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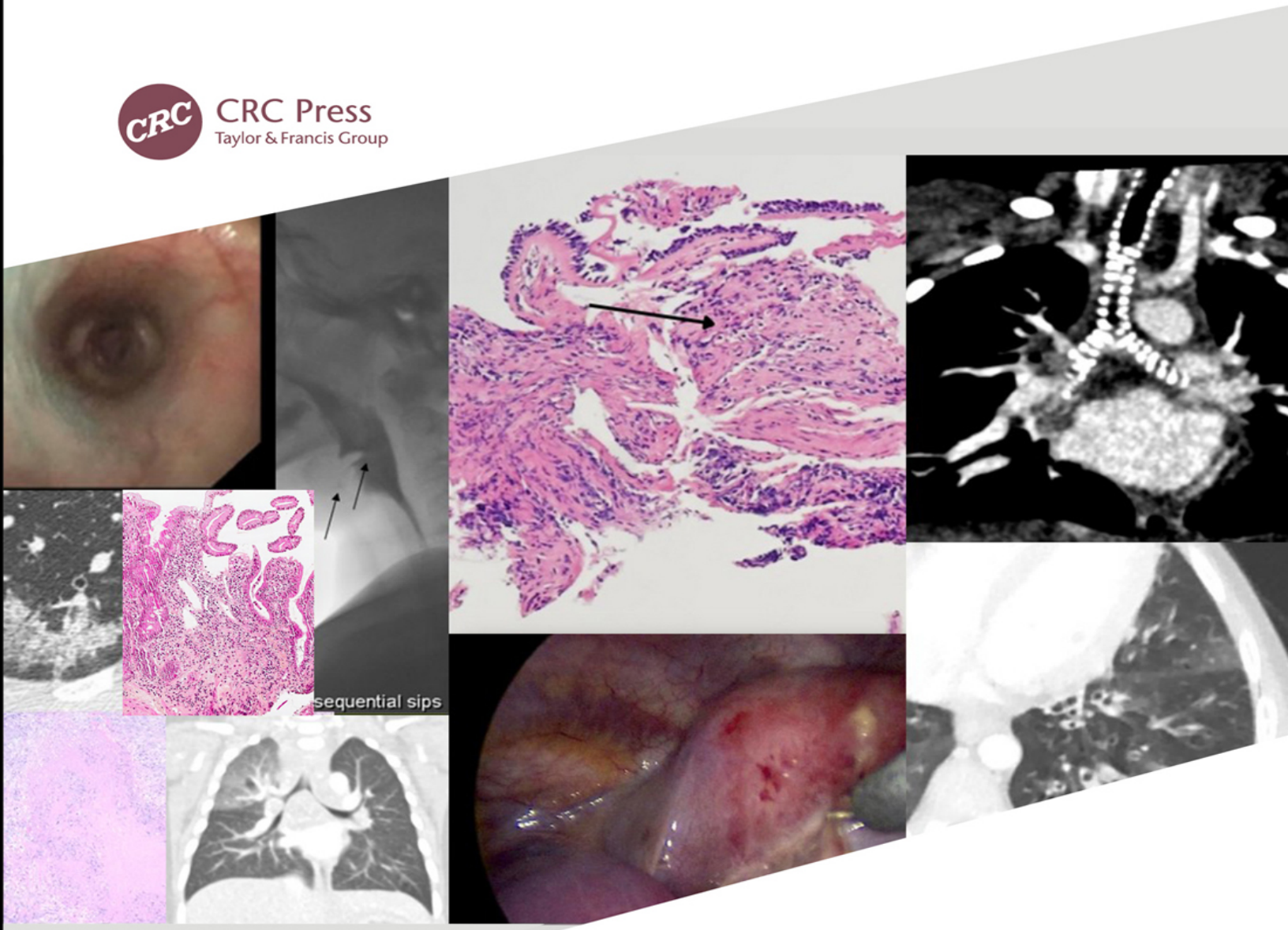

Challenging Cases in Paediatric Respiratory Medicine

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Thomas Semple

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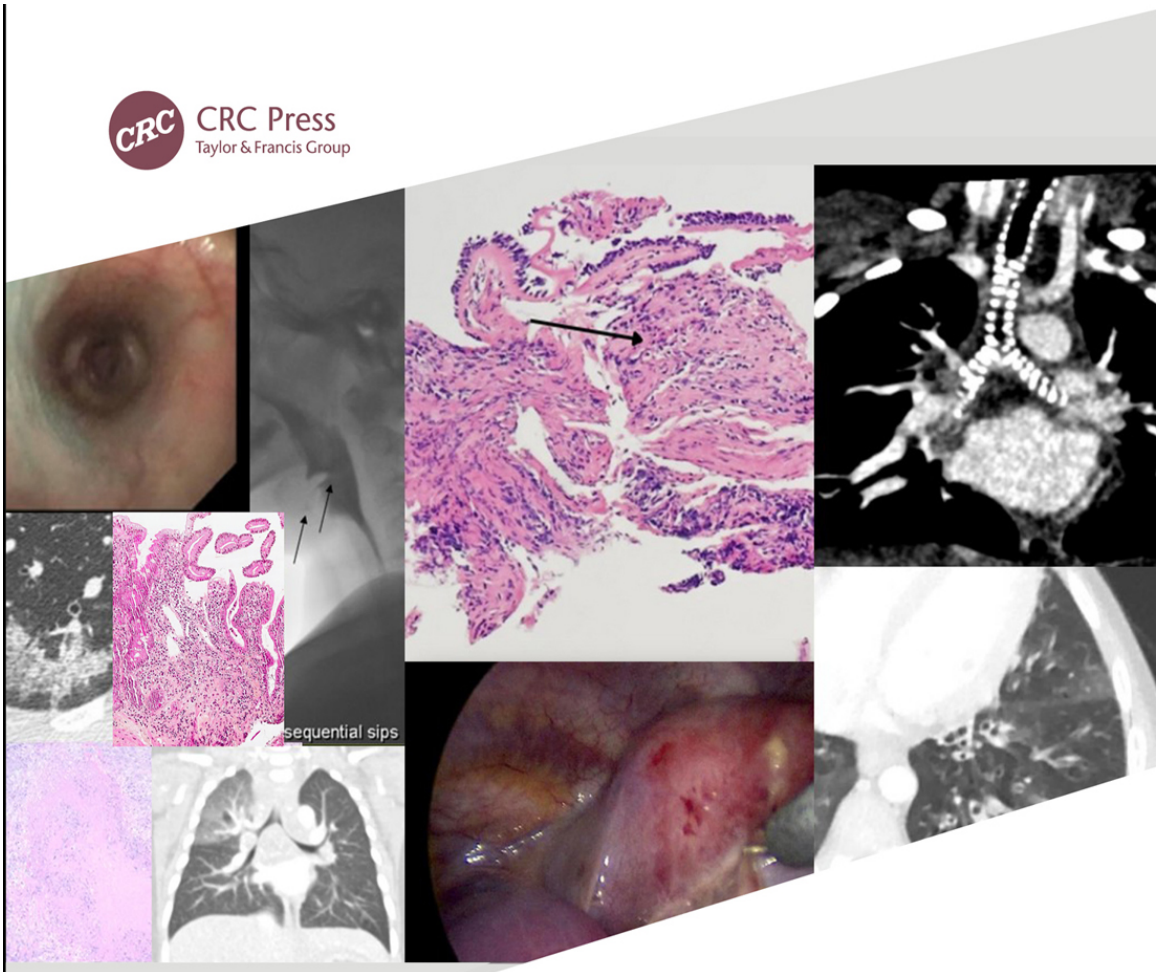

Challenging Cases in Paediatric Respiratory Medicine

EDITED BY
Andrew Bush
Thomas Semple

Challenging Cases in Paediatric Respiratory Medicine

When a few doctors get together, they always start discussing their fascinating cases, and one can learn a lot from the diagnostic journey, including the blind alleys, taken by others. Yet case report publications are rare because they are not cited. These challenging cases in paediatric respiratory medicine from around the world are chosen to illustrate important learning points. The format is a case scenario followed by the diagnosis, treatment outcomes, learning points, and references for bibliography.

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Challenging Cases in Paediatric Respiratory Medicine

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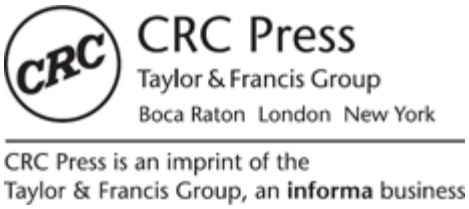

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PREFACE

The world of paediatric respiratory medicine is very small. A child can cross the world in less than 24 hours, well within the incubation period of many infectious diseases. Respiratory paediatricians need to know more than just what is common in their particular location. A sick child from Brazil can turn up in a London hospital, and a Canadian child to a healthcare facility in India, and the challenge for paediatric pulmonologists is to know about respiratory disease in children the world over. The idea for this book came from the INSPiRED meetings. This is the only truly international congress dedicated to children's respiratory disease and brings together doctors of all levels of seniority and healthcare professionals from all over the world for scientific and clinical discussions. The case presentation sessions are always well attended and there is always lively debate. The purpose of this book is to bring together diagnostic and management problems from across the world. The format is a brief introduction, and then the progress of the child is set out as it evolved in real life, with questions for the reader to consider until the final diagnosis is reached. There are extensive illustrations of diagnostic tests including imaging and pathology. Each chapter has a succinct bibliography list. As well as reporting puzzling problems, the book also gives a taste of the constraints under which some colleagues operate. Not all tests are available everywhere, and for those in high-income settings, some of these cases are a salutary reminder of how lucky some of us are. Some of the problems do not have a really clear-cut solution, again reflecting real life, and this is why case discussions are so fascinating. Perhaps you will disagree with some diagnostic pathways and conclusions, but that is meant to be part of the fun – when we disagree, we learn and grow. We hope this book will stretch your mind and your horizons wherever you practice, and you will get as much value out of reading it as we did compiling it.

Finally, we would like to thank all those who submitted these great cases, without whom there would be no book; it was a pleasure to work with you all. Thanks also for the patience of Kanchi Shridhar and Shivangi Pramanik and to the publishers for their efforts compiling this volume. Above all, thanks to our long-suffering wives and families to whom we owe so much!

EDITORS

Andrew Bush's research interests include the invasive and non-invasive measurement of airway inflammation in children, in particular the use of endobronchial biopsy in the management of severe asthma, and clinical physiology, especially respiratory mass spectrometry. He has supervised more than 50 MD and PhD degrees, co-authored more than 800 papers in peer-reviewed journals, and written nearly 150 chapters in books and monographs. He is Deputy Editor of the *American Journal of Respiratory and Critical Care Medicine*. He has served as Guidelines Director of the European Respiratory Society and Chair of the Publications Committee. He is also an Emeritus NIHR Senior Investigator. Major recent awards include the British Thoracic Society Medal (2022, the first paediatrician to be so honoured); the 2024 James Spence Medal and an Honorary Life Fellowship, the highest honour of the Royal College of Paediatrics and Child Health (RCPCH); and the 2024 ERS Presidential Award.

Thomas Semple took up a consultant position at the Royal Brompton in 2018 having completed an MDres at Imperial College (supervised by Jane Davies, Simon Padley, and Claire Hogg) applying structural and functional respiratory MRI to children and adults with cystic fibrosis. Prior to this, he studied respiratory and cardiac imaging with Dr Cathy Owens and Dr Michael Rubens, and he has also had the honour of working alongside Prof Bush and the entire Royal Brompton Paediatric Respiratory team, as well as the wider London Paediatric Respiratory Group reviewing cases, not just from in and around London but from around the world. His research interests include the translation of subspecialty cardiorespiratory imaging techniques from adult practice into paediatrics; the development and optimisation of oxygen-enhanced MR imaging of respiratory physiology; and radiation protection in paediatric CT. He has published peer-reviewed

original research and review papers covering the length and breadth of adult and paediatric respiratory and cardiac imaging practice, written chapters for multiple textbooks, lectured and taught on many courses around the world, and sits on international task forces for both respiratory and cardiac imaging. He is, however, most proud of his recent PhD students and the energy with which they strive to improve and advance practice in paediatric respiratory imaging as well as the increasingly international work of the Royal Brompton's Paediatric Respiratory Multidisciplinary Team.

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CHAPTER 1 A YOUNG GIRL WITH AN INCIDENTALLY DISCOVERED MASS ON A CHEST RADIOGRAPH

Warot Chitanuntavitaya and Prakarn Tovichien

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INTRODUCTION

Here we present the case of an apparently healthy 12-year-old girl in whom a mass was an incidental finding upon a routine check-up chest X-ray. We discuss the differential diagnoses of mediastinal masses, the investigations, and the outcomes in what turned out to be an unusual disease.

CASE PRESENTATION

In Thailand, due to the high prevalence of pulmonary tuberculosis, some schools include chest X-rays in the annual health check-up. Following check-up chest X-rays, a previously healthy 12-year-old girl was found to have a well-defined, lobulated soft tissue mass in the left paratracheal area. The mass measured 6.1 × 4.3 cm and caused a slight pressure effect on the left lateral wall of the trachea (Figure 1.1A). She was advised to undergo further tests at a specialized hospital. She reported no chronic cough, breathing difficulty, or chest pain. There was no family history of genetic diseases or consanguinity. A comprehensive physical exam indicated normal findings, including equal pulses and no significant differences in four-limb blood pressure.

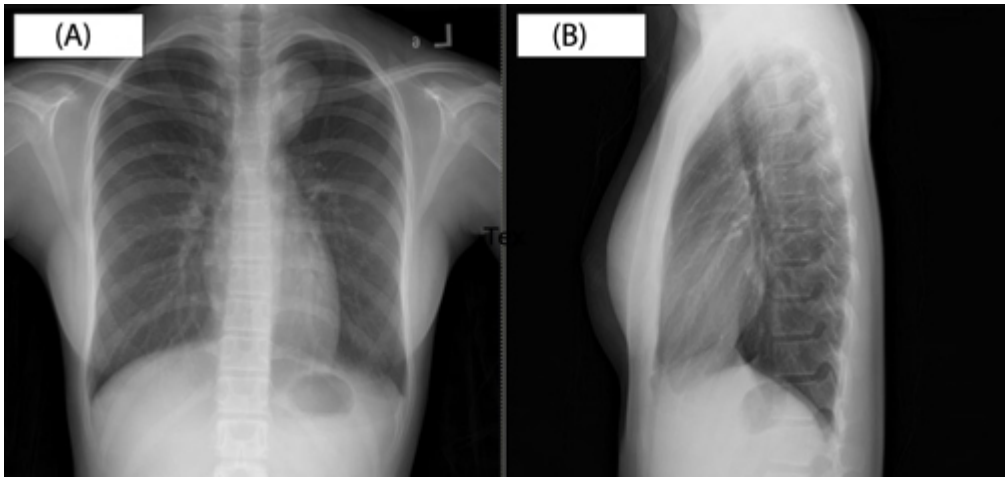

Figure 1.1 (A) A posteroanterior chest X-ray revealed a well-defined, lobulated soft tissue mass at the left paratracheal area. The mass measures 6.1 × 4.3 cm and causes a slight effect on the left lateral wall of the trachea. There is no rib notching, and the heart is normal in size and shape with no signs of left ventricular enlargement as might be seen in aortic coarctation. (B) A lateral chest X-ray revealed a single, superior mediastinal mass.⏎

QUESTION 1: *What are your differential diagnoses?*

The International Thymic Malignancy Interest Group (ITMIG) categorizes mediastinal masses into three compartments using primarily CT imaging: prevascular (anterior), visceral (middle), and paravertebral (posterior) (Figure 1.2). This classification scheme enhances the description of mediastinal abnormalities and generates potential differential diagnoses.[1,2]

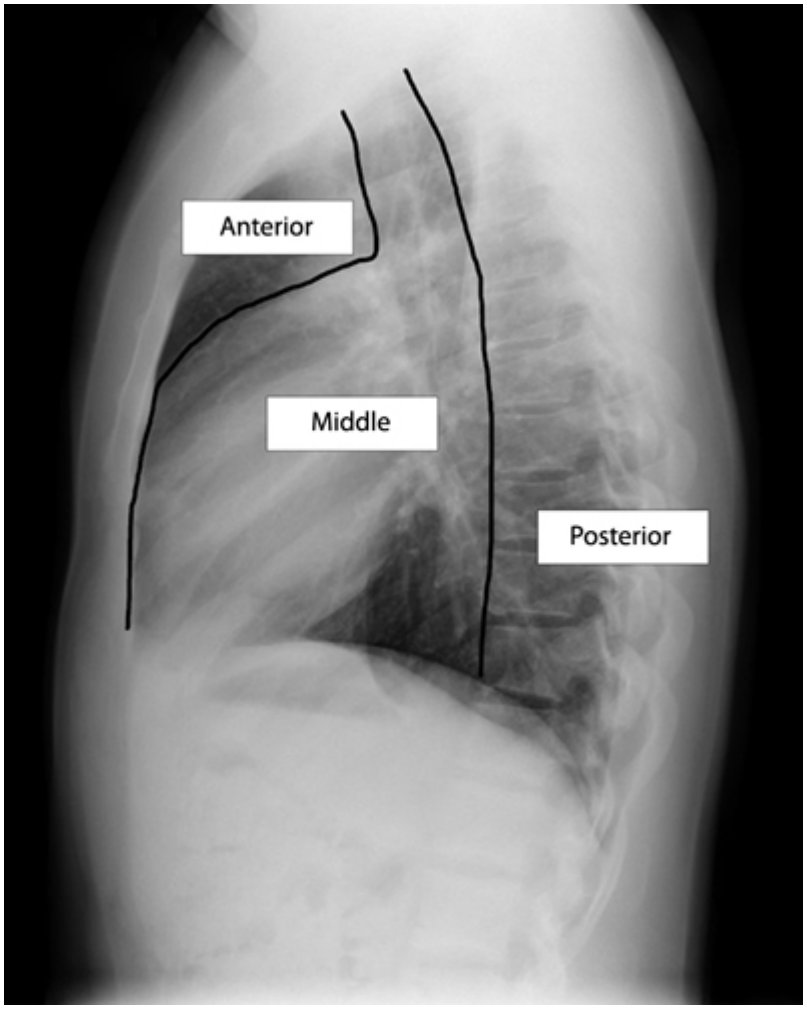

Figure 1.2 A normal lateral chest X-ray illustrating each mediastinal compartment.⏎

The paravertebral (posterior) compartment's boundaries are defined as follows: superiorly, by the thoracic inlet; inferiorly, by the diaphragm; anteriorly, by the posterior boundaries of the visceral compartment; and posterolaterally, by a vertical line along the posterior margin of the chest wall at the lateral aspect of the transverse processes.[2] This compartment contains the descending thoracic aorta, oesophagus, azygos and hemiazygos veins, thoracic duct, lymph nodes, adipose tissues, vagus and splanchnic nerves, and autonomic ganglia.[3] However, this compartmentalization can be less useful when a lesion is positioned as superiorly as the one presented.

