PCN catheter indicated no malignancy. Doctors diagnosed the patient with Calculus pyonephrosis and malignant tumor to be excluded. An open radical nephrectomy was then performed. His kidney was markedly enlarged with a thinning renal cortex. There was an unintentional spillage of gelatinous material because of the two PCN procedures. Therefore, the doctors only performed a nephrectomy without a total ureterectomy. After opening the kidney, there were polypoids, gelatinous material, and stones filling the renal pelvis. Histologically, the tumor was detected in intestinal metaplasia and glandular acini with multiple extracellular mucins. Immunohistochemistry revealed that tumor markers CDX2, CEA, villin, and ki67 (60%) were positive and tumor markers CA125, MUC6, CK7, CD20, GATA3, S100P, and SATB2 were negative. The histologic diagnosis of primary mucinous adenocarcinoma of the renal pelvis was conducted. This patient was advised to undergo adjuvant chemotherapy because of the spillage of gelatinous material during surgery, but he refused. After 1 year of follow-up, the patient reported no discomfort, and a computed tomography scan indicated no sign of recurrence. Upon testing the serum tumor markers it indicated that CEA was 3.57 ng/mL depicts a timeline of the diagnosis, interventions, and outcomes [1].

Differential Diagnosis

1. Calculus pyonephrosis—Calculus pyonephrosis and primary mucinous adenocarcinoma of renal pelvis both drain mucinous material on PCN. Histopathological analysis can help differentiate calculus pyonephrosis from primary mucinous adenocarcinoma of the renal pelvis.
2. Ureteropelvic junction stenosis with stones in the renal pelvis—Urologist must consider a possibility of primary mucinous adenocarcinoma of renal pelvis in patients presenting with renal stones accompanied by severe hydronephrosis and chronic inflammation.

Discussion

Mucinous adenocarcinoma is usually of colorectal and ovarian origin. It is characterized by abundant mucus production [2, 3]. As seen in the patient above, percutaneous nephrostomy drained gelatinous material. Multiple renal pelvic calculi, stenosis of the ureter, and severe hydronephrosis were seen, along with cortical thinning. These features made it easy to diagnose Calculus pyonephrosis. PCN can also cause iatrogenic spillage and tumor cell seeding. It is essential to be cautious before conducting PCN for pyonephrosis and consider the possibility of malignancy. The most common presenting features are flank pain, hematuria, abdominal mass, and discomfort. All the features except for mass do not indicate malignancy. Out of all the total cases reported, it has been studied that only 20% of the cases showed elevated tumor marker CEA 19-9.

Plan of Action, the Points Clinician Should Consider, Pitfalls to Avoid, and Pearls of Knowledge to Consider

Taking careful history, physical examination, and measuring tumor marker levels accompanied by CT scans can improve the diagnosis accuracy rates. Primary adenocarcinoma of the renal pelvis or ureter is a rare entity. Urologists should always have a window of suspicion whenever mucinous material is seen on a nephrostomy tube. No standard treatment has been established so far. It has been studied for pelvis tumor nephroureterectomy with a bladder cuff accompanied by chemotherapy can improve the prognosis [7]. No surgical procedures have been proposed for this tumor yet. Only after a histopathological analysis, a definitive diagnosis of primary mucinous adenocarcinoma can be made [8]. Primary mucinous adenocarcinoma has a lousy prognosis, and most of the patients die within 2–5 years of follow-up [9].

Conclusion

Although on percutaneous nephrostomy, Calculus pyonephrosis and primary mucinous adenocarcinoma drain gelatinous material, it is worth noting that it can be differentiated. Common clinical presentation of Mucinous Adenocarcinoma are flank pain and abdominal pain [10]. If the lesion bleeds when touched, it's possibly a pelvic tumor, while a lesion in pyonephrosis does not bleed easily.

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Chapter 52
Kidney Inflammatory Myofibroblastic Tumor Misdiagnosed as a Metastatic Malignancy

Maria Mohammed Javed Shaikh

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Create an appropriate differential diagnosis in patients presenting with symptoms of gross hematuria.
2. Evaluate clinical and radiological evidence to come up with a diagnosis of kidney inflammatory myofibroblastic tumor.
3. Confirm the diagnosis based on immunohistochemical and microscopic analyses.
4. Discuss the identification and early treatment of infectious causes of inflammatory myofibroblastic tumors of the kidney.
5. Emphasize the need for follow-up to prevent recurrence and metastasis.

Introduction

An inflammatory myofibroblastic tumor (IMT) is also called an inflammatory pseudotumor. It is a mesenchymal tumor characterized by spindle cells from fibroblasts and infiltration of different types of inflammatory cells [1]. Only 48 cases of IMT have been reported so far from 1972 to 2019. The first-ever case of IMT was reported in 1937. From the published databases, it was reviewed that out of a total of 48 cases, 37 occurred in the renal parenchyma, and the other 11 cases occurred in the renal pelvis. It occurs equally in both men and women. It can occur in a wide range of age groups from 3 to 75 years old. It was found that 73% of the cases occurred in the age

M. M. J. Shaikh (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: maria.shaikh@martinus.edu

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population over 40 years old. Only five cases accounted for in children below 14 years old. There is no sex predilection of this disease. The most common location of IMT is the lungs; extrapulmonary sites include the head, neck, liver, retroperitoneum, ventricles, bladder, and spinal canal [2–10]. In the genitourinary system, the most common site is the bladder [11]. The kidney is an unusual site for IMT. Fifty percent of cases involve the left kidney and the remaining 50% of the cases in the right kidney. IMT was notably found to be more commonly occurring in the upper pole of the kidney than in the lower pole. The literature suggests that spindle cell proliferation is reactive hyperplasia that occurs due to chronic inflammation, surgery, or trauma. However, etiological factors are still unknown. Long-standing nephrolithiasis is also suspected as one of the causes of IMT. IMT was initially thought to be an inflammatory pseudotumor. However, later research classifies this as a borderline neoplasm because it was found that spindle cells were the main part of these tumors [1]. As per a few scholars, IMT has been redefined as low-grade neoplasm. It is crucial to identify these tumors and treat them as it has a potential for metastasis, is locally invasive, and can recur. It is challenging to diagnose it preoperatively because it is a rare entity involving the kidneys and is often missed by the physician and misdiagnosed as a malignant disease both clinically and pathologically [4, 5]. It occurs equally in both men and women. It can occur in a wide range of age groups. It is more often diagnosed in children than adults of both sexes equally. However, extrapulmonary forms occur more commonly in adult women [2]. Most commonly it clinically presents mainly as lower back pain and abdominal pain. Other clinical presentations include hematuria, anemia, recurrent high fever, abdominal discomfort, lethargy, and weight loss. It can also be an incidental finding in imaging. The tumor size reviewed ranged from 1.5 cm to 13.5 cm. In clinical practice, the first-line treatment is surgical resection of the lesion. In patients with bilateral masses, single kidney, or renal insufficiency, a biopsy with intraoperative pathological assessment was highly suggested by some authors to avoid needless removal. However, it is still disputable as the diagnosis can be made only post nephrectomy [22]. It is linked to the anaplastic lymphoma kinase (ALK) gene, located on 2p53 in 50% of cases. Fusion partners are clathrin heavy chain, tropomyosin, and ran-binding protein, correction-genes that have been seen in patients who are ALK-positive. Fusion proteins involved with ALK-negative genes are reactive oxygen species (ROS-1) and platelet-derived growth factor (PDGF) genes [12, 13]. ALK-positive cases are more commonly found in children. Herein, we discuss a case of renal IMT in a patient with a history of long-standing nephrolithiasis to improve the understanding of the disease and impart the patients with better treatment and management.

Clinical Case Presentation

A 77-year-old female with a past medical history of bilateral renal calculus for 15 years was admitted to the urology department. She complained of recurrent painless gross hematuria for 1 month. At the time, doctors treated her with cephalosporin, which was not effective. Computed tomography (CT) imaging showed a mixed

density and slightly heterogeneous enhancement of the lesion in the middle pole of the left kidney and adrenal enlargement ipsilaterally. The patient underwent surgical treatment by retroperitoneoscopic left radical nephrectomy plus adrenalectomy. On microscopy, a large number of typical spindle cells surrounded by plasma cells and lymphocytes were observed. Immunohistochemical analyses indicated that these spindle cells were positive for vimentin, cytokeratin (CK), Ki-67, CK7, cluster of differentiation (CD) 34, and CD31 and focally positive for CD10 and anaplastic lymphoma kinase (ALK-1). So, a definitive diagnosis of IMT was made. The patient improved after the operation, and no recurrence or metastasis was noted during the 22-month follow-up. Laboratory investigation showed mild anemia and infection on routine blood work, with a hemoglobin level of 10.0 g/dL and a leukocyte count of 12.2 × 109 cells/L. On urinalysis, it showed a large number of red blood cells. Other laboratory results were within the normal limits, and no malignant cells were noted in three urine cytopathologic analyses. On imaging, only bilateral renal calculus was noted on abdominal ultrasound; however, no space-occupying lesions were noted. CT imaging showed a slightly heterogeneously enhancing mass in the middle pole of the left kidney and an ipsilateral adrenal enlargement, which was suspected as potential metastasis. Treatment-radical nephrectomy was performed retroperitoneoscopically on the left kidney along with adrenalectomy [1].

Differential Diagnosis

1. Renal cell carcinoma—IMT is a benign tumor and has little potential for metastasis; however renal cell carcinoma can spread hematogenously.
2. Angiomyolipoma—Angiomyolipoma consists of fat and muscle cells; however, kidney IMT is composed of inflammatory cells, spindle cells, and fibroblasts. Moreover, angiomyolipoma has been linked to TSC1 and TSC2 genes.
3. Xanthogranuloma—Xanthogranuloma is caused by chronic nephrolithiasis and infection. Biopsy will help differentiate xanthogranuloma from kidney IMT.

Discussion

IMT is a rare type of renal mesenchymal tumor composed mainly of spindle cells and various inflammatory cells. It can occur in a wide range of age groups between 3 and 75 years [7, 8]. Seventy-three percent of the cases reported were found in people 40 years old. According to scholars, IMT can also be caused by Epstein-Barr virus [8]; others are found to be associated with hep B virus infection [9]. Etiological factors could be autoimmune or infectious. Some infectious causes with *Mycobacterium tuberculosis* and *Eikenella corrodens* have also been reported [14, 15]. IMT of kidneys does not have distinctive clinical and radiological features making it difficult to diagnose. IMT in kidneys is slow-growing, occurring in middle-aged and elderly patients. It is usually confined to a single organ. It most

commonly manifests as pain and hematuria. A few cases presented with anemia, weight loss, fever, night sweats, and thrombocytosis, all of which resolved after treatment gradually. It is imperative to differentiate renal IMT from renal malignant disease. It lacks distinctive radiologic features, causing misinterpretation as a malignancy. It appears as hypoechoic and intratumoral vascular distribution on ultrasound, making it difficult to differentiate from malignancy [16]. CT and magnetic resonance imaging (MRI) are better for the diagnosis of kidney masses. Cystic renal IMT should be differentiated from cystic renal cancer [17]. The conclusion diagnosis usually depends on histopathological and immunohistochemical stains. On immunohistochemical stain, it usually appears as spindle cells with collagen, infiltrating lymphocytes, and plasma cells. The above case was misdiagnosed as malignant renal disease metastasized to the ipsilateral adrenal gland. In addition to surgery, chemotherapy should also be used as adjuvant therapy. Radiotherapy is mainly used in IMT involving the head and neck. It has been studied that high-dose fractionated radiotherapy is very effective for skull and nasopharyngeal IMT [18]. For ALK-positive cases, target therapy ALK inhibitors like crizotinib can be considered [19]. For ALK-negative cases, nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce the tumor size and cure the disease [20]. Antibiotics can be used for infectious causes of IMT [21]. Corticosteroids are used in younger patients with bilateral renal IMT. Radiotherapy is an option when NSAIDs, steroids, and surgery fail to control IMT in the kidneys effectively.

Conclusion

The kidney is an unusual site for IMT neoplasm. Physicians need to be aware of the possibility of IMT in the differential diagnosis while evaluating renal masses to avoid misdiagnosis. Although IMT is not a malignant disease, it is reported to be associated with renal cell carcinoma, which should be considered in the management and prognosis of the patient. Surgery and adjuvant target and chemotherapy are considered to be first-line treatments. As there is a possibility of recurrence and metastasis, follow-up is crucial.

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Part X
Neurology

Chapter 53
Guillain–Barré Syndrome Misdiagnosed as Posterior Circulation Stroke

John Michael Baratta

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Demonstrate appropriate understanding of signs and symptoms of the condition that were presented in this case.
2. Enumerate the various diagnostic techniques to rule out the differential diagnosis of this condition.
3. Discuss the various treatment modalities of this condition.
4. Describe the course of development of this condition by studying this case presentation.
5. Discuss the symptomatology of this condition.

Introduction

Guillain–Barré syndrome is an acute, demyelinating polyneuropathy which originates through autoimmune mechanisms following an infectious illness [1]. It is most traditionally associated with sequelae of *Campylobacter* infection, although other triggers including a variety of infections and vaccinations have been implicated [2, 3]. Due to damage to the myelin of peripheral nerves, affected patients often develop bilateral, ascending weakness, sensory impairments, and loss of deep tendon reflexes. While the course can progress insidiously, it is most concerning

J. M. Baratta (✉)
Department of Physical Medicine and Rehabilitation, Medical Director of Stroke Rehabilitation, University of North Carolina School of Medicine, Chapel Hill, NC, USA
e-mail: john_baratta@med.unc.edu

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when rapid neurological decline leads to respiratory compromise. As with other autoimmune diseases, Guillain–Barré syndrome predominantly affects females. It is the most common paralytic neuropathy, estimated to affect 100,000 per year across the globe [4]. The syndrome can be heterogeneous and further complicated by disease variants, thereby raising the risk of misdiagnosis particularly in early stages of the illness.

This case presents a man who was evaluated for acute neurological findings. Initial workup was most consistent with posterior circulation stroke, and management was initiated accordingly. It was not until the patient's neurological status decompensated that Guillain–Barré syndrome became a concern. Guillain–Barré syndrome was confirmed with further neurological workup including lumbar puncture and electrodiagnostic studies.

Clinical Case Presentation

"A 53-year-old man presented with left-arm weakness, glossolalia, and right eyelid droop for a duration of 3 h. He had a sore throat and stuffy nose 10 days earlier. Other than having hypertension and gout, his medical history was unremarkable. None of his family members had experienced similar symptoms. On admission, his vital signs were normal, and his higher mental functions were appropriate for his age. Neurological examination showed dysarthria, right eyelid droop, left facial droop, and a left-held tongue. No nystagmus, ophthalmoplegia, ataxia, or hearing loss was noticed. His muscle strength was 4/5 in the left upper limb (in both the proximal and distal muscles). There was no sensory function deficit. Deep tendon reflexes were present and symmetrical. The results of coordination tests and gait tests were normal, and plantar responses were normal bilaterally. The results of the rest of his physical examination were normal. The results of his brain CT examination were normal. In summary, he was managed as having a posterior circulation infarct. The patient and his family did not agree to intravenous thrombolysis because of the risk of bleeding. Eight hours after he was admitted, his condition deteriorated, with quadriplegia and bilateral peripheral facial palsy. Immediately, cranial magnetic resonance imaging (MRI) with magnetic resonance angiography was performed, but no abnormal manifestations were found. Cervical and thoracic spinal MRI were also performed, and the results were normal. Because of his unremarkable neuroimaging results, Guillain–Barré became the primary working diagnosis. The following day, he developed bilateral ophthalmoplegia, dysphagia, dyspnea, and numbness in all extremities, and he underwent tracheotomy to prevent a worsening of his acute respiratory failure. Lumbar puncture was performed, and cerebrospinal fluid (CSF) analysis showed that the protein level was 0.87 g/L (normal values: 0.25–0.47 g/L), while the white blood cell count was 5 × 106/L (normal values: 0–8 × 106/L). Anti-ganglioside antibody analysis of the serum and CSF revealed high levels of anti-GQ1b. The blots for other anti-gangliosides (anti-GM1, anti-GM2, anti-GM3, anti-GD1a, anti-GD1b, and anti-GT1b) were negative. Nerve

conduction study (NCS) results showed that the amplitudes of the bilateral facial, median, ulnar, and right peroneal (fibular) motor nerves were reduced; the occurrence rates of the F wave in the left median nerve and ulnar nerve were reduced; the F wave was absent in the right median nerve; and the rest of the testing revealed normal results. Unfortunately, the H wave could not be detected in either leg due to the limitations of the patient's posture. According to the NCS results, mild to moderate damage to multiple motor nerves was considered. The patient received intravenous immunoglobulin (0.4 kg/day) for 5 days. Three weeks after admission, at discharge, his dysphagia, dyspnea, facial paralysis, ocular movement disorder, and leg weakness had recovered almost completely, but his arms were still moderately impaired, with a power of 4/5 (in both the proximal and the distal muscles). When the patient was discharged, he no longer needed a ventilator and could breathe normally. The patient had to be flown home, and due to safety concerns, the patient was discharged with a tracheotomy. Fortunately, the patient recovered well without any sequelae after two years of follow-up." [5]

Differential Diagnosis

- Stroke
- Brain tumor
- Seizure
- Conversion disorder
- Complicated migraine
- Metabolic derangement
- Vestibular dysfunction
- Polyneuropathy

What Was Misdiagnosed in This Case and Why?

The patient in this case was diagnosed with a posterior circulation stroke after appropriate initial workup which included general and neurological physical exam and CT imaging of the head. The results of this initial evaluation were most consistent with stroke. It was not until the patient subsequently declined that an alternate diagnosis of atypical Guillain–Barré syndrome became more apparent.

Discussion

The heterogenous presentations Guillain–Barré syndrome and variant conditions can lead to diagnostic challenges for clinicians. While the syndrome classically presents with progressive, ascending flaccidity and loss of reflexes, symptoms can be variable particularly early in the disease process. Numerous disease variants further complicate the diagnosis. For example, the Miller–Fisher variant often presents with prominent ophthalmoplegia in addition to limb ataxia and loss of deep tendon reflexes [6]. The pharyngeal-cervical-brachial variant can be seen with progressive oropharyngeal and cervicobrachial weakness accompanied by upper extremity areflexia [7].

Diagnosis of Guillain–Barre syndrome is made with careful history-taking and examination. A history of progressive, ascending loss of strength and sensation accompanied by diminished reflexes is convincing [8]. Lumbar puncture should be performed on all patients with suspected Guillain–Barre and typically demonstrates albuminocytologic dissociation defined as an elevation of CSF protein without an elevation in white blood cells [9]. Electrodiagnostic studies, including nerve conduction study and electromyography, can be helpful for diagnosis, often showing delay of nerve transmission through an absent or reduced H response, F wave, and abnormal upper extremity sensory nerve action potential combined with a normal sural sensory nerve action potential [10].

Treatment is multipronged and frequently includes high-dose steroids, intravenous immunoglobulin, and plasmapheresis. Supportive care is necessary for those with nutritional and respiratory deficiencies, potentially involving provision of parenteral feeding and mechanical ventilation [11]. Mortality typically involves respiratory failure and is estimated at 3–10%. Symptoms typically peak at 4 weeks after disease onset and gradually remit with time. At 6 months after disease onset, 20% of patients are still unable to ambulate [12]. Pain, fatigue, and other functional impairments may continue for months or years.

Conclusion

Guillain–Barré syndrome is the most common paralytic neuropathy globally. While initial symptoms classically include ascending weakness and areflexia, the presentation can be heterogeneous leading to diagnostic challenges. A thorough history and physical examination along with frequent re-evaluation are critical for patients presenting with acute neurological concerns. Appropriate diagnosis is necessary for timely administration of immunomodulating treatments to minimize disease progression.

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Chapter 54
Stroke Misdiagnosed as Benign Positional Paroxysmal Vertigo

John Michael Baratta

Introduction

Stroke is a leading cause of disability and death both in the United States and globally. Efficient and accurate evaluation of a person with suspected stroke is particularly important given the rapid destruction of neurons, lending to the saying "time is brain." [1] Newer interventions for stroke, including intravenous tissue-type plasminogen activator (IV tPA) and mechanical thrombectomy, can dramatically improve mortality as well as neurological and functional outcomes.

In the United States, it is estimated that 800,000 people suffer a stroke annually, with a total cost exceeding 40 billion dollars. Stroke is classically associated with facial droop, arm or leg weakness, and speech difficulties; however in many cases stroke does not present typically. There are often nonspecific symptoms such as dizziness or transient numbness that increase the risk of misdiagnosis. In the United States, it is estimated that there are up to 165,000 missed stroke diagnoses annually. Inability to diagnose stroke in the emergency department may lead to failure of acute intervention and secondary prevention therapy resulting in higher risk of mortality and morbidity. The risks of a missed stroke diagnosis are higher for younger, female, and non-White patients [2, 3].

Most frequently error occurs in posterior circulation infarcts with presenting symptoms such as nausea, headache, and dizziness. Identifying symptoms like these that are not specific but accompanied by neurologic signs such as ataxia and Horner syndrome will reduce the rate of misdiagnosis. Additional symptoms which can help

J. M. Baratta (✉)
Department of Physical Medicine and Rehabilitation, Medical Director of Stroke Rehabilitation, University of North Carolina School of Medicine, Chapel Hill, NC, USA
e-mail: john_baratta@med.unc.edu

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with stroke identification include crossed motor sensory problems, oculomotor nerve palsies, and visual field defecits [2].

Initial presentation of stroke can be variable and can include arm or leg weakness, facial droop, slurred speech, gait instability, confusion, and headache. Due to the complex nature of the central and peripheral nervous systems, stroke mimics are a frequent concern. Stroke mimics can vary widely and include seizure, metabolic derangement, complicated migraine, vestibular dysfunction, and polyneuropathy. A thorough review of the history, physical examination, and diagnostic studies is critical to achieving the proper diagnosis and initiating appropriate, timely management. In this case, the 50-year-old patient checked himself into the emergency department for a 3-week history of frequent episodes of gait imbalance, nausea, blurred vision, and tinnitus.

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Articulate ideas about the signs and symptoms of case presentation in this condition.
2. Discuss an alternative diagnosis of stroke.
3. Enumerate the various diagnostic techniques used in the investigation of this condition.
4. Discuss why this condition is often misdiagnosed with presentation of its symptoms.

Clinical Case Presentation

A 50-year-old male with a history of smoking and alcohol use presented to the emergency department with recurring episodes of gait imbalance, nausea, blurred vision, and tinnitus. Episodes had occurred for approximately 3 weeks, lasting for several seconds to minutes, and resolved spontaneously. The patient underwent thorough physical examination. A head computed tomography was done showing normal findings. He was discharged from the emergency department with a diagnosis of benign positional paroxysmal vertigo. Over the following weeks, his condition deteriorated instead of improving, with progressive development and worsening of diplopia and dysgraphia. Repeat brain computed tomography demonstrated multiple bilateral cerebellar infarctions, and he was subsequently admitted to the hospital for further evaluation and management.

On hospital day 1, the patient developed left rapid phase nystagmus which progressed to rapid right phase and then bilateral nystagmus. He also had left-sided dysmetria that became right-sided and then bilateral. He also expressed concerns about dysgraphia. On hospital day 3, the patient developed dysarthria and later was started on a statin and dual antiplatelet therapy containing aspirin and clopidogrel.

During the admission, he underwent carotid Doppler ultrasound and blood testing, including cholesterol, hemoglobin A1C, and autoimmunity labs, which were unrevealing. A transesophageal echocardiogram was normal, ruling out a patent foramen ovale and intracardiac thrombus. Computed tomography angiography findings revealed bilateral vertebral artery (VA) occlusions. The patient underwent interventional angiography for atheromatous stenosis greater than 50% at the right V4 segment and VA ostium. Retrograde flow with total occlusion of the distal left VA segment was noted. A vascular stent was placed in the right V4 segment with 30% of residual stenosis.

After the procedure, the patient's status improved substantially. He was noted to have substantial reductions in nystagmus and balance impairment. The patient improved to the point that he could return to walking and performing activities of daily living independently. He was discharged with dual antiplatelet therapy. After 1 year he had recovered well with minor residual effects of mild dysgraphia and slowed cognition.

[Case source: Costa, Ana et al. "A Patient With (Initially) Non-Persistent Vertigo - A Posterior Circulation Stroke Case." Cureus vol. 14,1 e21468. 21 Jan. 2022, doi:10.7759/cureus.21468]

Differential Diagnosis

1. Benign paroxysmal positional vertigo
2. Brain tumor
3. Functional neurological disorder
4. Seizures
5. Migraine

What Was Misdiagnosed in This Case and Why?

The patient was diagnosed with a benign paroxysmal positional vertigo after initial workup which included computed tomography head which was negative for stroke. More sensitive imaging, such as magnetic resonance imaging brain, was not performed during the initial workup. Further diagnostic testing was completed when the patient's symptoms worsened over the following weeks. Interventional angiography demonstrated bilateral vertebral artery stenosis which had resulted in substantially reduced flow and was likely the source of thromboembolic events.

Discussion

Stroke is a heterogeneous disease as well as a leading cause of death and disability [4]. Depending on its etiology and location, acute stroke can present with a variety of symptoms including arm or leg weakness, facial droop, slurred speech, gait instability, confusion, and headache [5]. The challenging nature of acute stroke presentations and numerous stroke mimics can lead even experienced clinicians to a misdiagnosis [6].

Efficient and accurate evaluation is critical for optimal stroke management, as key acute ischemic stroke interventions, such as intravenous tissue-type plasminogen activator and mechanical thrombectomy, are time-limited [7]. For this reason, many medical centers have developed acute stroke management pathways to minimize wait times for patients with stroke-like symptoms to undergo critical components of the evaluation, such as head imaging and neurology consultation [8]. Implementation of acute stroke interventions can provide the patient a substantial benefit in acute survival rates and long-term neurological sequelae [9]. Evaluation of patients with acute stroke-like symptoms should include emergent head imaging [8]. This is most often done with computed tomography as it is faster and less expensive to perform than other modalities but still sufficient to evaluate for a hemorrhagic event. It should be noted, however, that a negative head computed tomography in the acute phase does not rule out an acute ischemic event given the poor sensitivity of this test in the acute phase of stroke [10]. In patients with unclear or fluctuating symptoms, magnetic resonance imaging or contrasted imaging modalities may be better able to determine the source of symptoms [11, 12]. In this case, it was not until magnetic resonance imaging and angiography were performed that the correct diagnosis of vertebral artery occlusion leading to posterior circulation stroke was made.

Conclusion

Evaluation of people with stroke-like symptoms can pose diagnostic challenges due to the heterogeneous nature of presentations. Initial workup should include head imaging such as computed tomography; however it should be noted that negative initial computed tomography should not rule out acute ischemic stroke. Other diagnostic imaging modalities, such as magnetic resonance imaging and angiography, should be considered for further evaluation of patients with an initial negative workup.

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Chapter 55
Primary Amoebic Meningoencephalitis Misdiagnosed as Pyogenic Meningitis

Sathish Venugopal

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Demonstrate an appropriate understanding of the condition and its causative organism.
2. Describe the conditions that present with a similar pattern as primary amoebic meningoencephalitis.
3. Articulate the knowledge of symptomatology and proper history of the patient to narrow down the diagnosis.
4. Discuss the course of disease, management techniques, and various treatment modalities to help patients recover quickly.
5. Enumerate the various diagnostic techniques from laboratory tests done to techniques like next-generation sequencing and polymerase chain reaction.

Introduction

This disease was first identified in 1899 caused by a protist pathogen called *Naegleria fowleri*. It causes fatal infection of the central nervous system that has acute phase infection and rapid progression. This condition arises when the organism, *Naegleria fowleri*, is accidentally introduced via nasal route. Through the cribriform plate, amoeba enters the central nervous system and advances along the cribriform plate, following the olfactory nerve. *Naegleria fowleri* is a thermophile,

S. Venugopal (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: sathish.venugopal@martinus.edu

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free-living amoeba; there are over 40 species of *Naegleria*, but only *Naegleria fowleri* infection results in primary amoebic meningoencephalitis. The incubation period varies anywhere from 2 to 15 days [1–3].

In most cases, death happens around 3 to 7 days from the onset of symptoms. *Naegleria fowleri*, upon entering the central nervous system, causes cerebral edema, necrosis, and herniation. The infection of *Naegleria fowleri* resembles that of acute bacterial meningitis. The mortality rate is above 95%, with the highest number of cases occurring in developed countries because cases occurring in developing countries go primarily undiagnosed. The signs and symptoms of primary amoebic meningoencephalitis present in two stages, mild and severe. The risk factors for primary amoebic meningoencephalitis are (1) geographic location, i.e., areas that have been diagnosed, (2) summer seasons, and (3) sex. Primary amoebic meningoencephalitis has been promulgated widely around the globe, including America, Australia, Thailand, Hong Kong, and Taiwan; about 300 cases in total have been reported so far in 50 years, since it was first identified. Because of the limited availability of diagnostic testing and clinical expertise, the signs and symptoms of primary amoebic meningoencephalitis were misinterpreted as common neurological infections such as bacterial and viral encephalitis. It is often misdiagnosed, as there is no definitive variation in diagnosis that exists to discriminate primary amoebic meningoencephalitis from bacterial meningoencephalitis. About <0.5% of diagnosed encephalitis deaths in the United States are because of primary amoebic meningoencephalitis. There are about 0–8 cases per year that are laboratory confirmed [3, 4]. So far, there were about 151 confirmed primary amoebic meningoencephalitis cases from 1962 to 2020, with only 4 known survivors. These infections are more prominent in 15 southern tier states of the United States, of which more than half of the infections are concentrated in Texas and Florida [5]. About 1676 cases of undetermined neuroinfectious disease deaths are within 2–22 years of age during 1999–2010 in which 49% (826/1676) happened in the months of July to September of each year, of which 23% (192/826) were reported in an included state of the southern United States. Of which, 52% (100/192) were male, and 48% (92/192) were female. Of the unspecified neuroinfectious deaths, an average of 16 (8 males and 8 females) suit the typical primary amoebic meningoencephalitis pattern of infection [3].

Apart from Antarctica, *Naegleria fowleri* was spotted in all the corners of the world. Among identified 381 global primary amoebic meningoencephalitis cases, this is believed to be an underestimation of the actual occurrence of primary amoebic meningoencephalitis cases worldwide. An approximation of about 16 cases per year in the United States has been estimated in a previous study, of which only 0–8 cases are reported annually. The most favorable period for primary amoebic meningoencephalitis infections is the summer months, i.e., July, August, and September, during which the water temperatures are high and water levels are low. In an environmental investigation of lakes and rivers where the patients swam, high water temperature, algal bloom, and poor water clarity have been recorded, and samples taken from this area were positive for *Naegleria fowleri*. In India, only 15 cases of

amoebic encephalitis have been identified. Worldwide data estimates that around 133 cases were reported from 1992 to 2014, out of which 10 were from India; about 97% of the victims died because of infection resulting in very few survivors. Of the identified 381 cases of primary amoebic meningoencephalitis from 1965 to 2016, 32 survived, and only 7 were laboratory-confirmed cases [6–9]. Of all those suffering from primary amoebic meningoencephalitis, most were previously healthy young males exposed to warm recreational water more commonly in lakes, ponds, and reservoirs in southern states of the United States during summer months. Differing from other free-living amoeba like *Acanthamoeba* and *Balamuthia* that affects the individuals who are immunocompromised, most of the *Naegleria fowleri* infections were present in young and immunocompetent individuals. However, in a place with high temperature like Africa, only less than ten cases of primary amoebic meningoencephalitis have been recorded. Even though *Naegleria fowleri* is a thermophilic organism, cases have also been identified in northern states of the United States, such as Kansas and Indiana; this change in existence and epidemiology of primary amoebic meningoencephalitis would indicate climate change. The change in geography, i.e., the reported cases outside of southern tier states, has raised concern and debates that regardless of its geography, primary amoebic meningoencephalitis should be made as a differential for meningitis [8, 10] (Fig. 55.1).