Some masses may not cause symptoms and are detected incidentally, while symptomatic masses are more commonly associated with malignancies. Symptoms linked to masses vary, ranging from common respiratory symptoms like cough, dyspnoea, palpable mass, and dysphagia to neurological symptoms, which may result from spinal cord or nerve root compression. In more severe cases with vascular compression, superior vena cava syndrome may occur.[3]

Paravertebral or posterior mediastinal masses account for 30%–40% of all paediatric mediastinal masses. Among these, 85%–90% are of neurogenic origin.[2] The approach primarily focuses on mass composition due to the limited structures originating in the paravertebral compartment. Soft-tissue lesions in this area include neurogenic neoplasms and extramedullary haematopoiesis. Neurogenic neoplasms typically appear as smooth, round masses on CT and are mostly benign. Extramedullary haematopoiesis usually enhances after intravenous contrast administration due to the high vascularity. Examples of neurogenic neoplasms include sympathetic ganglion tumours, peripheral nerve sheath neoplasms, or neuroendocrine neoplasms.[2] Cystic lesions in this compartment encompass intrathoracic meningoceles, mediastinal or paraspinal abscesses, and pancreatic pseudocysts. Aortic coarctation can result in the typical ‘Figure 1.3 sign’ appearance and if severe and long standing enough can result in rib notching as well as signs of left ventricular enlargement. Rarer vascular malformations or aneurysms should also be included in the differential diagnoses, particularly in the more superior mediastinum.

QUESTION 2: *What investigations would you do next?*

It is important to carefully evaluate chest radiography when assessing mediastinal masses. The lateral chest radiograph plays a valuable role in identifying lesions that might not be apparent on the posteroanterior radiograph and in locating them within one of the previously described compartments. Lesions in the retrosternal space or overlying the upper thoracic spine may not be apparent on posteroanterior radiographs. Nevertheless, CT and MRI are the preferred imaging techniques for a more in-depth assessment of the characteristics of the mass and its interactions

with adjacent structures. They help to narrow the list of differential diagnoses.

A lateral chest X-ray of this case revealed a single superior mediastinal mass located relatively posteriorly (Figure 1.1B). Subsequent contrast-enhanced CT imaging showed a focal abnormality with a lobulated contour, clearly vascular, measuring 3.0 × 2.2 cm, probably originating from the left superolateral aspect of the aortic isthmus, indicating a likely saccular thoracic aortic aneurysm. An associated tortuous course of the corresponding aortic segment was seen. Additionally, no signs of thickened walls of the aorta, perilesional fat stranding, signs of vasculitis, or obvious mediastinal haematoma were reported (Figure 1.3).

A thoracic aortic aneurysm (TAA) is a serious health concern, as evidenced by nearly 10,000 related fatalities in the US in 2019. More than 95% of individuals with TAAs show no symptoms until the condition progresses to dissection or rupture, making early identification challenging. The general definition of an aortic aneurysm is an enlargement of an artery to a size that is at least 1.5 times greater than its anticipated normal diameter. However, there are exceptions to this definition, especially regarding aneurysms of the ascending thoracic aorta and the aortic root.[4, 5, 6] To be classified as a true aneurysm, all three layers of the aorta—the inner tunica intima, the central media, and the outermost adventitia—must be involved. Approximately 60% of TAAs affect the aortic root or ascending aorta, with the remaining cases impacting the descending aorta.[5] In our case, the abnormality affected the distal arch to descending aorta, exactly where a coarctation or ductal aneurysm would be found. Regarding morphology, TAAs are categorized as fusiform and saccular, with the former being more common and characterized by symmetric dilatation, while the latter exhibits localized outpouching.[5],[7]

The electrocardiogram of this child showed a normal sinus rhythm and a heart rate of 76 bpm with no significant abnormalities. Subsequent transthoracic echocardiography (TTE) revealed a 3 cm aneurysm in the proximal descending thoracic aorta with normal cardiac anatomy. There was no family history of aortic diseases, connective tissue disorders, or

sudden cardiac deaths. Additionally, laboratory results indicated normal findings for the complete blood count, serum electrolytes, and liver and kidney function.

QUESTION 3: *What is the cause of a thoracic aortic aneurysm?*

The commonly suggested pathogenesis for a thoracic aortic aneurysm involves a condition known as cystic medial necrosis, which is a degenerative process characterized by the breakdown of elastin fibres and smooth muscle cells within the tunica media.[5,8] Consequently, the aorta becomes dilated, increasing the risk of complications. Risk factors for TAA include age, hypertension, hypercholesterolaemia, smoking, and heritable genetic variants. The disease may follow an autosomal dominant inheritance pattern, with about 1 in 5 patients with TAA or dissection reporting a positive familial background of TAA.[5,6] However, in this case, there is no family history of the disease, and the patient does not exhibit any sign of genetic diseases related to TAA, including Marfan syndrome, Loyes–Dietz syndrome, Ehlers–Danlos syndrome, Turner syndrome, or other risk factors[5] (Box 1.1). The position would also be consistent with a ductal aneurysm. Other diagnostic considerations would include syphilis and a mycotic aneurysm, but there was nothing to suggest these diagnoses.

Box 1.1: Genetic syndromes associated with TAA

- *Marfan syndrome (FBN1)*: Ectopia lentis, dural ectasia, overgrowth of long bones
- *Loyes–Dietz syndrome (TGFBR1/TGFBR2)*: Bifid uvula, cleft palate, arterial tortuosity, hypertelorism, craniosynostosis, skeletal features, aneurysms/dissections of other arteries
- *Ehlers–Danlos syndrome (COL3A1)*: Thin, translucent skin, gastrointestinal rupture, rupture of the gravid uterus, rupture of medium and large arteries
- *Turner syndrome (45, X karyotype)*: Short stature, primary amenorrhoea, bicuspid aortic valve, aortic coarctation, webbed neck, locked set ears, low hairline, broad chest

- *Familial TAA*
- *TGFBR2*: Thin translucent skin, arterial tortuosity, arterial aneurysms
- *MYH11*: Patent ductus arteriosus
- *ACTA2*: Livedo reticularis**,** iris flocculi, patent ductus arteriosus, bicuspid aortic valve
- *MYLK*

Larger aneurysms grow faster than smaller ones, with the growth rate of the thoracic aorta being relatively slow, progressing at an approximate rate of 0.19 cm per year. As the diameter of TAAs reaches or exceeds 4.5 cm, a significant escalation in the risk of dissection is observed, emphasizing the importance of monitoring and timely intervention to mitigate the associated risk and mortality.[4]

QUESTION 4: *What is your plan for treatment?*

TAAs are most often diagnosed incidentally, given the absence of general population screening recommendations. Nonetheless, guidelines suggest screening for first-degree relatives of individuals with a history of TAA or aortic dissection. Screening involves both aortic imaging and genetic testing. The 2022 American College of Cardiology (ACC) and American Heart Association (AHA) "Guideline for the Diagnosis and Management of Aortic Disease" recommends follow-up imaging with TTE, computed tomography (CT), or magnetic resonance imaging (MRI) within 6 to 12 months after the time of diagnosis to determine the rate of aortic enlargement. If stable, surveillance imaging every 6 to 24 months is reasonable.[9]

The goal of the treatment of the TAA is to minimize the risk of adverse aortic complications. The approach to management depends on the underlying cause and the size of the aneurysm at the time of diagnosis. Non-surgical management includes medical therapy and risk factor modification. Healthy lifestyle modification such as smoking cessation and

blood pressure control benefits both overall cardiovascular health and the prognosis of aortic aneurysms.[4] For TAA patients with a systolic blood pressure (SBP) of ≥130 mmHg or a diastolic blood pressure (DBP) ≥80 mmHg, the use of antihypertensive medications is beneficial. Achieving blood pressure goal typically involves using beta-blockers. Adjunctive angiotensin receptor blockers (ARBs) are considered if there are no contraindications.[4] For this patient, we advised the avoidance of environmental smoke and pollution. As this patient had normal blood pressure, no antihypertensive treatment was prescribed.

Deciding when to have surgery and which surgical approach to take for TAA can be complex. Both clinicians and patients must consider their perspectives in the decision-making process.[10] The risks of future aortic complications compared to those of surgery must be evaluated. According to Class I recommendations from the 2022 ACC/AHA guideline, surgery for TAA is recommended for patients with aneurysm-related symptoms, regardless of aneurysm size. In adults, surgery is recommended for asymptomatic patients with an aneurysm diameter of ≥5.5 cm. Surgery is also recommended for asymptomatic patients with an aneurysm diameter of <5.5 cm if the aneurysm grows by ≥0.3 cm/year in 2 consecutive years or by ≥0.5 cm in one year. Patients with Marfan syndrome, who are at higher risk of aortic dissection, may undergo surgery if their aneurysm diameter is ≥5.0 cm.[4] Size cut-offs for surgical intervention are considerably less well established in paediatric practice.

Surgical options for treating descending TAA include endovascular and open repair. For patients without Marfan syndrome, Loeys–Dietz syndrome, or vascular Ehlers–Danlos syndrome, and whose aneurysms meet intervention criteria suitable for endovascular repair, thoracic endovascular aortic repair (TEVAR) is the recommended choice over open surgery. However, open surgery may be a reasonable option for individuals with a life expectancy of ≥10 years, especially in high-volume centres, due to limited long-term data on aortic-specific mortality rates in young patients post-TEVAR.[4]

A comprehensive approach ensured the patient's understanding of the disease, treatment, and the need for surgery. Following shared decision-making, the patient and parents chose surgery due to concerns about possible rupture. The 3.2 cm saccular aneurysm was successfully removed with end-to-end anastomosis through a limited left axillary thoracotomy, and tissue samples were sent for pathological examination. Intraoperative findings revealed a 3 cm saccular aneurysm in the proximal descending thoracic aorta and moderate adhesion without pleural effusion in the left thoracic cavity. A left-sided drainage tube was inserted and retained for 7 days to remove residual blood or fluid.

On the second day after surgery, the patient developed a fever without specific symptoms related to any organ. After administering intravenous empirical piperacillin/tazobactam, tests were conducted to investigate the possible source of infection, which showed no growth in blood, sputum, or urine cultures. The fever subsided within the next day, and antibiotic treatment was continued for a total of 7 days.

A postoperative echocardiogram on day 3 confirmed that the left ventricular function was normal, with no signs of valve stenosis or regurgitation. The pathology of the excised aortic aneurysm included myointimal thickening, myxoid change, calcifications, and medial destruction. These findings definitively indicate the presence of a true thoracic aortic aneurysm without any clear underlying causes.

QUESTION 5: *What is your plan for follow-up?*

Post-surgery surveillance recommendations differ between endovascular and open repair. Patients who have undergone TEVAR should undergo CT surveillance at 1 and 12 months, then annually if stable. MRI is a good alternative for patients concerned about long-term radiation exposure or those allergic to contrast. For patients undergoing open repair, it is reasonable to have CT or MRI surveillance in the first year after surgery, then every 5 years.[4]

KEY LEARNING POINTS

Our case highlights the clinical significance of TAAs. They are often diagnosed incidentally, with few symptoms, yet carry a high mortality rate. Abnormal findings on a screening chest radiograph should prompt further evaluation, starting with a lateral chest radiograph. This imaging modality provides detailed anatomical and morphological insights into the lesion. Subsequent CT or MRI scans are preferred to assess the lesion and its interactions with surrounding organs comprehensively. Shared decision-making is crucial, ensuring an optimal approach tailored to both timing and preferred treatment strategies for TAAs.

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CHAPTER 2 THE BOY WHO COUGHS WHEN VOMITING AND VOMITS WHEN COUGHING

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INTRODUCTION

All children cough, and most children do not have any underlying pathology. The clinical challenge is to determine which coughing child requires detailed investigation to rule out significant pathology. A 6-year-old boy presented with a 9-month history of chronic wet cough. This case illustrates the approach and evaluation for chronic cough in children, and the variety of treatment strategies that may be required.

CASE PRESENTATION

The patient is a 6-year-old boy of Chinese ancestry, with a past medical history of allergic rhinitis treated with intranasal steroids, and whose developmental milestones had been attained appropriately. He was referred to the respiratory outpatient clinic for chronic wet cough which had persisted for the past 9 months. The cough was worse at night but also occurred during the day. It appeared to worsen with exertion and with episodes of respiratory infection. Previously, he had been treated with two separate courses of oral co-amoxiclav (clavulanic acid; Augmentin) each of 7 days duration by a general practitioner. He had also been started on inhaled fluticasone 100 mcg/day by the general paediatrician for the past 2 months with slight improvement in cough, but he still experienced daily

including nocturnal wet cough. He did not have any previous wheezing episodes. His mother had a history of allergic rhinitis and atopic dermatitis.

Respiratory examination was normal with clear lung fields. There was no digital clubbing, Harrison's sulci, or chest wall deformities. Voluntary cough was wet. Neurological examination was normal and he was not dysmorphic. He was growing along the 25th centile for weight and height. Serum eosinophils were not elevated, and a chest X-ray (CXR) done previously was normal. He was sensitised to house dust mite allergen on skin prick test.

QUESTION 1: *What are the possible causes of chronic cough in this patient?*

Chronic cough in children is defined as the presence of daily cough for more than 4 weeks. Although children with post-viral or "nonspecific" cough may sometimes have cough for weeks following a viral or bacterial respiratory tract infection, the long duration of this child's cough points towards a "specific" cough, i.e., one that is associated with underlying pathology. Furthermore, the child presented with a wet phlegmy cough, which in itself is considered a red flag with a positive likelihood ratio of 26.2 (95% confidence interval: 3.8–181.5) for specific cough requiring treatment or reflecting underlying pathology. It is always useful for the clinician to hear the cough rather than rely on descriptions, either in person (including a voluntary cough if age-appropriate) or via audio recordings taken by the parents, to accurately characterise the nature of the cough.

In general, wet cough is associated with airway infections such as protracted bacterial bronchitis (PBB), chronic suppurative lung disease (CSLD, which includes cystic fibrosis, primary ciliary dyskinesia, and bronchiectasis), recurrent aspiration, or structural airway anomalies. Dry cough is associated with post-viral cough and atopic conditions – asthma or allergic rhinitis. This child had chronic wet cough, so PBB is the most likely differential diagnosis. Although antibiotics are the empiric treatment for PBB, the suggested duration of treatment is 2 weeks or more rather than a 7-day course. Another possible diagnosis would be that of asthma, as

there is diurnal variability, exercise-induced symptoms, sensitisation to house dust mite allergen, and a personal and family history of atopy. However, blood eosinophil count was not raised, and the symptoms persisted even after treatment with inhaled corticosteroids (ICS). Recurrent aspiration can be considered, especially if the child has a pre-existing neurological or neuromuscular condition. Other more serious pathologies such as bronchiectasis, structural airway anomalies (such as a congenital pulmonary airway malformation [CPAM] causing recurrent infections), immunodeficiency, primary ciliary dyskinesia, or cystic fibrosis should be considered if symptoms do not improve. However, in the absence of concerning symptoms (such as loss of weight, recurrent fevers, haemoptysis, or persistence of cough with adequate antibiotic treatment) and signs (such as growth failure, abnormal lung findings, chest wall deformities, digital clubbing, or situs inversus), and a normal chest X-ray, these are less likely.

The patient was treated empirically with a 2-week course of oral Augmentin for PBB. Although his cough became less phlegmy, he still continued coughing daily. As he had allergic sensitisation and a personal and family history of atopy, and there were symptoms suggesting reactive airway disease such as diurnal variability and exercise-induced symptoms, his dose of inhaled fluticasone was raised to 200 mcg/day. Despite these measures, on review 3 months later, his chronic wet cough had returned. Further history was obtained that he had experienced recurrent vomiting since around 3 years of age, and this exacerbation was accompanied by an increase in vomiting frequency, both prior to and following cough episodes. Chest X-ray was done which suggested peribronchial thickening and tram-track opacities in the right lower zone (Figure 2.1).

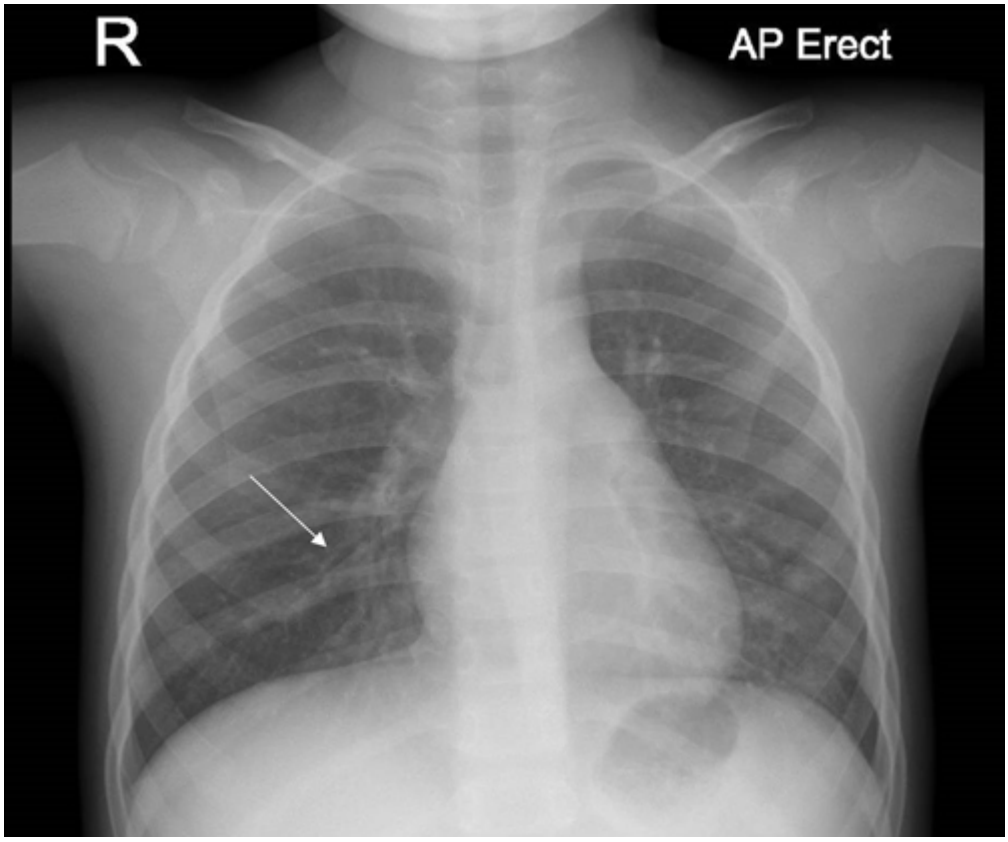

Figure 2.1 CXR showing peribronchial thickening and tram-track opacities in the right lower zone (arrow) and a hyperinflated right lung base with reduced lung markings compared to the left and widening of the right costophrenic angle.

QUESTION 2: *How should the patient be further investigated?*

For children with chronic cough, the recommended initial investigations are a chest X-ray and, if age appropriate, spirometry. However, this patient was not able to perform spirometry as he could not grasp the technique. As there is a chronic productive cough, a cough swab or sputum culture to look for infection should also be considered.

PBB has been defined as a chronic wet or productive cough with no symptoms or signs to suggest another cause and that resolves following 2 weeks of an appropriate oral antibiotic, typically Augmentin. In some

patients, the cough resolves only after 4 weeks of oral antibiotics (PBB-extended). However, if the cough persists after 4 weeks of appropriate antibiotics, further investigation with flexible bronchoscopy including quantitative cultures and sensitivities, and possibly chest CT, should be performed. One study found that 83.8% of children with persistent wet cough not responding to at least 4 weeks of antibiotics had bronchiectasis, compared with 25% of those whose cough resolved after antibiotics.

Although this patient had only received 2 weeks of oral Augmentin, he had received two shorter courses of the same antibiotic earlier in the disease course. More importantly, there were tram-track opacities on chest X-ray which can be seen in patients with bronchiectasis, and there was a history of recurrent vomiting which can contribute to recurrent aspiration and chronic airway infection. Hence, he was planned for further investigation with flexible bronchoscopy and bronchoalveolar lavage (BAL). A diagnostic and therapeutic trial of low- to medium-dose ICS (at least 200 mcg/day fluticasone or equivalent) should be sufficient to show improvement in most children with asthma. Supportive investigations, such as a full blood count for serum eosinophils, serum IgE, skin prick testing to common environmental allergens, and chest X-ray, should be performed, preferably before starting ICS or increasing the dose further.

The patient was admitted for further evaluation. Serum IgE was raised (264 IU/mL) and serum eosinophils were elevated (740×10^6/L). Lymphocyte subsets and serum IgG/A/M, done as a screen for underlying immunodeficiency, were normal. Flexible bronchoscopy was performed, and the airways were structurally normal with loose mucopurulent secretions seen in both lower lobes. Lower respiratory cultures grew normal flora. Polymerase chain reaction (PCR) testing from BAL fluid was positive for adenovirus and mycoplasma. He was treated with intravenous ceftriaxone followed by oral Augmentin for a total of 3 weeks, and oral clarithromycin for 2 weeks. Cytology from the BAL fluid was positive for lipid-laden macrophages.

QUESTION 3: *How does the presence of lipid-laden macrophages affect the differential diagnosis?*

Lipid-laden macrophages in the BAL fluid are thought to be an indicator of pulmonary aspiration or gastroesophageal reflux, as lipid-containing food or gastric contents entering the lung should be phagocytosed by alveolar macrophages. However, other endogenous processes, such as the breakdown of surfactant and other lipids, can also cause phagocytosis of lipids by macrophages, and lipid-laden macrophages are a nonspecific finding. There is also evidence that lipid-laden macrophages may instead reflect parenchymal inflammation and correlate with airway neutrophilia, and one paediatric study found that the mean lipid-laden macrophage index (LLMI) was comparable between patients with recurrent aspiration (mean LLMI 52.5) and other diagnoses such as asthma, cystic fibrosis, recurrent pneumonia, and the immunocompromised child (LLMI 48.5, 51.9, 63.9, and 77.2, respectively). To further complicate matters, there is no standardised reporting criteria for the frequency of lipid-laden macrophages, and no standardised cutoff value for quantitative markers such as the LLMI that would indicate aspiration; it has been variously defined as 85–165/400 over multiple studies. Furthermore, studies have shown significant intra- and inter-rater variability among pathologists when calculating the LLMI. Therefore, the presence of lipid-laden macrophages or the LLMI (if used) is not a specific or sensitive marker for aspiration. However, it may be used as a qualitative indicator together with relevant clinical symptoms to suggest that recurrent aspiration may be taking place.

In this patient with a history of recurrent vomiting associated with an increase in the frequency of productive cough, recurrent aspiration should be excluded. Conditions that may cause or exacerbate aspiration, such as oropharyngeal dysphagia, gastroesophageal reflux (GER), or structural abnormalities such as laryngeal cleft or H-type tracheoesophageal fistula, should be ruled out.

The patient was referred to the gastroenterologist and otolaryngologist. A rigid laryngobronchoscopy showed a grade 1 laryngeal cleft and no tracheoesophageal fistula, and the laryngeal cleft was surgically repaired. Oesophagogastroduodenoscopy (OGD) showed normal upper endoscopy without hiatal hernia. He was empirically started on oral omeprazole for GER. He was also referred to a speech therapist. Further history was

obtained that he tends to eat large portions very quickly – he was able to complete an adult-sized meal in 10 minutes! Videofluoroscopic Swallow Study (VFSS) was done which showed mild oropharyngeal dysphagia (Figure 2.2). He was advised to use compensatory strategies such as eating more slowly and in smaller boluses, water flushes with solids, and a neutral or chin tuck positioning when eating.

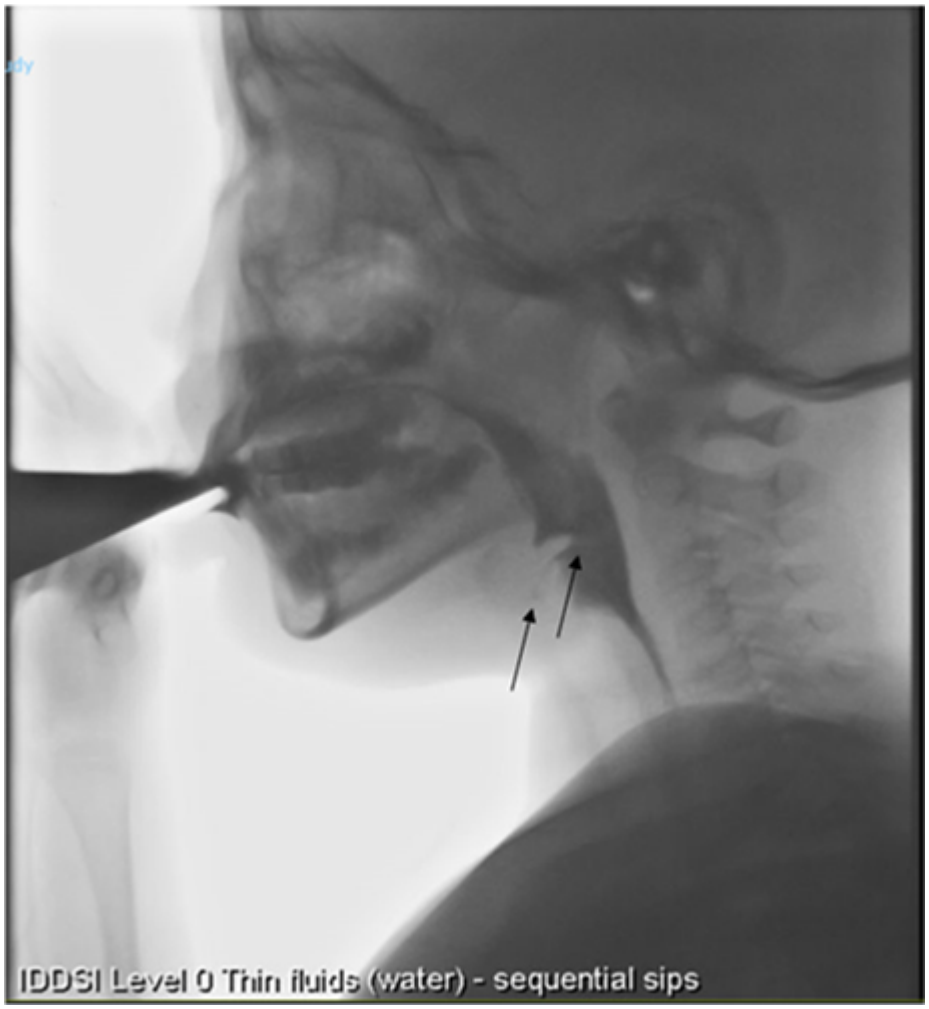

Figure 2.2 VFSS with penetration of fluid into the laryngeal vestibule, shown by contrast lining the underside of the epiglottis all the way from the tip to the base (arrows). However, there is no contrast demonstrated on or below the vocal cords to confirm frank aspiration.⏎

A CT thorax was done 6 weeks after the initial bronchoscopy and 2 weeks after the laryngeal cleft repair. It was normal with no features of bronchiectasis (Figure 2.3) and no persistence of the overinflation demonstrated on the CXR. Post-repair of the laryngeal cleft and after following the compensatory strategies for oropharyngeal dysphagia, his cough significantly improved, with only an occasional dry cough. The frequency of his vomiting also improved. He also gained weight up to the 75th centile for his age. As his symptoms had improved, his ICS dose was gradually weaned down over the next 7 months and eventually discontinued. However, 1 month after discontinuing ICS, his cough returned; he now complained of daily nocturnal cough as well as cough with exertion. At this review, he was able to perform his first spirometry which showed significant bronchodilator reversibility in both large and small airways, supporting the diagnosis of asthma. He was restarted on ICS–LABA (fluticasone 200 mcg/day with salmeterol) and has remained well since with no recurrence of cough.

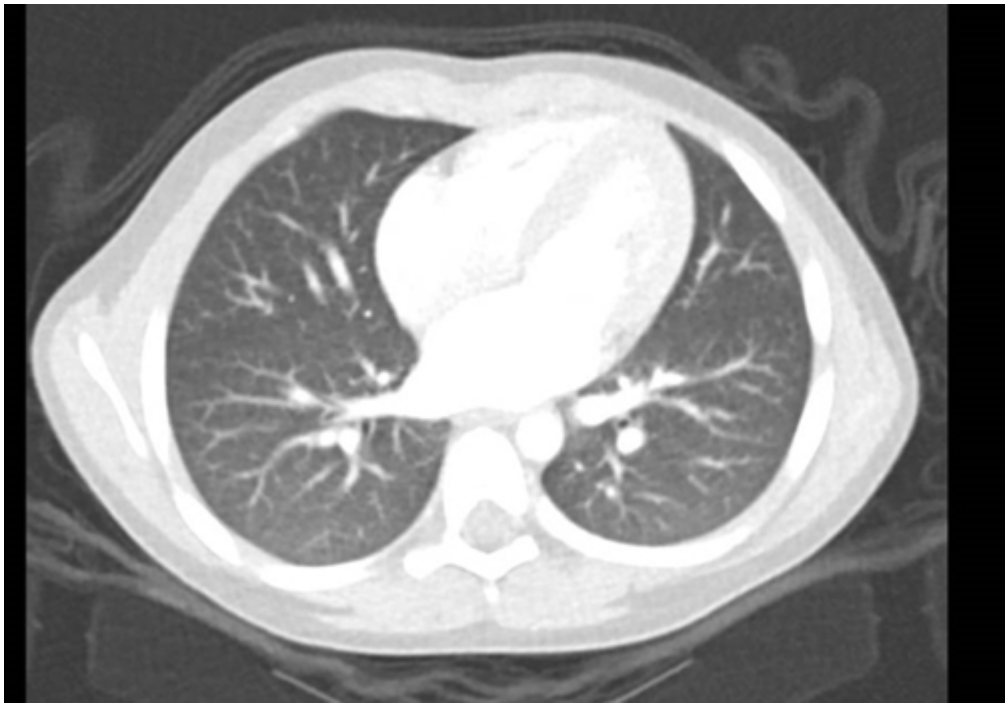

Figure 2.3 Normal CT thorax with no bronchiectasis, large airways thickening or mucus plugging, and no

mosaic attenuation to suggest persistence of the marked hyperinflation demonstrated on the CXR.⏎

QUESTION 4: *How can recurrent aspiration be managed, and how does it relate to asthma?*

Aspiration means that foreign material has entered the lower airways. Usually, this involves aspiration of swallowed food, oropharyngeal secretions, and/or gastric contents. It usually occurs in concert with an unsafe swallow and an inability to protect the airway, which is frequently seen in children with neurological or neuromuscular disorders that affect swallowing but can also be found in otherwise healthy children. A review of healthy children with dysphagia found that recurrent respiratory infection or pneumonia predicted swallowing difficulties on VFSS or fibreoptic endoscopic evaluation of swallow (FESS). Other comorbidities that should be excluded in neurologically normal children include GER and structural abnormalities such as laryngomalacia, laryngeal cleft, tracheoesophageal fistula, or cleft palate. This patient was treated with behaviour modification and surgical repair of the laryngeal cleft, which resulted in improvement of his symptoms. Other treatment strategies include modification of oral food or liquid consistency, treatment of reflux with proton pump inhibitors (PPIs), enteral feeding with or without fundoplication, and repair of specific laryngotracheal abnormalities.

Aspiration can cause bronchospasm and wheeze. However, the relationship between aspiration and asthma is less clear. GER is also more prevalent in asthma, and one of the proposed mechanisms by which GER worsens asthma is via the shared vagal innervation of the oesophagus and the bronchial tree, causing vagal stimulation of the oesophagus by acid to also result in bronchoconstriction. However, multiple trials targeting reflux in adults with asthma have failed to show a convincing benefit. Studies involving PPI treatment in children and infants with asthma did not show any improvement in asthma symptoms or lung function, even in those with a positive oesophageal pH study prior to treatment. Furthermore, a recent randomised controlled trial on the effect of lansoprazole in children with

poorly controlled asthma found increased adverse effects in the form of more frequent respiratory infections while on lansoprazole. Conversely, an older study reported that 91% of 235 children with severe asthma on oral steroids and symptomatic GER who were treated with a Nissen fundoplication noted subjective improvement in asthma symptoms by 2 weeks postoperatively, and many were weaned off their oral and inhaled steroids postoperatively. Although this can be considered for a selected group of severe asthma patients with medically refractory GER, this needs to be balanced against the significant risks inherent in surgical treatment. Currently, there is no evidence for the routine treatment of reflux in the management of children with asthma.

KEY LEARNING POINTS

The patient is a 6-year-old boy who presented with chronic wet cough contributed to by recurrent aspiration resulting from oropharyngeal dysphagia and a grade 1 laryngeal cleft, as well as asthma. The cough only resolved after all factors had been completely addressed: recurrent aspiration via surgical repair of the laryngeal cleft, compensatory strategies for oropharyngeal dysphagia, and antibiotics; and asthma via treatment with ICS.

The important learning points from this case are:

- The investigation and management of chronic cough and its multifactorial nature. Specifically, chronic ($\geq$4 weeks) wet cough is a red flag which mandates further investigation.
- The investigation and management of recurrent aspiration, and the importance of a multidisciplinary aerodigestive team in selected cases.
- The importance of a cautious diagnostic and therapeutic trial of inhaled corticosteroids in the diagnosis of patients who are unable to perform spirometry. These should be discontinued if there is no response.