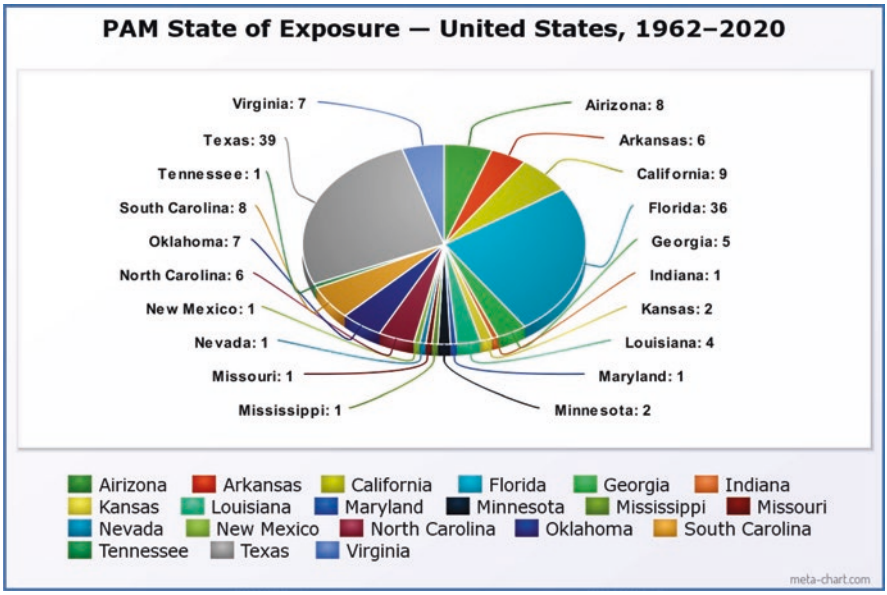

Fig. 55.1 Shows the data on the primary amoebic meningoencephalitis exposure places in the United States [11]

Clinical Case Presentation

The patient is a 36-year-old male from the countryside who was admitted to Dayanand Medical College & Hospital, Ludhiana, India, in a partially comatose state. The patient had a severe frontal headache, neck stiffness, intermittent fever with body pain, nausea, vomiting, and left hemiplegia. On reviewing the patient's history, it was known that he was a farmer with a history of opium use for the past 3 years and no significant medical history. On further investigation, it was found that the patient had a habit of taking bath in the village pond. The patient had an episode of syncopal attack 2 months back but regained consciousness after a while. There was significant weight loss in the last 2 months. As per the patient's medical notes, he was complaining of sudden onset of left arm and leg weakness. A week before admission, the patient was conscious, was responsive to command, and had a regular appetite. At first, he was admitted to a private nursing home, where his condition started to deteriorate; he started losing his sensorium and stopped responding to commands. There he had two episodes of seizures, but it was controlled with the help of medication. On physical examination, the patient's temperature was 102 F, blood pressure 130/80 mmHg, and pulse rate of 88 and deeply comatose. The patient's pupils were constricted, and no papilledema was present. Computed tomography scan was done after the lumbar puncture procedure; cerebrospinal fluid was slightly turbid, collected in a sterile vial and sent to the laboratory for investigation.

On a computed tomography scan, it was revealed that there was a hypodensity in the brain stem up to the hypothalamus without any enhancement. The fourth ventricle was normal; in the right parasellar region, sphenoid sinus, and prepontine cistern, a soft tissue density was seen with evidence of erosion in the lateral wall of sella and adjacent portion of the greater wing of sphenoid, with soft tissue mass touching the basilar artery. The patient was diagnosed with a fungal infection of sphenoid sinus involvement and brain stem infarct. On laboratory data a total leukocyte count was 6800/mm^3 including 69% neutrophils, 25% lymphocytes, 2% eosinophils, and 4% monocytes, platelets were 210×10^9/L, and erythrocyte sedimentation rate was 21 mm/h. The patient's hemoglobin concentration was 12.5 g/dl. Peripheral blood film was negative for malarial parasites. A rapid test was negative for human immunodeficiency virus. The cerebrospinal fluid was slightly turbid, and in biochemical analysis, glucose level was 36 mg/dl, and proteins 110 mg/dl. On cerebrospinal fluid cytology, the presence of total white blood cell count was 90/mm^3, predominantly polymorphonuclear leukocytes. A provisional diagnosis of pyogenic meningitis was given to the patient. Gram stain was negative for bacteria and fungus, and India ink was negative for *Cryptococcus neoformans*. Some organisms on wet preparation of cerebrospinal fluid resembled *Naegleria fowleri* in the trophozoite stage. On staining, this organism with Giemsa stains a sky-blue cytoplasm with very pink nuclei and pseudopodia resembling *Naegleria fowleri.* There was no growth of fungus or bacteria on the pyogenic culture of cerebrospinal fluid done by the BacT Alert system (Organon Teknika, USA). The cerebrospinal fluid was

Table 55.1 The patient's laboratory results

Parameter	Results	Reference range
Total leukocyte count Neutrophils—69% Lymphocyte—25% Eosinophils—2% Monocytes—4%	6800 cells/mm^3	4000–11,000 cells/mm^3 of blood
Platelets	210×10^9 cells/L	150 to 400×10^9 cells/L
Erythrocyte sedimentation rate	21 mm/h	0 to 22 mm/h for men and 0 to 29 mm/h for women
Hemoglobin concentration	12.5 g/dl	13.2 to 16.6 g/dl for men 11.6 to 15 g/dl for women
Glucose level (CSF)	36 mg/dl	50 to 80 mg/100 mL
Total leukocyte count (CSF)	90/mm^3	0–5 leukocytes/mm^3
Proteins (CSF)	110 mg/dl	18 to 58 mg/dl

negative for acid-fast bacilli or malignant cells. With the evidence of amoeba in cerebrospinal fluid, the patient was given a clinical diagnosis of primary amoebic meningoencephalitis. The fully expanded organism had a significantly consistent limax shape; the organism was broader in the anterior part and narrower in the posterior portion. In the anterior end, there was a single pseudopod that was not clear in agar culture preparation. The posterior end was narrow during motile, and sometimes a small number of intertwined debris was seen. Development of the uroid process was observed and reported; rounded, dormant forms and binary fission of vegetative trophozoites were also noted. Binucleate and uninucleate amoebae were also noted. Cerebrospinal fluid/agar culture with the trophozoite forms was changed to a test tube with 2.5 ml of distilled sterile water and incubated at 37 C for about 16–20 h. On microscopic observation of wet preparation, morphogenesis of amoeboid form to free swimming flagellates was noted. Pear-shaped body with two flagella helps the organism in forward motion. Some of the flagellates changed back to the amoeboid state after incubating for longer duration. In Table 55.1 shows the test results done in the patient.

Differential Diagnosis

1. Bacterial meningitis/encephalitis/pyogenic meningitis: Initially in our case, the patient exhibited symptoms such as severe frontal headache, neck stiffness, intermittent fever with body pain, nausea, and vomiting which are similar to the most common symptoms of bacterial meningitis including fever, neck stiffness, and headache; moreover on cerebrospinal fluid cytology, the total leukocyte count was 90/mm^3, predominantly with polymorphonuclear leukocytes which gave the provisional diagnosis of pyogenic meningitis [12].

2. Viral meningitis/encephalitis: In viral meningitis/encephalitis, there are common symptoms such as fever, headache, nausea, vomiting, confusion, and altered mental status and more severe symptoms such as seizure, weakness, and coma. Some of these mild and severe symptoms are seen in our patients. Both viral and bacterial meningitis are clinically overlapping making them difficult to distinguish. Since primary amoebic meningoencephalitis resembles both viral and bacterial meningitis in symptoms, proper diagnostic technique and detailed history of the patient can help to distinguish [13].
3. Tuberculous meningitis: Tuberculous meningitis exhibits symptoms such as malaise, fatigue, anorexia and vomiting, headache, and fever. It is almost impossible for us to determine between tuberculous meningitis and bacterial meningitis in acute presentation. Rarely a person with tuberculous meningitis can show symptoms such as progressive dementia (change in one's personality) and social withdrawal [14].

What Was Misdiagnosed in This Case and Why?

The shortfall of knowledge on primary amoebic meningoencephalitis indicates that there is almost limited or no awareness among the clinicians and laboratories, regarding the infection leading to misdiagnosis of cases. Without a detailed history of exposure, it is challenging to identify primary amoebic meningoencephalitis, which presents as meningitis clinically. In our case, the preliminary diagnosis was given as fungal infection with involvement of sphenoid sinus and brain stem infarct, but later, based on the cerebrospinal fluid cytology, a provisional diagnosis suggestive of pyogenic meningitis was made; as the wet preparation of cerebrospinal fluid revealed, trophozoites of *Naegleria fowleri* have pointed toward the final diagnosis of primary amoebic meningoencephalitis. Symptoms such as headache, high-grade fever, photophobia, lethargy, confusion with an altered level of consciousness, and seizures should raise a suspicion of primary amoebic meningoencephalitis infection; among these most of the symptoms were exhibited by our patient. Death in most cases was due to increased intracranial pressure. Since the presentation of primary amoebic meningoencephalitis is often identical to bacterial meningitis, prompt identification is often too late, which increases the risk of death from infection due to cerebral edema [8, 10].

Discussion

In this, we have discussed a fatal case of primary amoebic meningoencephalitis, in which the patient had a habit of bathing in the village pond. *Naegleria fowleri* can be ingested into the nasal cavity by swimming or bathing in water contaminated with the organism and via nasal irrigation as shown in Fig. 55.2. The amoeba sticks

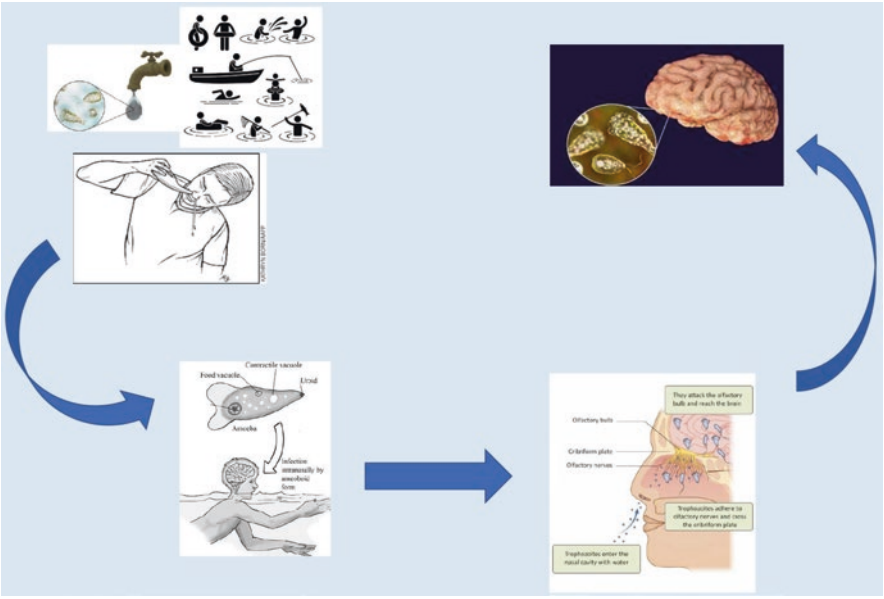

Fig. 55.2 This figure shows the various activities leading to primary amoebic meningoencephalitis infection and route of entry for *Naegleria fowleri*

to the mucosa of the nasal cavity which enters the central nervous system via the olfactory nerve and reaches the olfactory bulb through the cribriform plate [9]. The signs and symptoms of the patient were frontal headache, neck stiffness, intermittent fever with body pain, nausea, vomiting, and left hemiplegia; the lesion will be primarily concentrated in the orbitofrontal base, temporal lobe, base of the brain, hypothalamus, midbrain, pons, medulla, and upper portion of the spinal cord. It is evidenced in computed tomography that there is damage to cisternae around the midbrain and subarachnoid space of the cerebral hemisphere. Fibropurulent leptomeningeal exudate with polymorphonuclear neutrophils, eosinophils, and a few lymphocytes and macrophages was seen microscopically in the cerebral hemisphere, brain stem, cerebellum, and upper portion of the spinal cord. Amoebic trophozoites without polymorphonuclear neutrophils and tropic amoebae are visible in necrotic neural tissue and Virchow-Robin spaces, respectively [15].

Diagnosing a case as primary amoebic encephalopathy increases the rate of mortality by more than 97% [8]. Primary amoebic meningoencephalitis has an acute course of infection with median incubation period of 5 days; often death occurs within 3 to 7 days from onset of symptoms [5]. In 1965 Fowler and Carter recorded the first case of primary amoebic meningoencephalitis; summer is the high point for infection with amoeba, during which most of the recreational water activities are recorded. Clinical symptoms seen with primary amoebic meningoencephalitis infection are pretty indistinguishable from acute bacterial meningitis, such as headache, fever, nausea and vomiting, altered consciousness, and seizures [2]. Even a

few cases presented with anorexia/weight loss and hemiplegia, which is also found in our case. In gross primarily young males are involved; these demographic groups are indulging in high-risk activities. Other than recreational activities, the practice of nasal irrigation among adults may result in *Naegleria fowleri* exposure [5]. Confirmed cases have a more rapid clinical course compared with suspect cases. The portal of entry is the olfactory epithelium, in which the sustentacular cells which line the olfactory neuroepithelium phagocytose the amoeba that enters the victim's nasal passage; they pass via porous cribriform plate into subarachnoid space and reach the brain parenchyma. The period of incubation varies with the size of inoculum and also with the virulence of infecting amoebic strain [8].

As proposed by the Centers for Disease Control and Prevention, the treatment for primary amoebic meningoencephalitis includes high doses of intravenous and intrathecal amphotericin with rifampin, azithromycin, miltefosine, and miconazole. Amphotericin and miltefosine were prescribed for the successful treatment of *Naegleria fowleri*-related primary amoebic meningoencephalitis. Amphotericin is an antifungal agent which also has an amoebicidal effect; it is used in the treatment of primary amoebic meningoencephalitis, but the rate of recovery with amphotericin is less than 5%, i.e., 15 recoveries/300 cases worldwide. Miltefosine, which is used in breast cancer and *Leishmania* infections, has now been suggested for primary amoebic meningoencephalitis infection. Timely diagnosis and triple regime treatment with intravenous amphotericin, fluconazole, and oral rifampin have been seen to be effective in primary amoebic meningoencephalitis patients. Even amphotericin has limits due to its dose-dependent nephrotoxicity and is capable of inducing anemia, fever, chills, vomiting, and headache in a number of patients. In recent research, it has been found that chlorpromazine has high potency and is faster-acting than amphotericin and voriconazole in eliminating *Naegleria fowleri* trophozoites. Another study revealed an effective, nontoxic drug called corifungin; it can kill both the pathogenic *Naegleria fowleri* and nonpathogenic *Naegleria gruberi*. *Naegleria fowleri* has a gene called nfa1 which is influential in its pathogenicity; attempts were made to develop a DNA (deoxyribonucleic acid) vaccine out of this gene using lentiviral vector pCDH [2, 3, 10, 15–17].

Plan of Action, the Points Clinician Should Consider, Pitfalls to Avoid, and Pearls of Knowledge to Consider

Initially he was admitted to a private nursing home, and then he was transferred to another medical facility since his sensorium started to get worse to the extent that he was not responsive to auditory stimuli. When admitted to another facility, computed tomography of the brain was done which revealed hypodensity of the hypothalamus and soft tissue density in parasellar region, sphenoid sinus, and prepontine cistern. With the observed abnormality in computed tomography at first, he was diagnosed with fungal infection with involvement of sphenoid sinus and brain stem infarct and was medicated with cefotaxime, dilantin, mannitol, and dexamethasone. After

laboratory data of total leukocyte count, platelets, erythrocyte sedimentation rate, and cerebrospinal fluid cytology, a provisional diagnosis of pyogenic meningitis was made. But no bacteria or fungi were visible in Gram smear and India ink preparation. Later, on a wet mount preparation of cerebrospinal fluid, organisms resembling trophozoites of *Naegleria fowleri* were found, and on Giemsa stain sky-blue cytoplasm and microscopic pink nuclei with pseudopodia similar to *Naegleria fowleri* were visible, which confirmed the diagnosis of primary amoebic meningoencephalitis. After that, he started on amphotericin, 40 mg for 6 hours with rifampicin and ceftazidime. Even though he was treated, there was no significant improvement in his condition. He was discharged roughly after 10 days in declining state against medical advice and died after a couple of days.

If Misdiagnosed, Was It Realized Later? How Was It Rectified?

Even though our case was misdiagnosed initially, laboratory investigations helped the physicians for a prompt and precise diagnosis, both of which are important in case of infections like primary amoebic meningoencephalitis. In one of the case studies, a new technique known as next-generation sequencing was used and played a vital role in the precise diagnosis of *Naegleria fowleri* infection, but in that case, the amoeba was absent in the culture. This should be taken as an example in the future for the culture-negative cases to use the next-generation sequencing technique for diagnosing primary amoebic meningoencephalitis in time. Therefore next-generation sequencing provides a rapid and accurate method for identifying the pathogen and should be considered in diagnosing diseases with unknown causes or cases with inadequate patient history. Diagnostic polymerase chain reaction, immunohistochemistry, and indirect immunofluorescence are methods that are mainly available for diagnosis; but absence of these advanced techniques should not delay the diagnosis. Rapid progression of meningoencephalitis in patients despite starting on intravenous antibiotic therapy should raise an alarm of primary amoebic meningoencephalitis. Molecular techniques like polymerase chain reaction and isothermal DNA amplification developed can be more helpful for specified spotting of *Naegleria fowleri* clinically. Currently, polymerase chain reaction is considered the gold standard for diagnosis and is even used by center of disease control for suspected primary amoebic meningoencephalitis cases [3, 8, 10].

Conclusion

Primary amoebic meningoencephalitis is a deadly infectious disease. This disease is still an unexplored one for developing and underdeveloped countries. Proper disease surveillance needs to be enforced in the developing and underdeveloped countries to identify it in patients at an early phase of infection. Climatic change is one

of the affecting factors in controlling this condition, even though *Naegleria fowleri* is a thermophilic organism; this disease is becoming prevalent even in cold temperate zones. Physicians at primary level and private medical practitioners should be made familiar with this disease to identify primary amoebic meningoencephalitis clinically and start treating them instead of waiting for laboratory results for confirmation; this will very much reduce the mortality of patients. Proper diagnostic criteria and guidelines should be formulated for better treatment and timely diagnosis.

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Chapter 56
Cotard Syndrome Misdiagnosed as Major Depressive Disorder

Sathish Venugopal

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Demonstrate an understanding of this condition and its various spectrums.
2. Enumerate the symptoms of the spectrum and differential diagnosis of Cotard syndrome.
3. Explain the course of disease development in the patient.
4. Restate the different variety of treatment modalities used such as pharmacotherapy and electroconvulsive therapy that are used to treat the condition.
5. Recognize the condition without any difficulty after going through this misdiagnosed clinical case presentation.

Introduction

We might have heard that "sound soul is one that dwells in a sound body" but with this condition making you wonder if you have soul or not, whether you are alive at all. In Paris, June 28, 1880, a French psychologist named Jules Cotard described an enthralling disease in his lecture given at the "Societe Medico-Psychologique" that is the medico-psychological society titled "Du delire hypocondriaque dans une forme grave de la melancholie anxieuse" literally translating as hypochondriac delirium in a severe form of anxious melancholy which was already recorded by Esququirol, Leuret, and some others. He detailed a case of a 43-year-old female

S. Venugopal (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: sathish.venugopal@martinus.edu

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named Mademoiselle X by him; she was not oriented to person, place, and time, stating that she was never born or existed; she also said that the world had ended and she was dead. She also stated that she was missing organs like the brain, nerves, and stomach; all she had were bones and skin. Cotard termed this condition "e delire de negations," or nihilistic delusion. A decade later, the disease was termed Cotard syndrome (delire de Cotard) by two French psychologists, Regis (1893) and Seglas (1897). Cotard, after a few years, described similar cases from ancient literature precisely, five demonomania from "Esquirol's des maladies mentales" (1838) in which these patients thought as if they had no flesh and blood and they would live on for eternity. It makes us question and offers the perception of neurocognitive mechanisms regarding our sense of existence and development of beliefs and consciousness. Nevertheless, around a century earlier, this was noted by Charles Bonnet, who mentioned a case of a woman in a geriatric population; she was paralyzed as if she had a stroke; after a while, when she recovered her ability to speak, she wanted her to be dressed and placed in a coffin. As a guesstimate it is mentioned in Cervantès' licenciado vidriera (1613) and earlier cases of so-called glass delusion [1–6].

This condition is very explicitly defined as monothematic delusions with distinguishing features of nihilistic beliefs of one's existence of body or life. It has been calculated that about less than 1% of elderly adults, 3% of older adults with depression, and less than 1% with psychotic disorders developed Cotard syndrome. It is widely seen that some patients with Cotard syndrome have a belief that their life or specific body parts were debilitated. Even though Cotard syndrome is rare and essential, it has not been included in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) and the International Classification of Diseases, tenth revision, clinical modification (ICD-10-CM). This is a rare and unique disease and neuropsychological mechanisms of this condition remain undisclosed [5, 7].

Cotard syndrome is sporadic and about 200 cases are known globally. Even though the symptoms are severe, people recover on treatment [8]. Nihilistic delusion exists in patients with schizophrenia, but its prevalence is rarely less than 1%. Schizophrenia and nihilistic delusion are both associated with the loss of one's inner self. About seven case series have been reported so far, which shows that it is a comorbidity with an increased chance of misdiagnosis/dismissal because of showing hypochondriac symptoms by health and mental health professionals [9].

Clinical Case Presentation

The patient L was 42 years old working as administrative assistant. Following his father's death, she was constantly visiting general practitioners for several trivial health ailments such as sneezing and vague abdominal pain. After 4 years, the mental health of the patient started to deteriorate. She became anxious, withdrawn, preoccupied, and sleep-deprived because of buzzing noises coming outside her ear. She was bothered by the thought that someone might try to hurt her. She was lethargic

due to lack of sleep because of which she was unable to concentrate, which made her quit her job. In a private psychiatrist practice, diagnosis of major depressive disorder was given. She was prescribed agomelatine 25 mg daily and zolpidem 10 mg daily. Upon evaluation by an otorhinolaryngologist, no issue was reported.

Even after being overseen by a psychiatrist, patient L's mental health keeps deteriorating, and there is no improvement on patients' insomnia. After 3 weeks of treatment, the patient stated that she felt like a zombie pinning it toward antidepressants. She was persuaded by the thought that her organs started to decay. There was lack of food intake and purging to show that the food she had was not able to get digested which made her more weak and lethargic. Moreover she was denying to micturate and defecate as it was the belief of the patient that her intestine and bladder were not functioning. As the patient's physical health continued to get worse, she was checked in to the public hospital in Klang Valley in September 2018. She was experiencing third-person auditory hallucination in which the voice was commenting on her actions. Patient L was paranoid that the fictional voice might try to hurt her. Neither any Schneiderian first-rank symptoms nor delusions of misidentification were noticed. There were not any features of depression, mania, or hypomania noted by the patient's family. There was no history of any significant psychiatric illnesses from either side of the patient's family. Patient was often associating her anxiety with her organs rotting and liquefying inside her. A differential of major depressive disorder with psychotic features, due to another medical condition and schizophrenia, was made. A detailed workup of the patient was done to eliminate possible causes by acquiring an elaborate history of fever, seizures, connective tissue disorders, illicit drug use, or any neurological deficits suggesting migraine, stroke, or meningitis. But all examinations of the patient were insignificant. Considering her first episode of psychosis featuring Cotard syndrome, she was given a diagnosis of schizophrenia and Cotard syndrome. Later, patient L was admitted and her decision-making capacity was compromised, so the patient's family was educated on available treatment concerning the disorder. After that, the psychiatrist and family decided for her to stay in the hospital for 1 to 2 weeks. She was treated for her condition with atypical antipsychotic risperidone 2 mg twice a day. Patient L has not shown adequate improvement on risperidone; even though she was on treatment, her nihilistic delusions remained the same during her stay in hospital. She demanded that she had to be assisted by a nurse each time she came toward the counter. Her physical examination was insignificant; on her mental health status examination, she had a direct effect, poor speech, apathy, inability to recognize reality (persecutory delusion), and hallucinatory behavior. She was later put on amisulpride 200 mg better than risperidone in effect. There was a slight improvement with patient L in her hygiene and meals after 2 weeks; she started to show signs and symptoms of Parkinson's disorder at a dose of 600 mg twice a day, which were resolved with 2 mg of trihexyphenidyl. She was still showing persisting symptoms of psychosis upon her discharge. Sadly she was again admitted after a week due to several unsuccessful suicide attempts; her nihilistic beliefs were still present such as she could not swallow, micturate, or defecate. She showed extrapyramidal side effects that manifest due to amisulpride and amenorrhea because of hyperprolactinemia (316.2 mU/l).

After discussion, a course of electroconvulsive therapy for acute stabilization of suicidal ideation and nihilistic beliefs was advised. Since she was experiencing extrapyramidal symptoms from amisulpride and her prolactin levels were high, her medication was changed to quetiapine immediate release 100 mg due to its positive effects on her profile. In referral to the Malaysian Mental Health Act 2001, the consent to start the treatment was obtained. A short course of bitemporal electroconvulsive therapy of six sessions for 2 weeks is given on alternative days, using the META SpECTrum 5000 machine (devised by Meta Corporation, USA) with a brief pulse width of 1.0 m/s (33 Hz).

Upon completion of six sessions of electroconvulsive therapy, the patient showed notable development in her condition. Three weeks later, she was discharged on quetiapine 400 mg. Her prolactin level was normalized, and her menstrual cycle was resumed after 3 months. No extrapyramidal symptoms were seen; after a year, she was compliant with the treatment and in full recovery with retaining her ability to do her instrumental activities of daily living.

Differential Diagnosis

1. Major depressive disorder
2. Depression
3. Capgras delusion

What Was Misdiagnosed in This Case and Why?

In this case, since the patient was showing symptoms that mimicked depressive disorder and lack of knowledge in the existence of this syndrome, she was misdiagnosed initially. The misdiagnosis is related due to clinical bias that develops due to unfamiliarity with psychiatric symptomatology; many difficulties are faced by patients as the psychiatric symptoms are being laughed at and reported as vague in the primary care setting. Without any denial, Cotard syndrome is a peculiar condition; its comorbidity with schizophrenia is another rarest form. Not including it in the diagnostic and statistical manual makes it difficult to recognize by clinicians and psychiatrists. Another reason is the scarcity of recognition and knowledge among primary healthcare physicians; medical specialists should have adequate psychiatric training and education. Health professionals at the primary level face difficulty in identifying and recognizing rare psychiatric conditions. Advancement in diagnosing psychiatric conditions can be made by adequate training courses and regular updates in psychiatry via more consultation-liaison visits. Besides this, conducting more study and writing case reports may help other clinicians and psychiatrists with more precise diagnosis and reduce misdiagnosing the patients, which leads to unwanted treatment [9, 10].

Discussion

Cotard syndrome comes under delusional misidentification syndromes (DMS); interference in neural circuits that influence self-perception gives rise to feelings of depersonalization. Moreover, a deep right frontal lesion could damage connections between the limbic region and frontal lobe that influence oneself, people, and places [5]. Two-factor delusional theory was put forward to describe monothematic delusions like Cotard syndrome that contain abnormalities that lead to the development of delusional beliefs. It is hypothesized that damage to the right frontal lobe impairs the belief evaluation system. Certain studies spot abnormal firing in the fusiform gyrus of the brain as shown in Fig. 56.1 as a reason for delusion [7]. Cotard syndrome is formerly explained in idiopathic psychiatric conditions, including schizophrenia and psychotic depression. It has shown a connection with neurologic conditions such as headache, seizures, sagittal sinus thrombosis, cerebral atrophy, infarction, encephalopathy, catatonia, Capgras syndrome, traumatic brain injury, arteriovenous malformations, multiple sclerosis, and neurodegenerative diseases [10, 11].

In this case, we see a 42-year-old female who was first misdiagnosed with major depressive disorder since she was exhibiting symptoms that were more leaning toward major depressive disorder. Moreover, the patient lost her father in 2014; over the next 4 years, she started becoming more withdrawn, anxious, preoccupied, and sleep-deprived, which correlates with the clinical signs of depressive disorder, which could have made the psychiatrist give a diagnosis of major depressive

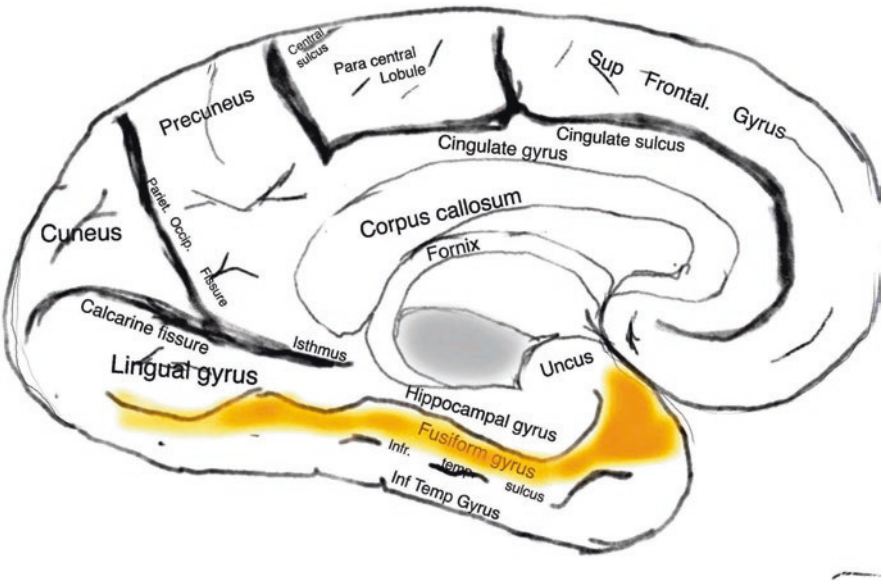

Fig. 56.1 Fusiform gyrus of the brain

disorder. In a study of Cotard syndrome conducted in 2011, it was evidenced that about 89% of documented cases show depression as a symptom [12]. She has been prescribed agomelatine 25 mg daily and zolpidem 10 mg daily to treat her insomnia and other symptoms.

Nevertheless, her mental health condition and insomnia worsened; she started showing nihilistic beliefs as having felt like a zombie and others such as her organs were rotting. Later, she developed psychotic episodes such as paranoid about getting harmed by an imaginary person and auditory hallucinations like buzzing noise outside her ear. With her episode of psychosis and characteristics of Cotard syndrome, she was diagnosed with schizophrenia and Cotard syndrome. The presence of Cotard syndrome in schizophrenia is infrequent because in a study by Stompe and Schanda, about (3 out of 346) 0.87% of patients were identified with schizophrenia and Cotard syndrome, i.e., the prevalence of both the conditions combined is less than 1%. The incident of Cotard syndrome in the setting of depression is rare, and it is too rare to see among patients with schizophrenia spectrum disorder. Pinpointing Cotard syndrome is complicated with the presence of psychosis, mainly in which delusions are common. To understand its rarity, we can see in a systematic chart review of 479 psychiatric inpatients over 2 years by Ramirez-Barmudez et al.; only 3 cases (0.62%) of Cotard syndrome were found out of 479 patients, of which 150 had a diagnosis of schizophrenia. However, not at least one case had the coexistence of Cotard syndrome and schizophrenia [7, 13].

In our case, patient L's second admittance to a psychiatric facility resulted from the infliction of self-harm. Violent aggression and self-harm behavior are present in schizophrenia patients; in a case of a 32-year-old patient with co-occurring Cotard syndrome and schizophrenia, she mutilated her nose in a case reported by Ghaffari Nejad et al. Caliyurt et al. reported a case in which a 27-year-old with Cotard syndrome associated with schizophrenia exhibited self-starvation as demonstrated in our case by patient L [7].

In a retrospective analysis of 100 cases by Berrios and Luque, three types of Cotard syndrome in accordance with clinical symptoms are:

1. Psychotic depression: In which patients project a picture of depression (melancholia), anxiety, a delusion of guilt, and paracusias.
2. Cotard syndrome type 1: It shows a clear picture of Cotard syndrome with hypochondriacal delusion, the nihilistic delusion of body and concepts of existence and suicidal ideation.
3. Cotard syndrome type 2 (mixed): In which anxiety, delusion of immortality, auditory hallucinations (paracusias), nihilistic delusion, and the idea of committing suicide are seen.

Our patient L most likely suffered from Cotard syndrome type 1, a pure form Cotard syndrome which is delusional in origin rather than secondary to any affective disorder. Classifying Cotard syndrome has its therapeutic value because antidepressants are ineffective in patients with type 1 Cotard syndrome [13–15].

Symptoms associated with Cotard syndrome can develop in three stages: (1) germination stage or prodromic stage with hypochondria and cenesthopathy, (2)

blooming stage with nihilistic delusion and delusion of immortality, and (3) chronic stage with change in the mood, either depressive type or paranoid type, and delire d enormite (delirium of enormity) as developed by Yamada [5, 14, 15]. As suggested by Yamada in our case, the patient was initially withdrawn and anxious and later developed nihilistic beliefs, symptoms related to somatic changes (organs are decaying), and observed changes in her mood developed over time.

Overall treatment involves managing the underlying medical or neurologic illness; behavioral and psychotherapy have yielded promising results in treating Cotard syndrome. There are two primary level treatments electroconvulsive therapy and antipsychotic medication. In electroconvulsive therapy an acute course of electric shocks is given to the patient's brain during general anesthesia. These shocks trigger seizures in the patient's brain and cause alteration in brain chemistry. It has been recorded to be safe in pregnant women showing severe refractory depression. Antipsychotic medication is commonly used to treat schizophrenia and has mood stabilizer effects that help decrease nihilistic beliefs/delusions. Haloperidol was found to be safe in treating pregnant women suffering from Cotard syndrome. Monotherapy with sulpiride 300 mg/day has been seen as effective in patients with schizophrenia and Cotard syndrome. In our case, patient L started to experience Parkinson's symptoms and extrapyramidal side effects at a dose of amisulpride 600 mg; she was switched to quetiapine 100 mg. De Risio with his colleagues and Sahoo evidenced overactivity of dopamine receptor binding, and Joseph reports advanced neuroimaging studies providing an association between schizophrenia and Cotard syndrome as in our case. Drugs like quetiapine, risperidone, aripiprazole, and citalopram which can decrease dopamine and act as dopamine antagonists have been used in our patients since our case is Cotard syndrome type 1, which is considered delusional in origin but not developed secondary to any affective disorder which shows hyperactivity of dopaminergic neurons that's why antipsychotics are more effective than antidepressants [9, 10, 11, 13, 16].