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CHAPTER 3 A NEONATE WITH BLEEDING AND TRACHEOBRONCHIAL CALCIFICATIONS

Suha Rizik, Lea Bentur, Noa Mandel-Shorer, and Ronen Bar-Yoseph

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Herein, we present a newborn with diffuse neonatal bleeding. The differential diagnosis and initial management are discussed. Tracheobronchial calcification demonstrated on chest X-ray and family history were the clues to the diagnosis. Neonatal airway calcifications are rare in neonates. Aetiologies and possible physiological consequences of airway calcification are discussed. The link between neonatal bleeding and airway calcification in this rare disease is elucidated and follow-up is provided.

CASE PRESENTATION

A term female infant was delivered by caesarean section due to fetal bradycardia. Antenatal scans were unremarkable until late-onset polyhydramnios was detected, for which no further investigations were undertaken. Both parents were healthy. At birth, the infant's Apgar scores were 4 and 7 at 1 and 5 minutes, respectively, and she required several hours of positive pressure ventilation for respiratory distress. On physical examination, the only dysmorphic feature noted was a depressed nasal bridge. Birth measurements included a weight of 3.5 kg (approximately 60th percentile) and an occipitofrontal circumference of 36 cm (97th percentile).

At 7 hours of life, she developed sudden pallor, hypotension, tachypnoea, tachycardia, and diffuse mucocutaneous bleeding.

QUESTION 1: *What is the differential diagnosis for bleeding in a neonate, and what are the initial diagnostic and therapeutic steps?*

Bleeding in a neonate is a potentially life-threatening presentation with a wide range of underlying causes. In the first days of life, one must consider disorders related to vitamin K deficiency, such as the various forms of haemorrhagic disease of the newborn, which can be precipitated or worsened by maternal medications such as warfarin. Congenital coagulation factor deficiencies, such as haemophilia A or B, factor XIII deficiency, or combined deficiencies of vitamin K–dependent factors, should also be in the differential. Platelet-related disorders, including neonatal alloimmune thrombocytopenia or congenital amegakaryocytic thrombocytopenia, may present with mucocutaneous bleeding and petechiae. More acute systemic conditions like disseminated intravascular coagulation, secondary to sepsis, hypoxia, or severe birth asphyxia, can produce a similar presentation, as can metabolic or hepatic diseases that impair synthesis of clotting factors.

The initial evaluation should include a coagulation profile – prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen – as well as a complete blood count with platelet count and basic liver function tests. A sepsis workup is warranted if infection is suspected.

Management begins with stabilization of the infant's airway, breathing, and circulation, while correcting coagulopathy with vitamin K administration.

In cases of severe bleeding, transfusion of fresh frozen plasma, cryoprecipitate, and/or platelet concentrates may be necessary. Definitive therapy is directed at the underlying cause once identified.

CASE EVOLUTION

Initial laboratory evaluation demonstrated a markedly prolonged PT (no clot formation), an INR of 1.34 (reference range 0.9–1.30), and an aPTT of 142 seconds (reference range 27–38). Fibrinogen was slightly reduced at 158 mg/dL (reference range 200–400), while the platelet count was within normal limits at 389×10^9/L (reference range 150–400). A chest radiograph performed due to respiratory distress showed diffuse linear calcifications along the tracheobronchial wall (Figure 3.1).

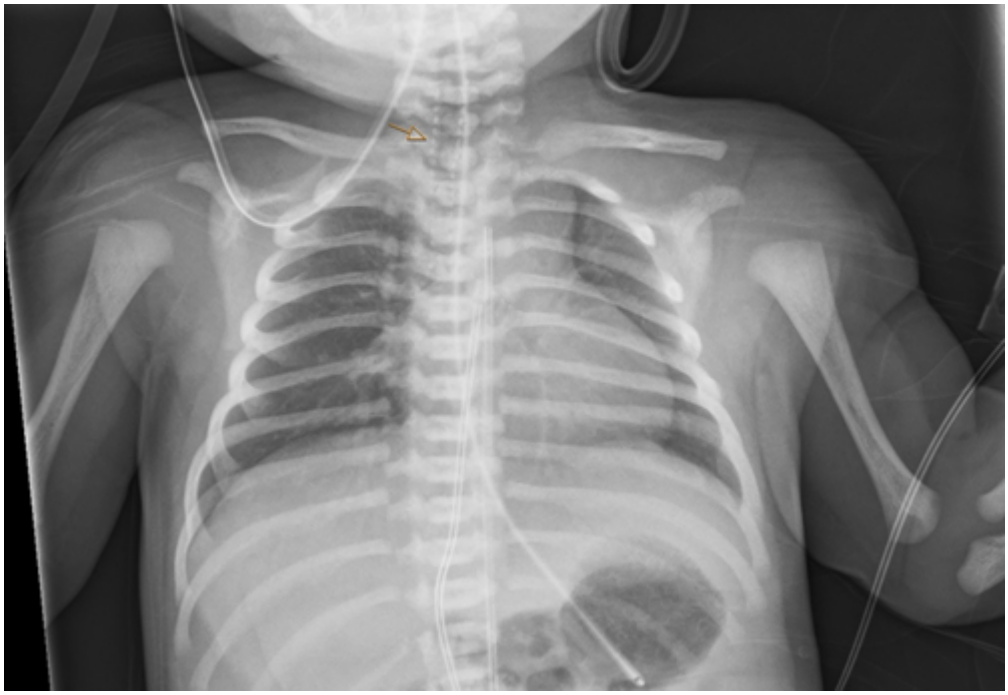

Figure 3.1 Frontal chest radiograph showing linear and nodular calcifications along the tracheal wall.

QUESTION 2: *What is the differential diagnosis of airway calcifications in infants?*

Airway calcifications in infancy are unusual and most often congenital. Keutel syndrome, caused by mutations in matrix Gla protein (MGP), is characterized by diffuse cartilage calcification and other skeletal abnormalities. Chondrodysplasia punctata, a heterogeneous group of disorders, may also present with airway calcification. Warfarin embryopathy can cause similar changes if the fetus is exposed in utero.

Metabolic and endocrine disorders such as hypervitaminosis D, chronic hypercalcaemia, and hypophosphatasia are less common causes. In older patients, airway calcification may follow chronic inflammation or be idiopathic, but in the neonatal period, an in utero process affecting cartilage mineralization is most likely.

QUESTION 3: *Is there a link between the two entities?*

Given the severity of the coagulopathy, the coexistence of airway calcifications suggested a unifying diagnosis affecting both coagulation and cartilage physiology. Conditions that disrupt the activation of vitamin K–dependent proteins can explain both. Gamma-glutamyl carboxylase (GGCX) deficiency and vitamin K epoxide reductase complex deficiency (VKORC1 mutations) are foremost among these, as both impair the gamma-carboxylation process needed for the function of coagulation factors and MGP. In this case, family history was revealing: an older relative had been diagnosed with GGCX deficiency. Genetic testing confirmed the presence of a homozygous pathogenic mutation in the GGCX gene in the newborn.

QUESTION 4: *Are there any consequences of airway calcifications? How can you evaluate physiological significance?*

Airway calcifications are common in adults; usually, no functional impairment is noticed. However, when it is extensive and associated with cartilage abnormality such as Keutel syndrome and chondrodysplasia punctata, physiological changes may occur.

In theory, mineralization of the normally flexible tracheobronchial cartilage can reduce airway compliance, limiting its ability to change calibre with intrathoracic pressure dynamics. This rigidity may predispose to turbulent airflow, increasing the risk of chronic cough, wheezing, or stridor. In severe cases, fixed narrowing of the airway can lead to obstructive symptoms, particularly during respiratory infections when mucosal swelling further compromises the lumen.

Physiological evaluation of airway calcifications includes clinical symptoms, airway diameter by imaging (chest X-ray, CT, and bronchoscopy), and flow-volume curve in pulmonary function tests, which can demonstrate flattening of the curve. MRI is less useful because calcification is very difficult to see.

In infancy, direct experience with advanced non-invasive techniques such as forced oscillation technique (FOT) or multiple breath washout (MBW) has not been reported in patients with airway calcifications. Nevertheless, FOT has been successfully applied in infants with central airway obstruction and may have the potential to detect altered airway resistance or reactance in this context, whereas MBW is primarily a marker of small-airway ventilation inhomogeneity and is unlikely to add substantial information in large-airway calcification.

FOLLOW-UP

Over the first year of life, the patient experienced intermittent noisy breathing and recurrent upper respiratory infections. Workup included bronchoscopy, which showed an irregular tracheal shape with anterior cartilaginous bulging (Figure 3.2).

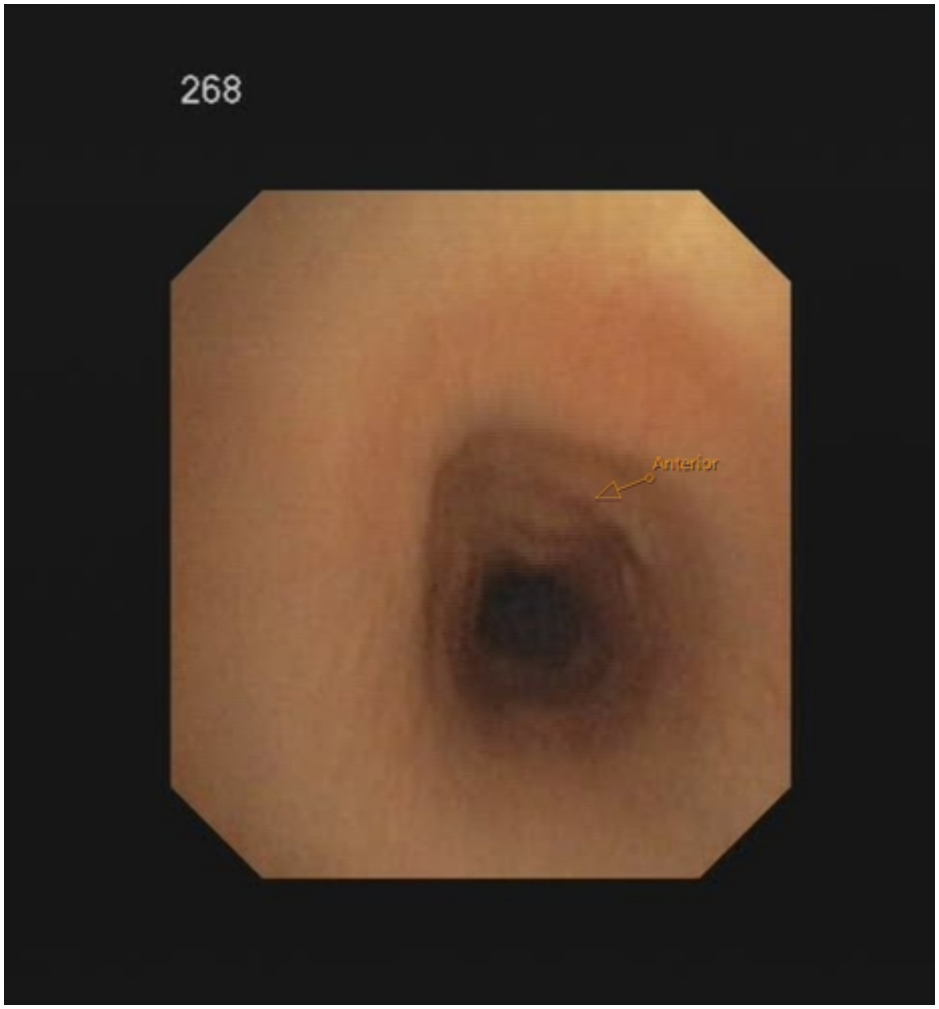

Figure 3.2 Bronchoscopy at 14 months revealed an irregular tracheal shape with anterior cartilaginous bulging.

Chest CT was done for further evaluation, which confirmed dense calcifications of the tracheal and bronchial cartilages (Figure 3.3).

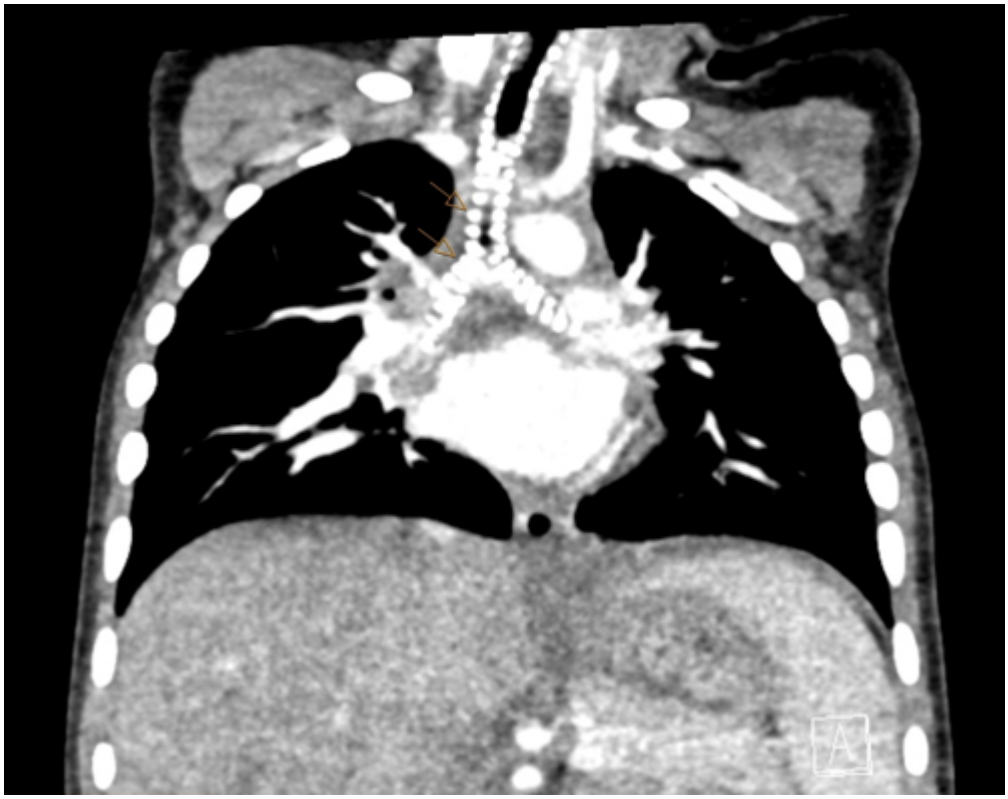

Figure 3.3 CT confirmed dense calcifications of the tracheal and bronchial cartilages.

The child was maintained on regular vitamin K supplementation, which normalized coagulation studies and prevented further bleeding episodes. During the first year of life, she received inhaled corticosteroids. It should be noted that there were no signs of eosinophilic inflammation. There was some improvement over time, but a cause-and-effect relationship between ICS treatment and improvement could not be established. Now, 4 years of age, her respiratory symptoms improved, with fewer episodes of noisy breathing and no episodes of respiratory distress requiring hospitalization. There were no further bleeding episodes, and she is thriving well.

Follow-up imaging (chest X-ray) demonstrated persistent but non-progressive calcifications. She continues to be monitored by a multidisciplinary team including paediatric pulmonology and haematology.

DISCUSSION

Gamma-glutamyl carboxylase is essential for activating vitamin K–dependent proteins by adding gamma-carboxyglutamic acid residues to specific glutamate residues. While coagulation factors II, VII, IX, and X require this modification to bind calcium and function in the clotting cascade, MGP – present in cartilage, vascular smooth muscle, and other tissues – also depends on gamma-carboxylation to inhibit calcification. In GGCX deficiency, non-functional MGP permits ectopic calcium deposition within cartilage, leading to airway calcification. Importantly, this process is not restricted to the tracheobronchial tree: articular cartilage is also affected, and patients can develop premature or progressive calcification of costal and peripheral joints, with radiographic findings resembling chondrocalcinosis. Clinically, this may manifest as joint stiffness**,** limited mobility**,** or early degenerative changes, reflecting the widespread role of MGP in preventing inappropriate mineralization of connective tissues.

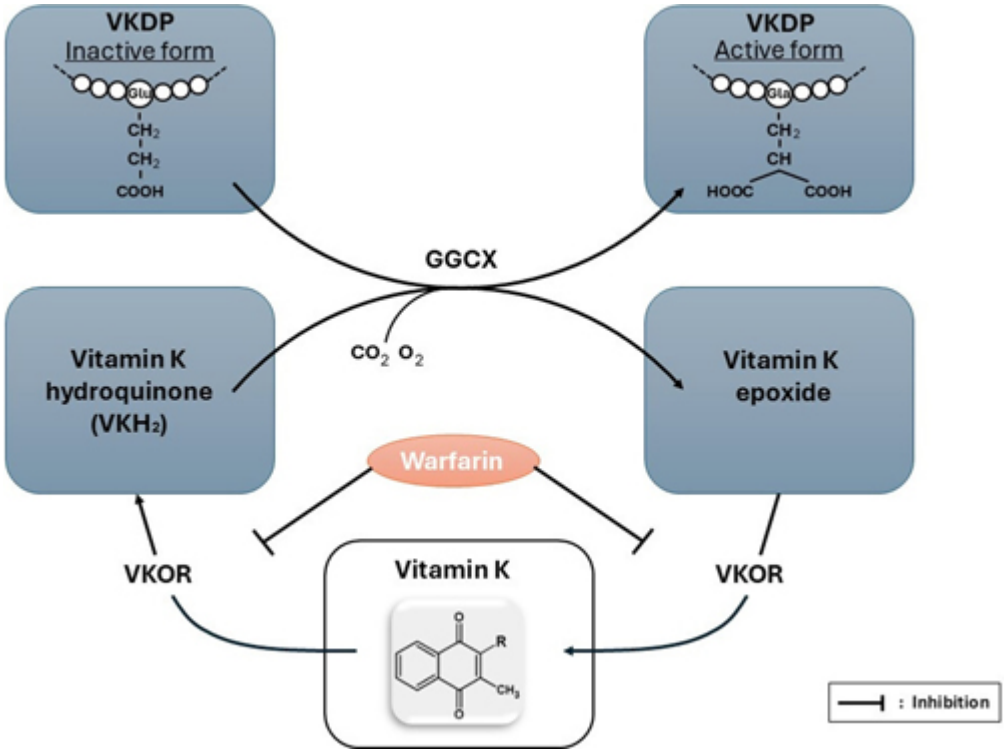

Figure 3.4 Vitamin K–dependent protein activation cascade. VKDP, vitamin K–dependent protein; GGCX, gamma-glutamyl carboxylase.

Adapted from Tsugawa and Shiraki (2020).

The physiologic implications in the respiratory system include potential airway stiffness, reduced compliance, and, in rare cases, fixed narrowing, although in many children calcifications remain stable or even regress over time.

KEY LEARNING POINTS

- GGCX deficiency is a rare but important cause of combined neonatal coagulopathy and cartilage calcification.
- Airway calcifications in infancy should prompt evaluation for congenital metabolic or genetic conditions.
- The pathophysiologic link lies in impaired gamma-carboxylation of both coagulation factors and MGP.
- Long-term management requires multidisciplinary follow-up, with attention to both haematologic stability and airway health.

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CHAPTER 4 A TALE OF TWO DIAGNOSES

Ciaran O'Toole and Siobhán B Carr

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INTRODUCTION

Having established an unequivocal cause for a respiratory presentation, it is easy to forget that there may be a second, associated diagnosis. Failure to remember this may lead to further morbidity as ongoing symptoms are wrongly attributed to the first (correct) diagnosis. We present a case in which neglect of this principle would have led to ongoing lung damage. The second learning point is that no screening test is 100% reliable, and false-negative screening tests are always possible.

HISTORY

A 6-month-old girl presented to a paediatric emergency department with cough, fast breathing and fever. Her parents reported her to usually have a wet cough which was worse in the morning on waking and after physical exertion. This had become more pronounced during the preceding 2 weeks, taking longer to clear and occurring more frequently throughout the day. She also had had 24 hours of fast breathing which was particularly worse when upset or on exertion. Temperatures measured at home on the day of admission ranged between 37.5°C and 38.5°C and prompted the presentation to hospital. She had had bowel motions three to five times a day, with no associated vomiting.

She was born vaginally at 37 weeks. She had opened her bowels at birth, and there was no recall at newborn screening. She was weighed at 2.3 kg

(9th centile), length was 46 cm (5th centile) and head circumference was 33 cm (25th centile). There was no relevant past medical history, and she was up to date with immunizations. She had been weaned onto soft foods alongside breast milk, and she occasionally coughed more after feeding.

On examination, she appeared pale with slightly sunken eyes. She had an increased work of breathing with tracheal tug, especially when upset. Coarse crackles were heard predominantly on the left side. Heart sounds were normal. Her pulse rate was 145 beats per minute, respiratory rate 55 breaths per minute, O_2 saturations 98% in room air, and temperature 38.4°C. Height on presentation to ED was 67 cm (0.4th to 2nd centile) and weight 6.2 kg (0.4th centile).

Due to the raised respiratory rate and abnormal examination findings, a chest X-ray was ordered by the attending team (Figure 4.1).

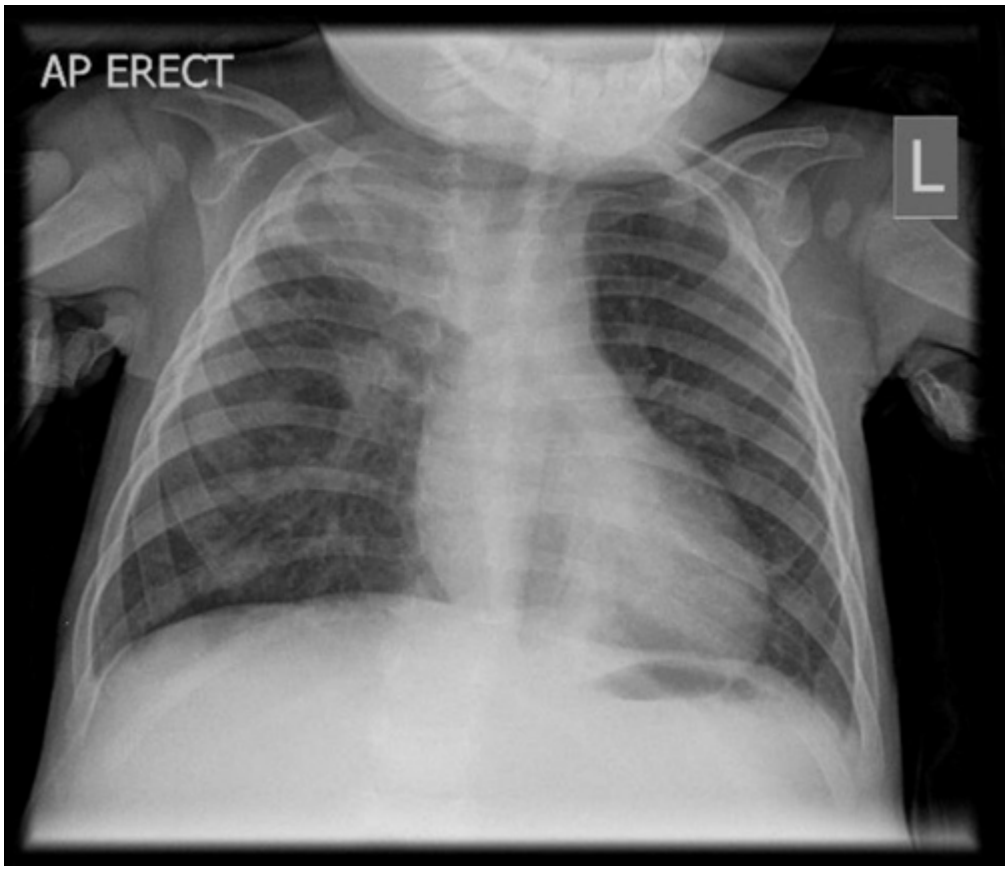

Figure 4.1 Chest X-ray obtained on admission.⏎

QUESTION 1: *What findings are demonstrated in this chest X-ray? What diagnosis are they consistent with?*

The predominant finding at this chest X-ray is the dense opacification and volume loss noted within the right upper lobe. There is also patchy consolidation and atelectasis within the left lower lobe medially, as shown by the obscuring of the diaphragmatic shadow behind the heart. Finally, there is peribronchial thickening in the perihilar regions and lower lobes bilaterally. In conjunction, this chest X-ray is suggestive of bilateral pneumonia, although it does not exclude other diagnoses.

QUESTION 2: *What are the possible differential diagnoses?*

The acute history of worsening cough and fevers described by parents, alongside examination findings of tachycardia, pallor and sunken eyes, raises the likelihood of a severe acute respiratory illness, such as bronchiolitis or pneumonia, with underlying dehydration. While likely responsible for the child's acute deterioration, the presence of bilateral pneumonia, decreasing growth centiles and prolonged history point towards an underlying chronic aetiology. Despite normal newborn screening, congenital respiratory conditions such as cystic fibrosis or primary ciliary dyskinesia should be considered due to the predominant respiratory symptoms, such as chronic cough. This could, however, also indicate an aspiration pathology. Causes include an unsafe swallow (most commonly neurological in origin), severe gastro-oesophageal reflux, or anatomic disorders such as laryngeal cleft or H-type fistula, although the absence of vomiting or feeding difficulties makes this less likely. An immunodeficiency disorder may present as an acute-on-chronic infection; however, a primary disorder such as severe combined immunodeficiency (SCID) would usually present with severe sepsis or skin changes, while the history does not convincingly offer any evidence for a secondary cause, such as HIV, medication-induced issues or prematurity of childhood.

QUESTION 3: *What are the first-line investigations that should be undertaken?*

First-line investigations requested by the paediatric emergency department are shown in Table 4.1. Full blood count shows raised white cells, predominantly due to lymphocytosis. Biochemistry demonstrated mild hyponatraemia, hypokalaemia, raised creatinine and CRP. Septic screen was sent, including blood cultures, pernasal swab for *Bordetella pertussis* and nasopharyngeal PCR analysis for respiratory viral panel, which was positive for rhinovirus.

Table 4.1 Baseline investigations requested in paediatric emergency department

Investigation	Result	Normal range
Full blood count		
White cell count	19.1×10^9/L	6–17
Neutrophils	5.7×10^9/L	1.5–8
Lymphocytes	10.1×10^9/L	3–9.5
Monocytes	2.4×10^9/L	0.5–1.5
Basophils	0.1×10^9/L	0–0.2
Biochemistry		
Sodium	134 mmol/L	135–145
Potassium	2.9 mmol/L	3.5–5.7
Urea	4.9 mmol/L	1.0–5.5
Creatinine	46 μmol/L	13–34
C-reactive protein	95 mg/L	<10
Vitamin D	36 nmol/L	<25 deficient 25–50 suboptimal >50 adequate
Respiratory viral panel	Rhinovirus positive on PCR	
Bordetella pertussis	Negative	
Blood culture	Negative	

She was admitted to the ward for acute management of her lower respiratory tract infection as well as further workup for underlying

pathology.

To screen for cystic fibrosis (CF), a sweat chloride was requested. This was found to be elevated at 94 mmol/L (<30 normal, 30–60 intermediate, 60+ elevated), raising the possibility of cystic fibrosis. Genetic analysis was homozygous for the CF disease-causing mutation F508del, while a faecal elastase was <15, indicating pancreatic insufficiency. Subsequent bronchoscopy revealed a normal trachea, some bronchomalacia, and thickened white secretions on the left side. Cytological analysis of bronchoalveolar lavage demonstrated neutrophilia, eosinophilia and increased mast cells. There was no bacterial growth on culture. Staining with Oil Red O showed some fat-laden macrophages. pH study was unremarkable, with no evidence of significant gastroesophageal reflux (Figure 4.2).

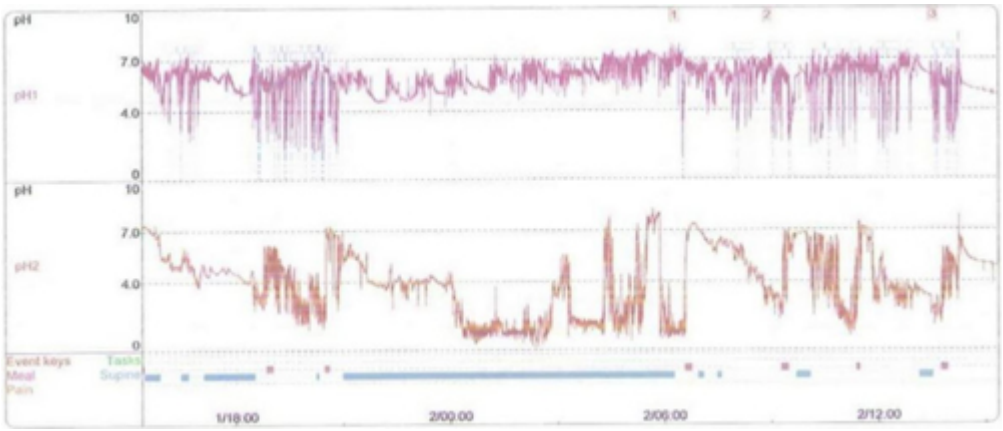

Figure 4.2 Twenty-four-hour pH monitoring study. Oesophageal pH < 4 for 5.2% of the study (upper trace). Gastric pH < 4 for 52.4% of the study (lower trace). No evidence of significant gastro-oesophageal reflux in this study.⏎

QUESTION 4: *What further management may be initiated for this child?*

Urgent referral to a cystic fibrosis specialist centre was indicated for initiation of CF-specific management and establishing long-term follow-up

within the outpatient setting. At the point of new diagnosis, this involves disease education with the patient and their family, review of initial investigations, and initiation of ongoing multidisciplinary team support. The healthcare professionals who would be involved in a child's care would include, but not be limited to, CF specialist clinician, nurse specialist, physiotherapist, dietitian, psychologist and pharmacist. Of particular importance in this case is the early initiation of regular chest physiotherapy and pancreatic enzyme replacement therapy, in addition to specialist microbiology input to guide appropriate antimicrobial agent selection.

Antibiotics were given intravenously for treatment of bilateral pneumonia; ceftazidime and tobramycin were chosen because of their coverage against *Pseudomonas aeruginosa.* Although there was no significant growth on bronchoscopy, bacteria can be missed depending on how many lobes are sampled. Oral flucloxacillin used as prophylaxis against *Staphylococcus aureus* was prescribed on discharge. In conjunction with chest physiotherapy, hypertonic saline 7% is used to clear thickened secretions and is often preceded by inhaled bronchodilator. Dornase alfa (RhDNase) is also given within this context, but its use is licensed only for children over the age of 6 years. Pancreatic enzyme replacement therapy (PERT in the form of Creon™) is indicated due to the poor weight gain secondary to pancreatic insufficiency. Homozygosity for F508del means this child would likely benefit from highly effective cystic fibrosis transmembrane conductance regulator therapy (CFTR modulators); however, most agents are unlicensed in infants and would be initiated later in childhood.

Following this management plan, her clinical state improved and she was discharged with arrangements for follow-up care to be provided at the regional CF centre. Her weight increased from the 2nd to 9th centile. However, her wet cough persisted, and her chest X-ray appearances were not improved on follow-up imaging at 3 months (Figure 4.3). She was readmitted for further investigation, where she was found to have positive upper airway cultures for *Pseudomonas aeruginosa*. She was initiated on long-term alternating courses of inhaled colistin and tobramycin.

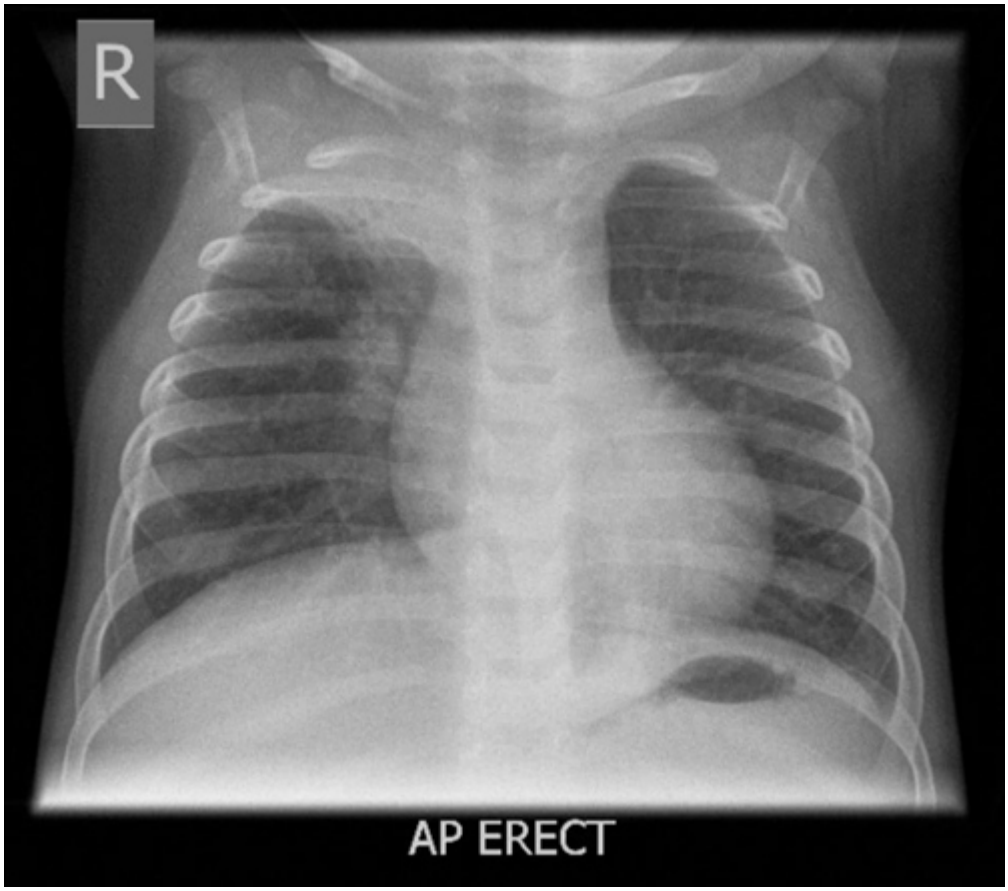

Figure 4.3 Repeat X-ray demonstrates worsening collapse and consolidation within the right lung apex. There is a further area of air space opacification within the right lower zone and the left retrocardiac region.⏎

Due to her mother reporting a worsening of her cough after drinking, videofluoroscopy was undertaken to evaluate her ability to safely swallow fluids of varying thickness in accordance with the International Dysphagia Diet Standardisation Initiative (IDDSI). Key images from this study at 20 months are shown in Figures 4.4–4.6.