Plan of Action

Based on her initial diagnosis done by a private practice psychiatrist as major depressive disorder, she has been prescribed agomelatine 25 mg and zolpidem 10 mg daily. Later on her admission to Klang Valley in September 2018, she got a differential diagnosis of major depressive disorder with psychotic features due to another medical condition and schizophrenia. However, after detailed workup was done to rule out differential by doing detailed history taking investigating the presence of fever, seizures, connective tissue disorder, substance abuse, or any other neurological abnormalities indicative of migraine, stroke, or meningitis; since all her tests were normal and taking her first psychotic episode into account with exhibiting features of Cotard syndrome, she was given a diagnosis of schizophrenia and Cotard syndrome. After that, she was advised for a hospital stay of 1 to 2 weeks, during which she was put on atypical antipsychotic risperidone 2 mg twice a day.

The patient had not displayed any significant improvement in her nihilistic beliefs on risperidone, so her medication was swapped to amisulpride 200 mg. There was a slight improvement in her personal hygiene and eating habits, but she started to develop signs and symptoms of Parkinson's disorder at a dose of amisulpride 600 mg; to resolve symptoms, trihexyphenidyl 2 mg was given. After a week, she was admitted to the facility again for expressing suicidal ideation and nihilistic beliefs. She still had extrapyramidal symptoms from amisulpride and amenorrhea due to hyperprolactinemia (316.2 mu/l). She has switched to quetiapine immediate release 100 mg due to its ability to neutralize the side effects of amisulpride. Then a decision was made to provide electroconvulsive therapy. Consent to initiate the course was obtained. Our patient was given six sessions over 2 weeks every other day.

If Misdiagnosed, Was It Realized Later? How Was It Rectified?

Cotard syndrome defines a set of well-marked symptoms of hypochondriasis that progress to nihilistic delusion, paving the way for the diagnosis of Cotard syndrome, as shown by Tomasetti and colleagues. Our patient L was not exhibiting any symptoms of existing neurological conditions; moreover, a detailed history was taken along with blood investigation and neuroimaging, which ruled out the differential neurological disorder. Diagnosis of schizophrenia was concluded in lieu of auditory hallucination of third-person aspect and persecutory delusion independent of affective symptoms. Association between Cotard syndrome and schizophrenia due to poor flow of information from the sensory cortex of the brain to the limbic system was put forth by Morgado and colleagues [9].

Conclusion

Clinicians and physicians at primary practice have to be trained and made aware of this condition so that this can be diagnosed earlier, and psychiatrists should be able to recognize and differentiate the symptoms so that patients will not be misdiagnosed and can prevent them undergoing unwanted treatment which will not burden them both financially and emotionally.

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Part XI
Oncology

Chapter 57
Colonic Cancer Misdiagnosed as Hemorrhoids

Junaid Hassan and Safeera Khan

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Identify the importance of early risk factor assessment and diagnostic assessment of the symptoms of colorectal carcinoma.
2. Review the policy to manage colorectal cancer based on risk factors and comorbidities.
3. Identify the high-risk population for early screening.
4. Consider the younger population with symptoms, strong family, and personal history.
5. Update healthcare professionals with new recommendations regarding colorectal cancer management, including diagnostic and therapeutic options.

Introduction

Colorectal cancer is the third most common cancer worldwide [1, 2]. In the United States, the second-leading cancer-related death is due to colorectal cancer [1]. According to the National Cancer Institute, more than 100,000 new cases of colon cancer and 40,000 cases of rectal cancer are diagnosed yearly. Of these 140,000 new colorectal cancer cases, roughly 50,000 cancer-related deaths occur [1]. Common symptoms and signs of colon cancer include blood in the stool, excessive diarrhea,

J. Hassan (✉)
M. Islam Medical & Dental College, Gujranwala, Pakistan

S. Khan
California Institute of Behavioral Neurosciences and Psychology, Fairfield, CA, USA

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constipation or change in bowel movement, fatigue, and/or rectal bleeding. According to a census by the Canadian Cancer Society, early diagnosis of rectal carcinoma leads to a 92% 5-year survival rate [1].

Although hereditary factors play a major role in the development of colorectal cancer, several other factors also serve as important risk factors. A sedentary lifestyle can also be a significant risk factor for colorectal cancer. Obesity, genetic predisposition, smoking, heavy alcohol consumption, and poor diet are other considerable risk factors [3]. Diet, especially red or processed meats and sugar-rich foods, may also cause colorectal cancer. Hereditary nonpolyposis colon cancer or Lynch syndrome also increases the risk of developing colorectal cancer [4]. Timely screening, diagnosis, and treatment, including immunotherapy and individual management of metastatic colorectal disease, can help save more patients' lives. Delayed and wrong diagnosis of colorectal cancer can be due to delayed or improper screening or delay in using the appropriate tools.

Misdiagnoses related to colorectal cancer are around 0.007% of the all-misdiagnosed cases in the United States and are not very commonly misdiagnosed as some other conditions. However, misdiagnosis causes severe and fatal outcomes [4]. If it is diagnosed late or misdiagnosed, leading to a delay in treatment, the survival rates are not high because of the progression of cancer. Colorectal cancer is misdiagnosed as other common intestinal diseases and conditions before reaching the final diagnosis and vice versa because of symptoms common to other intestinal conditions. Some of these conditions are not serious, but some are acute emergencies. A missed diagnosis of colorectal cancer may present later as an acute abdomen requiring emergency surgical interventions like the development of intussusception at the site of cancer. Several colorectal carcinomas are diagnosed at the time when they present as an acute abdomen.

Several factors play a major role in the misdiagnosis, age being one of the major ones. Since it is a common disease in the older population, younger patients are more at risk of not being fully investigated and of misdiagnosis. The percentage of misdiagnosed colorectal cancer may even be higher as medical records may not completely cover the magnitude of the numbers and amounts of misdiagnoses. Early screening and diagnosis are the keys to preventing the development of colorectal carcinoma. Despite having many available screening tools and methods, they still do not accurately detect colon cancer with 100% accuracy. This causes misdiagnosis, thus leading to severe consequences down the road.

Hemorrhoids, the infected or swollen dilated veins around the anus, may present both externally and internally. Internal hemorrhoids are commonly associated with a misdiagnosis of colon cancer [4]. Hemorrhoids present with bleeding per rectum and change in bowel habits and stool consistency. Internal hemorrhoids are not visible easily but cause all these symptoms and therefore are one of the commonest misdiagnoses of colorectal carcinoma.

Clinical Case Presentation

A 31-year-old female visited her primary care physician complaining of bleeding per rectum and hard stools with hematochezia. She had no significant relevant medical history. After a physical and digital rectal examination, her physician diagnosed external hemorrhoids that were negative for occult blood. She was advised to increase the dietary fiber intake and that a colonoscopy may be needed but not ordered or advised.

She presented the second time with a similar complaint of bleeding per rectum 11 months later. Her bloodwork, which included a complete blood count, was normal. This time she was scheduled for a colonoscopy the next week. The gastroenterologist reported a single mild internal hemorrhoid and a normal cecum and colon. He also noted that the colon was well-prepared for the exam, and the cecal area was viewed with a pediatric scope from a short distance. During the procedure, a single image was taken.

She presented again to her cardiologist and family physician with a complaint of hard stools and blood on the toilet paper. The physician associated the symptoms with hemorrhoids. The fourth visit yielded the same diagnosis as hemorrhoids, and if symptoms persist, another gastroenterology consult will be done. She was also seen with fatigue but no change in weight.

The patient presented to the emergency department a year later with severe abdominal pain, nausea, and vomiting with severe anemia. She was transfused three pints of packed red blood cells. Computerized tomography (CT) scan showed free fluid in the abdomen and two hepatic lesions. Emergency surgery was performed, and a right-sided colectomy and resection of hepatic lesions were done. Histopathology diagnosed moderately differentiated mucinous adenocarcinoma, positive lymph nodes, and (stage IV) liver metastases. Despite ongoing treatment, the patient died 9 months later.

Differential Diagnosis

Colorectal cancer is commonly misdiagnosed with other conditions before reaching the final diagnosis [5]. These conditions include:

1. Hemorrhoids: Internal hemorrhoids are the swollen blood vessels above the pectinate line and may have features like rectal bleeding, itching, and lumps at the anal opening resembling polyps like the colorectal cancer presentation.
2. Inflammatory bowel disease (IBD): IBD, including Crohn's disease and ulcerative colitis, presents with some similar symptoms, like rectal bleeding and constipation alternating with diarrhea. Patients with inflammatory bowel disease risk developing cancer because of increased cellular turnover and inflammation.

3. Irritable bowel syndrome (IBS): Abdominal bloating, feeling of incomplete stool evacuation and mucus in stool, and relief of symptoms after a bowel movement are some of the symptoms that may be similar to colorectal cancer. However, unlike IBD, there is no increased cancer risk in IBS patients.
4. Diverticulitis: Diverticulitis and colon cancer both present with colonic wall thickening on CT scan; hence, colorectal cancer is commonly misdiagnosed as diverticulitis if the diagnosis is made according to radiological findings.
5. Familial adenomatous polyposis is a familial, hereditary precancerous condition with several hundred to thousand polyps throughout the colon. If not treated, these polyps can become cancerous.
6. Ischemic colitis: Ischemic colitis is painful ischemia of the colon; however, during investigations like colonoscopy, it may look like ulceration, a narrowed colon, or growth, which may mimic colorectal carcinoma.

The age of the patient is a common factor, playing a major role in the misdiagnosis of colorectal cancer. According to one report by Colorectal Cancer Alliance, many doctors disregarded the concern of younger patients between the ages of 19 and 39 compared to patients aged 40–50. Women with symptoms and concerns about cancer were dismissed more by their doctors than men. Patients have to visit many doctors and make multiple appointments before reaching a diagnosis. Thirty-nine percent of patients visited two physicians, 19% visited three, and 17% visited four or more before reaching the final diagnosis [2].

What Was Misdiagnosed in the Case, and Why?

Several factors contributed to the misdiagnosis. The patient presented with symptoms common to several diseases, like changes in bowel habits and stool consistency. These symptoms are shared with other conditions like irritable bowel syndrome (IBS) and IBD. The blood in stool is also a symptom that can present other conditions like hemorrhoids.

Another misdiagnosis was an overreliance on previously normal findings and a narrow diagnostic focus. However, a colonoscopy was scheduled and conducted during one of her previous visits and showed a normal result related to the colon and the presence of hemorrhoids. This led to an overlooking on the part of the treating physicians despite having repeated and related symptoms. The symptoms were not evaluated further, and a repeat colonoscopy was not requested.

In this case, the bowel was well-prepared when the colonoscopy was conducted. This may have given the advantage of properly viewing all the colon along with the cecum. The cecum was viewed from a distance while conducting a colonoscopy, which may have led to missed findings. Also, only one image was taken, limiting their ability to view the imaging later and pick up any missed findings. The presence of internal hemorrhoid and bleeding per rectum as presentation led to overlooking or casual examination of the rest of the colon.

Discussion

The patient's age plays a major role in screening for the disease. Colorectal screening is part of a regular screening program in several developed countries; however, it is started after a certain age. Genetic factors are also considered to play a major role, and people with a family history of colorectal cancer are scheduled for relatively early screening. Females, especially younger females, are more prone to be misdiagnosed because of the less risk. They are not screened regularly, so many early cancers will be missed. Even when a female presents, a high index of suspicion is not there because of the low risk. Therefore, the diagnostic and screening process is started late and leads to either misdiagnosis or late diagnosis when the disease has already metastasized.

Colonoscopy is the gold standard for screening and diagnosing adenomatous polyps and colorectal carcinoma. A colonoscopy may be normal when the cancer is not fully developed; a polyp takes around 3 years to develop into colorectal cancer. Therefore, the results of colonoscopy during this phase may be normal. Therefore, in the presence of symptoms, even if the results of colonoscopy are normal, follow-up should be proper with a repeat endoscopy in the plan and sigmoidoscopy [6, 7].

In the presence or persistence of these symptoms, with or without another definitive diagnosis, adequate screening should be incorporated into clinical practice. In the case of a coexisting diagnosis, the symptoms or the findings while screening may bring the index of suspicion to a lower level leading to no further diagnostic effort and a missed or misdiagnosis.

Another case that the patient narrated showed a similar scenario; however, the outcome was not as severe as the patient was diagnosed when he could be treated. The patient, Robin McGee, presented to two physicians and a surgeon with rectal bleeding and pain. She was also not advised of immediate and early colonoscopy. She had her colonoscopy done after 18 months, considering her younger age (under age 50) and lower risk of colorectal cancer. She was diagnosed after 18 months, and after a colonoscopy, when she was diagnosed with stage IV colorectal cancer, treatment was started. She improved, but after 7 years of follow-up, growth was missed again, and it took 6 months to start chemotherapy [8].

Plan of Action, the Points to Consider, Pitfalls to Avoid, and Pearls of Knowledge to Consider

1. People, including the younger population, who are experiencing symptoms should undergo screening and be included in screening programs to reach the disease's early diagnosis in the curable stage. Timely screening, early diagnosis, and treatment, including immunotherapy and personalized medicine for metastatic colorectal patients, can reduce disease incidence and control at an early stage.

2. There are more chances of missed diagnosis in a population under 50 years of age and female patients. They should be given equal consideration by clinicians while investigating their symptoms, keeping a high index of suspicion while treating their symptoms [7, 8].
3. A strong family history, personal history of colorectal cancer and polyp, and history of inflammatory bowel disease, FAP, and hereditary nonpolyposis colorectal cancer (HNPCC) are common risk factors. These people may need early screening and a more vigilant approach.
4. A suboptimal colonoscopy may lead to missed findings. The colon must be visualized with proper focus on the cecum, ileocecal valve, appendiceal orifice, and terminal ileum. Multiple images should be taken for review later so that no finding is missed accidentally. There should be proper and adequate bowel preparation before the procedure [9].
5. The government should decide on the policy of producing processed meat and dietary recommendations according to the information provided by health experts considering all risks and benefits.
6. There are some investigations like double contrast barium enema (DCBE), which have a high rate of missing cancers. Now it is time to reconsider their use to detect colorectal cancers.
7. Colonoscopic surveillance in individuals has a chance of missed adenomas. Chromoendoscopy for adenoma detection is unique in its use, but still, a large trial to provide this new technique to improve cancer prevention [4].
8. For patients presenting with hematochezia, a colonoscopy may miss the pathological lesions or colorectal carcinoma, as the lesions may be located below the sigmoid colon. Therefore, the first choice of diagnosis in patients with hematochezia should be sigmoidoscopy [10].

Conclusion

Colorectal carcinoma is a condition that, if diagnosed early, is treatable but, if missed or misdiagnosed, may later present with more serious symptoms and/or metastasis which may not be treatable at that time. The symptoms present in other conditions may delay the screening and diagnostic process. Since the disease is common in the older male population, there is a greater chance of missing it in the younger population, especially younger females. A high index of suspicion is needed while diagnosing bleeding per rectum and other intestinal symptoms, even when they coexist with other diagnoses or are missing symptoms like weight loss. Early screening and colonoscopy/sigmoidoscopy with proper preparation and technique may pick colorectal carcinoma at a time when it is treatable.

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Chapter 58
Malignant Melanoma Misdiagnosed as Diabetic Foot Ulcer

Junaid Hassan and Safeera Khan

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Discuss the importance of focusing on typical and atypical presentations of malignant melanoma.
2. Analyze and highlight the importance of appropriate and timely steps in evaluating and diagnosing a patient with symptoms that may cause suspicion of melanoma.
3. Outline the importance of early diagnosis and the consequences of misdiagnosis leading to delayed treatment.

Introduction

Malignant melanoma is a dangerous type of skin cancer. It accounts for around 4% of all skin cancers; although the percentage is not very high, it has the highest death rate of about 79–80% due to skin cancers [1]. Melanoma is formed when skin damage triggers the mutations in the skin. If diagnosed early, it can be treated by resecting and removing the affected area, in which case no further treatment will be needed. However, if diagnosed late, it can be fatal as the cancer cells can multiply and spread quickly throughout the body. Around 8800 patients die due to melanoma annually, and the morbidity of malignant melanoma is increasing faster than other types of skin cancers [2].

J. Hassan (✉)
Department of Surgery, M. Islam Medical & Dental College, Gujranwala, Pakistan

S. Khan
California Institute of Behavioral Neurosciences and Psychology, Fairfield, CA, USA

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Melanoma occurs in the melanocytes throughout the body. It occurs in pigmented areas like the pigmented moles, pigmented part of the eye or intestines, etc. There are several risk factors for melanoma development. The most common is exposure to ultraviolet light that triggers melanoma formation. Some other risk factors include age, race, economic status, h/o previous melanoma, number of nevi, sunbed use, or FAMM syndrome (familial atypical mole and melanoma syndrome). Early prevention treatment is especially needed in people with fair skin, red or blonde hair, and blue eyes because of the invasive nature of malignant melanoma in this population.

There are different types of malignant melanomas. Acral lentiginous melanoma is a form of melanomas involving hands and feet that forms around 7% of all malignant melanoma [3]. It does not exhibit any classic symptoms of melanomas that are associated with ABCDE (asymmetry, border, color, diameter, evolution). It occurs at unusual sites and is morphologically different, making it frequently misdiagnosed melanoma. Because of this, the patient may undergo a longer and inadequate treatment/therapy [4, 5]. The rate of misdiagnosis of ALM is about 25–36% [6, 7]. One of the common presentations of this type of melanoma presents with ulcer and, therefore, can be misdiagnosed with other ulcer-forming conditions like venous ulcer, diabetic foot ulcer, or vasculitis [8]. Patients with ulcerated melanoma have a shorter life expectancy for disease-free survival than the ones who have non-ulcerated melanoma [8, 9]. When ulceration is present in cancer, it upstages the staging of cancer, and is an independent risk factor that is used when staging cancer to assess prognosis [8, 9].

Clinical Case Presentation

A 78-year-old diabetic female presented with ulcers on her foot for the past 6 months. She had type 2 diabetes for the past 8 years and had developed complications like diabetic neuropathy and peripheral arterial disease. She had a history of poorly controlled diabetes. On examination, there were two 0.5 cm ulcers on her right heel. There was a pigmented margin, and one of these two ulcers had red granulation tissue. The area around the ulcer had callus; no erythema, edema, oozing, or other signs of infection were observed. There was minor pain at the wound site. A diagnosis of diabetic foot ulcer was made.

She was given antibiotics, wound debridement, daily dressing changes, and medications for neuropathy and peripheral arterial disease for 2 weeks. However, despite the treatment, the ulcer failed to improve. This prompted further workup and conducting of an incisional biopsy. Histopathology was performed and showed tumoral cells positive for HMB45 and S100 and partly positive for Ki-67. Finally, a diagnosis of malignant melanoma was made with a Breslow thickness of 1.6 mm. There was no metastasis at that time. Wide excision of the incisal margin of 2 cm was done with skin grafting and biotherapy. The lesion was healed [10].

Differential Diagnosis

Malignant melanoma can frequently be misdiagnosed as other nonhealing ulcers, warts, blisters, hyperkeratotic lesions, onychomycosis, foreign bodies, pyogenic granules, benign nevi, and tinea pedis [12].

Malignant melanoma is commonly misdiagnosed with other conditions before reaching the final diagnosis. These conditions include:

1. Diabetic ulcers—Chronic uncontrolled diabetes may cause the development of foot ulcers. In the case of a nonhealing ulcer with uncontrolled diabetes, the first diagnosis clinicians consider is diabetic foot; however, a biopsy should be considered if the ulcer is nonhealing despite the medical treatment. Acral lentiginous melanoma, because of its unusual site, can be missed or misdiagnosed in diabetics.
2. Venous ulcers—Venous ulcers develop due to venous stasis and may not heal if the stasis is not relieved. Chronic nonhealing venous ulcers may become cancerous, called Marjolin's ulcers. A biopsy should be done to identify the type of cancer, malignant melanoma.
3. Tinea pedis—Tinea pedis or fungal infection of the foot can sometimes appear as an ulcer with the macerated surrounding skin, esp. interdigital tinea pedis. Because of the unusual site, acral lentiginous melanoma can often be misdiagnosed with conditions like tinea pedis and delay the diagnosis.
4. Onychomycosis—It is the fungal infection of the toenail that may resemble the subungual type of melanoma that starts under the nail. Onychomycosis may cause missed or delayed diagnosis of subungual melanoma; therefore, careful examination is crucial to prevent serious outcomes of delayed diagnosis.
5. Melanocytic nevi (darkly pigmented moles)—Moles or melanocytic nevi are a cluster of cells that are benign but, over the years, may tend to become malignant; therefore it should be screened if any changes are observed. They are considered biomarkers of an increased risk of cutaneous melanoma.
6. Pigmented basal cell carcinoma (an uncommon variant of basal cell carcinoma).
7. Dermatofibroma—It is a common benign skin tumor; because of its color, the hemosiderotic dermatofibroma can be misdiagnosed as various melanocytic lesions and some vascular tumors.
8. Subungual hematoma—A small hematoma under the toenail similar to a scab may look like melanoma and can easily delay further management because of the misdiagnosis.
9. Tinea nigra—It is a dark patch of infected skin most common on the skin extremities of the body and usually occurs in tropical climates. It can mimic acral lentiginous melanoma; clinicians should do a thorough exam and microscopy to rule out acral lentiginous melanoma.

What Was Misdiagnosed in the Case and Why?

The patient presented with a nonhealing ulcer common to several other conditions like diabetic ulcers, vasculitis, and venous ulcers. She was a known diabetic whose diabetes remained uncontrolled and had developed several complications like diabetic neuropathy and vascular complications. Based on the history and the appearance, the ulcer seemed similar to the other common types of ulcers. This history and comorbidities led to the initial misdiagnosis of the ulcer as a diabetic ulcer.

For the diagnosis of melanoma, a weighted 7-point checklist is used with major features worth two points, like a change in size, irregular shape, and minor features worth each point like largest diameter equal to or more than 7, inflammation, oozing, and change in sensation.

In the mentioned case, the ulcer persisted for more than 6 months; there was no significant change in the size and shape of the ulcer. Also, there were no signs of infection or oozing. The size of the ulcer was also 0.5, which is less than 7. This lack of the main diagnostic points, the history of uncontrolled diabetes, and the lack of sensations led to the misdiagnosis of the ulcer as a diabetic ulcer.

Discussion

Several conditions present with ulceration, particularly ulcers on the feet. The features of these ulcers, along with a history of other relevant symptoms, lead to the diagnosis of these conditions. Melanomas may be present in various parts of the body. The melanoma found on feet, if present as an ulcer, may be misdiagnosed as several other ulcer-causing conditions. Acral lentiginous melanoma, if misdiagnosed, is reported to have a poor prognosis because of delayed diagnosis and improper or inadequate treatment [9–11]. Several factors may contribute to the delayed treatment, including an incomplete history and inadequate biopsy [12]. In the presence of other coexisting symptoms or conditions, foot lesions or smaller ulcers are often overlooked because the incidence of AML is low. Therefore, melanoma is often a missed diagnosis or misdiagnosed.

Suppose no obvious causes of the ulcer or comorbidities are found, like any history of trauma, uncontrolled diabetes, peripheral arterial disease, or diabetic neuropathy. In that case, the clinician should schedule an early biopsy. However, even in the case of any of these obvious causes and coexisting symptoms, the index of suspicion should be kept high, and an early follow-up should be requested to avoid misdiagnosis as in the case being discussed. If the ulcer doesn't respond quickly to the treatment, an alternate diagnosis should be thought of, and further workup like a biopsy should be requested. The clinician's high level of suspicion may avoid misdiagnosis or a delayed diagnosis and can help start early treatment and increase the 5-year survival rate [12].

Diagnosing the cause of a foot ulcer early is important to avoid a misdiagnosis. However, many causes of a foot ulcer cause severe discomfort and affect the quality of life but are manageable. However, melanoma can have severe consequences if diagnosed late by reducing the patient's life expectancy, whereas if diagnosed early is easily cured in early stages. Therefore, recommending proper investigations and involving dermatologists and pathologists early can help avoid misdiagnosis.

Diabetic foot ulcers (DFU) are a common but serious complication of diabetes and may co-exist with ulceration caused by other etiological factors. Often, patients fail to inform doctors about new lesions on their feet. Therefore, it is important for physicians to thoroughly examine the feet each time patients present to more easily detect these lesions.

Plan of Action, the Points to Consider, Pitfalls to Avoid, and Pearls of Knowledge to Consider

1. The clinicians must maintain a high level of suspicion to diagnose melanoma and distinguish it from other benign skin conditions. This will prompt the clinician to do a proper physical exam and request the relevant test early.
2. A biopsy should be requested even when the suspicion level is low, esp. if there is a delayed response to the treatment.
3. A follow-up visit should be scheduled early if an alternate benign diagnosis is made to observe if the treatment is working. If there is no treatment response, a biopsy should be done immediately.
4. Pathologists and dermatologists should be consulted early to avoid any delays in the diagnosis.
5. Any changes in the ulcer's size, shape, and other features should be documented on every follow-up, even if the risk of melanoma is low.

Conclusion

Malignant melanoma may develop in various parts of bodies and may also present in different forms. It can also present as a nonhealing ulcer on the foot and may be confused with several other benign conditions. Another comorbidity like diabetes or vascular disease may lead to an alternate diagnosis of diabetic foot ulcers or venous ulcers. A high suspicion index is needed for a proper and early evaluation. A biopsy should always be requested in case of a foot ulcer that is not responding to treatment or if the ulcer has atypical features like pigmentation and the presence of granulation tissue. The patient's 5-year survival rate can be significantly prolonged if diagnosed early.

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Chapter 59
Multiple Myeloma Misdiagnosed as Rheumatoid Arthritis

Safeera Khan and Junaid Hassan

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Discuss the importance of focusing on typical and atypical presentations of multiple myeloma and the pathophysiology.
2. Discuss and highlight the importance of appropriate and timely steps in evaluating and diagnosing a patient with symptoms that may cause suspicion of multiple myeloma.
3. Outline the importance of early diagnosis and the consequences of misdiagnosis leading to delayed treatment.

Introduction

Multiple myeloma (MM) is one of the hematopoietic cancers that account for approximately 10% of all hematologic malignancies [1]. The lifetime risk of MM in the United States is 1 in 132 (0.76%) and has a 30% 10-year survival rate in patients under 60 years of age [2, 3]. Hematopoietic cancers (HCs) , more commonly called blood cancers, are the malignancies of the hematopoietic stem cells. They are commonly caused by or are associated with chromosomal abnormalities such as translocations [4, 5]. Blood cancers affect both the structure and function of the blood cells because of changes in their precursor cells. Hematopoietic stem cells are the

S. Khan (✉)
California Institute of Behavioral Neurosciences and Psychology, Fairfield, CA, USA

J. Hassan
M. Islam Medical & Dental College, Gujranwala, Pakistan

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primitive cells or precursor cells that can develop into all types of bloodlines. These bloodlines can be the myeloid lineage or the lymphoid lineage. These hematopoietic stem cells can be found in peripheral blood, bone marrow, or umbilical cord.

Blood cancers are divided into three main groups, leukemias, lymphomas, and myelomas. Leukemias, also called liquid tumors, may start in bone marrows and be of either lymphoid or myeloid series. On the other hand, lymphoid cancers are solid tumors where a transformed lymphocyte can create a solid tumor. In myelomas, the transformed cells are fully differentiated plasma cells that may present as scattered or dispersed malignant cells or as a solid mass within the bone marrow. Plasma cells are white blood cells that produce antibodies (immunoglobulins) to help the body fight infection. Most of these are associated with gross chromosomal abnormalities [4]. As a result of these mutations, the abnormal plasma cells begin to divide uncontrollably and make several more plasma cells leading to either the precancerous condition called monoclonal gammopathy of undetermined significance (MGUS) or multiple cancerous myelomas. MGUS also may develop into multiple myeloma later. These myeloma cells can form tumors in bones called plasmacytomas; it may be a solitary plasmacytoma, several plasmacytomas, or multiple myeloma. If formed outside of the bones, they are called extramedullary plasmacytomas.

Common risk factors for multiple myeloma include a weakened immune system, a family history of multiple myeloma, and being overweight. Since plasma cells produce antibodies that help fight infection, the high build-up of abnormal plasma cells causes the production of abnormal antibodies, causing decreased ability to fight infection. Plasma cells also affect other cell lines and may cause a build-up of abnormal blood cells, affecting the functioning of other blood cells and causing symptoms like anemia, fatigue, etc. The increased number of myeloma cells can also distort the balance of certain minerals in the body leading to other symptoms. The myeloma cells can also lead to bone damage and high calcium levels in the blood because of their abnormal proteins called M-protein. These abnormal proteins can also affect other organs, such as the kidneys.

Multiple myeloma may or may not have the symptoms of the disease. Smoldering (indolent) multiple myeloma is when there are no symptoms. This is a transitioning stage between MGUS and the active multiple myeloma with symptoms. People with smoldering multiple myeloma have at least one of the following features: Plasma cells make up 10% or more of the blood cells in the bone marrow or the plasma M-protein level of 30 g/L or more [5].

Active multiple myeloma or multiple myeloma with symptoms may have M-protein in the blood or urine. Plasma cells make up 10% or more of the blood cells in the bone marrow. A plasmacytoma in the bone or soft tissue. It may also present anemia, kidney failure, or high blood calcium (hypercalcemia). Osteolytic lesions made by abnormal plasma cells can also be seen on X-rays. Light-chain myeloma is another type of myeloma [5].

Myeloma is diagnosed by physical examination, blood tests, urine tests, a bone marrow biopsy, X-rays, and other more specialized bone imaging tests. An atypical manifestation of the absence of M-protein with nonspecific symptoms may lead to

the misdiagnosis. It could put an even greater challenge on the diagnosis and subsequently cause a delay in treatment.

A review conducted by Mayo Clinic revealed the most common presentations of multiple myeloma and the percentage of their presence. Anemia was found to be 73%, bone pain 58%, elevated creatinine (48%), fatigue (32%), hypercalcemia (28%), and weight loss (24%). The International Myeloma Working Group 2 suggested the acronym "CRAB" for hypercalcemia, renal insufficiency, anemia, and bone lesions to diagnose multiple myeloma. However, up to 20% of patients may have none of these "CRAB" features as their presenting symptoms. They may have atypical symptoms like hyperviscosity syndrome, amyloidosis, hemorrhage, coagulopathy, etc. In such patients, diagnostic challenges may lead to misdiagnosis and potentially serious consequences because of malaligned management plans [6]. Bone pain, the commonest symptom involving the smaller joints, can mimic rheumatoid arthritis. Therefore, diagnosing the condition early will help start the treatment early and prevent serious outcomes of the disease.

Clinical Case Presentation

A 58-year-old male presented to his physician with arthralgia of the hands, wrists, and elbow. His symptoms started 6 months ago and have gradually worsened since then. He had difficulty making fists and had swelling of his hands and wrists. He also had morning stiffness lasting more than 30 min. He had no history of fevers, chills, weight loss, decreased appetite, or night sweats. Systemic examination was negative for alopecia, dry eyes, mouth sores, and skin rash. The patient had no travel history, history of tick bites, or sick contacts. He was a nonsmoker with occasional consumption of alcohol. The patient was diagnosed previously with osteoarthritis as well. He also had a surgical history of bilateral shoulder replacement for severe osteoarthritis, right-sided carpal tunnel repair, and laminectomy of the cervical and lumbar spine. There was no lymphadenopathy, and no bruises were observed. The musculoskeletal exam showed bilaterally swollen, warm, and tender wrists with synovitis of the second to fifth metacarpophalangeal and proximal interphalangeal regions. He also had 30-degree fixed contractures of the elbow. No signs of psoriasis or nail changes were observed.

On lab investigations, white blood cells were found to be 12,000/mm; hemoglobin was 9.7 g/dl, and hematocrit was 30.9%. His C-reactive protein (CRP) was 40 mg per liter (reference = less than 8), and erythrocyte sedimentation rate (ESR) was 50 mm per hour (reference range = 0–15). His liver function tests, calcium, thyroid functions, uric acid, renal function, and urinalysis were normal as well, along with normal levels of the antinuclear antibody (ANA) , rheumatoid factor (RF) , anti-cyclic citrullinated peptide (anti-CCP) antibodies, and angiotensin-converting enzyme, hepatitis B panel, and hepatitis C antibody level.