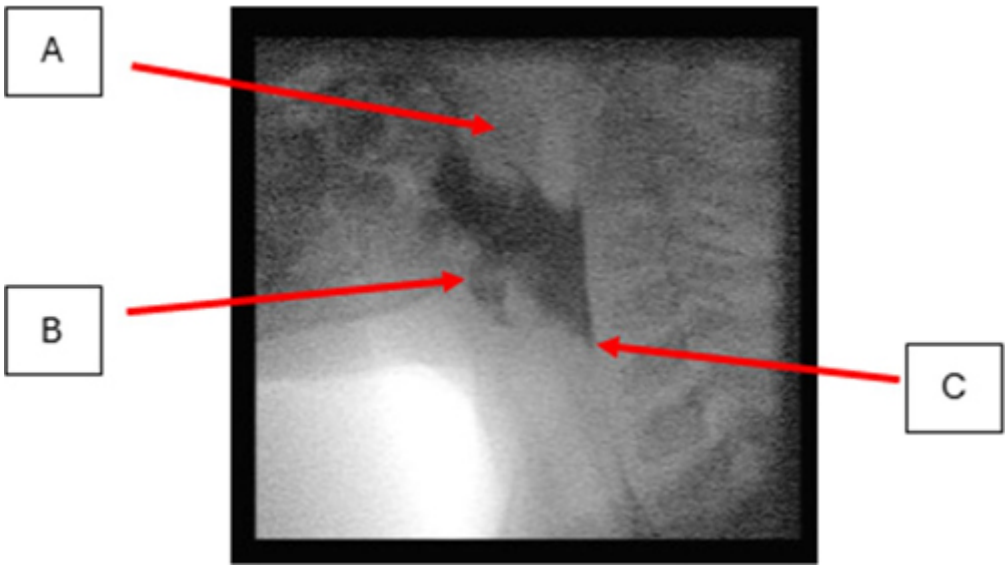

Figure 4.4 IDDSI fluid Level 1 “slightly thick.”

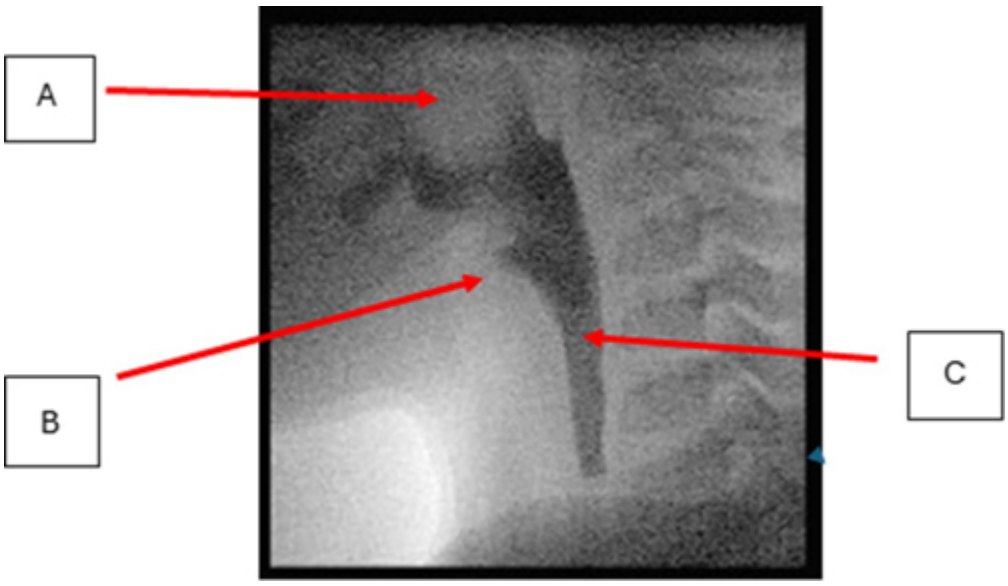

Figure 4.5 IDDSI fluid Level 2 “mildly thick fluids.”

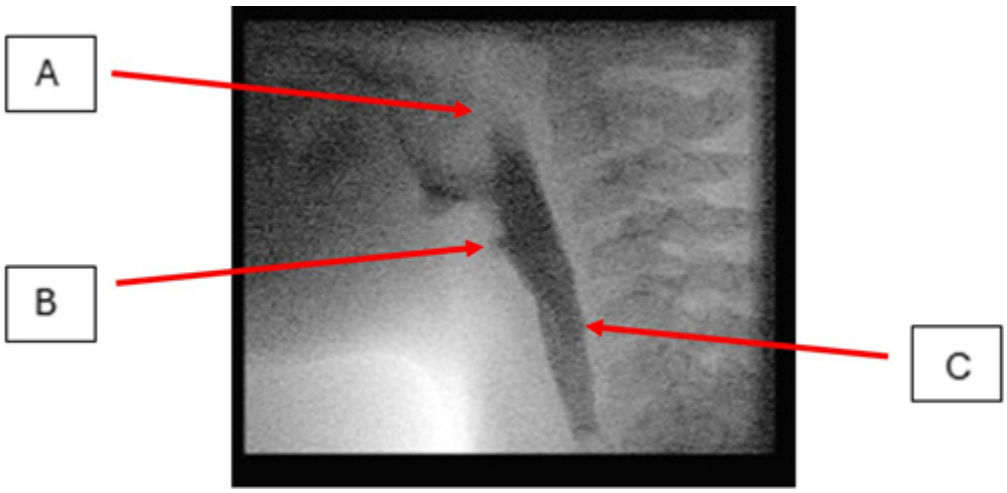

Figure 4.6 IDDSI fluid Level 3 "moderately thick fluids."⏎

QUESTION 5: *What are the key findings with these images? What is the diagnosis?*

Images from the Videofluoroscopic Swallow Study demonstrate a posterior pharyngeal filling defect present at all consistencies, labelled as "A." The defect is likely a result of enlarged palatine tonsillar tissue, a bilateral structure which is situated laterally within the oropharynx. Adenoid enlargement is less likely; this would be suggested by a forward displacement of the soft palate observed during the swallow study.

The filling defect described resulted in an obstruction of the bolus through the pharynx and, at thinner consistencies, an observed penetration of the bolus into the glottis (label "B"). It can be difficult to assess using still imaging alone whether the penetration represents deviation of contrast from the oesophagus ("C") into the valleculae (physiological depressions at the base of the tongue) or into the larynx (pathological entrance into the airway). Hence, full radiological assessment relies on the dynamic imaging of several swallows not reproduced here. In this case, the absence of contrast penetration below the level of the vocal cords excludes a true radiological definition of aspiration pathology.

Although extremely thick fluids (IDDSI Level 4) appeared to be safe on videofluoroscopy, it would not have been realistic for this child to drink the volume of fluids she required daily if only taking fluids with a high viscosity. Hence, a joint plan made in liaison with a speech and language therapist (SALT) to manage her aspiration risk included both thickened fluids and cooled boiled water, with regular monitoring to assess ongoing swallow safety and respiratory complications.

Following these measures, in addition to long-term antibiotic courses, her parents reported a significant improvement in her cough over the following months. She is now 3 years old and has been initiated on highly effective modulator therapy as part of her ongoing CF care, with height and weight centiles within the 25th–50th centile range.

DISCUSSION

There are two main learning points that can be taken from this case:

1. Never forget that no screening test is perfect, and that there is always a possibility of a false negative.
2. Never forget the possibility of a second diagnosis.

Starting with the former, screening for CF is usually carried out shortly after birth, as part of a panel of diseases screened for on a routine heel prick blood sample at 7–10 days of age. Specific testing protocol and cut-off levels vary across European countries, due to variations in resources available to the respective healthcare systems as well as differences in ethnic composition of populations. All protocols currently use immunoreactive trypsinogen (IRT) as the primary screening test with sweat chloride usually used to confirm a diagnosis. Heterozygous carriers of CF can have a raised IRT, as can babies who are born with a low birth weight; hence, IRT is not diagnostic in isolation. Further tiers of testing are used variably to achieve an acceptable PPV, such as CFTR mutation analysis of blood spot or second IRT testing on a repeat blood spot.

In England, IRT is initially measured twice using two discrete samples from the same blood spot (Figure 4.7). The main cut-off value is set at the 99.5th centile for IRT, which gives a sensitivity of 97% in the test's ability to detect CF. The preliminary cut-off value is set to 10 ng/mL below this level and is employed as a means of minimising the effect of volumetric variability of blood-spot discs and variability in IRT assays. Children with two levels above these absolute-value thresholds (48 μg/L and 58 μg/L for GSP assays; 55 μg/L and 65 μg/L for Auto Delfia assays) undergo genetic analysis for the four commonest CFTR variants in the UK population. If two variants are detected, the child is referred to a specialist centre for diagnostic confirmation, made using clinical assessment and sweat chloride. If only one variant is recognised, an expanded panel is used. If no further variants are detected using the expanded panel, a day 21 IRT is taken, with onward referral for CF diagnosis if this is raised. This unique aspect of the NHS England protocol acts to identify babies with CF who have particularly rare CFTR variants but is associated with a poor PPV (5%–10%).

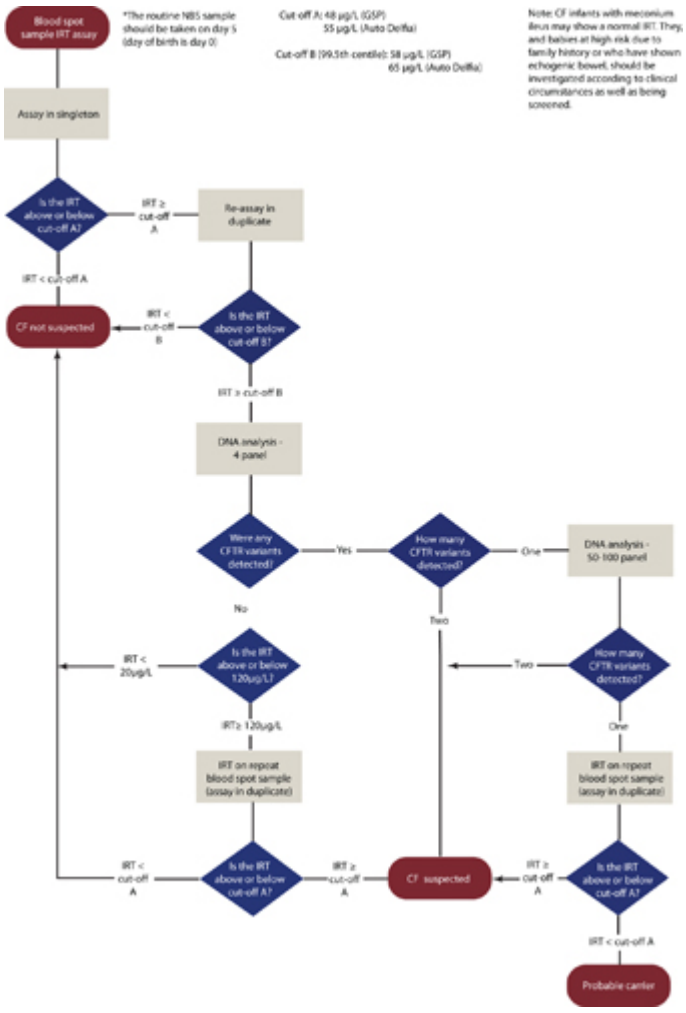

Figure 4.7 UK Cystic Fibrosis Screening algorithm. (Contains public sector information licensed under the Open Government Licence V3.0. Accessed via https://www.gov.uk/government/publications/cystic-fibrosis-screening-laboratory-handbook/cystic-fibrosis-screening-laboratory-handbook.)⏎

In the case of this child, her day 5 IRT was measured at 52 µg/L (with a local threshold used of 60 µg/L). In accordance with local protocol, she was not investigated further at birth, and a diagnosis of CF was deemed not likely. Retesting of the original sample 9 months later demonstrated a mean IRT of 27 µg/L, a reduction secondary to degradation of the sample from storage at room temperature, a result which is not inconsistent with the

original result. Causes for a biologic false-negative IRT include certain CFTR mutations, such as the R117H variant (with a poly-T intronic mutation) or meconium ileus. It is for this reason that babies identified as having echogenic bowel on antenatal testing or present with meconium during the first days of life should be investigated irrespective of IRT, although none of these were present in this child. An alternative explanation is seasonal and reagent variability, with one retrospective analysis of IRT results in 2007 finding these factors to influence the levels measured.

Second, this case highlights the need for diagnostic flexibility in the management of a persistently unwell child, even after a cause has been identified for the initial respiratory presentation. It is likely that the initial non-resolution of her pneumonia was attributed to a positive culture for *Pseudomonas aeruginosa*, given the association of chronic infection with loss of lung function, poor weight gain and lower quality of life. Treatment is difficult, due to the adaptation of the microorganism to the CF airway, which makes it less susceptible to eradication and shifts the aim of treatment to reducing bacterial density. Alternating nebulised colistin and tobramycin was used in this child, with the former recommended more commonly within UK CF guidelines due to the low risk of resistance even after prolonged use. Long-term azithromycin is also currently recommended for children over the age of 6 years, even in the absence of *Pseudomonas aeruginosa* infection, for its immune-modulatory and antimicrobial effects.

Despite this, a persistently unwell child requires reassessment and challenging of the management plan. The main key to uncovering the second diagnosis of an unsafe swallow in this case was the parental history of coughing that was worse after feeding.

A child with an unsafe swallow may be symptomatic on drinking thin fluids, with a cough, splutter or choking noted by parents, while other children are asymptomatic, termed “silent aspiration.” When this diagnosis is suspected, liaison with speech and language therapists is recommended, and a videofluoroscopy swallow assessment can be used to confirm the diagnosis. This child was identified as having a posterior pharyngeal wall

filling defect likely caused by enlarged tonsillar tissue, primarily disrupting the pharyngeal phase of swallowing and resulting in aspiration into the lung. Aspiration may be associated with repeated growth of coliform bacteria and fat-laden macrophages in bronchoalveolar lavage fluid – the latter of which was noted in this child at bronchoscopy. However, fat-laden macrophages are a very nonspecific finding. In addition to thickening fluids and pre-boiling drinking water, management strategies also include slowing down feeding and ensuring an upright position during drinking.

A further important differential for persistent airway inflammation in this context is gastro-oesophageal reflux disease (GERD). It is estimated that approximately half of infants with CF will have an abnormal dual probe 24-hour pH study at 4 months of age. However, determining whether reflux is clinically significant is more difficult. Reflux may certainly cause lung disease or be caused by lung disease or be an inconsequential finding, although this will typically self-resolve by 18 months. Given the potential impact on lung health, there is often a low threshold to treat with proton pump inhibitors as first line when suspected clinically. However, the association in population studies of this treatment with respiratory infection should also be considered.

KEY LEARNING POINTS

- An acute illness may be the first presentation of an underlying chronic illness.
- An unwell child despite treatment requires reassessment of the working diagnosis.
- No screening test is completely accurate.

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CHAPTER 5 A CHILD WITH INTERSTITIAL LUNG DISEASE AND HEPATIC CIRRHOSIS

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INTRODUCTION

In recent years, genetic variants have increasingly been found to be the underlying cause of childhood interstitial lung disease (chILD). Diagnosing these rarities is important because some have very specific and effective therapies, for example, JAK inhibitors for chILD due to STAT3 mutations.

Here, we present a patient with recurrent viral lower respiratory tract symptoms, congenital CMV pneumonia, interstitial lung disease, *Mycobacterium tuberculosis* (MTB) infection, hepatic cirrhosis, monocytosis, and haemophagocytic lymphohistiocytosis (HLH)-like symptoms to illustrate the diagnostic complexities of rare diseases that often need to be addressed.

CASE PRESENTATION

A 2.5-month-old female infant was admitted to the emergency department with respiratory distress and fever persisting for 3 days. On examination, her oxygen saturation was 84% on room air, and bilateral crackles were noted on auscultation. A posterior–anterior (PA) chest X-ray revealed bilateral ground-glass opacities (Figure 5.1). Laboratory findings showed

anaemia (haemoglobin: 8.8 g/dL) and thrombocytopenia (platelet count: 81,000/μL). The direct Coombs test was positive (+4), indicating autoimmune haemolytic anaemia. Liver function tests showed mildly elevated alanine aminotransferase (ALT) (46 U/L) and aspartate transferase (AST) (55 U/L), and lactate dehydrogenase (LDH) was significantly elevated at 1072 U/L. Inflammatory markers were also elevated, with ferritin at 4049 ng/mL, C-reactive protein (CRP) at 43 mg/L, and an erythrocyte sedimentation rate (ESR) of 36 mm/h. The patient had a history of a full-term, uncomplicated vaginal delivery at 38 weeks with no neonatal intensive care unit (NICU) admission. She had one episode of an afebrile seizure at 28 days of age, and an electroencephalography (EEG) performed at that time was normal. Family history revealed that both parents were healthy and from the same village, but no consanguinity was known, with no known family history of similar symptoms. The infant's height and weight were between the 10th and 25th percentile for her age.

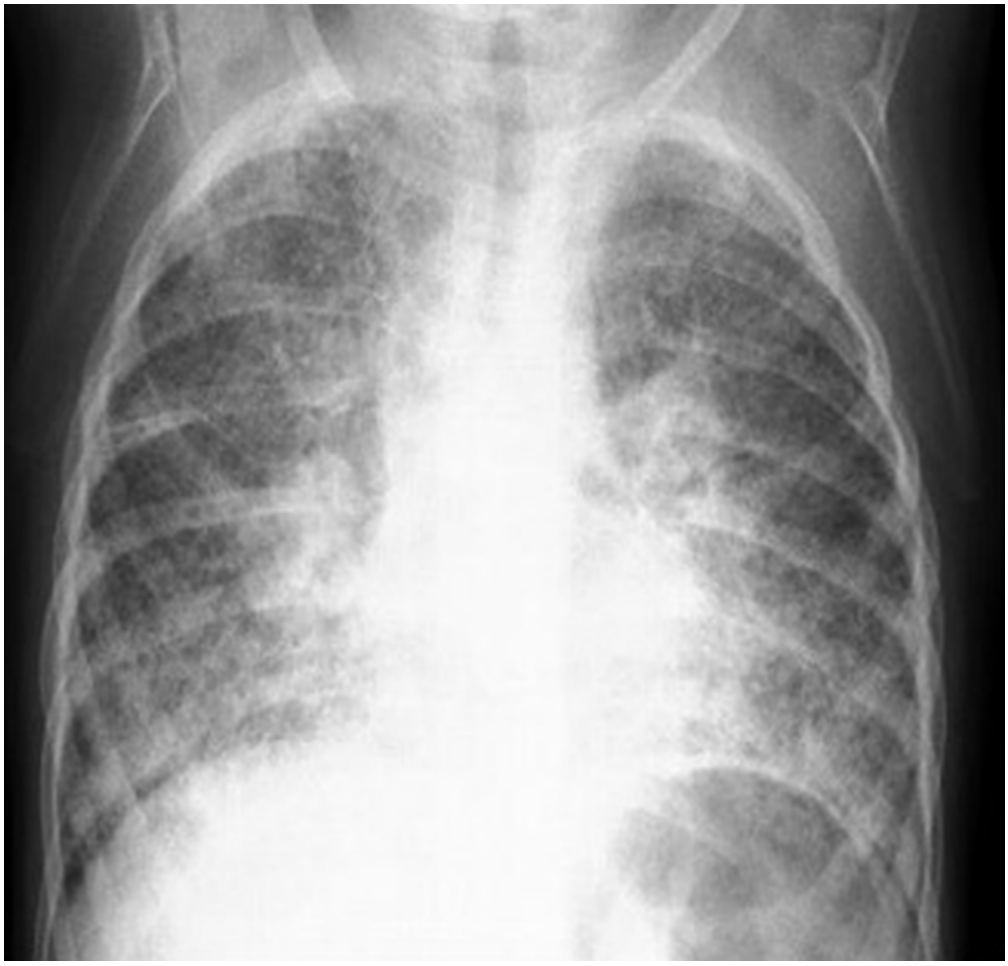

Figure 5.1 Posterior–anterior chest X-ray revealed bilateral ground-glass opacities and reticular densities.⏎

QUESTION 1: *What are the likeliest diagnoses? What investigations would you do next?*

Could this be cystic fibrosis, tuberculosis, viral pneumonia, or a primary immunodeficiency?

The patient underwent several diagnostic tests, including tuberculosis (TB) screening, which was negative for acid-fast bacilli (AFB), polymerase chain reaction (PCR), and culture. The TB tests were performed on bronchoalveolar lavage (BAL) fluid. The sweat test showed a result of 35 (macroduct type). Baseline immunological tests, including IgG, IgM, IgA,

and IgE, were within normal limits, and antibody responses to vaccines were also found to be normal. However, cytomegalovirus (CMV) testing revealed positive results, with CMV IgM levels at 3.54 μ/dL (cut-off: <0.7 negative, >0.9 positive), blood CMV DNA at 536 copies/mL, and urine CMV DNA at 26,200 copies/mL. Rubella IgM and toxoplasma IgM were negative. Given the positive CMV findings and the clinical presentation, congenital CMV with lung involvement was considered, and the patient was started on ganciclovir for 28 days. Additionally, bronchoalveolar lavage (BAL) revealed a CMV DNA load of 201,000 copies/mL, and brain computed tomography (CT) showed bilateral calcifications in the basal ganglia (Figure 5.2).

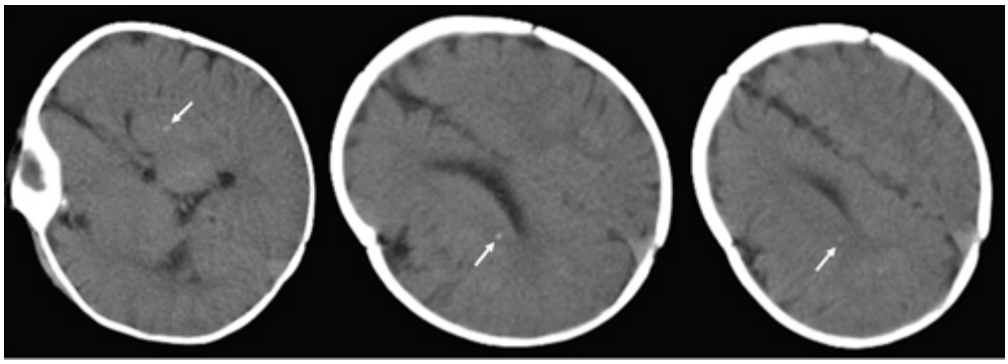

Figure 5.2 Brain CT showed bilateral a few calcifications (arrows) in the basal ganglia.⏎

By the time the patient was 2.5 years old, she had been hospitalized six more times due to high fever, recurrent lower respiratory tract infections, and acute phase reactant elevations. The patient's physical examination revealed growth retardation and pectus carinatum deformity, and she had an atypical facial appearance (round face, anterior hairline, narrow forehead, synophrys, bulbous nasal tip, prominent philtrum, micrognathia) (Figure 5.3). She had intercostal retraction and clubbing. Diffuse crackles were heard on auscultation. Oxygen via nasal cannula was continued, and based on the suspicion of an immune dysregulation syndrome, immunoglobulin replacement therapy (IGRT) was initiated.

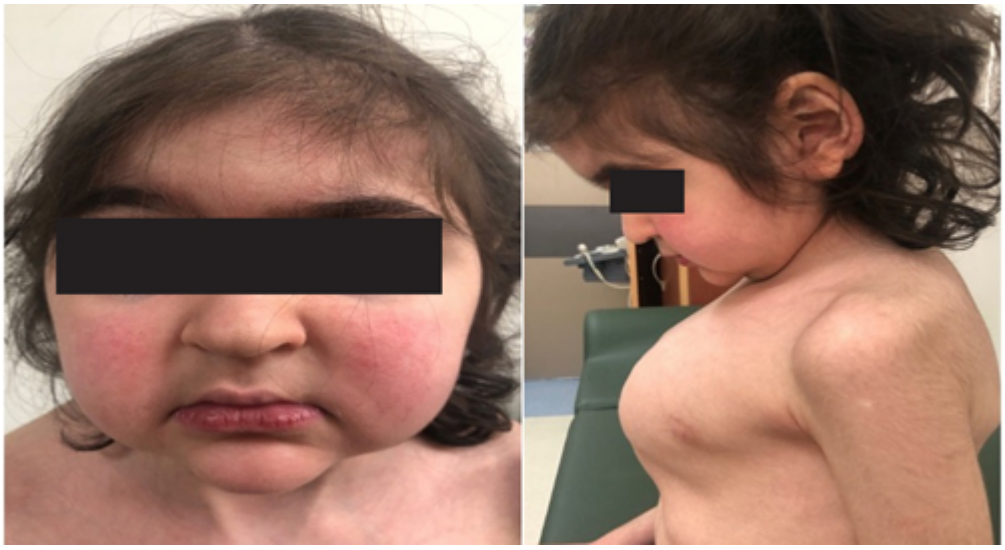

Figure 5.3 The patient had an atypical facial appearance.

(Photographs published with permission of the family.)

A thorax CT was performed because bilateral diffuse infiltrates, suspicion of cysts, ground-glass opacity, and mediastinal widening were observed on posteroanterior chest radiograph. CT demonstrated diffuse ground-glass opacification and subpleural cysts on both lungs as well as lymphadenopathy in the mediastinum and bilateral hilum (Figure 5.4).

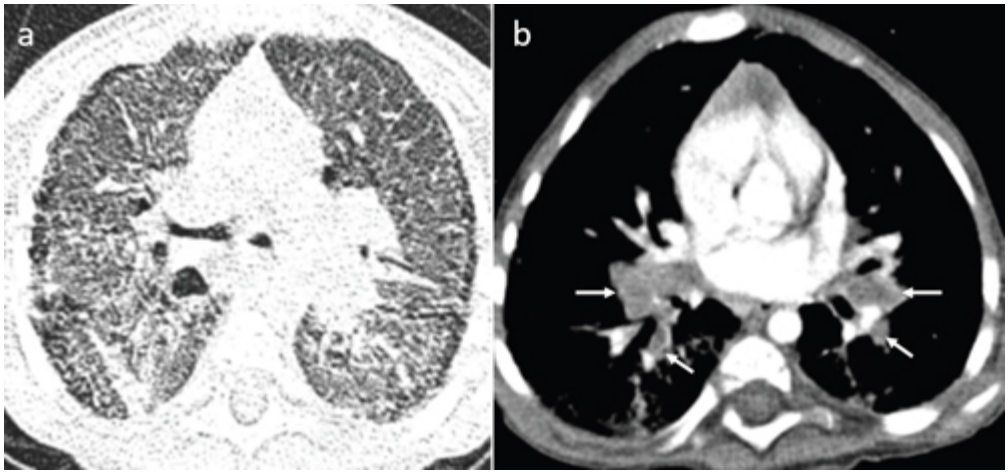

Figure 5.4 Thorax CT showed (a) diffuse ground-glass opacification, peripheral subpleural milimetric cysts on both lungs, and (b) lymphadenopathies (arrows) in the bilateral hilum.

QUESTION 2: *What would you recommend for the next step?*

Genetic evaluation? Lung biopsy? Treatment? Detailed immunological examination?

Since the patient had ongoing hypoxia, respiratory symptoms, and diffuse radiological changes, she met the criteria for chILD, and methylprednisolone at 1 mg/kg/day and hydroxychloroquine 6 mg/kg/day was empirically commenced. Genetic causes of chILD were considered. Surfactant protein disorders are a leading cause of chILD in infants. Diagnosis is typically confirmed through genetic testing, which is available clinically. Clinical manifestations can range from severe, rapidly fatal neonatal lung disease to the eventual development of pulmonary fibrosis in adulthood. The inheritance patterns, disease progression, and prognosis differ depending on the specific gene and, in some cases, the mutation involved. Surfactant protein (Sp)B, SpC, ATP binding cassette subfamily A member 3 (ABCA3), and brain–thyroid–lung syndrome (NKX2.1/TTF-1) genetic tests were sent and no mutation was detected. Peripheral blood cytogenetic analysis: 46, XX. The family did not give consent for a lung biopsy.

Immunophenotyping of peripheral blood lymphocyte subpopulations was normal. No pathological variant was detected in the primary immunodeficiency genetic panel. Familial Mediterranean fever (FMF) is a common monogenic autoinflammatory disease, characterized by recurrent febrile episodes, acute abdominal pain, and inflammation, especially in children from the Mediterranean region. Diagnosis is confirmed through the detection of mutations in the Mediterranean fever (*MEFV*) gene, particularly in exon 10. Colchicine is the main treatment, preventing attacks and reducing the risk of secondary amyloidosis, a severe complication that

can develop later in life. The patient underwent an FMF gene panel and *MEFV* gene: exon 10 M680I G/C heterogeneous/missense mutation was detected confirming this diagnosis. Colchicine treatment was started because of the clinical picture. This was the first diagnosis made in this child.

When the steroid dose was reduced, the patient experienced a recurrence of pulmonary exacerbations, accompanied by hypoxia, fever, and respiratory distress, which required hospitalization. As a result, mycophenolate mofetil was added to the treatment regimen as a steroid-sparing agent. A follow-up chest CT was unchanged, and a purified protein derivative (PPD) was 12 mm. The result was considered positive because the patient had a history of systemic corticosteroid use for 1.5 years. AFB, MTB culture, and PCR sent from the BAL sample were negative. Anti-TB treatment was started because of the clinical findings.

In the abdominal sections partially included in the follow-up thorax CT showed irregularities in the liver contour and slight heterogeneity in the parenchym (Figure 5.5). Therefore, abdominal magnetic resonance imaging (MRI) was performed, and it was determined that the liver was enlarged, had nodular contours and heterogeneous parenchyma, suggesting chronic liver disease (Figure 5.6). Further testing was conducted to evaluate chronic liver disease and liver cirrhosis. Anti-liver kidney microsomal antibody (anti-LKM), anti-nuclear antibody, anti-mitochondrial antibody, anti-smooth muscle antibody, and anti-dsDNA were negative; and ceruloplasmin and alpha-1 antitrypsin level were normal. EBV VCA Ig M, parvovirus B19 Ig M, and herpes simplex type 2 Ig M was negative; hepatic markers were normal; 24-hour urine copper was normal; and anti-gliadin antibody, anti-endomysium antibody, anti-gliadin Ig A, and anti-tissue transglutaminase (tTG) was negative.

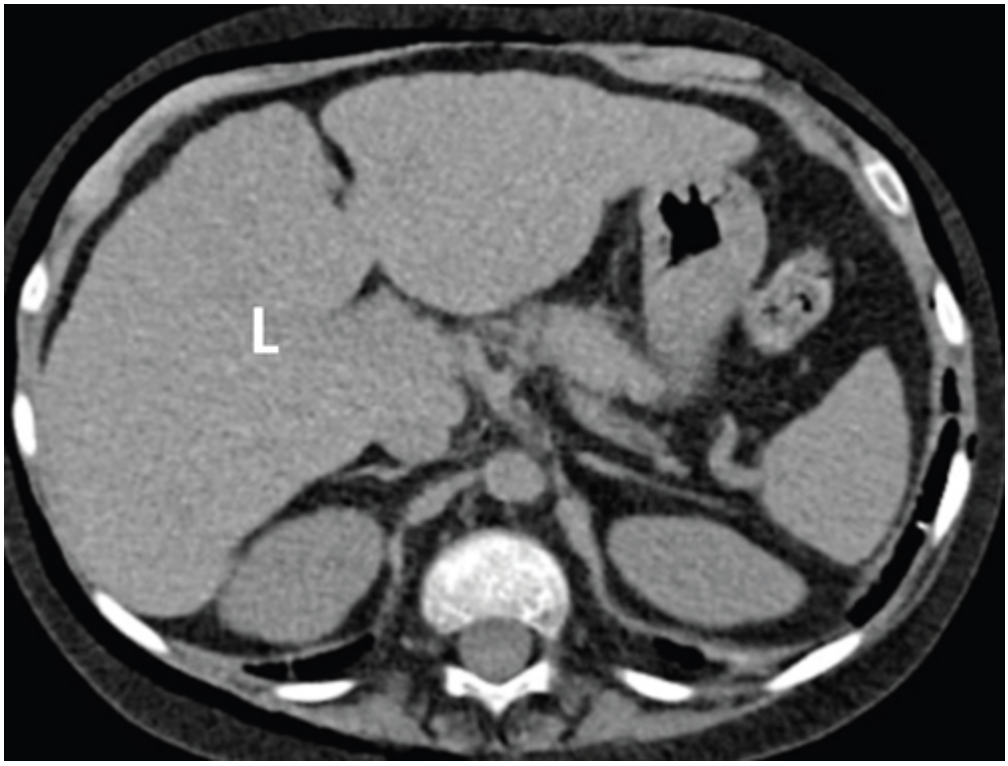

Figure 5.5 CT scan showed contour irregularity and slight heterogeneity of the liver (L).

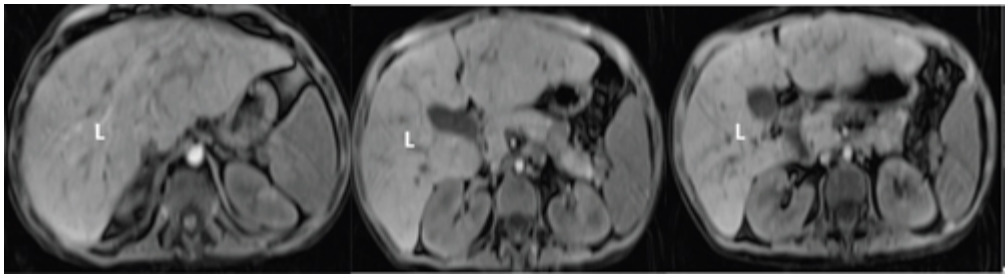

Figure 5.6 T1-weighted abdomen MR images demonstrated an enlarged liver (L) with nodular contours and heterogeneous parenchyma consistent with chronic liver disease.

In summary, this child is found to have systemic autoinflammatory diseases, chILD, and hepatic cirrhosis.

QUESTION 3: *What is your next step?*

Advanced genetic immunological evaluation? Whole exome sequencing (WES)? New treatments? Liver biopsy? Ask the parents again about a lung and mediastinal lymph node biopsy?

The patient was analysed in detail for genetic immunoregulation syndromes. Inherited mutations in the lipopolysaccharide-responsive beige-like anchor (*LRBA*) gene led to a recessive immune dysregulation syndrome in humans, characterized by memory B-cell and antibody deficiencies, commonly presenting as common variable immunodeficiency (CVID). Affected individuals may also experience inflammatory bowel disease, enlarged spleen and lymph nodes, accumulation of activated T cells, and autoimmune disorders. *LRBA* plays a critical, cell autonomous role in facilitating the accumulation of cytotoxic T-lymphocyte antigen-4 (CTLA-4) in CD4 effector T cells and FOXP3+ T-regulatory cells (Tregs), which is essential for immune regulation. FOXP3, *LRBA*, and CTLA-4 expression was examined regarding immune dysregulation, and no abnormal results were found.