The patient was previously treated with analgesics by his physician and was also seen by a rheumatologist. He was initially treated with prednisone 20 mg/day and

methotrexate and then 20 mg/week for 3 months with no response. He was then started on antitumor necrosis factor inhibitors. During his follow-up visit after 6 months, he showed the same symptoms. Alternate TNF inhibitors were started with no improvement as well. X-rays of the joints were done, which showed mild degenerative changes only. An MRI of the right hand was done, which showed synovial thickening of radiocarpal joint and MCP joints with flexor tendon tenosynovitis consistent with inflammatory arthropathy. He also revealed a family history of primary amyloidosis in his mother.

Since his serum calcium, uric acid, and creatinine remained normal during RA treatment, protein electrophoresis (SPEP) and urine protein electrophoresis were sent. The serum protein electrophoresis (SPEP) was positive for M-band. The patient was referred to a hematologist for further evaluation and underwent a bone marrow biopsy. His biopsy showed more than 40% plasma cells, which were Congo red stain negative. These findings were consistent with MM. FISH analysis was positive for monosomy 13 in 88% of the cells. Ultimately a diagnosis of multiple myeloma was made, and he was then started on bortezomib and dexamethasone. A 6-month follow-up showed complete resolution of joint swelling; there was a significant improvement in pain in the hands, wrists, and elbows. His MM remained controlled with chemotherapy, and a bone marrow transplant was not needed [7].

Differential Diagnosis

Multiple myeloma is commonly misdiagnosed with other conditions before reaching the final diagnosis. These conditions include:

1. Arthritis: Arthritis can be of different types, and almost all types present with joint pain, stiffness, swelling, and decreased range of motion. Since multiple myeloma also causes similar symptoms and may cause back pain and stiffness, it can easily be misdiagnosed as arthritis.
2. Back injury: Any injury to the back may cause localized back pain and stiffness confusing it with multiple myeloma.
3. Pneumonia: Multiple myeloma may present with fever, frequent infections, backache, and bone pain, including in the chest which may mimic pneumonia. Therefore, a careful history and thorough exam are needed.
4. Kidney disease: Kidney damage can result from multiple myeloma because of M-protein. However, kidney damage caused by other medical conditions may present similar conditions to multiple myeloma-related kidney damage, like fatigue, lack of appetite, and painful, swollen feet. Frequent urination may distinguish between kidney damage due to chronic kidney disease and multiple myeloma-related kidney injuries.
5. Amyloidosis: Amyloidosis is the accumulation of amyloid in different body tissues like skin, heart, nerves, etc. Amyloid of various types, “light-chain

immunoglobulins," is one of the types and is associated with the disease "light-chain amyloidosis." This amyloidosis is called "primary amyloidosis." This is similar to multiple myeloma, where light-chain immunoglobulins are produced and can easily misdiagnose the condition.

6. Lyme disease: Lyme disease is a vector-borne disease transmitted by a tick bite and may present with symptoms like fever, joint pains, rash, numbness of hands and feet, fatigue, and headache. Multiple myeloma can present with these symptoms and, therefore, can easily be mistaken for Lyme disease; therefore, a careful history of tick bites should be asked to rule it out.
7. Monoclonal gammopathy of undetermined significance (MGUS) : Monoclonal gammopathy of undetermined significance is asymptomatic but has the monoclonal protein in the blood, which may cause a misdiagnosis. It doesn't affect the well-being of the patient.
8. Waldenstrom macroglobulinemia: This is the malignancy of B-cell lymphocytes producing a monoclonal immunoglobulin. These B-lymphocytes replace the normal bone marrow cells and affect their normal functioning causing anemia and other blood cell deficiency. The large monoclonal IgM monoclonal protein is called macroglobulin. This antibody makes it very similar to multiple myeloma.
9. Solitary plasmacytoma: A discrete, solitary mass of plasma cells produces antibodies and may occur in different places or organs. If present in bone, it is called solitary bone plasmacytoma and may present with bone pain or fractures like multiple myeloma. It needs regular follow-up as it may progress to multiple myeloma over the years.
10. POEMS syndrome: POEMS syndrome is a paraneoplastic syndrome and an uncommon marrow disorder. It occurs because of the body's immune response to cancer, like glomeruloid hemangiomas. It is called POEMS syndrome because of its characteristics, signs, and symptoms: peripheral neuropathy, organ enlargement, endocrine gland dysfunction, monoclonal plasma cell tumors, monoclonal immunoglobulin, and skin changes. Peripheral neuropathy and bone alterations are the reasons for misdiagnosing multiple myeloma as POEMS syndrome. The bone alterations are, however, different from the classic bone changes in multiple myeloma.
11. Metastatic carcinoma: Any other carcinomas, if metastasized to bones, cause weakened bones and bone pain. If not thoroughly investigated, symptoms may misdiagnose multiple myeloma and miss the primary tumor.

What Was Misdiagnosed in the Case and Why?

The patient presented with symptoms common to rheumatic diseases, like rheumatoid arthritis, and had a history of osteoporosis. He also had contractures of his elbow joint, which misled the physicians that the disease was rheumatological.

Another factor leading to misdiagnosis was an overreliance on previously normal findings and a narrow diagnostic focus. However, protein electrophoresis and urine protein electrophoresis were ultimately sent, leading to the diagnosis.

Discussion

Plasmacytomas form in the bones and lead to bone pain and other symptoms common to several rheumatological diseases. At times, the symptoms are so similar to common rheumatological conditions that an early diagnosis of those diseases is made, and treatment for them is started. However, this prevents the physicians from considering an alternative diagnosis and conducting further tests. A review focusing on such presentations showed that hands and wrists were the most commonly involved joints in patients of MM that mimics rheumatoid arthritis. However, most of these patients had negative rheumatoid factor (RF). This case shows an atypical presentation of MM that mimicked rheumatoid arthritis and consequently misled the physicians into diagnosing it as rheumatoid arthritis and treating it as that. This misdiagnosis caused a delay in diagnosing a cancerous condition, a life-threatening malignancy, and hence delay in its treatment. This highlights an important point of reconsidering and re-evaluating the initial diagnosis of rheumatoid arthritis if the patient is not responding to the treatment [7].

Many patients do not have the well-known risk factors for multiple myeloma. One of these risk factors includes old age, as most individuals diagnosed with the condition are in their 60s. However, some patients present with these symptoms at an early age and therefore need a proper evaluation if present with these symptoms. Family history is another important risk factor of the condition that can be picked up early and prompt early investigation, as the ones having a sibling, parent, or a close relative with multiple myeloma are at increased risk of developing the disease in their lifetime. Males are more commonly diagnosed with multiple myeloma than females, but this gender-based difference is not that stark. Racial differences also tend to play a role in increasing the risk of developing the disease. African Americans are more likely to develop multiple myeloma than Asian Americans. Patients with monoclonal gammopathy of undetermined significance (MGUS) with more monoclonal protein in the bone marrow and blood are at higher risk.

Shem et al. studied four patients with hematological malignancies mimicking rheumatoid arthritis or other rheumatic conditions. These patients between the ages of 20 years and 62 years presented with rheumatic syndromes and were later diagnosed with hematological malignancies. Two of them were diagnosed with polyarthritis. One of these cases was diagnosed with multiple myeloma and amyloidosis; the other was diagnosed with angioimmunoblastic T-cell lymphoma. The third patient was initially diagnosed with migratory arthritis and then eventually with acute myeloid leukemia. The fourth patient was diagnosed with giant cell arteritis and eventually with anaplastic large cell T-lymphoma. All these patients responded well to corticosteroids given for their initial diagnosis. These cases highlight the

importance of considering an alternate diagnosis in the presence of atypical symptoms, even if the corticosteroids show a good response. This may be a major diagnostic pitfall giving a false perception of a correct diagnosis, hence delaying the actual diagnosis [8].

Although an overall 5-year survival rate is 54% after the cancer diagnosis, 5% of the multiple myeloma cases diagnosed early have a higher survival rate. Seventy-five percent are alive after 5 years of diagnosis. However, around 95% of the cases are diagnosed at a later stage when cancer has already spread, which reduces the 5-year survival rate from 75% to 53% [9]. Misdiagnosis can delay the diagnosis and increase the mortality rate significantly, highlighting the importance of vigilant investigation and working up these symptoms.

The Plan of Action, Points to Consider, Pitfalls to Avoid, and Pearls of Knowledge

1. The most important and the first step in evaluating and diagnosing multiple myeloma is good history-taking to evaluate the presence of the risk factors. Focusing on nonspecific symptoms like fatigue or pain is also important while evaluating the patient.
2. A history of symptoms similar to the other significant and severe conditions should also be sought. At times there may be a family history of any other condition that is similar but not the same hematological malignancy.
3. The consultation for the nonspecific symptoms should be sought early and needs to be properly documented along with relevant history-taking, duration of the symptoms, the pattern of the symptoms, examination, and lab findings; this documentation will help during follow-up and in deciding when to evaluate further and when to consider a misdiagnosis if a patient fails to respond to treatment.
4. In the initial diagnosis of any rheumatological condition, a good response to corticosteroids can be a major diagnostic pitfall in patients with hematological malignancies. In such conditions, physicians should look out for subtle clinical and laboratory findings; if present, the clinician should look out for any occult hematological malignancy.

Conclusion

Multiple myeloma has a variety of symptoms; some are typical, and some atypical symptoms. The atypical symptoms are frequently misdiagnosed as rheumatic conditions and as rheumatoid arthritis. Thus, multiple myeloma arthropathy features symmetric RF-negative nonerosive polyarthritis, and therefore an index of suspicion of hematological malignancy should be kept high. Therefore, arthropathy is a

frequently underdiagnosed presenting symptom of multiple myeloma. A thorough history, including the family history of the presence of multiple myeloma in families and the typical and nontypical symptoms in families, is important. Also, early urine electrophoresis and plasma electrophoresis can prevent misdiagnosis.

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Part XII
Psychiatry

Chapter 60
Bipolar Disorder Misdiagnosed as Major Depressive Disorder

Aemil Palm and Carla Rodriguez

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Analyze ways in which bipolar disorder can be more accurately diagnosed and prevent misdiagnosis.
2. Discuss why bipolar disorder is often misdiagnosed or goes undiagnosed.
3. Enumerate the consequences of misdiagnosing bipolar disorder.
4. Analyze the similarities and differences between bipolar disorder and major depressive disorder.
5. Critique the current diagnostic criteria of bipolar disorder.

Introduction

Bipolar disorder (BD) is a psychiatric affective illness characterized by moderate to severe mood swings that mainly present themselves in definable episodes. Although both depressive and manic episodes are possible, according to DSM V criteria, only once a patient has presented with a manic or a hypomanic episode may they be diagnosed with BP. A manic episode is an elevated mood state lasting for 1 week and must include at least three of the following symptoms:

A. Palm (✉) · C. Rodriguez
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: aemil.palm@martinus.edu; carla.rodriguez@martinus.edu

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1. Inflated self-esteem or grandiosity
2. Decreased need for sleep (e.g., feels rested after only 3 h of sleep)
3. Increased talkativeness
4. Racing thoughts
5. Distractibility
6. Increase in goal-directed activity or psychomotor agitation
7. Engaging in activities that hold the potential for painful consequences, e.g., unrestrained buying sprees

Note that there is a subclassification in the diagnosis of bipolar disorder: bipolar disorder II, in which hypomania is present as opposed to mania. Criteria for this diagnosis are met when there is evidence of a milder manic episode that typically has a shorter duration (4 days or less) [1].

Approximately 2.8% of US adults have bipolar disorder, with a lifetime prevalence of 2.9% [2]. The lifetime prevalence of unipolar depression is 3.5 times greater than bipolar depression, making it by far the more common disorder [3, 4]. The etiology of BD is an area that requires more study. Investigation of serotonin transport genes has yielded promising results of association with BD, but more research is required [5].

Clinical Case Presentation

A 25-year-old female presents to an outpatient department with psychiatric symptoms that have been refractory to treatment for the last 5 years. She reports difficulty expressing herself during interpersonal interactions and weeps during the consultation.

This patient has undergone a diverse course of pharmacological treatments for the last 3 years. These consisted of lamotrigine 100 mg/day and moclobemide 600 mg/day for the last 1.5 years. Despite these treatments, the patient reported no improvement in her symptoms, including melancholy, apathy, and food aversion. In contrast, she also felt exasperation, restlessness, and an overwhelming urge to wander outside her household, especially at night. She reported greater self-assuredness, greater sociability, aggression, and inappropriate laughter during these periods.

The patient recalled that her symptoms arose during a sixth-grade class at school when she had started to wear spectacles. She felt embarrassed, anhedonic, and apathetic even on joyous occasions; her appetite and sleep schedule, however, were normal. Her symptoms worsened when she went to a university, where she reported less free time and less social interaction fulfillment. She recalled experiencing being uncomfortable in crowded places such as lecture halls, libraries, and cafeterias. Similar to her younger years, she felt apathy and also lethargy. In addition, she also started to overeat, stayed in bed all day, and experienced periods of agitation. It was at this time that a psychiatrist diagnosed her with depression and prescribed her

fluoxetine 20 mg/day and trifluoperazine 1 mg/day. She admits that she did not consistently adhere to her medication regimen. After 1 year of symptoms resistant to medication, she sought treatment at a university's psychiatric day outpatient clinic, where she was given a diagnosis of bipolar disorder type II and a new regimen consisting of valproic acid 1000 mg/d and sertraline 50 mg/day. She adhered to this regimen for 1 year but reported feeling too mellow and elected to stop her regimen, feeling that she no longer needed it.

Additionally, another psychiatrist claimed that she did not have bipolar disorder (BD); they reasoned that BD is difficult to diagnose and that her previous treatment regimen should not be changed; these conflicting narratives confused the patient, and this confusion also influenced her decision to stop taking the drugs. After a short time, the patient started to experience uncontrollable bouts of crying and sought consultation with another psychiatrist who, upon hearing that she had been previously diagnosed with BD, prescribed her lithium. Due to nausea caused by the lithium, she also elected to stop taking lithium. Five months after this, she sought the help of yet another psychiatrist with complaints of uncontrollable crying and general feelings of apathy. The patient was given lamotrigine and moclobemide but failed to adhere to the treatment regimen properly; subsequently, her symptoms did not improve.

The findings from the psychiatric evaluation of the patient were as follows: Her physical appearance corresponded to her biological age. She was dressed casually with disheveled hair, she was bashful and apprehensive, and she had difficulty expressing herself. Her mental status examination revealed that she was alert and oriented, with no apparent issues relating to attention, memory, or perception. She had a flat affect and expressed a lack of self-esteem. No psychosis or suicidal ideation was detected, and her symptoms seemed to be at least partially egodystonic. A thorough laboratory analysis, which included thyroid tests, yielded normal results. A brain CT yielded no abnormal findings. The patient underwent psychometric evaluations and received the following results: Young Mania Rating Scale, 2/60; Hamilton Depression Rating Scale, 23/51; Avoidance Rating, 62/96; and Liebowitz Social Phobia-Anxiety Rating, 76/96. The MMPI results described her as being withdrawn socially with a low activity level, shy, and not being able to interact with others.

During the evaluation, the patient expressed herself using an analogy; there were times when she laughed for no reason, which she understood as not being very healthy. She continued that her laughter felt like "cream on spinach" where the cream (laughter) was "fine, but it felt very awkward because it was on spinach."

The patient was ultimately diagnosed with "bipolar mood disorder, unspecified type" in accordance with the DSM V criteria due to several factors: (1) onset of symptoms during adolescence, (2) atypical depressive episodes and chronicity, (3) psychomotor agitation, and symptoms very similar to (but not completely meeting the criteria for) (4) hypomania. Additionally, the patient was diagnosed with a social anxiety disorder because of her avoidant nature, anxiety symptoms in social situations (especially around strangers), and general aversion to social situations.

Because of other signs such as mood swings, low self-esteem, lack of meaningful relationships, frequent change of psychiatrist, and low adherence to treatment, the patient was evaluated for personality disorders but did not satisfy the diagnostic criteria for any specific personality disorder. Dysthymia was also considered as a diagnosis, but seeing as how her social phobias and antidepressant-induced hypomania could not be ruled out, it was decided that the diagnosis of bipolar was clinically satisfactory.

The diagnosis was discussed in detail with the patient, and she was advised to take lamotrigine and moclobemide regularly. Subsequent to follow-ups, her valproic acid dosage was increased up to 1000 mg/day, and her lamotrigine dosage was halved. The patient also attended regular individual psychotherapy sessions, which aided in the partial remission of her depressive symptoms. The patient subsequently began to work as a private tutor for high school students, which indicates a considerable improvement in her social functioning. The patient herself stated that she believes her issues with interpersonal communication have diminished greatly [6].

Differential Diagnosis

1. Major depressive disorder—The patient presented with classic symptoms of unipolar depression and was even diagnosed with it initially. However, the patient also presented with classic symptoms of (hypo)mania (psychomotor agitation, uncontrolled laughter, grandiosity, aggressiveness), making BD the stronger diagnosis.
2. Unspecified personality disorder—Due to low self-esteem, frequent changes of their psychiatrist, and low medication adherence, the patient was evaluated for personality disorders but did not meet DSM criteria for any of these.
3. Dysthymia—Although dysthymia is a good differential diagnosis, BD is a better fitting diagnosis in this case, especially because the patient's hypomanic episodes could not be ruled out.

What Was Misdiagnosed in This Case, and Why?

Initially, the patient was diagnosed with depression. The depression proved to be treatment-resistant, and the patient was diagnosed with bipolar disorder type II. Due to conflicting narratives from her psychiatrists, one of them stating that she did not have BD and should not take medication, the patient felt confused and decided to quit her medication regimen, at which point her symptoms worsened. Ultimately, the patient was diagnosed with bipolar disorder: unspecified type, as well as social anxiety disorder. The diagnosis was thoroughly discussed with the patient so as to avoid another instance of confusion, and the patient also attended psychotherapy sessions and followed up regularly, both of which improved her prognosis.

Discussion

Patients with bipolar disorder spend half of their lives symptomatic, and the majority of symptoms are depressive symptoms [7]. Bipolar disorder initially presents with a depressive episode in up to 78.7% of cases that were initially misdiagnosed [7, 8]. In one study (Fig. 1) with 177 patients diagnosed with BD, 136 (76.8%) reported a previous misdiagnosis. Of the 136 misdiagnoses, the most common misdiagnosis was depression at 96 (70.6%). That means that 54.2% of bipolar patients are likely to have been initially misdiagnosed with unipolar depression [7].

The aforementioned statistics speak to a larger issue than clinical error. In the event that a patient who in actuality has BD presents with no detectable mania but a depressive episode, their symptom profile would be nearly identical to a patient suffering from unipolar depression. Because of the aforementioned DSM diagnostic criterion, which states that a manic episode must have occurred in order for a patient to be diagnosed with BD, patients who may have BD but have not yet had a manic episode (e.g., the aforementioned 78.7% of initially misdiagnosed patients) will not receive the proper diagnosis. Oftentimes for these patients, the period between initial treatment and correct diagnosis can last more than 10 years [9, 10].

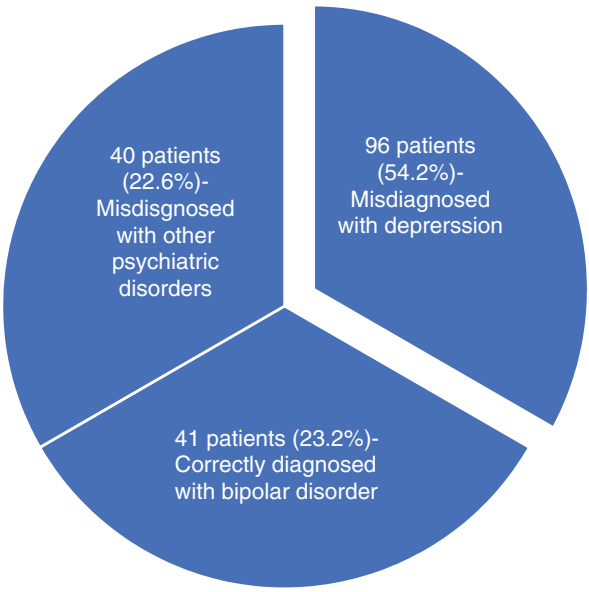

Fig. 60.1 Distribution of bipolar patients who were misdiagnosed and correctly diagnosed [7]

Plan of Action, Points the Clinician Should Consider, Pitfalls to Avoid, and Pearls of Knowledge to Consider

1. The clinician should be alert to any symptoms the patient describes that point toward mania. Even if the patient is presenting in a depressive state, the clinician should inquire if the patient has had any episodes of markedly elevated mood, decreased need for sleep, hypersexuality, or impulsivity [1].
2. Patients with bipolar disorder tend to have a family history of psychiatric disorders. The clinician should inquire about psychiatric illness in the patient's family. Additionally, the clinician should also inquire about the patient's interpersonal relationships and social network [8, 11, 12].
3. Bipolar patients tend to have more incidents of psychiatric hospitalizations than unipolar depression patients. The clinician should inquire about any previous psychiatric hospitalizations [8, 10–12].
4. The mean age of onset in bipolar disorder is younger (22 years) than in unipolar depression (26 years) [4, 8, 11, 12].
5. Bipolar patients tend to have a history of treatment-resistant depression [8, 12].

Conclusion

Bipolar disorder is often initially misdiagnosed as major depressive disorder (unipolar depression), leading to unrealistic expectations regarding prognosis and incorrect pharmacotherapy. Current diagnostic criteria are not sophisticated or nuanced enough to differentiate major depressive disorder from a suspected case of bipolar disorder without previous manic episodes. Therefore, careful history-taking combined with psychometric analysis and consistent patient follow-ups are vital in detecting potentially misdiagnosed cases.

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Chapter 61
Schizoaffective Disorder Bipolar Type Misdiagnosed as Bipolar I with Psychotic Features

Jonathan Seok

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Create an appropriate differential diagnosis in patients presenting with schizoaffective disorder (SZA) by considering all relevant details of the medical history together with proper SZA screening and diagnostic tools.
2. Enumerate the new parameters of the DSM-5 in order to discuss both the changes made and how it assists providers in making the correct diagnosis of SZA.
3. Evaluate the different components of the medical history and physical examination which indicate the most appropriate screening and diagnostic tools so the most correct course of further diagnostic procedures needed to reach a definitive diagnosis can be reached.
4. Appreciate the consequences of a misdiagnosis or delay in reaching a correct diagnosis for the individual patient prognosis.
5. Discuss the relationship between bipolar type 1 disorder with psychotic features and SZA to correctly diagnose SZA between the two.
6. Apply the knowledge gained from the case in a clinical setting where appropriate.

J. Seok (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: jonathan.seok@martinus.edu

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Introduction

Schizoaffective disorder is a serious psychiatric disorder in which people interpret reality abnormally and have an unstable mood. There are two types: bipolar type and depressive type. This case report will focus on schizoaffective disorder bipolar type. Schizoaffective disorder bipolar type patients experience symptoms of both schizophrenia and a mood disorder like bipolar disorder. Schizoaffective disorder may present in some individuals as a combination of delusions, hallucinations, and very disordered thinking and behavior which will impair daily functioning and can be disabling like schizophrenia. In addition to the schizophrenia-like symptoms, people with schizoaffective disorder also have mood symptoms of mania, hypomania, mixed episode (mania and depression), or depression and tend to be episodic rather than continuous. It is estimated that the disorder affects 0.3 to 0.8% of people, but it is one of the most misdiagnosed mental health disorders [1]. There are diagnostic tools to help providers diagnose patients with SZA, but the DSM-5 will need to be followed closely in order to make a proper diagnosis. Recent endophenotype studies have also shown that there is a possible genetic difference between the schizophrenia disorders [2]. This further validates the DSM-5′s changes to schizoaffective disorder criteria for diagnosis. The patient in the case study reported a multitude of clinical symptoms that can be misinterpreted for bipolar disorder type [3].

Clinical Case Presentation

A 50-year-old African American female presented to the hospital with a "history of bizarre delusions, hallucinations, disorganized behavior, and disorganized speech." [3] She has been experiencing these symptoms for the past 1.5 months and was unable to tell the providers why she was in the psychiatric unit. She does not have depression, homicidal, or suicidal ideations. Her past medical history showed that she had previously had a history with acute myeloid leukemia (in remission), diabetes type 2, epilepsy, HIV, and hypertension. The patient was previously diagnosed with bipolar type 1 disorder with psychotic features.

During the physical examination, her vitals were stable. She was asked about a scar on the right knee, and the patient said the scar was a recent wound that occurred when homeless people recently broke into one of her homes and attacked her (hallucinations). She kept insisting that the scar was still bleeding even though it had healed [3]. The patient looked poorly groomed and unkempt.

Upon examining her mental status, her behavior was childish but she was also very cooperative. She could read, comprehend, and repeat as well as name things and knew what day and time it was. She was unable to write a complete sentence nor was she able to recognize a person or situation. The patient was experiencing euphoria, but her affect was appropriate to the content [3]. Her thought content

included grandiose delusions and an overabundance of thought [3], while her thought process consisted of loosening of associations, talking quickly and erratically, and unable to keep on topic.

During the initial presentation, the patient was manic and showed aggression when she was not believed [3]. The patient would share extreme delusions that she was a child celebrity and also believed she was the daughter of the US president. She would remove her clothing in public, talking quickly and erratically jumping rapidly between ideas, engaged in movements that served no purpose, as well as an extreme need to share her ideas [3]. These symptoms were also observed by the nursing home she resided in prior to her admission to the psychiatry unit. These hallucinations, delusions, disorganized speech, and grossly disorganized behavior were present for 2 weeks in the absence of her mood symptoms. After evaluation the patient was diagnosed with schizoaffective disorder, bipolar type, according to the DSM-5 criteria after being closely monitored. Her mood episodes were initially reported to be present for most of her illness. This is why her disorder was confused with bipolar disorder with psychotic features and initially misdiagnosed. The patient was treated with a combination of drugs. They consisted of an antipsychotic (quetiapine 100 mg) with a mood stabilizer (valproic acid 500 mg) and an antidepressant (sertraline 50 mg) which is used to treat roughly 18% of schizoaffective patients. Paliperidone is the normal first-line antipsychotic for schizoaffective disorder, but due to the patient's limited finances, the drug could not be used in the treatment. After consultation with a social worker, the patient was sent back to her nursing home a week later with reconciled medications and scheduled cognitive behavioral therapy [3].

Differential Diagnosis

1. Schizoaffective disorder bipolar type [4]

   The correct diagnosis and rationale can be seen below in the discussion section.
2. Bipolar I disorder with psychotic features [4, 5]

   The patient has mood episodes and has had them since the start of her illness. This mood episode where the patient was manic and easily distracted can be confused with bipolar disorder with psychotic features. The hallucinations, delusions, and confused thinking are all signs of bipolar I disorder with psychotic features. The reason why this is schizoaffective disorder bipolar type rather than bipolar I disorder with psychotic features is due to the timing of the symptoms. The schizophrenic symptoms do not present when the patient is having the mood episode. This is the key difference between schizoaffective disorder bipolar type and bipolar disorder with psychotic features. The schizophrenic symptoms also appear when the patient is not having mood symptoms or remains present after the mood symptoms improve. It is this timeframe of when symptoms arise that clearly distinguishes the two disorders.

3. Schizophrenia [4, 6]

   Like bipolar disorder, schizophrenic symptoms present in patients with schizoaffective disorder bipolar type. The similar symptoms make distinguishing schizophrenia difficult from schizoaffective disorder bipolar type. A lack of mood disorders would instantly rule out schizophrenia, but the patient in this case has mood disorder symptoms which makes schizophrenia unlikely and the two previous differential diagnoses more likely.
4. Major depressive disorder with psychotic features [6]

   The patient does not present with depressive symptoms. If the patient had SZA depressive type, then this differential would be more likely and higher on the list. It is important to distinguish between the two types of schizoaffective disorder to make sure the correct one is diagnosed. The lack of depressive symptoms in the case is key here. The case had an excellent medical history on the patient as well as a detailed list of current symptoms highlighting the importance of history taking and prognosis in diagnosing schizoaffective disorder properly.

Discussion

The African American female patient "presented with a history of bizarre delusions, hallucinations, disorganized behavior, and disorganized speech for the past one and a half months." She was admitted to the hospital and put in the psychiatric ward. On initial interview and based on the symptoms, the initial diagnosis seems to point toward the bipolar I with psychotic features which is what she was previously diagnosed with or schizophrenia [3].

Schizoaffective disorder (SZA) bipolar type is characterized by abnormal thought processes and an unstable mood [7]. There are two types depending on the mood disorder (bipolar and depressive) and the patient in this case had the bipolar version. The most important distinguishing symptomology in order to properly diagnose schizoaffective disorder is the appearance of psychotic symptoms for at least 2 weeks without any mood symptoms [7].

The bipolar type is distinguished by symptoms of mania, hypomania, or mixed episode similar to bipolar type I. Importantly, she denied any depression, homicidal, or suicidal ideations. This is an important part of the medical interview as it helps distinguish what type of mood disorder she has [3]. In this case, the lack of depression and/or suicidal ideation allows for depressive mood disorders to be removed from the differential [4].

When she was initially admitted, "the patient was manic, easily distracted, and demonstrated aggression for not believing her." During the initial stay, the patient presents with symptoms of a mood disorder [3].

The common schizophrenic symptoms of the disorder include hallucinations, delusions, and disorganized speech and thinking. Patients will also experience

auditory hallucinations which usually present as "hearing voices." [8] The onset of mood symptoms begins in young adulthood as it usually occurs with mood disorders; the onset of schizophrenic symptoms will then confirm the schizoaffective disorder (SZA) diagnosis. Other schizophrenic features include psychological symptoms such as catatonia and negative symptoms (socially withdrawn, muteness, apathy).

She states she constantly claims that her beach home is being burglarized, thinks that her father is the president of the United States, that she is 10 years old, and that she is a celebrity as well as other grandiose delusions. She also believes that an old scar on her leg is bleeding even though it is not. She exhibits childlike behavior and is unable to complete thoughts or speak proper phrases. She had a global increase in the quantity of thoughts, and her thought process showed signs of loosening of associations as well as flight of ideas and tangentiality. Her grooming and appearance were both poor [3].

As the patient presents with both bipolar and schizophrenic symptoms at the same time and as the diagnosis of bipolar I with psychotic features was already on the patient's chart, it would be very easy for most providers to miss the actual underlying diagnosis [3].

Upon further interviewing and observation of the patient at the hospital as well as by interviewing the staff at the nursing home the patient stays at, there was a key indicator that the patient was misdiagnosed. The patient's "hallucinations (burglars attacking her in her beach home and seeing blood on her knee), delusions, disorganized speech, and grossly disorganized behavior were present for two weeks in the absence of her mood symptoms." [3] It is this absence for 2 weeks that is critical to changing the diagnosis to schizoaffective disorder (SZA) bipolar type. This highlights the importance of a thorough and complete interview of both the patient and the patient's caretakers and background check for patients with disorders that lie on the schizophrenic spectrum as well as the importance of holding and observing the patient.

The patient's vital signs were stable. She had also been previously diagnosed with type 2 diabetes, hypertension, HIV, epilepsy, and acute myeloid leukemia (in remission) [3].

In order to confirm this diagnosis, we need to use the DSM-5 criteria to ensure the change from bipolar type 1 with psychotic features to schizoaffective disorder (SZA) bipolar type. Due to the provider's in-depth interview of both the patient and caretaker in the case, the DSM-5 criteria can be easily compared to, and the patient had met almost all the criteria for SZA bipolar type. Additionally, the provider could have also used the Self-assessment of Negative Symptoms (SNS) and the Patient Assessment Questionnaire (PAQ) . The SNS would help screen for the schizophrenic symptoms, and the PAQ would help screen for general distress and side effects. Both of which would help providers fill in the criteria for the DSM-5 [9]. Based on the DSM-5 criteria, the patient should be correctly diagnosed with schizoaffective disorder (SZA) bipolar type.

Plan of Action, the Points Clinician Should Consider, Pitfalls to Avoid, and Pearls of Knowledge to Consider

The diagnosis of schizoaffective disorder (SZA) bipolar type involves ruling out other mental health disorders on the list of differential diagnosis. This also includes ruling out symptoms that may be caused by substance abuse, prescription medication, or other medical issues. Ways to do this include physical exams, tests and screenings, psychiatric evaluations, and most importantly diagnostic criteria using DSM-5. Using the PAQ and/or SNS helps providers gather data points to help fill in the criteria but cannot be solely used for diagnosis.

This patient had a complete psychiatric and neurologic evaluation done for her, and key aspects of the patient's history were uncovered and reevaluated by interviewing the patient's caregivers. This is important to keep in mind and remember as the patient may not always be reliable due to the symptoms of delusion and other schizophrenic symptoms [10].

In addition, her admission to the hospital and observation was another key and critical element to properly diagnosing her as the extended stay allowed for providers to witness the absence of mood disorder symptoms for 2 weeks which pointed to SZA bipolar type instead [3].

The patient's medication included sertraline, quetiapine, and valproic acid. The patient was treated with what is known as a combination therapy of drugs. In this case, she is being treated with a combination of an antipsychotic with a mood stabilizer and an antidepressant [3, 10] which is used to treat 18% of SZA patients. The US Food and Drug Administration recommends paliperidone as the first-line antipsychotic for schizoaffective disorder [4, 10], but the patient could not afford paliperidone, and it was not used in the treatment of the case patient. Along with medication she was assigned a social worker and a cognitive therapist. The patient was discharged back to her nursing home after a week with reconciled medications.

However it is now recommended that patients with SZA bipolar type not take antidepressants like sertraline. The provider needs to rule out bipolar disorder before starting an antidepressant because this can risk making a manic episode worse [4, 8].

Second opinions at a specialized schizophrenia clinic after initial diagnosis are wise efforts to reduce the risk of misdiagnosis and ensure prompt and appropriate patient treatment. These clinics also specialize in schizoaffective disorders and are better able to identify the sometimes-subtle differences between these disorders [6].

What Was Misdiagnosed in This Case and Why?

Patient was initially misdiagnosed by a previous provider. This was primarily due to her mood episodes that were present for the majority of her illness when she was initially diagnosed. This is why her disorder was confused with bipolar disorder

with psychotic features instead of schizoaffective disorder, bipolar type. This misdiagnosis can be prevented by observing a patient for a longer period of time or by looking for a lack of mood disorders when the patient comes back for follow-ups. Treating this mental disorder early may help get symptoms under control before more serious complications develop and may help improve the patient's long-term outlook [6], making correct diagnosis critical in this case.

Conclusion

Living with SZA bipolar type can be a long-term challenge and it is a serious mental health condition. Patients must seek treatment. Schizoaffective disorder bipolar type is commonly misdiagnosed as bipolar I with psychotic features as both present with schizophrenic and bipolar symptoms. Do not confuse a patient's diagnosis by looking at the timeframe in which different symptoms arise. Be ready to get a good history and listen carefully for red flags during the interview as well as interview caretakers, friends, and family for a complete medical history [3]. Then by using the DSM-5 criteria along with other screening and diagnostic tools, the patient can be properly diagnosed with SZA bipolar type. In most cases, SZA bipolar type improves with medications. Therapy and social work can also help patients in managing their SZA. With proper treatment and medication, patients with SZA can manage symptoms and lead a normal and fulfilled life.

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Chapter 62
Borderline Personality Disorder Misdiagnosed as Bipolar Disorder

Aemil Palm and Carla Rodriguez

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Compare and contrast the differences and similarities between the clinical presentations of bipolar disorder (BD) and borderline personality disorder (BPD).
2. Discuss why borderline personality disorder is often misdiagnosed as bipolar disorder.
3. Assess the consequences of misdiagnosis of borderline personality disorder as bipolar disorder.
4. Distinguish nuanced concepts of patient history, especially when attempting to differentiate bipolar disorder and borderline personality disorder.
5. Analyze the statistical data that distinguishes bipolar disorder and borderline personality disorder.

Introduction

Borderline personality disorder (BPD) is defined by the American Psychiatric Association's DSM-V criteria as "a pervasive pattern of instability of interpersonal relationships, self-image and affects, and marked impulsivity beginning by

A. Palm (✉) · C. Rodriguez
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: aemil.palm@martinus.edu; carla.rodriguez@martinus.edu

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early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

1. Frantic efforts to avoid real or imagined abandonment (Note: Do not include suicidal or self-mutilating behavior covered in Criterion 5).
2. A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation.
3. Identity disturbance: markedly and persistently unstable self-image or sense of self.
4. Impulsivity in at least two areas that are potentially self-damaging (e.g. spending, sex, substance abuse, reckless driving, binge eating). (Note: Do not include suicidal or self-mutilating behavior covered in Criterion 5).
5. Recurrent suicidal behavior, gestures, threats, or self-mutilating behavior.
6. Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
7. Chronic feelings of emptiness.
8. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights).
9. Transient, stress-related paranoid ideation or severe dissociative symptoms [1]."

Borderline personality disorder is found in approximately 1–6% of the general population [2]. Although BPD and BD are most often separately diagnosed in 80–90% of cases, 20% of people with borderline personality disorder have comorbid bipolar disorder, and 15% of people with BD have comorbid BPD, a higher-than-expected comorbidity rate for disorders that are often separately diagnosed. This suggests that the number of people with underlying BPD may be much higher than thought [7]. The etiology and pathophysiology of borderline personality disorder are still obscure. Studies on the association of 5-hydroxytryptamine receptor 2A (HTR2A) gene variants, as well as on serotonin transporter genes, serotonin receptor genes, and tryptophan hydroxylase genes, have yielded inconclusive results [3, 4]. Despite a low association with studied genetic variants, the heritability of BPD has been estimated at 40%. This could mean that the etiology of BPD is more associated with genetic plasticity than genetic vulnerability [4].

Clinical Case Presentation

A 29-year-old female patient was admitted to a psychiatric hospital by the police after she had consumed five alcoholic beverages and texted a male friend repeatedly, stating that she wanted to commit suicide. The patient was docile and responsive the following day during her psychiatric consultation but could not fully recall what had happened the previous day. The patient was diagnosed with bipolar

disorder in the past and confirmed that she had experienced symptoms that point toward manic episodes, such as intense mood; irritability; increased libido; racing thoughts; hyposomnia; hasty, disorganized thoughts; feelings of grandeur; and rapid, frenzy speech. She also demonstrated impulsiveness and displayed mood swings. The patient herself admits to having issues with her affect (more so with feelings of loneliness and rage), disinhibited actions (suicidality, improper sexual conduct, and drug abuse), and social interactions (feelings of abandonment, overdependency, and entitlement). The patient elucidated several sources of stress in her life, including marital problems and a strained relationship with her own mother. She has three children and is married to a husband, who the patient said would always remain loyal to her despite her infidelity during her manic episodes. The patient denies a previous diagnosis of borderline personality disorder; however, she made it known that she had a history of self-mutilation, anorexia for 3 years in adolescence, and two attempted suicides via medication overdose, one at age 15 and one at age 21. After the first interview with the patient, the psychiatric team concluded that the patient was currently suffering from a depressive episode directly related to her previously diagnosed bipolar disorder. She was restarted on quetiapine, which the patient reports had a positive impact in the past, and in addition, she was started on lithium. The patient remained compliant with her treatment during the 4-day inpatient hospitalization period, and her new diagnosis of borderline personality disorder was disclosed to and discussed with her [2].

Differential Diagnosis

1. Bipolar disorder—The patient was previously diagnosed with BD. However, the enduring pattern of behavior that the patient presented with since adolescence is not typical of BD.
2. Alcohol abuse—In the initial presentation of the patient, she had consumed five alcoholic beverages. However, this does not explain the enduring pattern of behavior of the patient when she was not intoxicated.

What Was Misdiagnosed in This Case, and Why?

The patient was correctly diagnosed with BD, but her other diagnosis of BPD was missed. The patient did meet DSM criteria for manic episodes, but there were other behavioral symptoms present that were not defined by those episodes. The symptoms occurred in an enduring pattern throughout the patient's life, even during the remission of manic episodes. Through diligent history-taking, the clinicians were able to spot the missed diagnosis.

Discussion

Approximately 40% of patients with BPD report being previously misdiagnosed with BD, compared with 10% of patients with other disorders [4, 6]. Interestingly, 20% of people with BPD have been diagnosed with comorbid bipolar disorder, and 15% of patients with bipolar disorder have comorbid BPD [5]. There are several overlapping symptoms of the two disorders, including suicidality, irritability, impulsivity, and mood instability [2]. Affective instability is also a core feature of both BD and BPD [2, 6]. Some experts believe that borderline and bipolar are two separate entities [2, 6], while others see them as coexisting on a spectrum [2, 7]. Despite their many similarities, they are different disorders that necessitate completely different treatments. BPD is treated with dialectical behavioral therapy, while BD is treated with various pharmacological treatments (antidepressants, mood stabilizers, lithium), which can all cause unnecessary adverse effects to misdiagnosed patients. Furthermore, a misdiagnosis would presumably delay the correct treatment of the patient, leaving them and loved ones with an unrealistic expectation of prognosis and causing feelings of hopelessness. Considering the fact that BPD has a good prognosis (65% of patients achieve remission in 4 years with proper treatment), knowing how to differentiate BPD from BD is vital [5, 6].

Plan of Action, Points the Clinician Should Consider, Pitfalls to Avoid, and Pearls of Knowledge to Consider

- Five out of nine diagnostic criteria for BPD might occur in hypomanic or manic episodes of BPD, making misdiagnosis or overdiagnosis quite easy, (Fig. 1) [7].
- Irritability is a hallmark of BD manic episodes, while frequent angry outbursts point more toward BPD [1]. It is easy to confuse irritability with angry outbursts. Irritability refers to a person's quickness to anger, while angry outbursts refer to heightened anger or disproportionally angry reaction.
- Mood changes in BD persist for days or weeks, and mood changes in BPD will change rapidly but only last for minutes or hours [7].
- An enduring pattern (especially outside of manic/depressive episodes) points more toward BPD, while definable "episodes" with periods of normalcy point more toward BD [10].
- Fear of abandonment and identity disturbance is a classic trait of BPD. A patient with BD might also suffer from these, but it is not considered pathognomonic to BD [1, 7, 10].
- Splitting (a defense mechanism characterized by idealization or devaluation of an object) is pathognomonic of BPD and is typically absent in BD [1].
- Hostility scores (Buss–Durkee Hostility Inventory) are higher in BPD patients than in BD [8–10].
- Impulsiveness scores using the Barratt Impulsiveness Scale (attentional, nonplanning, and motor) are markedly higher in patients with BPD [8, 10].

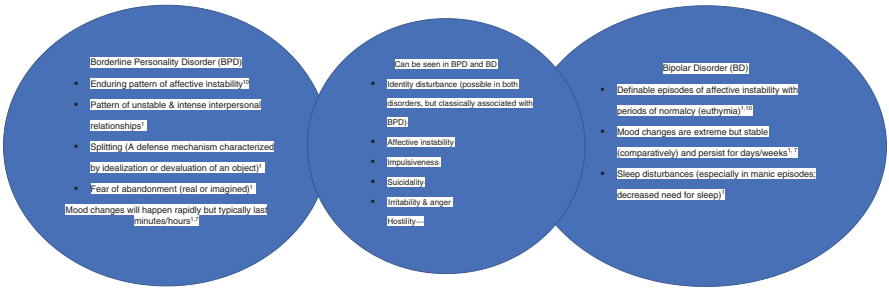

Fig. 62.1 Similarities and differences in the clinical features of borderline personality disorder and bipolar disorder

If Misdiagnosed, Was It Realized Later?

The clinicians, in this case, realized that the patient had an enduring pattern of behavior even outside of her manic episodes that pointed toward borderline personality disorder. They also determined that the abnormal behavior was not the result of alcohol misuse. Therefore, they added a diagnosis of borderline personality disorder in addition to the patient's preexisting bipolar disorder diagnosis [2].

Conclusion

The majority of BPD misdiagnoses are initially diagnosed as BD because of remarkably similar symptomatology. The consequences of this misdiagnosis can be minimized through careful and complete patient history, as well as a thorough understanding of the nuances that set the two disorders apart.

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Chapter 63
Generalized Anxiety Disorder Misdiagnosed as Nonspecific Physical Pain

Jonathan Seok

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Create an appropriate differential diagnosis in patients presenting with generalized anxiety disorder (GAD) by considering all relevant details of the medical history together with proper GAD screening and diagnostic tools.
2. Evaluate the different components of the medical history and physical examination which indicate the most appropriate screening and diagnostic tools so the most correct course of further diagnostic procedures needed to reach a definitive diagnosis can be reached.
3. Discuss the relationship between nonspecific physical pain and GAD.
4. Apply the knowledge gained from the case in a clinical setting where appropriate.

Introduction

The most common mental health disorder in the United States and the world is generalized anxiety disorder (GAD). GAD is a disorder where the patient has unfocused worry and anxiety that is not related to current situations or events, although it can be exasperated by certain and current situations of at least

J. Seok (✉)
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: jonathan.seok@martinus.edu

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6 months or more [1]. As per the Anxiety and Depression Association of America (ADAA) , GAD affects 6.8 million adults or 3.1% of the US population [2]. Generalized anxiety disorder can adversely impact a patient's life and disrupt daily living. The research shows that GAD is often misdiagnosed with symptoms often ascribed to physical causes [3]. However, there is no brief clinical measure for assessing GAD [4]. Generalized anxiety disorder is not only misdiagnosed but also often associated with other mental health disorders that involve anxiety such as bipolar disorder (comorbidities) [4–6]. Many of the body's systems can be affected by GAD, including the cardiac, pulmonary, and neurological, but it also affects the musculoskeletal system. This is because the disorder can appear in several different ways, incorporating physical characteristics in addition to mental and behavioral ones. The patient in the case study reported musculoskeletal symptoms that can be misinterpreted for actual musculoskeletal issues rather than GAD [7].

Clinical Case Presentation

A 28-year-old white female presents to the clinic with "complaints of joint pain (arthralgia) and intermittent low back pain." [7] The patient does not know or remember how she injured herself. She is currently a second year graduate student who cannot sleep at night and is unable to get quality sleep or rest, and she believes that this is making her feel "restless" or "on edge." [7] She is constantly worrying about her performance in school, her family, and her mother as the patient has recently been diagnosed with stage IV small cell carcinoma. The patient also presents with throbbing headaches that last for a couple of hours at night time and further keep her awake. She is tense most of the day, which in turn causes her to be stiff. She also cannot pay attention in class and has trouble finishing her homework [7]. Subjective symptoms are reported as joint pain, lower back pain, headache, muscle stiffness, difficulty sleeping, and difficulty paying attention for approximately a year.

Her comorbidities include hypertension, 10+ alcoholic beverages per week (which indicates possible substance abuse), and depression. The patient was previously diagnosed with posttraumatic stress disorder (PTSD) and treated with cognitive behavioral therapy (CBT) in February of 2000. The patient was assessed for GAD by taking the GAD-7 (16/21), the Penn State Worry Questionnaire (PSWQ) (64/80), and the McGill Pain Questionnaire (42/78). Her score on the Oswestry Disability Index (ODI) was 38% [7]. Subjective symptoms are as follows: heart rate of 98 bpm (tachycardia), blood pressure of 146/92 mmHg (hypertension), and a respiratory rate of 24 bpm. She also presented with palpable muscle tightness in upper trapezius, forward flexed head, and increased kyphosis. Patient appears to be heavily sweating and her hands are cold and clammy to touch [7].

Differential Diagnosis

Given the medical history of the patient, the most probable differential diagnosis could be as follows:

1. Chronic non-cancer or nonspecific physical pain: The patient presents with "joint pain, low back pain, headache, and muscle stiffness" which are common symptoms of chronic non-cancer or nonspecific physical pain. Chronic non-cancer pain is "moderate or severe pain that lasts six or more months is attributed to conditions such as neuropathic pain, rheumatoid arthritis, lower back pain, osteoarthritis, fibromyalgia and a range of several other conditions." [8] However, the lack of a specific injury or "lack of recall of any mechanism of injury" [7] as well as a lack of rheumatic disorder is an indicator making the chronic pain more likely secondary to the primary diagnosis of GAD.
2. Bipolar disorder: The patient states that she is "restless" and "on edge." [7] This could be interpreted as a mood swing which is a symptom of bipolar disorder. Studies have shown that overactive moods can be subjectively mislabeled as "mood swings" and thus leading to a common misdiagnosis of bipolar disorder [5, 9]. However by closely following the DSM-5, the patient in the case meets all the criteria of GAD, and the correct diagnosis of GAD was made.
3. Endocrine disorder: It is important to rule out endocrine disorders such as pheochromocytoma or hyperthyroidism before diagnosing GAD [10, 11]. There is a biochemical basis of anxiety, and it presents with many endocrine diseases with muscle weakness, pain, and stiffness as common symptoms [6] of endocrine disorders. The tachycardia and hypertension are also both signs of an endocrine disorder [7]. While the case does not indicate the patient's lab values, lab work will help exclude endocrine disorders as the primary cause of this patient's symptoms.
4. Chronic fatigue syndrome (CFS) : The patient presents complaints of physical pain unrelated to injury that could be considered as part of the clinical manifestations of CFS but does not present the key feature of debilitating fatigue that according to the CDC (Centers for Disease Control and Prevention) criteria is necessary for a diagnosis.
5. Somatic symptom disorder (SSD) : Although the patient presents with physical pain and constant worry, the DSM-5 criteria are not met as the patient's anxiety is not coming from the symptoms she is presenting but from different aspects of her personal life.

What Was Misdiagnosed in This Case and Why?

The patient reported many symptoms that are consistent with musculoskeletal (MSK) deficits which initially led to diagnosing the patient with a MSK issue; however after a thorough clinical history and physical exam, alternative diagnoses were considered, and the right diagnosis was ultimately made.

Discussion

The patient reported "joint pain, low back pain, headache, muscle stiffness, difficulty sleeping and paying attention for approximately a year." [7] On initial interview and based on the physical symptoms, the initial diagnosis seems to point toward the nonspecific physical pain. Generalized anxiety disorder (GAD) is characterized by excessive and persistent worry that is difficult to control. GAD also causes significant distress or impairment and occurs on more days than not for at least 6 months [12]. Other features include psychological symptoms such as apprehension and irritability and physical (or somatic) symptoms such as increased fatigue and muscular tension [3]. Physical and somatic symptoms are seen in generalized anxiety disorder. Upon further interviewing, there were some additional key red flags such as "restless" and "on edge" to describe her current state [7]. She had also been previously diagnosed with PTSD and treated with cognitive behavioral therapy. She is constantly worried about her performance in graduate school and her mother. The patient's mother was recently diagnosed with stage IV small cell carcinoma. Her constant worrying about her mother's health and her inability to pay attention in class and her difficulty finishing her school work help providers' make the correct diagnosis [7, 8]. This information further provides evidence for GAD rather than nonspecific physical pain as the patient has major stressors in her life [3] and also highlights the importance of a thorough and complete interview. After further physical exam, hypertension, tachycardia, and increased respiratory rate are all reported in the case [3, 7]. Patient appears to be profusely sweating and hands are cold and clammy to touch. These are all symptoms found in GAD rather than nonspecific physical pain [3, 4]. Palpable muscle tightness in the upper trapezius and forward flexed head along with increased kyphosis result from the GAD. While the relationship is poorly understood, the lack of a direct cause of the tightness or kyphosis points to GAD rather than other causes [7, 13]. In order to confirm this diagnosis, we need to use the GAD-7 scale as a means to measure anxiety. Due to the provider's in-depth interview in the case, the GAD-7 scale can be filled in, and the patient had a "significantly high" score on the GAD-7. Additionally the provider also used the Penn State Worry Questionnaire and the McGill Pain Questionnaire [7]. These additional diagnostic tools reinforced the initial diagnosis of GAD from the GAD-7 survey. The scores from the survey coupled her history and symptoms show that the patient has signs that are consistent with a GAD [7, 9, 12]. The results of the outcome measures along with her significant medical history point to GAD along with other possible comorbidities.

Plan of Action, the Points Clinician Should Consider, Pitfalls to Avoid, and Pearls of Knowledge to Consider

Screening and monitoring tools can be used by providers to help make the correct diagnosis, and a few were used to successfully diagnose the patient in the case. The GAD-7 is a free diagnostic tool and the most common screening to diagnose GAD. Once successfully diagnosed, good prognosis may require a combination of treatments specific to the individual patient [3].

Stress management techniques such as meditation, deep breathing, progressive muscle relaxation techniques, exercise, and modifying her diet [7] could lead to reduction in GAD symptoms. The provider recommended a reduction in the patient's alcohol consumption and educated her on alcoholism and the effects that it has on the mind and the body [14]. Her primary care provider prescribed her paxil, a selective serotonin reuptake inhibitor to increase her levels of serotonin, which greatly improved her motivation for therapy. Within 2–3 weeks her active range of motion improved, and the scores on her outcome measures decreased significantly [7]. However other medications such as but not limited to buspirone, hydroxyzine, abecarnil, and other antidepressants can be used to effectively treat GAD [10]. Duloxetine has also shown promise in reducing GAD symptoms [15]. Benzodiazepines have been shown to be effective in treating GAD, but a study found that benzodiazepines increased the risk of dependence, sedation, and both work and traffic accidents [14]. Other anxiety disorders, depression [1], or substance abuse often accompany GAD [14], which rarely occurs alone; co-occurring conditions must also be treated with appropriate therapies [7]. These comorbidities need to be properly diagnosed along with GAD and not misdiagnosed as GAD by using the proper screening and diagnostic tools.

Conclusion

Living with generalized anxiety disorder can manifest as a long-term challenge. In many cases, it occurs contemporaneously with other anxiety or mood disorders. Generalized anxiety disorder can often be misdiagnosed as chronic non-cancer or nonspecific physical pain. Many of the body's systems can be affected by GAD. Do not confuse a patient's MSK issues with GAD by looking for pain without a specific cause. Be ready to get a good history and listen carefully for red flags during the interview as well as the elevated respiratory rate and heartbeat during the physical exam [9]. Lab work can also further rule out endocrine issues [11]. Then by using the correct diagnostic tool of the GAD-7 along with other screening and diagnostic tools, the patient can be properly diagnosed with GAD. In most cases, GAD improves with psychotherapeutic intervention or pharmacotherapy. An adjustment to lifestyle changes, learning coping skills and using relaxation techniques also can help. In this case, physical therapy was used in conjunction with therapy and medication in order to relieve the MSK issues secondary to GAD [7].

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Part XIII
Pulmonology

Chapter 64
Chronic Beryllium Disease Misdiagnosed as Sarcoidosis

Abdulla Khan and Jose Luis Ferrero

Learning Objectives
By the end of this section, the clinician will be able to:

1. Discuss the presentation, pathologic progression, and nature of the disease.
2. Recognize the prevalence of misdiagnosed cases of CBD among the population.
3. Discuss and analyze the consequence and importance of timely diagnosis and its effect on the prognosis of the disease.
4. Enumerate the diagnostic criteria and challenges in diagnosing a patient with CBD.
5. Analyze up-to-date diagnostic techniques such as biomarkers and their importance.
6. Delineate the diagnostic challenges and common errors that a physician might encounter when evaluating a patient with CBD.

Introduction

Occupational respiratory disorders are work-related lung diseases that are caused by long-term exposure to a variety of toxic particulates, hazardous chemicals, and fumes. Berylliosis or chronic beryllium disease (CBD) is an occupational

A. Khan (✉) · J. L. Ferrero
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: abdulla.khan@martinus.edu; luis.ferrero@martinus.edu

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hypersensitivity granulomatous disease caused by exposure to beryllium (Be) and is characterized by the formation of noncaseating, non-necrotizing granulomas predominantly in the lungs and skin [1]. Be being an integral component is used in many manufacturing industries such as metal and alloy, aerospace, ceramic, defense, computer microchips, automotive industry, jewelry making, and dental laboratories, thereby increasing the risk of exposure among the population [1, 2]. CBD is one of the most commonly misdiagnosed occupation-related lung diseases and is present in 2–5% of beryllium-exposed workers [1]. Misdiagnosis of CBD is attributable to the varying clinical course (asymptomatic → severe respiratory failure) of the disease and the inconsistent onset of action (acute → 20 years or more) [3]. It is most commonly misdiagnosed as sarcoidosis (systemic granulomatous inflammatory disease) because of its strong clinical and pathologic association with CBD followed by idiopathic pulmonary fibrosis (IPF) and hypersensitivity pneumonitis [4]. Hence a detailed occupational history and multidisciplinary approach are necessary for formulating an accurate diagnosis. Here we present a case of a 27-year-old dental technician who presented to the ER in respiratory distress and was initially misdiagnosed as having sarcoidosis and managed with IV corticosteroids [5]. Upon further investigation, a diagnosis of CBD was confirmed.

Clinical Case Presentation

The case reports of a 27-year-old female dental technician who presented to the ER in severe respiratory distress. Six months before admission, she presented with dyspnea, weakness, nausea/vomiting, and diarrhea and reported a weight loss of about 12 kg. She was treated with Prozac as her medical history and chest X-ray findings were unexceptional. The initial study was unexceptional, and radiologic examination consisting of chest X-ray and computed tomography (CT) later revealed an increased interstitial pattern in addition to hilar lymphadenopathy. Echocardiography showed a significant increase in pulmonary pressure (90 mmHg), tricuspid valve insufficiency, and right atrial and ventricular enlargement. Blood work showed elevated hepatic enzymes; arterial blood gas (ABG) analysis reported pCO_2 = 38.9, pO_2 = 67, and pH = 7.358; and serologic examination was negative for all other diseases that were tested for (HIV, hepatitis B, hepatitis C). Pulmonary function test (PFT) was conducted reporting the following results (refer to Table 64.1).

Pulmonary function results were suggestive of a restrictive lung disease pattern with decreased diffusing capacity of the lung which required the use of high oxygen flow. An open lung biopsy was performed, and the histopathological analysis revealed the presence of abundant noncaseating granuloma, favoring the diagnosis of sarcoidosis which was managed with intravenous hydrocortisone followed by 60 mg of Meticorten (oral prednisone). The patient's condition improved and the mediastinal lymphadenopathy was resolved. Similar cases have been observed in other dental technicians [6], which were conspicuous and demanded a re-evaluation

Table 64.1 Pulmonary function test result

PFT parameter	% Predicted
FEV1	48
FVC	44
FEV1/FVC	95
TLC	53
DLCO	24
DLCO/vacuum aspiration	46

FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; FEV1/FVC, absolute ratio; DLCO, diffusing capacity of the lungs for CO

because of the patient's occupational history. Chemical analysis of the patient's sputum revealed abundant particles of clay minerals. Beryllium Lymphocyte Transformation Test (BeLTT) showed a 5.90 and 2.54 index (normal <1.7) at 10-4 M and 10-5 M of BeSO4, respectively. A genetic study revealed that the patient was homozygous for HLA-DPB1-Glu69, confirming the diagnosis of chronic beryllium disease.

Differential Diagnosis

1. Sarcoidosis—It is a multisystem noncaseating granulomatous inflammatory disease of unknown etiology characterized by the formation of reticular opacities in the lung and bilateral hilar lymphadenopathy. Biopsy of the affected lung tissue and a negative reaction to BeLTT is helpful in distinguishing it from berylliosis.
2. Idiopathic pulmonary fibrosis—Lung disease of unknown etiology characterized by progressive fibrosis of the pulmonary interstitium leading to a decline in pulmonary function. Peripheral distribution of bilateral fibrosis patterns on computed tomography differentiates it from CBD.
3. Hypersensitivity pneumonitis—It is a nonatopic, non-asthmatic inflammatory pulmonary disease characterized by prolonged exposure to antigen resulting in a hypersensitivity reaction. A positive hypersensitivity pneumonitis antibody panel is supportive in differentiating it from berylliosis.
4. Tuberculosis—It is an infectious disease caused by *Mycobacterium tuberculosis* bacteria mainly affecting the lungs characterized by the formation of caseating granuloma. Chest X-ray pattern for tuberculosis and a tuberculin skin test (Mantoux test) help us to differentiate it from berylliosis.
5. Asthma—It is a chronic inflammatory disease of the respiratory system characterized by bronchial hypersensitivity followed by reversible airway obstruction and narrowing of the airways. Pulmonary function test shows an obstructive lung pattern rather than restrictive type which is found in patients with CBD.

Discussion

Berylliosis or chronic beryllium disease (CBD) is a noninfectious granulomatous disease caused by the exposure to Be metal or its salts leading to symptoms such as nonproductive cough, dyspnea on exertion, weight loss, chest pain, and fatigue. CBD is a metal-induced delayed type IV hypersensitivity reaction characterized by beryllium sensitization due to recurrent exposure (formation of specific CD4+ memory T cells). Memory CD4+ T cells are reactivated upon subsequent exposure resulting in the release of multiple cytokines and chemokines causing the aggregation of T cells, macrophages, and plasma cells to form noncaseating granulomas and pulmonary fibrosis [1, 7, 8]. Epigenetic factors such as age, sex, race, and ethnicity also predispose to an increased susceptibility to pulmonary disease from beryllium exposure [9]. Genetic susceptibility to BeS (beryllium sensitization) and CBD has been found in many studies associated with polymorphism of the HLA-DP ß1 chain gene [10]. The presence of a similar pathognomonic lesion (epithelioid granuloma) and indistinguishable clinical manifestations in patients with both diseases makes it challenging to distinguish CBD from sarcoidosis [11]. Sarcoidosis is a systemic granulomatous inflammatory disease [12] characterized by the formation of noncaseating granuloma with an incidence rate of 14.5 per 100,000 citizens in the United States [13]. Remarkably, nearly 6% of the people diagnosed with sarcoidosis may have CBD [1] similar to the clinical case presented. It is an exceptional case of misdiagnosis caused by the deficient history taking that might have caused the delay in diagnosis and management of the patient. A definitive diagnosis of CBD is established based on the patient's occupational history and specific diagnostic criteria and tests. The criteria are as follows: [7, 14]

1. Exclusion of all other known granulomatous diseases
2. A previous history of exposure, either direct or indirect contact (family members exposed to Be, industrial accidents)
3. Histopathologic evidence of the presence of granuloma in the affected tissue
4. Evidence of immunological reactivity to Be via BeLTT (Beryllium Lymphocyte Transformation Test)
5. Consistent clinical, radiographic (chest X-ray, HRCT), and physiologic features of CBD

Another factor in the misdiagnosis of CBD is a low sensitivity (68.3%) of the BeLTT despite its high specificity (96.9%) [10], which eventually warrants the use of other noninvasive, accurate diagnostic tools such as the use of genomic biomarkers. The ongoing gene expression studies have found that expression of IFN-γ (interferon gamma), CD55 (cluster of differentiation 55/complement decay accelerating factor), RNase 3 (ribonuclease 3), TNF-α (tumor necrosis factor alpha), and CXCL9 (chemokine {C-X-C motif} ligand 9) are some biomarkers that can be used to distinguish between CBD and sarcoidosis. In CBD, the biomarkers CD55 and TNF-α were overexpressed, and CXCL9 was under-expressed [10, 15]. The diagnosis of CBD is further complicated by the lack of certified testing centers across the

United States that detects beryllium sensitization and the eventual development of a multisystemic disease suggesting a diagnosis of sarcoidosis rather than CBD. Therefore, a fastidious evaluation of the patient history and clinical manifestation is necessary to avoid misdiagnosis of CBD.

Management goals of CBD focus on improving patient survival by decreasing the progression of the disease and improving the symptoms. Apart from organ transplantation, no cure has been found yet to manage CBD. Corticosteroids are gold standard in the treatment of CBD. The use of inhaled corticosteroids has given evidence of stabilizing the decline in pulmonary function and shown improvements in symptoms (cough) [16]. Most cases require lifelong follow-up with chest X-ray, physical exams, and PFTs. Oxygen supplementation, vaccination, pulmonary rehabilitation, and lifestyle changes with exercise and diet are supportive in managing the patient with CBD. Prevention can be attained by reducing exposure with the help of a respirator (protective mask) and replacing the material with much safer ones.

Conclusion

Chronic beryllium disease misdiagnosis is not an infrequent finding among patients diagnosed with sarcoidosis. Clinicians must conduct a thorough physical examination and a meticulous assessment of the patient's history (occupational background) since it is critical to avoid misdiagnosis of CBD. Hence continuous medical surveillance and frequent inspection by the respective authorities are necessary to keep the incidence of disease under check.

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Chapter 65
Idiopathic Pulmonary Fibrosis Misdiagnosed as Sputum-Negative Tuberculosis

Abdulla Khan and Jose Luis Ferrero

Learning Objectives
By the end of this section, the clinician will be able to:

1. Review the presentation, pathologic progression, and nature of the disease.
2. Recognize the prevalence of misdiagnosed cases of IPF and understand the importance of a multidisciplinary care team in the management of the disease.
3. Discuss and analyze the importance of a timely diagnosis and its effect on the prognosis of the disease.
4. Discuss and enumerate the international guidelines and diagnostic algorithm in diagnosing a patient with IPF.
5. Explain the up-to-date diagnostic techniques such as biomarkers and their importance in the definitive diagnosis of IPF.
6. Delineate the diagnostic challenges and common errors that a physician might encounter when evaluating a patient with idiopathic pulmonary fibrosis.

Introduction

Interstitial lung diseases (ILDs) conform a group of restrictive respiratory disorders affecting the interstitial areas of the lung, which support the alveolar epithelium, such as the basement membrane, pulmonary capillary endothelium, and

A. Khan (✉) ·J. L. Ferrero
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: abdulla.khan@martinus.edu

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perivascular and perilymphatic tissues. In most cases, it is due to an abnormality in structural remodeling after an injury leading to fibrosis and scarring of the lung tissue [1]. The injury could be due to exposure to chemicals (chemotherapy, medications), occupational/environmental (organic/inorganic fumes, toxic dust, radiation), or due to an underlying autoimmune disease (rheumatoid arthritis, systemic lupus erythematosus, scleroderma) or due to an unknown etiology. Idiopathic pulmonary fibrosis (IPF) is an ILD with an unknown underlying cause characterized by progressive fibrosis of the pulmonary interstitium and persistent decline in pulmonary function leading to respiratory failure. It is one of the common forms of ILD, usually presented either in the fifth or sixth decade of life, with a global incidence at an estimated rate of 2.8–9.3 per 100,000 per year in North America and Europe [2].

Regardless of the numerous advancements in medicine, diagnosis and management of IPF persists as a significant challenge even to experienced clinicians, due to the indistinguishable nature of the disease, poor prognosis, and high mortality rate with a reported mean survival age of only 2–3 years [2]. Hence diagnosis and management of IPF require a quick, multidisciplinary approach to minimize diagnostic uncertainty. Awareness of these conditions must be the norm for nonspecialized members of the health-care team and not only for practitioners with a specialization.

Here we report a case of a 55-year-old patient who was initially misdiagnosed with negative sputum tuberculosis and treated with antitubercular drug regimen without any favorable outcome [3]. Studies have shown that more than 50% of the patients with IPF are initially misdiagnosed [2], with other respiratory illnesses such as bronchitis, pneumonia, tuberculosis, asthma, chronic obstructive pulmonary disease (COPD), and emphysema, which also account for the diagnostic delay, hence the poor prognosis of the disease.

Clinical Case Presentation

The case reports of a 55-year-old male textile trader who presented to the clinic with the chief complaint of breathlessness for 3 years and dry cough for the past 2.5 years. The patient was diagnosed with tuberculosis 2 months prior to the presentation and reported to have started treatment with antituberculosis medication with no significant symptomatic relief. General physical examination was unremarkable and vital signs were stable with SPO_2 of 96% on room air. Comprehensive systemic examinations were normal except for significant end-inspiratory bi-basal velcro-like crackles on thoracic examination. Chest X-ray shows streaky and patchy opacities in the lower zone bilaterally, and computed tomography (CT) of the lung revealed extensive nodular opacities/ground-glass appearance with honeycombing of the soft tissue of the entire lung field.

Pulmonary function test (PFT) was performed which showed a restrictive lung pattern with the following results (refer to Table 65.1):

Table 65.1 Pulmonary function test result

PFT parameter	Predicted	Value	% Predicted
FEV1	3.21	2.63	81.93%
FVC	3.92	2.64	67.34%
FEV1/FVC	79.11	99.77	126.11%

FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; FEV1/FVC, absolute ratio

Histopathologic examination of the lung tissue through lung tissue biopsy revealed moderate lymphocytic infiltration of the lung parenchyma with associated patchy interstitial fibrosis and adjacent areas of normal tissue.

After a complete evaluation, the patient was diagnosed with idiopathic pulmonary fibrosis (IPF). Management was initiated on tablet prednisolone 1 mg/kg daily, tablet rabeprazole 40 mg 12 hourly, and supplements for bone health.

Differential Diagnosis

1. Chronic hypersensitivity pneumonitis (CHP) —Hypersensitivity pneumonitis is a nonatopic, non-asthmatic inflammatory pulmonary disease caused by prolonged repetitive inhalation of antigens from the environment. Although both the diseases have similar radiologic and histopathologic presentation, presence of features such as bridging fibrosis, lymphoid aggregation, and intraluminal fibrosis can be helpful in differentiating CHP from IPF.
2. Asbestosis—It is an interstitial lung disease caused by inhalation of asbestos fibers predominantly seen in people who work in close contact with asbestos. The fibers cause inflammation followed by fibrosis and scar formation. The fibrosis appears coarser in CT findings, and presence of asbestos bodies differentiates it from IPF.
3. Desquamative interstitial pneumonia—It is characterized by extensive alveolar infiltration of macrophages followed by interstitial inflammation and fibrosis. It is predominantly found among cigarette smokers (90% cases) during the fourth or fifth decade of life. Smoking cessation and avoidance of second-hand smoking are essential for better prognosis of the disease.
4. Drug-induced pulmonary fibrosis—Cytotoxic drugs such as bleomycin and noncytotoxic drugs such as amiodarone are commonly found to induce pulmonary fibrosis. Proper history taking is necessary in order to rule out the differential.
5. Respiratory bronchiolitis interstitial lung disease—A mild inflammatory pulmonary disorder prevalent invariably among former heavy smokers/current smokers. It is characterized by accumulation of yellow-brown pigmented macrophages within the lumen of respiratory bronchioles associated with submucosal and peribronchiolar inflammation, which can be used to differentiate it from IPF.

Discussion

Idiopathic pulmonary fibrosis (IPF) is one of the most lethal diseases among other ILDs, which may further progress into respiratory failure due to cumulative fibrosis and destruction of the lung architecture. Although the exact etiology of IPF is still unknown, exposure to tobacco smoke, environmental pollutants, chronic aspiration due to GERD (gastroesophageal reflux disease), and medications (bleomycin, cyclophosphamide, nitrofurantoin) are some of the prevalent risk factors [4].

The case mentioned here described a patient diagnosed with sputum-negative tuberculosis due to nonspecific clinical manifestation and who was started on anti-tubercular drug regimen without any significant relief [3]. The case is prototypical of misdiagnosis as the initial diagnosis was made on the disease prevalence and its clinical correlation with IPF. According to studies conducted, patients diagnosed with IPF possess five times increased risk for incidence of tuberculosis than the general population [5]. Furthermore, patients in TB-endemic areas usually undergo empirical antitubercular treatment even if the sputum/smear test is negative for *Mycobacterium tuberculosis* which may further lead to diagnostic delay and accounts for the poor prognosis of the disease [6].

Genetic predisposition (Fig. 65.1) can also be established in some familial cases of pulmonary fibrosis based on mutations in the telomerase genes (e.g., TERT), surfactant genes (e.g., SFTPA2), mucin genes (e.g., MUC5B), and surfactant proteins SPC and SPA [7]. Therefore, a meticulous evaluation of the patient history is a prerequisite for the correct and complete diagnosis of IPF.

Diagnosis of IPF is quite challenging which is attributable to the complexity of the disease and the presentation of nonspecific symptoms that could misdirect to the

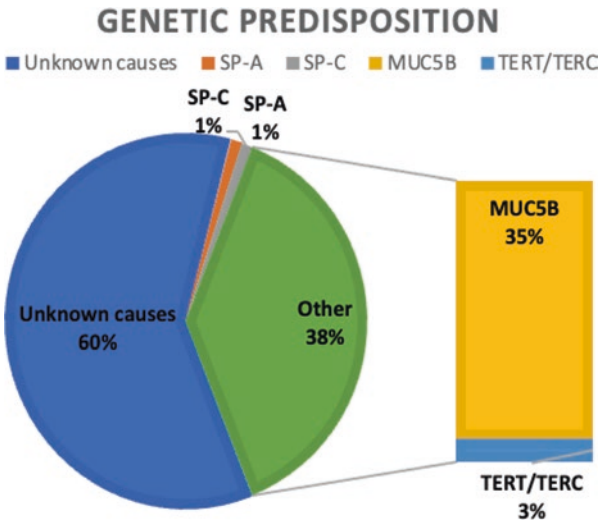

Fig. 65.1 Genetic predisposition among patients with idiopathic pulmonary fibrosis

large number of potential mimickers of IPF. Thus, a diagnostic algorithm (Fig. 65.2) and a specific set of evidence-based guidelines must be implemented to diagnose and manage IPF [8].

Diagnostic Criteria [9]

1. Exclusion of all other known causes of interstitial lung disease (domestic and occupational environmental exposures, connective tissue diseases, and drug toxicity)
2. The presence of UIP (usual interstitial pneumonia) pattern (refer to Table 65.2) on HRCT (high-resolution computed tomography)
3. Specific combinations of HRCT and histopathologic pattern in patients subjected to surgical lung biopsy

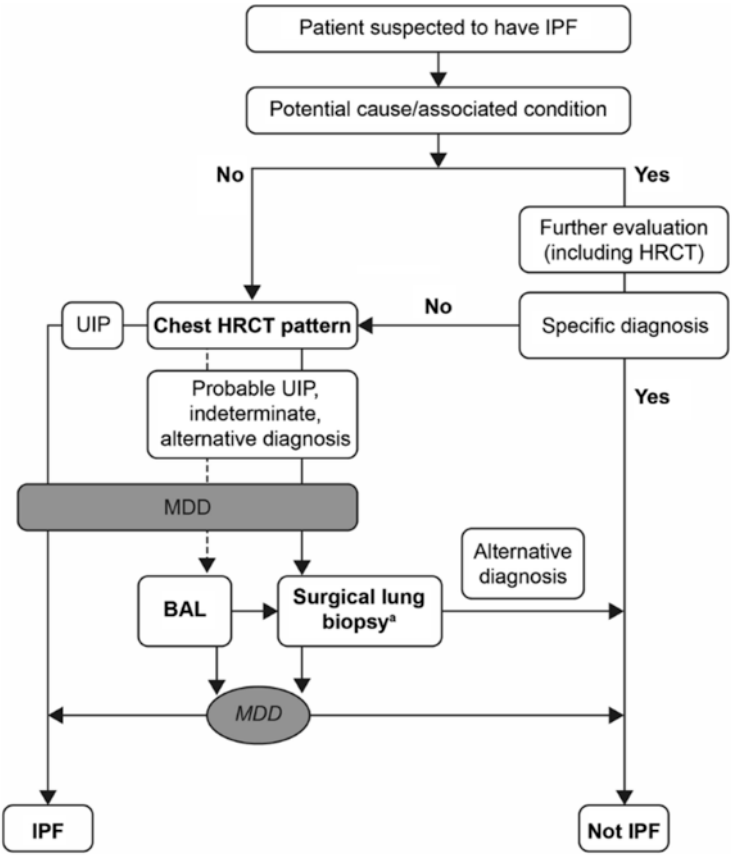

Fig. 65.2 Diagnostic algorithm for IPF. Source: https://link.springer.com/article/10.1007/s12325-018-0857-z. UIP, usual interstitial pneumonia; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; MDD, multidisciplinary discussion; BAL, bronchoalveolar lavage

Table 65.2 HRCT criteria for UIP pattern

HRCT criteria for UIP pattern		
UIP pattern (all 4 features)	*Possible UIP* pattern (all 3 features)	*Inconsistent UIP* pattern (any of the features)
Predominant fibrosis in the sub pleural and basal compartment of lungs	Predominant fibrosis in the sub pleural and basal compartment of lungs	Predominant fibrosis in the upper/mid lung or in the peribronchovascular areas of lung
Reticular Abnormality, often heterogenous distribution	Reticular Abnormality with often heterogenous distribution	Extensive ground glass abnormality (extent > reticular abnormality)
Honeycombing with or without traction bronchiectasis—present		Profuse micronodules (bilateral, predominantly upper lobes)
	Absence of features inconsistent with UIP pattern (refer column 3)	Discrete cysts (multiple, bilateral, away from areas of honey-combing)
Absence of features inconsistent with UIP pattern (refer column 3)		Diffuse mosaic attenuation/air-trapping (bilateral and in ≥ 3 lobes)

UIP, usual interstitial pneumonia; HRCT, high-resolution computed tomography

Usual interstitial pneumonia (UIP) is more of a histopathologic term rather than a disease and is often used interchangeably with IPF but not synonymous, as UIP is often observed in many other diseases such as hypersensitivity pneumonitis, drug toxicity, familial variants of IPF, etc.

Although UIP patterns on HRCT are suggestive of IPF in 50–60% of patients with diffuse lung diseases [9], the remaining patients do not reveal a typical UIP pattern that warrants a surgical lung biopsy for a definitive diagnosis. In most cases, the specific histopathologic classification (refer to Table 65.3) reveals a UIP pattern. In some cases, the biopsies may be identified as non-classifiable fibrosis (other than the UIP pattern); thereafter the diagnosis is made after a cautious evaluation and discussion by the multidisciplinary team (MDT).

The use of genetic and molecular biomarkers is also established in increasing the precision of the diagnosis of IPF [4]. Thanks to the advancements in genetic and molecular biomarker profiling of IPF, several biomarkers have been identified and classified based on their association with the underlying pathogenesis of the disease. Hence, analyzing the potential biomarkers of IPF may aid in diagnosing and evaluating the prognosis/trajectory of the disease:

- A mutation in the TERT/TERC, MUC5B, peripheral blood markers such as KL-6, surfactant protein SP-A, and SP-D are characteristics of telomere dysfunction that increase the epithelial cell's susceptibility to injury in addition to the impaired cell repair.
- Biomarkers such as CCL18, YKL-40, CXCL13, TLR-3, anti-HSP70, and CD28CD4T cells are immune-mediated subtypes due to compromised innate and adaptive immunity.
- Abnormal pulmonary remodeling mediated by biomarkers such as MMP1 and MMP7, periostin, osteopontin, circulating fibrocytes, and markers of MMP

Table 65.3 Histopathologic criteria for UIP pattern

Histopathologic criteria for UIP pattern			
UIP pattern (all 4 features)	*Probable UIP* pattern	*Possible UIP* pattern (all 3 features)	*Not UIP* pattern (any of the features)
Dense fibrosis and architectural distortion with/without honeycombing, predominantly sub pleural or paraseptal distribution	Evidence of marked fibrosis/architectural distortion with/without honeycombing	Patchy/Diffuse fibrosis of the lung parenchyma with/without interstitial inflammation	Formation of Hyaline membranes[a]
			Organizing Pneumonia[b]
	Absence of either patchy involvement or fibroblastic foci, but not both		Evidences of Granulomas[b]
Patchy fibrotic infiltration of the lung parenchyma		Absence of other criteria for UIP (refer column 1)	Marked Interstitial Inflammatory cell infiltration away from the regions of honeycombing
Presence of fibroblastic foci	Absence of features against diagnosis of UIP suggesting alternate diagnosis (refer column 4) *OR* Honey combing only	Absence of features except a diagnosis of UIP or suggesting an alternative diagnosis (refer column 4)	Predominant airway centered charges
Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (refer column 4)			Other features suggestive of alternative diagnosis

UIP, usual interstitial pneumonia; HRCT, high-resolution computed tomography
[a]Can be associated with acute exacerbation of idiopathic pulmonary fibrosis
[b]Isolated or occasional granuloma and/or mild form of organizing pneumonia may be found in lung biopsied otherwise UIP pattern

activity (generated by extracellular matrix turnover) may be an essential factor in assessing the progression of the IPF.

The main challenges faced in the diagnosis of IPF are due to delays in diagnosis, ruling out alternative diagnoses, and challenges faced in obtaining a surgical lung biopsy [10]. Since IPF is a complex disease with a poor prognosis, early diagnosis is essential, and delay in diagnosis poses a severe threat to the patient. The rationale varies from the challenging nature of the patient to undergo a surgical biopsy to the lack of experienced physicians. Hence all cases with suspected IPF are warranted for referral to specialists, and this is a major obstacle among patients in under-reserved areas where the accessibility to such specialists is laborious contributing to diagnostic delay of the disease.

Management of IPF primarily focuses on improving the patient's survival and quality of life. Pirfenidone and nintedanib (tyrosine kinase inhibitors) are two anti-fibrotic drugs approved for use in patients with IPF [7]. Although the medications are not curative, they are essential in slowing the disease progression. A previously used drug regimen known as triple immunosuppressive therapy for IPF (azathioprine, prednisolone, and N-acetylcysteine) has been discontinued due to the increased incidence of hospitalizations and death [9]. In addition, PFT (pulmonary function test) should be conducted every 3 to 6 months based on the presentation of

symptoms and disease progression. Supportive therapy includes smoke cessation, oxygen supplementation, proton pump inhibitors for GERD, and a pulmonary rehabilitation program including exercise training, occupational therapy, nutritional changes, and social counseling.

Conclusion

The misdiagnosis of idiopathic pulmonary fibrosis (IPF) is well established among the population with ILD, and an early diagnosis is evident in improving the prognosis of the disease. Physicians must conduct a thorough, comprehensive patient history (family and social) which aids in ruling out the differentials. Participation of a multidisciplinary team (MDT) comprising pulmonologists, radiologists, pathologists with additional input from the occupational physician, and specialist nurse can enhance the diagnosis of IPF, avoid unnecessary testing, and help optimize patient management. Despite various challenges, extensive research in understanding the underlying pathogenic mechanism and genetic studies in the future could help identify the cause(s) of IPF, detect disease in preclinical/early stages, help improve the survival and quality of life, or in due course find the ultimate cure for IPF.

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Part XIV
Rheumatology

Chapter 66
How to Differentiate Chronic Widespread Pain in Order to Reduce Misdiagnosis of Fibromyalgia

Kosha Geslaghi and Brandon Krout

Learning Objectives
By the end of this presentation, the clinician will be able to:

1. Discuss the clinical presentation of both FM and CWP.
2. Differentiate between FM and CWP through the clinical assessment chart provided by this chapter.
3. Enumerate the differential diagnoses and how to tell them apart from FM.
4. Analyze why FM is highly misdiagnosed.

Introduction

Despite extensive interest and examination over the past three decades, fibromyalgia syndrome (FM) continues to insight debate and raise challenges at many fronts of medicine [1, 2]. A few disputed and continually evolving points concerning FM are the clinical usefulness and legitimacy of the diagnostic label FM, the nosological classification, diagnostic criteria, suggested etiology and pathophysiology, and more [3–7]. The difficulty of diagnosis, uncertainty between physical signs and symptoms, and social stigma all contribute to an overall difficulty by clinicians to treat a patient with FM [17]. Now physicians are still reporting uncertainties about how to diagnose FM [8, 9, 17]. This uncertainty translates into patient stressors, frustration, and even dissatisfaction due to pain and lack of sleep caused by the condition [10]. Further compounding the burden that FM places on patients is the

K. Geslaghi (✉) · B. Krout
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: kosha.geslaghi@martinus.edu; brandon.krout@martinus.edu

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time to establish a diagnosis. This process often extends to many years with many clinic visits, investigations, invasive tests, and special consultations which all contribute to the personal, social, and financial burdens of FM [9–11]. An early and definitive diagnosis of FM has several advantages for each individual patient: the diagnostic classification legitimizes the subjective symptoms and provides reassurance and peace of mind; patients are better able to manage with their health status [9], and patients can access guidelines-based on their own treatments [12]. In contrast, there is increasing recognition of misdiagnosis of FM [13–15]. The aims of this chapter overview are to outline the prevalence and potential reasons for the misdiagnosis of FM and to give clinical guidance to enable the clinician to achieve a more accurate diagnosis of FM, thus leading toward a more positive outcome for the patient.

Clinical Case Presentation

There are a vast number of clinical situations that are associated with chronic widespread pain (CWP) . Therefore it is on the physician to always consider a differential diagnosis when evaluating a patient with a diffuse pain syndrome. The differential diagnosis of CWP has been examined in detail in a recent review titled appropriately "Diagnostic Confounders of Chronic Widespread Pain." [16] In general, conditions that may share similarities with FM can be categorized into neurologic, non-rheumatic medical conditions, rheumatic, mental health disorders, and drug-related negative effects. *The conclusion of the review is that the misdiagnosis of FM most likely occurs in the setting of early undiagnosed rheumatic diseases before the appearance of abnormalities on physical exam or lab testings*. For example, preclinical rheumatoid arthritis could be present with body pain, fatigue, and even muscle weakness in the months preceding onset of appreciable joint swelling [17]. Polymyalgia rheumatica should always be considered in an older person presenting with a new onset of diffuse pain, although there is usually prominent stiffness and complaints are more focused toward the limb girdle regions. The early stages of inflammatory spondyloarthritis, especially in the setting of multiple sites of enthesopathy [18], should be considered. Non-inflammatory musculoskeletal conditions should include myofascial pain syndromes. In the category of other medical illnesses, consideration of the following conditions should be given: endocrine disease or metabolic disorder (hypothyroidism, hyperparathyroidism, acromegaly, vitamin D deficiency), gastrointestinal disease (celiac and non-gluten sensitivity), infectious diseases (Lyme disease, hepatitis C, and immunodeficiency disease), and the early stages of a malignancy such as multiple myeloma, metastatic cancer, and leukemia/lymphoma [16]. Neurological diseases with a pain component include multiple sclerosis, Parkinson's disease, and peripheral neuropathy. Spinal stenosis, although most commonly associated with claudicant-type pain, can present in a

more ill-defined way and may be difficult for a patient to clearly describe. Even though weakness is the most common symptom of myopathy, this may be less prominent than diffuse pain in patients. Some cases have reported the misdiagnosis of FM in patients with myopathies [19]. A medication history is always required in diffuse pain, with an ever-growing list of drugs leading to myalgias and arthralgias. The most common drugs are the statins, opioids, chemotherapeutic agents, aromatase inhibitors, and bisphosphonates [16]. The foundation for examining a patient with CWP is an in-depth history and physical examination, which could be followed by specifically directed investigations as indicated in Table 66.1 and Fig. 66.1 [20].

Table 66.1 Fibromyalgia cues in the health history

Fibromyalgia cues in the health history
• Family history of early chronic pain, e.g., low back pain, "rheumatism," etc.
• Personal history of pain in childhood and adolescence
• Long history of local pain
• Onset of widespread pain related to physical and/or psychosocial stress
• Pain characteristics that include neuropathic-like pain quality (burning pain). Aggravated by weather changes, tension, poor sleep, stress
• General hypersensitivity to touch, smell, noise, taste
• Hypervigilance
• Multiple somatic symptoms (gastrointestinal, urology, gynecology, neurology) with previous diagnosis of functional dyspepsia, irritable bowel syndrome, painful bladder syndrome, tension headache, migraine, temporomandibular disorder
• High symptom-related emotional strain

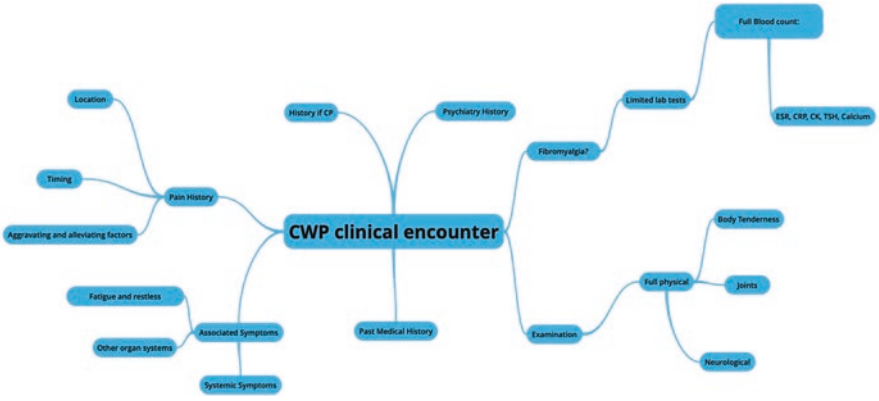

Fig. 66.1 Decision-based approached thought web of clinical findings for chronic widespread pain

Differential Diagnosis

1. Myofascial pain syndrome—A chronic *pain* syndrome caused by muscle tension, injury, or repetitive motion and characterized by the presence of trigger points in muscles and/or *fascia* (small tender knots).
2. Polymyalgia rheumatica—A chronic inflammatory rheumatic disease of unknown etiology that mainly affects women above the age of 50. Patients typically present with pain in their shoulders, hips, or neck; morning stiffness; and systemic symptoms (e.g., fatigue, malaise, and depressed mood). Ten to twenty percent of patients with polymyalgia rheumatica go on to develop giant cell arteritis.
3. Hypothyroid myopathy—A complication of hypothyroidism that manifests as proximal weakness with elevated creatine kinase levels. Clinically, the symptoms are very similar to those of polymyositis (progressive proximal muscle weakness), so all patients with suspected polymyositis should be evaluated for hypothyroidism.
4. Complex regional pain syndrome—A condition typically characterized by severe, debilitating pain of the extremities with associated sensory, motor, and/or autonomic changes. Typically associated with a specific precipitating trauma and restricted to a specific nerve territory. The underlying mechanism is unknown but thought to be related to inflammation and dysfunction of pain perception.

What Was Misdiagnosed in This Case and Why?

Fibromyalgia is being misdiagnosed for a multiple of reasons, but the general reason why is that clinicians fail to observe the common clinical indicators of FM, leading to the misdiagnosis of FM.

Discussion

The pillar for evaluating a patient with CWP is a comprehensive history and physical examination, which may be followed by specifically directed investigations (Table 66.1) [11]. History: As a first step, the location of chronic pain can be assessed. In the case of CWP, further questioning regarding associated symptoms of tiredness even after sleep and fatigue should be looked at. Positive responses in the setting of CWP would identify the condition as an FM-type syndrome. Attention must be given to the timing of onset and evolution of symptoms, report of any triggering event, and alleviating or aggravating factors. In the context of FM's familial association, a family history of first-degree relatives should be documented. For a person presenting with CWP, especially as a new symptom, a medication history

must be explored to ensure that the medication's adverse effect is not the cause of the pain complaint. Medications that should be considered include lipid-lowering agents in statins, aromatase inhibitors, bisphosphonates, and paradoxically even opioids. Therefore a history of current medication use is obligatory. Physical examination: A physical examination is required specifically to examine for evidence of structural joint abnormality, muscle weakness, neurological abnormality, or evidence of endocrine disease. The physical examination should be within normal limits for the patient's age. Clues that may point to a diagnosis of FM are soft tissue and generalized body tenderness. Although the tender point examination was used in the past to establish a diagnosis of FM, this finding is no longer incorporated into the physical examination because of poor validity and poor reproducibility. Some patients may demonstrate dysesthesia on light touch, myofascial induration, or joint hypermobility. Additional testing: No confirmatory blood tests, imaging, or histological analysis is available for FM. A limited number of laboratory tests will allow for screening for medical conditions that can mimic FM symptoms. The 2016 criteria require a widespread pain index (WPI) of between four (2011 required three) and six pain sites and symptom severity (SS) score of $\geq$9. In addition, generalized pain, as defined by pain occurring in at least four of five body regions except for the face and the abdomen, should be present [19]. The Fibromyalgia Survey Questionnaire (also called polysymptomatic distress scale, PSD) capturing the 2011 (21) and 2016 (21) diagnostic criteria of FM can be completed by the patient to further complement the clinical assessment and can be used to give some indication of the severity of the condition. In most cases, a definite diagnosis can be effectively established based on the history, a physical examination that demonstrates general tenderness, the absence of some other pathology that could explain pain and fatigue, and normal basic laboratory tests. The standards of good medical practice state that the physician must always consider a differential diagnosis for any patient presenting with a diffuse pain complaint. This has been covered in the section on misdiagnosis of FM. FM may coexist with other pain syndromes. Patients diagnosed with FM may also experience other painful conditions that are mostly distinct from FM and are generally classified as overlapping pain conditions. Notably, the 2011 [20] and 2016 [20] criteria include headache and abdominal pain in the somatic symptom score, increasing the probability that patients with migraine or tension headaches or irritable bowel syndrome will meet FM criteria. Even when the ACR 1990 classification criteria [21] are used for diagnosis, many patients with FM meet the criteria of some other function. Recent studies have demonstrated that treatment of visceral pain comorbidities (endometriosis, IBS, primary dysmenorrhea) reduced FM pain [14–16]. Therefore, FM patients should be screened for other pain syndromes, and a questionnaire that captures somatic symptom burden, such as the Patient Health Questionnaire (PHQ) [15, 18–20]. The coexistence of FM with some other medical condition that could act as a pain generator may influence the outcome of the other condition in particular and the global health outcome in general. There are two considerations when FM coexists with some other condition: firstly, the underlying condition should be treated according to best practice, e.g., for osteoarthritis or mechanical back pain; secondly, there

must be an appreciation that concomitant FM may affect the outcome of the underlying condition. This has been shown for a surgical outcome that is less favorable for patients with osteoarthritis of the knee and comorbid FM [20]. FM may coexist with mental health disorders. Depression is another FM symptom identified in the somatic symptom scale of the Fibromyalgia Symptom Questionnaire. Depending on the clinical setting, up to 80% of FM patients meet the criteria of depressive and anxiety disorder. FM's severity (number and intensity of symptoms and degree of disability) is substantially determined by comorbid mental disorders [5]. A screening of FM patients for psychological distress either by questions such as "Over the last 2 weeks, how often have you been feeling down, depressed, or hopeless" and "Feeling nervous, anxious or on edge" or questionnaires (e.g., PHQ 4) [21] is recommended by some FM guidelines. Severe comorbid mental disorders require the inclusion of a mental health specialist in the management of FM [19]. The severity of FM as a chronic disorder for patients with the full expression of FM are at the end of a continuum of multiple pain sites and other somatic and psychological symptoms [20]. As for other diseases defined by continuous variables, such as hypertension, diabetes, or depression, there is currently no absolute point defining where FM begins. Cutoff points for diagnosing continuum disorders are defined by expert consensus and based on clinical studies. The higher the cutoff point for a diagnosis, the lower the prevalence. The 2016 diagnostic criteria for FM [21] increased the requirements needed to meet the widespread pain criterion compared to the 2011 diagnostic criteria [21]. Thus, potential FM cases in the general German population decreased from 2.1% [21] to 1.9% (Wolfe 2018, submitted). In addition, longitudinal studies of patients with CWP and/or fibromyalgia have demonstrated that some patients report fluctuation in symptoms over time and thus oscillate around the cutoff points, at times being FM positive or FM negative [19–21]. FM's waxing and waning nature might explain some discrepancies between the prevalence of criteria identified FM and clinical FM. There is no internationally accepted grading of the severity of FM, but clinical wisdom requires the treating physician to assess severity to direct treatment options [4]. Most gradings suggest a distinction between mild, moderate, and severe forms of FM based on the intensity of symptoms and the degree of limitation in daily functioning. It, therefore, follows that a stepwise management approach can be based on the severity of FM. Mild forms require primarily education and advice (regular physical and social activities) with perhaps the occasional use of drug therapy for episodes of exacerbation and can be managed in primary care. More severe forms require multicomponent (exercise, psychological therapies, drugs) and multidisciplinary therapies [12, 18]. Therefore, for the follow-up of patients diagnosed with FM, a "continuum" assessment, e.g., by questions about general well-being (e.g., on a 0–10 scale or a Likert scale of "the same," "better," or "worse") or by symptom questionnaires such as the PSD [20] or the PHQ 15 [21], might be more appropriate [19] than the determination of whether a patient meets FMS criteria or not at a particular time point [21].

Plan of Action, Pitfalls to Avoid, and Pearls of Knowledge to Consider

1. Know all the clinical manifestations of FM.
2. Incorporate a multisystemic approach when diagnosing FM.
3. Create a plan of action when doing an examination of a new patient.
4. Avoid coming into the examination with an idea of diagnosis.
5. Review current up-to-date criteria for diagnosing FM.
6. Have the patient fill appropriate questionnaires when there is CWP.
7. Consider mental distress as a possible indicator of FM not just CWP.

Conclusion

Fibromyalgia syndrome (FM) is an enigma. Even with the gradual acceptance of the validity of FM, it has continued to be misdiagnosed by clinicians. Evidence-based interdisciplinary guidelines have presented a comprehensive clinical assessment to avoid misdiagnosis. A patient with chronic pain should be screened for CWP. Those with CWP should be examined for presence of additional major symptoms of FM: unrefreshed sleep and fatigue. A complete medical history and complete physical examination are mandatory in the evaluation of a patient with CWP in order to conclude the diagnosis of FM. Mild and limited simple laboratory testing is recommended to screen for possible other diseases. When taking into consideration of the differential diagnosis of FM, special attention should be paid to the presence of other chronic pain that is overlapping conditions and of mental disorders. FM on its own as a diagnosis is rare, as almost all patients with FM meet criteria for other overlapping pain conditions or mental disorders. The intensity of FM should be assessed in order to direct treatment approaches and help inform the likely outcome for an individual patient.

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Chapter 67
Rheumatoid Arthritis Misdiagnosed as Gout

Kosha Geslaghi and Brandon Krout

Learning Objectives
By the end of this presentation, the clinician should be able to:

1. Correctly differentiate between gout and rheumatoid arthritis.
2. Discuss how to correctly identify radiographic images of gout in patients.
3. Explain the symptomatology of gout and rheumatoid arthritis.
4. Summarize the effects of diuretics in patients who may be presenting with the same clinical manifestations of gout.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease with an etiology that is not well understood. RA is characterized by symmetric polyarthritis, the most common form being chronic and inflammatory [1, 2, 4, 6–8]. Since active RA often ends in articular cartilage and bone destruction and functional disability, it is crucial to diagnose and treat this disease early before damage ensues [1, 2, 4, 9]. As RA is a systemic disease, if left untreated, it may also lead to a variety of articular symptoms and subcutaneous nodules, including fatigue, lung involvement, peripheral neuropathy, pericarditis, vasculitis, and hematologic abnormalities [1, 2, 4, 5].

A different, metabolic disease that is often a cause for misdiagnosis in RA patients is gout. The most prevalent demographic for patients with gout and RA overlap which can lead to misdiagnosis, i.e., a middle-aged to elderly males or

K. Geslaghi (✉) · B. Krout
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: kosha.geslaghi@martinus.edu; brandon.krout@martinus.edu

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postmenopausal females. Gout is a metabolic disease with a main demographic of middle-aged to elderly men and postmenopausal women. Gout results from an increase of urate with hyperuricemia [1, 2, 4]. It is identified by episodic acute arthritis or chronic arthritis caused by deposition of monosodium urate crystals in joints and connective tissue tophi [2, 4]. There is the risk for deposition of monosodium urate crystals in kidney interstitium or uric acid nephrolithiasis [1, 2, 4].

In recent years, the atypical presentation of gout in the elderly has started to be acknowledged in greater frequency [1, 2]. Gout observed in older patients is often a subacute, symmetric polyarthritis missing in classic podagra [1–4]. Early development of tophi in a patient with symmetric gouty arthritis can lead to the misdiagnosis of rheumatoid arthritis with rheumatoid nodules; this results in inappropriate management of a condition that is generally treated with very positive results [1, 2]. The crystals found in gout are that of a buildup of uric acid which crystallizes in the synovial fluid; however, RA being an autoimmune disorder, there is a buildup of granulated tissue in the synovial spaces. The following case will demonstrate these points as well as the challenging clinical problems frequently encapsulating the effective diagnosis and treatment of gout in the most common demographic: that of the elderly.

Clinical Case Presentation

A 74-year-old elderly woman arrived into the emergency room after 10 days of weakness, diarrhea, and anorexia. She described 4 years of arthritis, occurring first in her ankles and later progressing to knees and hands, with the development of deformities and soft tissue nodules [1, 2]. There were no signs of morning stiffness and acute attacks of arthritis. The patient's past medical history was significant for hypertension, two myocardial infarctions, and renal insufficiency [10–13]. A diagnosis of rheumatoid arthritis had been made [1, 2]. Treatment with nonsteroidal anti-inflammatory agents (NSAIDS) was initiated. Two weeks prior to admission, she noted increasing pain in all joints, swelling of hands and knees, and resultant inability to ambulate [1, 2]. Her medications included prazosin, diltiazem, furosemide, indomethacin, and acetaminophen with codeine. System review revealed no cough, chest pain, or fever. She did note recent weight gain.

On examination the patient was fully oriented, with BP 200/100 mm Hg, pulse 104, respirations 28, and temperature 102 F. Soft tissue nodules were present on the fingers and were prominent around the proximal and distal interphalangeal joints. Cardiopulmonary exam showed a diffuse ventricular impulse and lowered breath sounds with left basilar egophony [1, 2]. No evident nodules were present on the olecranon or pinnae. Joint exam revealed warm knees with a 3+ effusion on the right limiting flexion and a 1+ effusion on the left with crepitance [1, 2]. Destruction of the metacarpophalangeal joint and proximal interphalangeal joints had caused a right hand flexion contracture and an asymmetric left hand deformity with ulnar deviation (Fig. 67.1). Bilateral hallux valgus deformities of the first metacarpophalangeal joints were present. Laboratory exam revealed Hgb 8.5 g/dL, WBC 11,500/mm3,

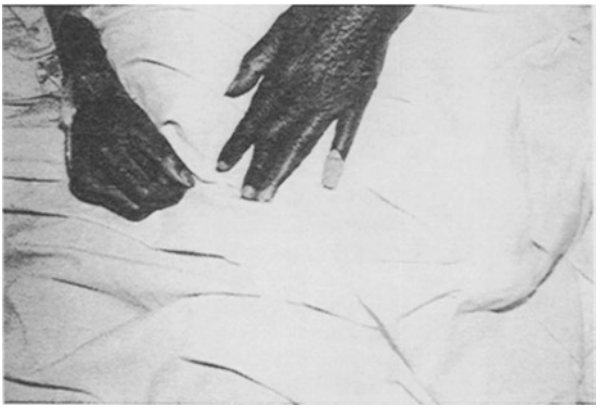

Fig. 67.1 Hands of a 74-year-old woman in full extension, asymmetric deformities of proximal interphalangeal and metacarpophalangeal joints, ulnar deviation, and flexion contractures on the right

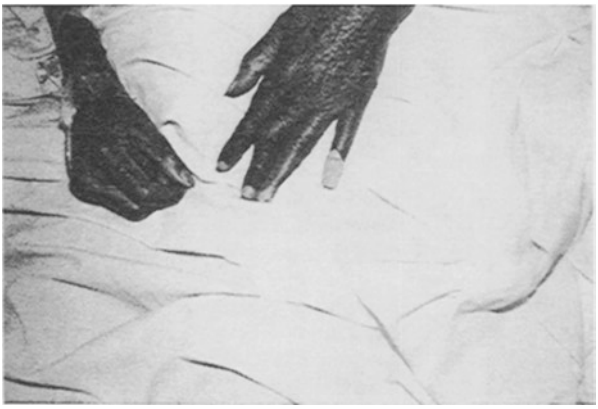

Fig. 67.2 Radiographs of patient's left hand in Fig. 67.1: preserved joint space in noninvolved joints and characteristic para-articular gout erosion with overhanging margin in the middle proximal interphalangeal

BUN 58 mg/dL, creatinine 3.0 mg/dL, uric acid 9.4 mg/dL, rheumatoid factor 1:1 O by latex fixation, normal cardiac isoenzymes, age-indeterminate infarction by ECG, cardiomegaly with cephalization of blood flow, and a predominant left lower lobe infiltrate on chest X-ray [1, 2]. Echocardiogram revealed a hypokinetic left ventricle with ejection fraction of 13%. On knee radiographs, changes of the patellofemoral compartment and a right knee effusion were present, without overt chondrocalcinosis or erosions. On left hand film, a soft tissue deformity and eccentric cortical erosion with overhanging margins of the involved proximal interphalangeal joint were present (Fig. 67.2) [1, 2]. Arthrocentesis of the right knee yielded copious opalescent fluid with a thick slurry of visible white particles [1, 2]. Polarizing microscopy

revealed a mass of needle-shaped crystals with both negative and positive birefringence. Intracellular crystals were present. When diluted 10× the synovial fluid revealed concentrations of uric acid 13.1 mg/dL, calcium 1.2 mg/dL, and glucose 10 mg/dL, confirming the predominant presence of monosodium urate crystals. The patient was treated on admission for congestive failure, hypertension, azotemia, and suspected pneumonia using erythromycin, prazosin, diltiazem, and azotemia; oral colchicine was begun without loading.

The diagnosis of gout rests on the identification of negatively birefringent intracellular crystals from synovial fluid or tophi [1, 2]. Supporting evidence, as in this case, may also include asymmetric joint involvement, soft tissue tophi, and periarticular osteolysis or classical marginal erosions outside the joint capsule.

Differential Diagnosis

1. Septic Arthritis—A joint infection that causes severe pain, swelling, erythema, warmth, and loss of function of the affected joint. Also frequently causes systemic signs such as fever. This condition is marked by its trademark fever prior to the onset of arthritis.
2. Osteoarthritis—A condition characterized by degeneration of the articular cartilage and the underlying bone as a result of chronic wear and tear. Usually occurs in the elderly but can be accelerated in patients with an underlying joint pathology and increased or abnormal biomechanical forces on the joint, including elevated body mass index. While this condition appears to be the same as RA, the risk factors of obesity differ from that of RA.
3. Psoriatic Arthritis—A seronegative inflammatory arthritis found in patients with psoriasis. In 60–80% of patients, psoriasis precedes the arthritis; in 15–20% of patients, arthritis appears before psoriasis. Other common symptoms include enthesitis particularly where the Achilles tendon attaches to the calcaneus, dactylitis, and nail changes.
4. Pseudogout—The acute form of calcium pyrophosphate crystal deposition disease. Manifests similarly to an acute gout flare, with sporadic episodes of monoarticular synovitis affecting large joints. Unlike gout, it can last for months and may be associated with systemic symptoms.

What Was Misdiagnosed in This Case and Why?

Diuretic gout was misdiagnosed as RA. The reason for this misdiagnosis was the diagnosing physician did not consider the effects of diuretics in patients with hypertension; the side effects of the aforementioned diuretic lead to accumulation of fluid in the proximal interphalangeal joints leading medical professionals to believe that it was RA caused by an autoimmune etiology.

Discussion

RA is known as a chronic inflammatory disease and its etiology is unknown. RA is characterized by polyarthritis and is the most prevalent form of inflammatory arthritis. Gout, however, causes arthritis-like pain but it is not an inflammatory disease. Gout occurs in response to the presence of monosodium urate (MSU) crystals in the joints.

The profile of the elderly gout patient has been classified as a thin 75-year-old woman with Heberden's nodes who is a teetotaler and uses diuretics [12, 13]. Accompanying this new profile for gout is the clinical history of a polyarticular arthritis involving both the upper and lower extremities, with subacute or no acute attacks [10, 11]. Gout in the elderly is strongly associated with diuretic use; the association reaches levels of 85%, 95%, and 100% in reports on gout in elderly women. All women were on diuretics and presented after the fifth decade with subacute attacks and often exuberant tophi, warranting the new label of diuretic-induced gout. A study emphasized renal insufficiency in 90% of all elderly gout patients, underscoring decrease in urate excretion as the cause of their gout [12]. Polyarticular gout in the setting of mild renal insufficiency and diuretic use may be the predominant form of gout in women. Early tophi are a unique characteristic of diuretic gout, often occurring within the first or second year of disease [1, 2, 13]. Urate deposition in the elderly shows a predilection for the sites of osteoarthritis in hand interphalangeal (IP) joints known as Heberden's and Bouchard's nodes. Several authors have demonstrated by crystal analysis that attacks of previously classified "inflammatory osteoarthritis," with clinical inflammation and erosive changes, are actually episodes of gouty arthritis in osteoarthritic IP joints. Development of tophi at osteoarthritic IP joints or in the soft tissue of the distal fingerpad may predate all attacks of gouty arthritis. It is therefore critical for the diagnosing physician to consider the side effects of medication on the patient population as the source for the current pathophysiology. This knowledge, combined with a focused physical exam, imaging, and synovial fluid analysis, is needed for a comprehensive medical workup of the presenting patient.

Plan of Action, the Points Clinician Should Consider, Pitfalls to Avoid, and Pearls of Knowledge to Consider

1. Create a framework when meeting new or referred patients.
2. Know all possible side effects of medication of patients, especially long-term medications.
3. Always refer to radiographic images before making diagnosis as well as clinical manifestations.
4. Running tests to confirm diagnosis may be invasive, but it would save the patient's time and energy in early diagnosis.

Conclusion

Rheumatoid arthritis is a very common diagnosis in the elderly patient population. As such, there are chances for error in assuming that a presenting patient who is elderly with symmetric polyarticular joint pain and nodules is suffering from rheumatoid or systemic arthritis. There must be a consideration of medication side effects, especially diuretics, for the proper patient workup. Diuretics can potentially lead to an increase of monosodium urate crystals in the kidneys and joint spaces, with resulting tophi formation and pain. A complete workup should include a detailed history, including medication review, physical examination, imaging, and serum studies. By using the various modalities offered to modern physicians, the misdiagnosis of gout can be significantly limited.

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Chapter 68
Spondyloarthritis: Gender-Based Symptomatology in Order to Reduce Misdiagnosis

Kosha Geslaghi and Brandon Krout

Learning Objectives
By the end of this presentation, the clinician should be able to:

1. Devise a framework for how to address new patients with the possible diagnosis of spondyloarthritis.
2. Illustrate the importance of a gender-based clinical approach to diagnosis.
3. Illustrate the reason for the greater prevalence in misdiagnosis among women.
4. Analyze appropriate diagnosis in both men and women in cases of spondyloarthritis.

Introduction

Somewhat like myocardial infarction, SA has been found to be a male disease, later in the thought to be a disease with sex differences in clinical symptomatology. For many years, it has been severely underdiagnosed in women [1–3].

SA subsumes a spectrum of diseases identified by inflammation affecting the sacroiliac joints, spine, or peripheral joints [4]. SA can be further subdivided into axial and peripheral [4]. AS is indicative to axial spondyloarthritis with radiographic damage of the sacroiliac joint, while non-radiographic axial spondyloarthritis refers to disease in the absence of radiographic damage [4]. The larger category of spondyloarthritis also involves peripheral involvement, including reactive psoriatic

K. Geslaghi (✉) · B. Krout
St. Martinus University Faculty of Medicine, Willemstad, Curacao
e-mail: kosha.geslaghi@martinus.edu; brandon.krout@martinus.edu

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arthritis, arthritis, and arthritis associated with inflammatory bowel disease [5]. In 1973 there was proven a strong association between AS and HLA-B27 [3, 6]; researchers discovered that other conditions were also associated with AS, proving that these diseases were part of the same pathology, now currently referred to as spondyloarthritis. AS was thought to be a rare disease in women [3, 7, 8]. It was not after 1975 that authors began to realize that AS and spondyloarthritis were not as rare in women as previously believed [1, 4, 9]. In 1961 Rome was the first to update the diagnostic criteria. In 1990, the classification criteria called the Amor and the European Spondyloarthritis International Society failed to note peripheral damage in publication. This halted the discovery that the incidence was not lower in women as previously thought. Assessment of Spondyloarthritis International Group (ASAS) in 2009 published classification criteria of differences of peripheral spondyloarthritis and axial spondyloarthritis; the target ASAS criteria for peripheral SA made the disease and its prevalence even more obvious in women. Patients can now be labeled as having AS, which includes AS and non-radiographic AS, and peripheral SA [3, 5, 10].

The classification of spondyloarthritis shows the changes that have happened in the understanding of spondyloarthritis. A rising and increasing number of physicians and health care workers are becoming aware that women can suffer from spondyloarthritis. Clinicians still link SA to the consultation and appearance of men, on the basis of their professional imaginary and learned diagnostic practices.

Clinical Case Presentation

Past ignorance of a different presentation of SA in women in comparison with men is likely the biggest contributing reason for there has been a decline in diagnostic suspicion, increased misdiagnosis in women [1]. Diagnosis of SA is based on a combination of record review, physical examination, and radiographic evidence. It must be noted that different symptoms can result in different presentations across the sexes which should be considered when making a diagnosis.

Diagnostic delay is well-known in spondyloarthritis; studies have noted an increase in time in deferral of diagnosis in women, as seen on Fig. 68.1 [2, 3, 11]. Patients reported having to explore a number of clinical possibilities by different medical specialists, including obtaining a different diagnosis, before finally spondyloarthritis is diagnosed [3, 12, 13]. Conceptually, with the recent advances in SA and with the goal and focus of avoiding any and all structural damage, early diagnosis and awareness and knowledge of sex differences have become achievable and most desirable. Figure 68.1 shows how women have to on average receive more than one diagnostic before getting the correct diagnosis of SA (Fig. 68.2) [3].

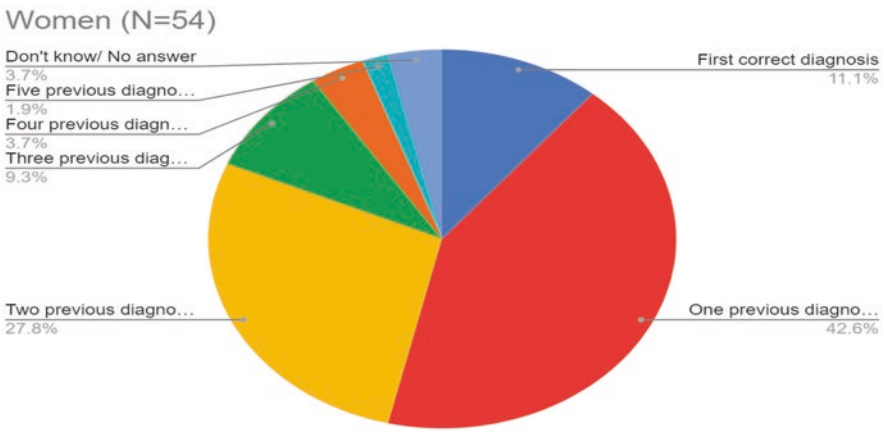

Fig. 68.1 Pie chart depicting frequency of consultation before correct diagnosis for women

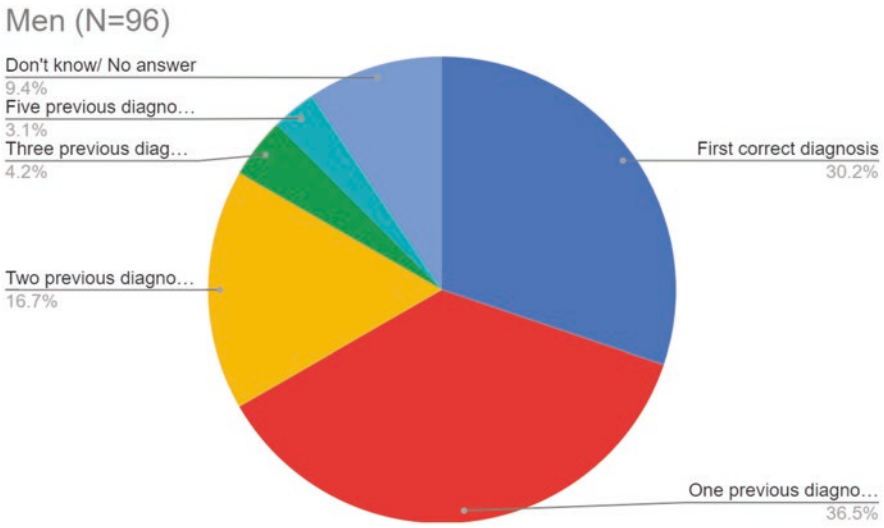

Fig. 68.2 Pie chart depicting frequency of consultation before correct diagnosis for men

Differential Diagnosis

1. Fibromyalgia—While both conditions are similar in terms of chronic pain being widespread or localized, these two conditions cannot be confused for one another based on two clinical criteria. First is HLA-B27 [6] being present in the laboratory reports for a patient suffering from spondyloarthritis. Secondly the referred area of pain is usually different in patients suffering from spondyloarthritis compared to fibromyalgia.

2. Osteophytes—Osteophyte is a bony outgrowth that can occur in inflamed or degenerating joints (e.g., from osteoarthritis, rheumatoid arthritis, joint ligament injury, ankylosing spondylitis). Can be asymptomatic or cause pain, joint deformity, tendinitis, restriction of joint movement, or compression of adjacent nerves. Visible on imaging as bony projections or spurs along the joint line. While this condition usually has underlying causes, radiographic images of the bony outgrowth will create a definitive diagnosis separating it from spondyloarthritis.
3. Vertebral Osteomyelitis—An infection of the vertebrae (e.g., due to hematogenous spread). Manifests with latent, nonspecific symptoms such as back and/or neck pain, spinal tenderness, and possibly fever. While this condition would have the closest clinical manifestation in terms of pain, the history of present illness would be completely different in vertebral osteomyelitis compared to spondyloarthritis.

What Was Misdiagnosed in This Case and Why?

Spondyloarthritis has a greater rate of misdiagnosis among women than men because of differences of the reported manifestations between the two sexes with spondyloarthritis as compared with their medical records (*show increased peripheral pain in women and elevated axial pain in men*). This suggests that health care or medical professionals' medical knowledge and understanding reflect what they expect. This would explain the higher misdiagnosis and diagnostic delay in women.

Discussion

Figures 68.1 and 68.2 [3] shows the correlation sex and diagnostic delay of SA, with a median of 7.5 years in women and 4 years in men *p*, which is concurrent with the medical delay than with the delay of patients (Table 68.1).

Findings confirm the existence of bias that has to do with gender in the diagnosis of spondyloarthritis. In the present case, in the time between the beginning of onset of spondyloarthritis symptoms and its diagnosis, female patients were misdiagnosed more times while experiencing an increased delay in reaching the final diagnosis of SA compared to male patients. Rheumatologists seem to have the symptoms referred by the patients that suit their prior preconceptions about spondyloarthritis in men and women. The most common preconception is that men have back pain and women have increased peripheral pain. Gender bias in spondyloarthritis may be understood as an indicator of gender inequity in the clinical practices, which is avoidable with an analysis of sex and gender interactions that points out how gender inequalities in medicine are still prevalent. Both sexes sought medical attention for pain. We observed a significant diagnosis delay in both sexes, significantly higher in

Table 68.1 Number of diagnoses before the spondyloarthritis diagnosis in a clinic of the General Hospital of Alicante

	Women ($N = 54$)	Men ($N = 96$)
First correct diagnosis	6 (11.1)	29 (30.2)
One previous diagnosis	23 (42.6)	35 (36.5)
Two previous diagnoses	15 (27.8)	16 (16.7)
Three previous diagnoses	5 (9.3)	4 (4.1)
Four previous diagnoses	2 (3.7)	0
Five previous diagnoses	1 (1.9)	3 (3.1)
Don't know/no answer	2 (3.7)	9 (9.4)

women. Even though women and men were waiting equally at the beginning of symptoms for their first visit to a medical professional, women had to wait longer than men until they received a definitive diagnosis of spondyloarthritis. Therefore, if both sexes sought medical attention simultaneously, sex differences in the delay in diagnosis are mainly the fault of the medial system and its literature [2]. This issue has typically been attributed to a lower level of clinical suspicion of the differences based on sex in clinical manifestations [10].

It is noteworthy that about one-third of men were given a correct diagnosis on the first clinic visit, compared to only one-tenth of women. According to the patients, there were no discoverable sex differences in back pain at the time of onset of the disease, although many women remembered peripheral symptoms. The difference in early diagnosis discovered between both sexes is likely due to physicians' differential diagnosis schemes about the presenting symptoms and from a general medical perspective. Until recently, spondyloarthritis was labeled as ankylosing spondylitis and taken to be a predominantly male and spinal disease [13]. This may be the reason why, during the visit to the first physician, male patients complaining of low back pain were recognized as having spondyloarthritis. In contrast, other possibilities were considered first in women, or spondyloarthritis was not considered. Those patients in which SA was not initially recognized followed pathways of greater complexity. They received an increased number of misdiagnoses before the final diagnosis of SA, likely explaining the longer diagnostic delay in women [3, 13].

An important query from the viewpoint of gender bias is, does the physician consider different alternatives in diagnosis. This means a different differential diagnosis in each sex. Data show that fibromyalgia and sciatica were diagnosed in more women than men. Conversely, the herniated disc had an increased rate of diagnosis in men than women, and bursitis and rheumatoid arthritis were considered only in women. These data agree with the texts and other literature, which has found an increased prevalence of fibromyalgia and rheumatoid arthritis in women [3, 13] and a higher expectation of herniated disc pathology in men because of increased occurrence in this population [3]. Most patients of both sexes attended primary care, which refers more patients to rheumatology. However, only one-fourth of female

and one-third of male patients were derived from the first visit to a nonrheumatological clinic. Men were referred to specialists more frequently than women.

Rheumatologists seem to have paid more special attention to the symptoms they would expect to occur, and their beliefs reflect their expectations.

Plan of Action, the Points Clinician Should Consider, Pitfalls to Avoid, and Pearls of Knowledge to Consider

1. Avoid dismissing a patient until all necessary tests are done.
2. Remember to properly refer when laboratory values coincide with possible diagnosis.
3. Confirm with past diagnosis, and find out why the patient is seeking a second opinion.
4. Pay special attention to women who suffer joint pain, due to an unknown cause or a misdiagnosed cause.
5. Always adapt to the change in resources in the field of medicine to better equip yourself for the change in any field not just rheumatology.
6. Consider spondyloarthritis in women also when presenting with diffused aching back pain.

Conclusion

The differences of clinical findings when comparing the two sexes with SA as compared with their medical files (*show increased peripheral pain in women and elevated axial pain in men*) suggest that the medical professionals' annotations reflect what they expect according to literature, teaching, or all other previous knowledge. This is a very likely explanation for the increased misdiagnosis and diagnostic delay in women with spondyloarthritis. In order to overcome this issue in clinical practice, a physician should consider all approaches when dealing with patients and consider a more tailored approach when addressing different genders. By reducing the amount of misdiagnosis, we save our patients years of pain and possible unnecessary invasive and sometimes painful tests.

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Part XV
Legal

Chapter 69
Legal Consequences of the Misdiagnosed Patient

James M. Ringer

Learning Objectives
By the end of this chapter, the clinician will be able to:

1. Define misdiagnosis and missed diagnosis.
2. Identify the basis of misdiagnosis or missed diagnosis as it relates to malpractice liability.
3. Enumerate the elements of legal liability for malpractice.
4. Discuss common examples of malpractice liability for misdiagnosis or missed diagnosis.

Introduction

One of the tenets attributed to the Hippocratic oath is "do no harm", meaning to provide quality medical care, diagnose the appropriate conditions, and find solutions to heal them. As discussed in the preceding clinical chapters, medical treatment is often based on the physician's judgment, which itself is the product of the doctor's education, training, and experience. Under the law, physicians are permitted a broad range of judgment in their professional duties. Physicians are trained to assess a patient's problem, diagnose it accurately, and provide efficacious management. It hardly needs repeating, but to the average nonprofessional and as viewed by the law, an accurate and prompt diagnosis is very important because it establishes an effective course of patient management. In most medical and surgical cases, a

J. M. Ringer (✉)
Meister Seelig & Fein LLP, New York, NY, USA
e-mail: jmr@msf-law.com

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timely diagnosis can literally mean the difference between life and death for patients. From a legal standpoint, errors in judgment may or may not be actionable, in other words, the product of a physician's medical malpractice.

Since the 1960s, the frequency of medical malpractice claims has increased, and today, lawsuits filed by aggrieved patients alleging malpractice by a physician are relatively common in the United States. One survey of specialty arthroplasty surgeons reported that more than 70% of respondents had been sued at least once for medical malpractice during their careers [1].

Medical malpractice occurs when a medical professional deviates from the accepted [2] norms of practice, resulting in either an affirmative act (misdiagnosis) or omission (missed diagnosis), which results in injury to the patient. However, failing to accurately diagnose a disease or condition right away does not automatically amount to medical malpractice. Doctors are not legally obligated to be perfect when it comes to making a diagnosis [1].

It is not enough that a doctor may have misdiagnosed or missed a diagnosis for a patient, but the plaintiff needs to show that their injuries would not have occurred [1] if the doctor properly diagnosed the condition. In other words, if the misdiagnosis did not directly contribute to the injury complained of by the patient, then no liability can attach for the error in diagnosis. Not all harms have a remedy in the law.

But, when the doctor does fail to diagnose or misdiagnoses a patient's condition by failing to meet the standards of care in their community, liability may arise. As a result, the injured patient—and sometimes their family—can bring a claim against the medical professional, and sometimes the facility or hospital that they work at, for monetary damages, including medical costs, any lost wages, and pain and suffering. Such damages may, depending on the particular circumstances of the patient (age, profession, degree of injury caused, and the like), total in the millions and even tens of millions of dollars.

The Lawyers Are Watching

While not every bad medical outcome is the result of malpractice, doctors can be sued when they make certain mistakes. Under the law, this means that the doctor failed to follow accepted medical practices in his/her efforts to diagnose a patient's condition, and as a result, the patient was harmed. In more concrete—less legalese—terms, to establish negligence in a failure to diagnose a case, a plaintiff needs to prove that the doctor breached the standard of medical care that a reasonable doctor would follow in his diagnostic efforts in the particular circumstances. Common examples include not performing the correct diagnostic testing [e.g., doing an X-ray instead of a computed tomography (CT scan) or misinterpreting testing results (e.g., failing to identify cancer tumors on a mammogram)] [1].

There are specialized attorneys who concentrate on pursuing medical malpractice cases. I am sure you have seen their television and print advertisements

informing potential clients of their right to pursue legal action against doctors and medical providers. Their practices are thriving.

Certain data indicates that there are millions of cases of misdiagnosis occurring; *BMJ Quality & Safety* published a study that found that at least 5% of outpatients receive an incorrect diagnosis from their physician [3]. Failing to diagnose is the most common lawsuit brought against doctors in the United States. About *1 in 20* adults in the United States, or *12 million* patients a year, are misdiagnosed. That means that about *5%* of adults are misdiagnosed by their doctors annually. Half of those misdiagnoses have harmful health implications.

In most jurisdictions, any licensed medical professional can be held liable to a patient for medical malpractice. This includes not only traditional providers like doctors, nurses, and physician's assistants but also nontraditional medical providers such as chiropractors, emergency medical technicians (EMTs) , and acupuncturists. The scope of potential defendants in medical malpractice claims also includes corporate/institutional healthcare providers such as hospitals, nursing homes, assisted living facilities, hospices, and urgent care providers [1]. Depending on the particular circumstances of the case, a medical provider or supervising institution may be liable for a missed or misdiagnosis, causing a patient that they treated to suffer.

Failure to diagnose and misdiagnosis of an illness or injury is the basis of many medical malpractice lawsuits. Even highly experienced and competent doctors make diagnostic errors, but to create malpractice liability the misdiagnosis or failure to diagnose must result in improper medical care, delayed treatment, or no treatment, which in turn must result in a worsening of the patient's medical condition in order for the malpractice to be actionable [4].

Hurdles to a Malpractice Lawsuit

When must the case be brought? There are time limitations imposed on filing a medical malpractice case, and the time period can vary from state to state. Often the period, called a statute of limitations, is 3 years. However, a majority of states follow the discovery rule for calculating limitation periods. Some jurisdictions have developed a comparatively strict interpretation of the discovery rule that is very plaintiff-friendly. This makes it easier for victims of malpractice to bring a lawsuit even when more than 3 years have passed since the alleged malpractice. In addition, certain jurisdictions also recognize an exception to the statute of limitations for children (minors under 18). When the victim of medical malpractice is a minor (under the age of 18) at the time the malpractice occurs, certain limitations periods are "tolled," and they have until their 21st birthday to file their claim.

In most jurisdictions, it is not enough for a plaintiff to claim that they suffered from the malpractice of a doctor. Because of the specialized nature of medical care, treatment, and disease diagnoses, most states require that another independent physician certify that they believe an act of malpractice occurred. The overwhelming majority of states have special rules that require medical malpractice

lawsuits to be supported by an initial certificate of merit. The certificate of merit is basically a signed statement from another doctor certifying that medical malpractice *may have occurred*. Without this "certificate of merit" from a qualified doctor, a medical malpractice claim will be automatically rejected or even dismissed.

What Is the Legal Standard of Care?

What is the legal standard? The physicians and hospital staff owe a duty to care for their patients to ensure that all the proper tests are done and properly read [5]. From the general practitioner to the most highly trained specialists, the standard is one of a reasonable physician of like training and background when presented with the patient's condition.

While the definition of "standard of care" can differ among jurisdictions and the concept can prove difficult in its application, the standard of care generally refers to the care that a reasonable, similarly situated professional would have provided to the patient [6]. Whether the doctor lived up to the standard of care will likely require an expert opinion. One of the issues the expert will examine is the defendant's doctor's differential diagnosis method. In order to establish a breach of a standard of professional care, expert witness testimony becomes essential since a jury of lay persons typically cannot understand the nuances of medical care.

What type of duty is owed? The duty of a medical practitioner generally (this will vary in text from State to State but is generally stated as): a medical practitioner is negligent if he/she fails to exercise the level of skill, knowledge, and care in diagnosis and treatment that other reasonably careful medical practitioners would possess and use in similar circumstances [7]. In other words, did the doctor act as any other reasonable practitioner when presented with a similar patient? This standard of a "reasonable practitioner" will depend on the level of skill of the doctor. Will a general practitioner (G.P.) be held to the same standard as a board-certified oncologist? Perhaps not, but then if a prudent G.P. would have referred the patient for certain testing or for a consultation with a specialist and didn't, that might be problematic.

Duty of a Specialist: involves three duties of care

1. The duty to have that degree of learning and skill ordinarily possessed by reputable physicians/specialists practicing in the same field and in the same or a similar locality and under similar circumstances
2. The duty to use the care and skill ordinarily used by reputable physicians/specialists practicing in the same field and in the same or a similar locality and under similar circumstances
3. The duty to use reasonable diligence and/or her best judgment in the exercise of skill and the application of learning

A failure to perform any one of these duties is negligence.

Misdiagnosis Versus Missed Diagnosis

To make a case of negligence or medical malpractice, the plaintiff/patient's legal team must prove that a similar professional in the same situation would have made the correct diagnosis. If an error is found in any diagnostic tests, then the liability may fall on a lab or lab worker instead of the diagnosing doctor [8]. If the error occurred in a hospital setting or in a clinic, the institution would likely be sued as well.

Misdiagnosis is not always negligent. It is possible for an error in diagnosis to be made even after a doctor took all reasonable steps to make the correct diagnosis. When a misdiagnosis is found to be negligent, it could be a doctor, a lab or lab technician, a nurse, a hospital, or any medical caregiver involved in the process that is responsible and liable for the mistake. But, at the core, a mistake is made that was avoidable through the exercise of ordinary reasonable care and prudence. Misdiagnosis and missed diagnosis are the leading causes of serious injuries and medical fatalities.

A *misdiagnosis* occurs when a doctor incorrectly identifies a patient's symptoms and assigns the wrong cure [9].

A misdiagnosis [10] refers to a doctor diagnosing a condition but not correctly. This could cause the real condition to worsen while the patient undergoes unneeded treatment.

Conditions often get misdiagnosed because symptoms overlap, such as chest pains getting diagnosed as a panic attack.

For example, a healthcare provider might diagnose the flu, but the patient really has Lyme disease [11].

A *missed diagnosis* happens when the physician fails to recognize signs of an illness at all and does not prescribe any treatments or recovery plans.

Missed diagnosis, or delayed diagnosis, means the doctor didn't diagnose a condition at all.

The patient doesn't get any treatment, and the doctor may tell them it's not serious or it's all in their head.

A commonly missed diagnosis is the experience of a woman who is sent to a gastroenterologist for stomach symptoms, but her real problem is ovarian cancer, which requires a gynecologist.

Both incidents can lead to the worsening of the condition's symptoms, serious harm, and potential death.

Why Does This Happen, and in What Cases?

Statistics show that more errors happen in outpatient care and emergency rooms (ERs), making up over 70% of diagnostic error cases. Doctors rarely have an established relationship with patients in these situations, which means they don't have the proper medical records, and ERs are often hurried.

Some illnesses can cause extensive harm that can cost a significant amount of money to remedy and treat. Some of the symptoms or complications would not have progressed if the doctor had identified the condition, symptom, or problem that the patient presented and had treated it correctly the first time.

When doctors do not timely diagnose conditions, a patient will lose valuable treatment time. Oftentimes, this can make the difference between life and death. For example, certain types of cancer must be treated without delay before they metastasize and spread. Pancreatic cancer is one example of difficult-to-diagnose cancer that is often discovered after it is too late to treat the patient. In other cases, doctors could miss the signs that may indicate an imminent heart attack.

Whether missed or delayed diagnosis is different from a misdiagnosis may, in certain instances, appear semantical, but in terms of patient suffering and the quantum of damages that might be recovered, there are real differences.

Missed Diagnosis: The patient may be treated, albeit for the wrong underlying condition.

Delayed Diagnosis: The patient's underlying illness is not diagnosed, and the patient is sent home with no apparent treatment.

Common misdiagnosis and missed diagnoses include:

- *Cancer*—Given the number of cancers a person can have, it can be difficult to narrow down the symptoms. However, if not diagnosed in a timely manner, cancer can progress and prove fatal.
- *Heart attack*—Doctors frequently fail to diagnose heart attacks because the symptoms can match those of other illnesses. Women, in particular, do not display common indications for the attack. Doctors who do not pay attention can easily fail to recognize the signs.
- *Stroke*—Strokes are one of the most common medical incidents in the United States. The National Institutes of Health in Bethesda, Maryland, estimate that about 10 to 20% of strokes are fatal. If not diagnosed appropriately, they can take an extensive toll on one's health [12].

Other Conditions

- Celiac disease—People often live with celiac disease without even knowing it. Experts believe that doctors misdiagnose or fail to diagnose about 83% of individuals with celiac disease.
- Thyroid conditions.
- Pulmonary embolism—33.5% of individuals experiencing a pulmonary embolism are sent home [13].
- Systemic lupus erythematosus.
- Fibromyalgia.

The severity of the injury, suffering, and remedial measures needed to restore the patient to health or abate or mitigate their pain and suffering will, in large measure, be the yardstick of the damages for which the physician who missed or misdiagnosed the underlying condition may be responsible.

Studies show a significant amount of harm that has come from doctors wrongfully diagnosing their patients. Experts estimate that an average of 12 million Americans are diagnosed incorrectly.

Diagnostic errors cause 10% of all patient deaths.

Specific cancers are misdiagnosed 44% of the time.

There are law firms that specialize in representing patients who claim to have suffered from such medical malpractice.

Exemplar Cases of Missed/Delayed and Misdiagnosed Cases

Prostate Cancer Misdiagnosis

In one reported instance, a plaintiff who was misdiagnosed as having prostate cancer was awarded in excess of $12 million dollars by a jury. The plaintiff, Rickie Lee Huitt, 65, consulted a urologist at The Iowa Clinic located in Iowa after receiving his prostate cancer screening results. The urologist ordered a biopsy, which was sent to the clinic's anatomical laboratory for interpretation. The pathologist, Dr. Joy Trueblood, reviewed Mr. Huitt's slides and concluded and reported that she found cancer on both sides of his prostate. Huitt then consulted a neurologist, on whose advice to survive the cancer diagnosis, Mr. Huitt underwent a radical prostatectomy. The surgery left Huitt with erectile dysfunction and incontinence [14].

Later, another pathologist examined Huitt's prostate and found no evidence of cancer in his prostate, which conclusion was then confirmed by the Mayo Clinic, Rochester, MN, by examining both the biopsy and the prostate specimens.

Both Huitt and his wife sued, the wife claiming loss of spousal services, The Iowa Clinic, and Dr. Trueblood, alleging that Dr. Trueblood had failed to follow standard procedure during her microscopic view of Huitt's biopsy specimens. They claimed that Dr. Trueblood didn't perform a proper and routine final "double check" to prevent Huitt from receiving another patient's cancer diagnosis and her mishandling of the requisition order forms. In this instance, the doctor did not misread the patient's results but rather mixed his results with those of a patient who did have prostate cancer.

This case is more than just poor paperwork. The injury to this patient, though, was the same as if the doctor had misread the biopsy results and diagnosed cancer where there was no such condition. *Huitt v. Iowa Clinic, P.C.*, No. LACL 139726 (Iowa Dist. Ct. Polk County).

Misdiagnosis Bladder Cancer in ER

The patient, 48-year-old Robert Klein, went to a hospital emergency room complaining of right flank pain, urinary burning, and blood in his urine. He was 48 years old at the time. A third-year resident, Dr. Lien Nguyen, ordered a CT scan. The CT

scan results revealed kidney stones and a bladder mass. Mr. Klein was discharged with instructions to see a urologist. More than 1 year later, after Klein's symptoms progressed, he underwent an ultrasound, again showing a mass on his bladder. Now, he was diagnosed with stage III bladder cancer and underwent an unsuccessful procedure to remove cancer. He later required the removal of his entire bladder.

Mr. Klein and his wife sued Dr. Nguyen and his supervising physician, Dr. Christopher Stromski, alleging that they failed to diagnose and treat his early bladder cancer, which was evident from that early CT scan. Mr. Klein alleged that the doctors failed to apprise Klein of the bladder mass and that this allowed his cancer to progress and later metastasize. The doctors rebutted this argument claiming that Mr. Klein himself had been negligent in failing to follow up with a urologist after having been directed to do so in the ER.

The jury returned a verdict of $10 million, which included $2 million to Klein's wife for loss of consortium. The jury found that Dr. Nguyen was 60% at fault, while Dr. Stromski was 25% at fault. The jury did hold Klein responsible at the rate of 15%. *Klein v. Nguyen*, No. 2017-C-02747 (Pa. Ct. Com. Pl. Lehigh County).

Breast Cancer Misdiagnosis

In the situation where there is a misdiagnosis of breast cancer, it is most likely that the patient's underlying illness was not discovered or was discovered late. Approximately 61% of breast cancer medical malpractice lawsuits are claims of misdiagnosis. But juries have found malpractice in a wide range of misdiagnosis cases.

The most commonly found malpractice is a doctor's failure to:

- Perform or analyze a diagnostic mammogram.
- Inform a patient of mammogram results.
- Perform or interpret an ultrasound.
- Perform or analyze a breast biopsy.
- Inform the patient of the results of a biopsy.
- Evaluate a breast lump correctly.
- Communicate with patient's other doctors to make sure cancer treatment needs are met.
- Properly monitor a breast tissue abnormality that is currently benign [15].

Exemplar Cases

In 2008, plaintiff Leanna Loud, a 39-year-old nurse, underwent a bilateral screening mammogram performed by Jeffrey Short, M.D., a radiologist at Charleston Radiologists, P.A. in Charleston, South Carolina. Dr. Short reviewed the

mammogram and discovered nodular calcifications in her right breast. He then concluded that these calcifications were benign. In 2010, Ms. Loud was diagnosed with advanced breast cancer. She then sued Dr. Short and Charleston Radiologists, P.A. for medical malpractice. Loud alleged that Short's failure to diagnose her developing breast cancer in 2008 allowed it to metastasize. At trial, Loud's oncology expert testified that Loud likely had early stage I cancer at her 2008 mammogram, and at that time, she had an 80+% chance of survival if given appropriate treatment in 2008. Dr. Short testified that the calcifications were scattered and should therefore be considered benign and were unrelated to her current metastatic cancer. Dr. Short's retained experts on mammography and oncology agreed that Loud's breast cancer developed subsequent to the 2008 mammogram and that the large calcifications were indicators of a benign mass.

The jury found that the defendants had been negligent. Ms. Loud was awarded $4.8 million in economic damages, along with $1.4 million in noneconomic damages. Her husband, William Loud, was awarded $700,000 in damages for loss of consortium. *Leanna Loud and William Loud v. Jeffrey Short, M.D. and Charleston Radiologists, P.A.*, No. 2013-CP-10-5902.

In a typical misdiagnosis case, a woman suspects she may have breast cancer and comes under the care of the defendant, a surgical breast oncologist. She undergoes a regular mammogram in order to determine whether or not she has breast cancer, and the defendant reviews her films himself, rather than having a radiologist do so, and tells her the results are normal and benign. Unfortunately, the defendant was wrong in his interpretations of the films causing the woman's cancer to go undetected. The tumor was nearly 8.5 cm when it was discovered. She brought this medical malpractice action against the defendant, alleging he was negligent in acting as a radiologist and departed from accepted practice in failing to detect and diagnose her cancer when she had the mammogram done. At trial, the jury determined the defendant was, in fact, at fault and returned a verdict to the plaintiff for $15 million [16].

In another case, in 2014, plaintiff Ann Domorad, 44, presented to the offices of Drs. Groover, Christie, and Merritt, in Washington D.C., for mammography and breast ultrasonography. The studies were examined by radiologist Dr. Bryan DeFranco, who interpreted both studies as demonstrating no suspicious masses, densities, or evidence of malignancy. Later that year, in 2014, Domorad was diagnosed with breast cancer after undergoing another mammography and breast ultrasonography. A biopsy revealed cancerous nodes and she underwent a surgical procedure that included a double mastectomy and reconstruction surgery. She claimed that the delay in diagnosis led her to undergo extensive treatment and surgeries, resulting in a shortened life expectancy. The jury found that DeFranco misread the diagnostic imagery taken on January 23, 2014, and that DeFranco and Doctors Groover, Christie, and Merritt were liable for Domorad's injuries. They awarded $640,000 to Ann Domorad for future medical expenses, as well as economic and noneconomic losses, and $40,000 to Robert Domorad for loss of consortium. *Ann Domorad and Robert Domorad v. Bryan A. DeFranco, M.D. and Doctors, Groover, Christie & Merritt P.C.*, No. 2015 CA 007137 [17].

In yet another case, a woman received a stage IV mammary carcinoma diagnosis. One year earlier, the radiologist interpreted her routine mammogram as normal. The woman underwent extensive treatments, including radiation therapy and multiple hospitalizations. She alleged negligence against the radiologist. She claimed she failed to suspect cancer and ordered additional tests. A District of Columbia jury awarded $14.3 million. *Leval v. Washington Radiology Associates (DC, 2019).*

Cardiac Misdiagnosis

Heart attacks have been a leading cause of death in the United States for decades, so doctors should be very familiar with the list of symptoms associated with them, including the differences between symptoms experienced by men and women [18]. In many cases, a "warning" heart attack occurs before a catastrophic event. When doctors quickly recognize the signs of a smaller heart attack, treatment is possible to help prevent a life-threatening event. When a doctor fails to recognize the signs of a heart attack [19] and the patient is injured as a result, a medical malpractice claim for failure to diagnose a heart attack may be appropriate [20]. Every year, over 600,000 people die of heart disease in the United States [21], making it the leading cause of death for both men and women. It accounts for around 25% of deaths nationwide. Heart conditions, including heart attacks, can be challenging to diagnose. When a patient presents with a heart attack and the physician fails to identify and treat it promptly, it also may be grounds for a claim of medical malpractice. When it causes severe damage to the heart muscle or even death, it may be a medical malpractice claim.

On October 16, 2013, plaintiff Terrea Holly, 26, went to the emergency room at Detroit Receiving Hospital, Detroit, MI, with high heart and respiratory rates and shortness of breath with exertion that had lasted for 5 days. After being evaluated and undergoing an electrocardiogram, she was released. However, her condition worsened the next day, and she was transported back to the hospital by ambulance. While at the hospital, she suffered cardiac arrest and was pronounced dead at 3:50 p.m. Holly's mother, Dushon Watkins, filed suit on behalf of Holly's estate, suing John Wilburn, M.D., the hospital, and its various legal entities. According to the lawsuit, Holly was evaluated by a resident on October 16 and was found to have high blood pressure, a high respiratory rate, and blood with an oxygen level of 94%. Dr. Wilburn, the attending physician, did an electrocardiogram and diagnosed her with a viral syndrome, also known as chronic fatigue syndrome; mild normocytic anemia, a condition that affects red blood cells; and dehydration. Wilburn discharged Holly after her condition improved with fluids and rested at the hospital. Holly returned home, but her shortness of breath continued and worsened the next day. She returned to the ER that afternoon via ambulance with the same symptoms, but her condition had severely deteriorated. The estate alleged several deviations from the accepted standard of care the first time Holly went to the ER, especially in light of clear indications of a pulmonary embolism at that visit. The estate argued

that the deviations included a failure to complete a full evaluation of Holly's condition, failing to include venous thromboembolism on the differential diagnosis, and failing to perform and review diagnostic tests to confirm the diagnosis. The jury determined that the hospital was negligent and deviated from the standard of care, resulting in Holly's death. The jury determined that the estate's damages *totaled $40 million*. The verdict was expected to be reduced pursuant to the state's cap on non-economic damages.

Failure to Diagnose Stroke in a Patient. On June 15, 2015, at approximately 8:20 p.m., Melanie J. Smith, 40, complained of a severe headache, slurred speech, dizziness, right-sided weakness, nausea, and vomiting while at her parents' home in Highland County. Her mother called 9-1-1 at approximately 8:25 p.m. and told the dispatcher she thought her daughter was having a stroke. An ambulance arrived at the home at approximately 9:05 p.m. Smith was transported to Augusta Health Hospital, Fishersville, V.A., by ambulance. She arrived at the emergency room at 10:42 p.m. The emergency room physician Antonio Baca was the physician in charge. On arrival at the emergency room, a nurse examined Smith and diagnosed her with a complex migraine headache. The nurse prescribed Smith medicine for the migraine headache. At 1:30 a.m., on June 16, 2015, a nurse ordered magnetic resonance imaging (MRI) of Smith. The MRI showed Smith had suffered an ischemic stroke. On June 19, 2015, Smith died of complications from the stroke. The estate's medical experts opined that Baca should have consulted a neurologist as soon as Smith arrived at the emergency room with a history of stroke symptoms. They opined that Baca departed from the standard of care by not initiating a stroke alert for Smith. According to the experts, if Smith had been given a tissue plasminogen activator (tPA) within the essential 4.5-hour window, it would have saved her life. The jury found Baca negligent and determined that the estate's damages *totaled $3.5 million*. *Tracy M. Smith, as personal representative of the Estate of Melanie J. Smith v. Antonio Baca, Stephen D. Turner, and Augusta Emergency Physicians*, No. CL-17894-00 [22].

Failure to Adequately Test. On March 6, 2009, Diane Miller, 49, presented to the emergency room at Memorial Healthcare in Owosso. She had complaints of chest pain radiating into her back and also had high blood pressure. Miller was treated by two emergency room physicians employed by Tri-County Emergency Physicians. After a number of tests were conducted, the physicians ruled out multiple causes for her complaints, except for pneumonia and aortic dissection (tear). The doctors ordered a diagnostic test that would have diagnosed an aortic dissection, but the patient was allergic to the contrast used with the computerized tomography (CT) scan. As a result, two less-comprehensive tests were administered, including a CT scan without contrast and a chest X-ray, both of which were nondiagnostic for aortic dissection. Miller was held in the emergency room for 7 to 8 hours. She was discharged on March 7, a Friday, at 3:45 a.m. with a diagnosis of pneumonia and instructions to follow up with her family physician the following week. She collapsed at 7:30 a.m. that same morning and died of a ruptured aortic dissection during transport to the hospital. Diane Miller died as a result of a ruptured aortic dissection. She was survived by her spouse, children, grandchildren, and sisters.

Miller had preexisting risk factors, including an enlarged heart (found on autopsy) and chronic obstructive pulmonary disease, resulting in a reduced life expectancy. The jury found the plaintiff and awarded a $750,000 verdict.

On June 9, 2012, plaintiff Charles Smith, 53, a laborer, was diagnosed with weakness on the left side of the body after suffering an acute stroke. As it turns out, 5 days earlier, Smith had presented to the emergency room at Geisinger Shamokin Area Community Hospital with complaints of pain in the left side of his chest, shortness of breath, headache, and numbness radiating into his left arm. Smith was seen by Dr. Jere Wagner. According to his medical history, he was at an increased risk for stroke because of both his family history and his own medical history, which included occlusion and stenosis of the carotid artery, high blood pressure, angina, and tobacco use. Dr. Wagner ordered blood work, one set of cardiac enzymes, a chest film, and an electrocardiogram and placed Smith on a heart monitor. Smith claimed that nothing in the record showed that Wagner performed a neurologic examination or upper extremity examination. After the tests were reported as normal, Smith was discharged with a diagnosis of noncardiac chest pain.

Four days later, Smith began experiencing weakness in his left leg and left arm, in addition to numbness in the left side of his face and decreased sensation on his left side. He presented to Geisinger Medical Center in Danville (an affiliate of Geisinger Shamokin Area Community Hospital), where he was admitted and diagnosed with an acute ischemic stroke. Smith sued Wagner and the Geisinger medical facilities, alleging that Wagner was negligent for failing to properly treat him on June 4, when he was exhibiting signs of a transient ischemic attack. The jury found that Wagner was negligent, and his negligence was a factual cause of harm to Smith, who was determined to receive $625,000 [23].

In case you wondered if all verdicts were against the physicians, on June 10, 2009, in the early morning hours, Bernard Poliner, 77, who had been undergoing chemotherapy treatment for multiple myeloma, fell down a flight of stairs at his split-level home in Bloomfield after having taken some sleeping medication. Although suffering a laceration to his scalp, he returned to bed and waited until morning to call his internist, Munish Kumar Shastri, M.D. Later that day, Poliner was seen by Dr. Shastri, who placed 11 sutures for the scalp laceration. Dr. Shastri performed a neurological examination and did not note any abnormalities. Dr. Shastri ordered a back X-ray, which revealed a T12 fracture that had occurred during the fall. No further treatment was provided for the scalp injury except the removal of the stitches about a week later. On day 6 following his fall and doctor's visit, Poliner began to deteriorate rapidly, with noted slurred speech and loss of consciousness. He was transported to an emergency room, and a CT scan revealed a massive subdural hematoma. An immediate craniotomy was performed, but Poliner died as a result of the brain bleed on June 27, 2009. The estate alleged that the standard of care required Dr. Shastri to obtain a CT scan and that, had one been timely performed, it would have revealed a small subdural hematoma in time for it to have been successfully treated, i.e., before the massive second related bleed. The

defense contended that the cause of death was an arterial brain bleed unrelated to the fall. The jury found for ProHealth Physicians and Shastri. A defense verdict was entered, and no damages were awarded.

Failure to Diagnose William's Disease. On December 17, 2012, Emilee Williams, 21, a graduate student, presented to Dr. Elene Pilapil at Mercy Clinic Springfield Communities with complaints of tremors, loss of balance, insomnia, difficulty concentrating, crying spells, and panic attacks. Dr. Pilapil diagnosed Williams with fatigue and depression with anxiety. He prescribed medication for anxiety and depression. On May 13, 2013, Williams returned to Pilapil with continuing complaints of resting tremors, difficulty with handwriting, and general weakness. Dr. Pilapil again determined that anxiety with depression was the cause of her symptoms and adjusted her medication.

Williams returned yet again on June 28 and reported she was having mental struggles, such as spells where she appeared inebriated and had a loss of balance, as well as fatigue and hand tremors. Dr. Pilapil, this time, ordered a magnetic resonance imaging (MRI) in August, which showed severe damage to the basal ganglia as a result of Wilson's disease, a rare inherited disorder that causes too much copper to accumulate in your liver, brain, and other vital organs [24]. A urine test on August 12 showed low ceruloplasmin as a result of Williams' excessive copper accumulation within her body. She sustained severe brain damage and impairments to her motor functions. Williams sued Dr. Pilapil and his employer Mercy Clinic Springfield Communities, alleging that the doctor failed to timely test her, failed to consider neurological diseases on a differential diagnosis, and failed to timely order a neurological consult and instead diagnosed anxiety without ordering testing to rule out the severe pathological cause of the patient's condition. As a result of her disease, Williams suffered temporary quadriplegia, rendering her totally disabled and requiring 24-hour care. The defense expert neurologist testified that even if Pilapil had begun treating Wilson's disease in December 2012, the outcome would have most likely been the same. The jury rendered a verdict for the plaintiff. The jury awarded total damages of $28,911,000 [25].

COVID Misdiagnosis

Any type of harm that results from the improper procedure may be considered negligence. Here are some examples of how negligence can lead to harm:

By studying rapidly evolving literature and news for emerging diagnosis issues, Singh and Gandhi developed names for the types of diagnostic errors in an effort to help clinicians, other healthcare personnel, and the public:

- Classic: A delayed COVID-19 diagnosis due to a lack of accessible tests or tests that read false-negative.

- Anomalous: A COVID-19 patient is misdiagnosed as non-COVID when they present uncharacteristic symptoms such as nausea and diarrhea, especially if they lack respiratory symptoms.
- Anchor: Assuming someone has COVID-19 when they may have another illness instead, such as bacterial pneumonia or sinusitis. Singh explains this can make their conditions worse, especially if the patient requires antibiotics.
- Secondary: Because COVID-19 is a new virus, clinicians may miss underlying or secondary conditions that it can cause, like blood clot-related lung complications. New inflammation syndromes in children are just being described, for example.
- Acute Collateral: Because some people fear venturing into hospitals or clinics due to potential exposure, many remain home even when they have a stroke or heart attack symptoms [26].

How Does a Patient Recover Damages in a Lawsuit?

As seen from the above exemplars, evidence of malpractice from misdiagnoses is predominantly established through the presentation of expert testimony. Depending on the specialty and illness, doctors retained as testifying experts present evidence of the level of care appropriate in the circumstances based on the patient and their presenting condition, the skill, training, and experience of the treating defendant and any institution involved and then ultimately the actual treatment afforded by those medical providers. These testifying doctors are paid by the respective parties based on a review of the medical records, patient examinations, and information from scientific studies or learned treatises.

Damages: Plaintiffs in cancer misdiagnosis cases must prove that they were actually harmed or injured by the failure to timely diagnose their cancer. In other words, the plaintiff needs to show that the misdiagnosis made their cancer less treatable or somehow changed their outlook to get compensation. This is often a contested issue of missed malignancy claims. Defense lawyers in cancer misdiagnosis lawsuits often argue that the plaintiff would have died even if the diagnosis had been timely made [27]. Patients in misdiagnosis cases claim to have been forced to undergo either unnecessary procedures or, in late-diagnosed cases, more invasive and drastic surgeries and treatments to try to address their illnesses.

Patients and their families may be able to recover some of the costs related to their misdiagnosis by filing a lawsuit. Some of the types of costs that can be awarded as part of a malpractice verdict include:

Economic damages like medical bills, lost income, cancer treatment costs, transportation to and from medical centers, and future expenses or losses resulting from your illness.

Noneconomic damage*s* such as pain and suffering, disfigurement, disability, loss of consortium/companionship, and other costs that do not have a strict monetary value.

The exact types of damages you can receive vary from state to state [28].

Moreover, many states have enacted laws that cap the maximum amount of certain types of damages that plaintiffs can get in malpractice cases.

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Part XVI
An Editor's Perspective

Chapter 70
Strategies to Avoid a Misdiagnosis

Hassaan Tohid

Introduction

The *Misdiagnosis Casebook in Clinical Medicine*, 1st Edition, is a thoughtful and well-represented educational resource. The determined and dedicated authors were guided by the editors, who spent months ensuring high-quality material intended to provide value to the reader. The casebook contains evidence-based knowledge to help clinicians avoid common diagnostic mistakes and aspires to serve as a guide to avoid a misdiagnosis pitfall. This writing project began in mid-2021 and culminated in late 2022. Thanks to the writing team and the publisher Springer Nature for making this book a reality.

The casebook contains 70 chapters, all of which contain common and unique clinical cases misdiagnosed by clinicians. This book will serve physicians, clinicians, academicians, medical students, nurses, and other healthcare providers who face the daily challenges of diagnosing clinical conditions with unique presentations. The ultimate goal of which is to benefit the patient.

A common human characteristic is to make mistakes; no one can claim that he/she does not make mistakes. However, the sign of a great learner is that he/she accepts the mistake and works toward improving the mistakes. This casebook will convey that all of us are human and make mistakes. Moreover, this casebook will serve as a helping tool to avoid many mistakes seen in clinical settings on an everyday basis.

The book's title and concept show that misdiagnosis during clinical care is possible and is not strange. Every clinician has misdiagnosed a disease at some point in his or her career, whether during student life, internship years, or post-internship

H. Tohid (✉)
California Institute of Behavioral Neurosciences and Psychology, Fairfield, CA, USA

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clinical career. Since we all are prone to making mistakes, how do we rectify our mistakes? Should we deny the mistake and refuse to accept what has happened? Should we shift the blame to a fellow clinician? Or do we accept our mistake and take absolute responsibility for the error? Should we deny it and hide the mistake from others? Or work toward the improvement of our mistakes? If we deny and do not accept, what we are doing is not the right thing to do and can lead to patient harm. This book will help clinicians around the globe in minimizing the errors that they would otherwise make without this book. Our goal is to mitigate errors and raise awareness that medical misdiagnoses are expected and possible, with the ultimate goal of serving the patients.

This chapter intends to address strategies clinicians may adopt to reduce the number of errors that may lead to a misdiagnosis.

How to Avoid Misdiagnosis?

A study demonstrated that approximately 21% of patients with unplanned hospitalizations within the first 2 weeks of a primary care visit had misdiagnosis [1]. Moreover, misdiagnosis also causes a substantial financial burden on our society. Therefore, avoiding misdiagnosis is essential in providing better healthcare to society. However, we must partially avoid misdiagnosis because human errors will last as long as there is life on this planet. However, we can mitigate the number of misdiagnoses by adopting specific strategies.

1. Attention

We must admit that misdiagnosis errors can only partially be avoided. Even after this book, clinicians will keep making mistakes, and misdiagnosis will remain one of the critical issues; however, the strategies mentioned in this chapter may reduce the chances of mistakes in misdiagnosis. I will address some evidence-based strategies and ideas that could play an instrumental role in avoiding misdiagnosis.

The first and foremost factor that may help clinicians avoid misdiagnosis is paying attention. Healthcare professionals at all levels must be cognizant of what is happening around them. They must be vigilant, carefully observe everything, and pay for all the signs and cues the patient provides during the clinical history. They must also pay attention while reading laboratory tests. Many problems related to a misdiagnosis can be resolved if the clinicians focus, concentrate, and pay attention to the patient, history, and findings. Nowadays, distractions such as smartphones can lead to severe errors. For example, when we were supposed to listen carefully to the patient, we became distracted. We are worried about sending or receiving a text message or how many "likes" we received on our social media posts. Who replied to us or liked our social media posts? This situation can easily cause misdiagnosis. Therefore, switching every distraction off, including cell phones, when with the patient and paying hundred percent attention to the patient can avoid or

reduce many errors, including misdiagnosis. The golden rule should be to pay hundred percent attention to the patient when with the patient.

2. Take Time
Another factor that can reduce errors and misdiagnosis is being patient and not being in a hurry to diagnose. We should take proper time, make sure the complete information is gathered, and analyze carefully. We should also spend time on the findings, such as clinical history and lab findings, and spend time "thinking." Ideally when we think, we should think on paper. Making fast and rash decisions can be wrong; patience is critical.

3. Consult with Others
No one knows everything. No one achieves anything alone. The idea of self-made successful people is a myth because we all need people. We all need other people's help and support. Even the most successful entrepreneur in the world cannot achieve anything alone. He has to hire people and has a team, different departments, and a coach or consultant to talk to. The same goes for any profession, including medicine. Teamwork and the help of others are way more important in medicine than in any other field because it is a matter of someone's life and death. It is imperative to involve as many people as possible. The new residents should consult their fellows and senior physicians in the hospital. The senior physicians should involve as many clinicians as possible to decide on a perplexing and challenging case. An important rule is always to seek advice and consult with others when in doubt.

Never think of yourself as someone who knows everything. Be willing to learn from others, and accept that no one is perfect.

4. Learning
Learning is a lifelong process, and we must develop a habit of lifelong learning. Take courses and classes; attend seminars and webinars, including continuing medical education (CME) hours; and keep improving and growing professionally. The number of misdiagnosed cases can be reduced significantly if everyone develops a habit of lifelong learning. Hospitals can also play an essential role in improving the quality of care by providing educational opportunities for all clinicians. Educational programs are one of the best ways to improve clinicians' knowledge.

5. Experience
A clinician's experience is one of the most valuable resources in the healthcare system today. Learning cannot compensate for the experience. To gain more insight and knowledge, young clinicians must practice lifelong learning and spend as much time with experienced clinicians as possible. In addition, patience is the key; new clinicians will also gain experience with time. The objective is to learn as much as possible, be patient, and resolve to gain more and more experience. They will 1 day realize that they make fewer mistakes and their diagnostic abilities have improved. They must realize that nothing happens overnight, and there is no shortcut. We all must be humble enough to accept the fact that there is always someone with more knowledge and experience around us.

6. Communication
We clinicians should strive to work on improving their communication skills. Better communication can reduce the cases of misdiagnosis [2]. Communication, as commonly believed, is not just speaking and conveying our message; it is just one component of communication. Communication consists of reading, writing, listening, and speaking. We all clinicians should strive to work on all four components of communication. We should highly focus on listening. We can easily misdiagnose any case if we can communicate our message to other clinicians and patients but cannot correctly listen. The same goes for reading and writing. There are plenty of courses and books that teach communication.

7. Audits
Clinical audits are another way that can help us reduce cases of misdiagnosis. Audits are standard in the United Kingdom, and young clinicians actively conduct clinical audits. I believe all the hospitals around the world should adopt the concept of clinical audits to improve the quality of care and minimize misdiagnosed cases [3].

8. Checklists
I learned the concept of writing daily goals and checklists, drastically changing my life. While working at a drug rehabilitation facility, I strictly adhered to writing daily checklists of tasks and followed them religiously. This not only improved the quality of my work but also improved my patients' well-being. I relied on the checklist, from the assessment to the diagnosis, and even during the therapy sessions.

One thing I learned that helped me change my life was that we should never trust our memory. We are humans, and we can make mistakes. Just like an airplane pilot relies on a checklist while taking off, flying, and landing, we clinicians must also rely on checklists because, just like a pilot, we are also responsible for other people's lives. One missed question or a missed step can misdiagnose a disease and be lethal for the patient. Therefore, all clinicians must rely on making and following a checklist to avoid mistakes [4].

9. Technology
No one can deny the fact that technology is the need of time. We need technology to improve all aspects of our lives now. It increases efficiency and productivity. The hospitals in rural areas of some developing countries where technology is not prevalent or present may face challenges in proper diagnosis and treatment. The governments should support the healthcare industry in those countries to adopt modern technology. Countries such as the United States, where technology is prevalent, must ensure proper training of staff and clinicians to operate better, handle, and read the findings by modern machines to reduce diagnostic errors [5]. Technology itself will only help if the clinicians and the staff working at a hospital are equipped with the knowledge and expertise to operate the machines and understand the findings provided by advanced technology such as function magnetic resonance imaging (fMRI) and other similar testing methods.

10. Kaizen Principle

The concept of Kaizen suggests "improvement." No one is perfect, and we all need improvement. In fact, if we are not improving and continuously learning and evolving, we are declining. Therefore, we must adopt the habit of continuous learning regardless of age and experience. Every year we see drastic advancements in research and technology; therefore, if we are not updating ourselves with current research in medicine and healthcare and are not aware of the recent advancements in technology, then we will be left behind, and we will struggle to diagnose cases which otherwise would have been easily diagnosed with the habit of continuous learning and being updated. The most experienced and knowledgeable clinicians develop the habit of reading new research and keep themselves updated. PubMed is a great source to read new and modern research that new clinicians can read to improve and enhance their knowledge. Moreover, they can explore certain scientific journals related to their specialty to be aware of recent research to improve their knowledge. All these resources are just one click away and can be accessed on computer or cellphones. In these times of smart phone technology, if we are not learning and improving, we have no one but ourselves to blame.

Conclusion

The challenges faced by clinicians from other fields in diagnosis will remain as long as we humans run the operations in healthcare. Mistakes are unavoidable, not just in medicine but in all fields. The main characteristic of a human is making mistakes. There are no guarantees that mistakes will never occur, but we can mitigate them by adopting specific strategies such as continuous learning, collaborative teamwork, and a belief in continuous improvement.

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