The immune response involving interferon (IFN) types I and III is critical for host defence against viral infections. Recent research has identified genetic defects in the type I IFN pathway that increase susceptibility to certain viral infections, including severe cases of COVID-19 linked to TLR3 and IRF7 mutations. Type II IFN (IFN-γ) is essential for combating infections caused by intracellular pathogens like mycobacteria. Genetic disorders affecting IFN-γ signalling have been observed in patients with atypical mycobacterial infections. Hence, next-generation whole exome sequencing analysis was performed using the Illumina platform. The analysis revealed a *ZNFX1* gene (ENST00000396105.1, c.1414_1415del) with a homozygous new frameshift zinc finger *NFX*-type containing 1 (*ZNFX1*) mutation causing a two-base pair deletion, the first time this has been described in the literature. Biallelic loss-of-function variations of this gene are associated with the “immunodeficiency 91 and

hyperinflammation" phenotype characterized by both recurrent infections and hyperinflammation with systemic involvement.

The *ZNFX1* gene encoding a member of RNA helicase superfamily-1 plays a role in antiviral immunity. Essentially, *NFX1* contributes to the early induction of IFN expression during RNA virus infections. This c.1414_1415del frameshift variant was expected to disrupt the protein product of the *ZNFX1* gene due to a nonsense-mediated decay mechanism. In the literature and the ClinVar database, there was no report related to this variant, and it was found only once in the GnomAD database. Therefore, this novel change was interpreted as likely pathogenic according to ACMG/AMP (American College of Medical Genetics and Genomics and the Association for Molecular Pathology) guideline criteria. The variant was found to be heterozygous in both parents. This is the second diagnosis in this child.

In conclusion, we report a novel homozygous variation in the *ZNFX1* gene, causing a frameshift change that likely introduces a truncation of the protein product. Since the *ZNFX1* is a relatively newly identified gene, reports on the genotype–phenotype correlation provide novel insights into its clinical implications and emphasize the re-evaluation of the undiagnosed patients considered for the *ZNFX1*-related disease. Understanding the molecular mechanisms and pathological effects of this mutation is of great importance for prospective treatment strategies and genetic counselling.

KEY LEARNING POINTS

- Detailed genetic examination is required in patients with susceptibility to viral infections and multisystemic involvement. If negative, evaluation should be repeated because new knowledge is constantly emerging.
- Interstitial lung diseases may be associated with immunodeficiency syndromes.
- Identification of new variants will guide genetic counselling and treatment strategies.

- The finding of one diagnosis (in this case, familial Mediterranean fever) does not exclude the presence of a second rare disease.

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CHAPTER 6 WHERE IS THIS BABY'S LEFT LUNG?

Liang Yi Justin Wee, Duo-Tong Cheng, and Chun Yi Ting

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INTRODUCTION

This is a 3-month-old infant who presented with chest X-ray findings of almost complete opacification of the left hemithorax, without significant infective symptoms. This case illustrates the approach to a large pleural effusion in a neonate and an uncommon solution to a rare problem.

CASE PRESENTATION

The patient is a 3-month-old boy of Chinese ancestry, with no past medical history, who presented to the emergency department with a history of cough for 4 days and tachypnoea for 2 days.

He was born at term via emergency lower segment caesarean section for poor progress after 12 hours of labour. His mother's antenatal scans were normal. His birth weight was appropriate for gestational age and there were no dysmorphic features seen at birth. There were no issues prior to discharge from the hospital and he had remained well until being admitted. He did not have any fever, and there was no known recent contact with anyone with an infectious illness. He had been unable to finish his usual milk feeds for the previous 3 days.

In the emergency department, he was noted to be tachycardic and tachypnoeic. Oxygen saturations were borderline (94%) in room air. He was afebrile and not oedematous. Respiratory examination showed decreased

breath sounds on the left side with stony dullness. Heart sounds were normal with no murmurs, and he was well perfused. He did not have any abdominal masses or dysmorphic features. A chest X-ray (CXR) showed almost complete opacification of the left hemithorax with a rightward mediastinal shift (Figure 6.1). He was admitted to the intensive care unit (ICU) and started on continuous positive airway pressure (CPAP).

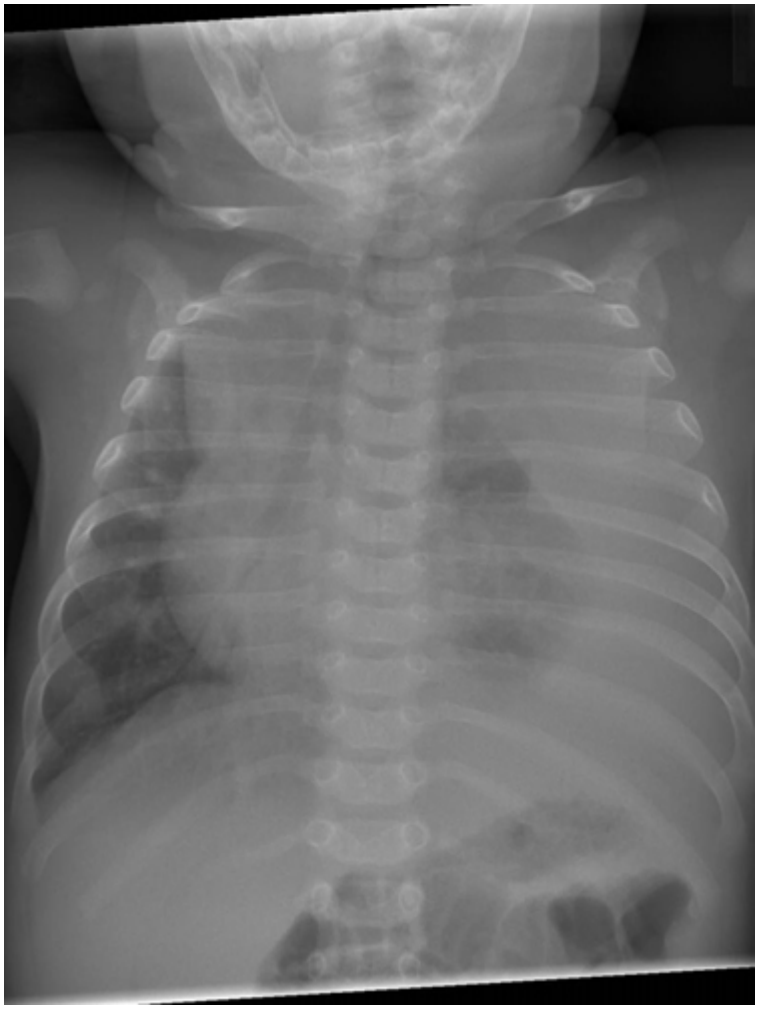

Figure 6.1 CXR on admission. There is near-complete opacification of the left hemithorax with a marked mediastinal shift to the right, consistent with a large left-sided pleural effusion.⏎

QUESTION 1: *What are the possible diagnoses in this patient?*

The CXR findings are consistent with a large pleural effusion in a neonate. The quickest and easiest way to confirm the presence of an effusion would be an ultrasound scan. Possible causes include congenital chylothorax, transudative effusions such as may be seen in congestive heart failure or hypoalbuminaemic states such as congenital nephrotic syndrome, or hydrops fetalis. However, the lack of generalised oedema would make hypoalbuminaemic states less likely, and hydrops fetalis would usually have been evident at birth. Infective causes, such as parapneumonic effusion or empyema, are very unlikely due to the lack of any fever. However, it is important to remember that a structural malformation, such as a large fluid-filled congenital pulmonary airway malformation (CPAM), or a lung mass such as a teratoma or pleuropulmonary blastoma, may also result in opacification of much of a hemithorax. Another possibility is congenital diaphragmatic hernia; although this would usually result in bowel loops or the gastric bubble being seen in the chest cavity, this is not always the case. Therefore, for the neonate with a "pleural effusion," more detailed imaging is required to further delineate the lesion before any drainage procedures are carried out. As such, a CT thorax (Figure 6.2) was done prior to drainage of the effusion.

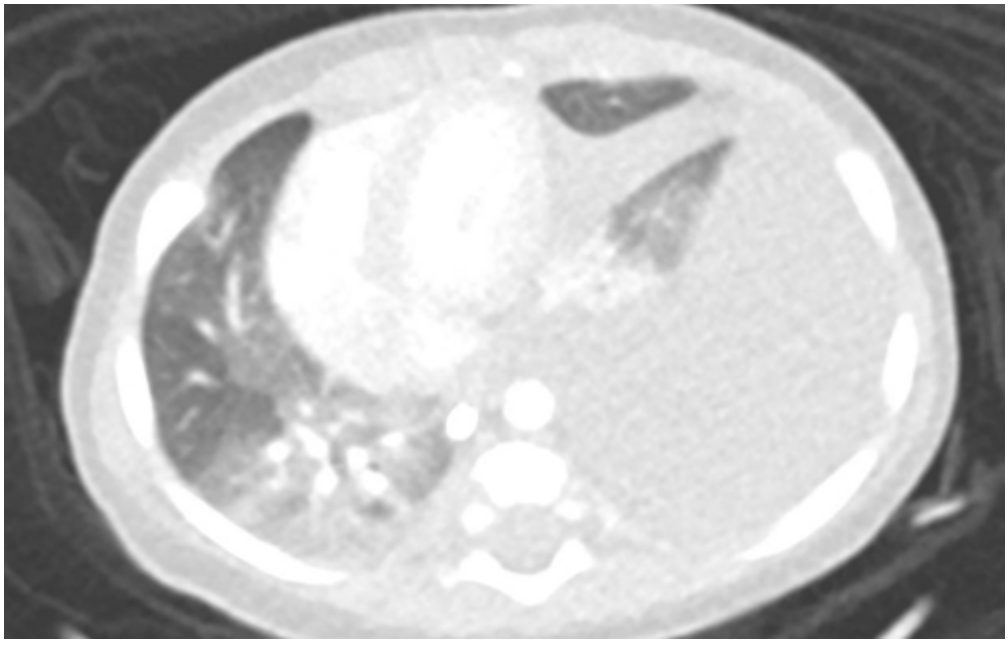

Figure 6.2 CT thorax showing the large pleural effusion, partly collapsed left lung and marked mediastinal shift to the right. There was no intrathoracic mass found.⏎

Chest drainage was performed under ultrasound guidance and the drainage fluid is shown in Figure 6.3.

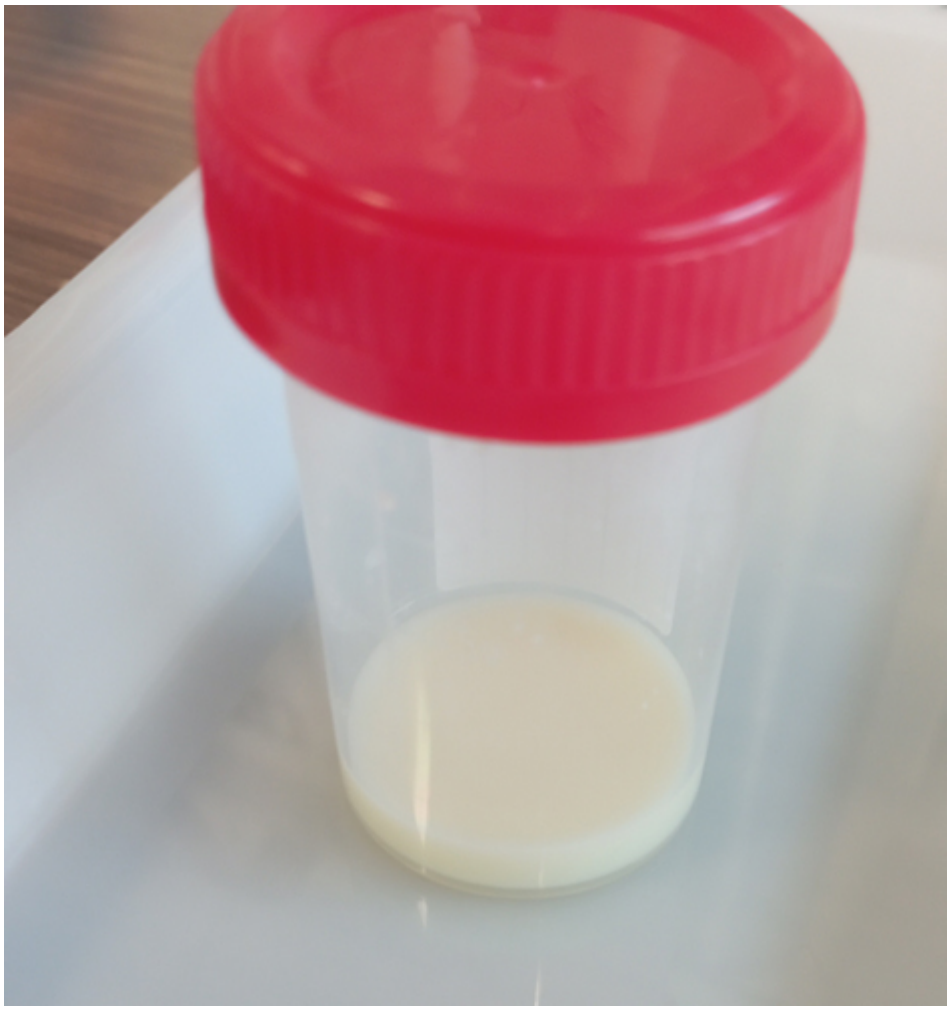

Figure 6.3 White, milky-appearing chest drainage fluid.⏎

QUESTION 2: *Based on the appearance of the drainage fluid, what is the likely cause of the pleural effusion? What further investigation and management are required?*

Figure 6.3 shows the classic white milky appearance of chylothorax.

Chylothorax is the accumulation of chyle in the pleural space, which usually results from compression, trauma, or malformation affecting the thoracic duct and lymphatics, causing a chyle leak. It is a rare condition, but in the first few days of life, it is the most common form of pleural effusion. The diagnosis of chylothorax is confirmed via laboratory studies from the pleural fluid. The confirmatory test is Sudan III staining of the pleural fluid, which shows chylomicrons. However, this test may not be available in all laboratories and is negative if the baby is not being fed. A simpler method is finding a pleural fluid triglyceride level of more than 1.1 mmol/L (levels between 0.56 and 1.1 mmol/L are equivocal). If the patient is fasting or has had poor dietary fat intake, the milky or turbid appearance may not be visualised, and there may not be a high triglyceride level, so a high-fat meal administered to the patient may be necessary for diagnosis. Chyle is rich in lymphocytes, and the differential count from the fluid is usually lymphocyte predominant (>80%). Pseudochylothorax occurs when there is accumulation of cholesterol but not triglycerides or chylomicrons in the pleural fluid; this usually occurs in a chronic pleural effusion. It can be distinguished from chylothorax by a pleural fluid cholesterol level of >200 mg/dL (5.18 mmol/L) and a triglyceride level of <50 mg/dL (0.56 mmol/L).

Chylothorax in children can be divided into traumatic and atraumatic causes. The following is a list of the possible underlying pathologies:

- Traumatic chylothorax is due to rupture or laceration of the thoracic duct and is a possible postoperative complication for any surgery involving the course of the thoracic duct – usually cardiac or intrathoracic, but sometimes even cervical or scoliosis surgery can cause chylothorax. Penetrating chest trauma or even non-accidental injury are other potential causes.
- Congenital or idiopathic chylothorax happens in the absence of prior surgery or other obvious inciting causes. The mechanism is unclear, but it may be due to stretching or rupture of the thoracic duct during the birth process from hyperextension of the spinal column or

increased systemic venous pressure. This is more likely in complicated or prolonged deliveries.

- Congenital abnormalities of the lymphatics, such as pulmonary lymphangiomatosis or pulmonary lymphangiectasia, can result in chylothorax. Lymphangiomatosis is a focal proliferation of well-differentiated lymphatic tissue, whereas in lymphangiectasia, there is diffuse dilatation of the interlobular and subpleural lymphatics.
- Syndromes such as Noonan syndrome (strongest genetic association), Down syndrome, Turner syndrome, or non-immune hydrops fetalis.
- Mass lesions compressing the thoracic duct, such as benign cysts or teratomas or malignant tumours such as teratoma, sarcoma, lymphoma, or neuroblastoma, can result in chyle leak.
- Increased central venous pressure can cause rupture of the thoracic duct and its collaterals. This may be seen in thrombosis or obstruction of the superior vena cava or subclavian vein, or right heart failure.
- Translocation of chylous ascites via the diaphragm.
- Drug-induced chylothorax (dasatinib).

Further investigation and management should be geared towards anticipating consequences of a prolonged chyle leak, as well as looking for a cause of the chylothorax. Lymphatic fluid contains lymphocytes, proteins such as immunoglobulins and clotting factors, fat-soluble vitamins and electrolytes, and prolonged leakage can result in deficiencies. Therefore, a baseline full blood count and blood film (to look for lymphopenia or blast cells), serum electrolytes, albumin, immunoglobulin levels, and prothrombin time and activated partial thromboplastin time should be done and repeated regularly thereafter. Further imaging including CT and/or MRI of the neck and the thorax should be done to look for mass lesions, pulmonary lymphangiomatosis, and pulmonary lymphangiectasis, and there is an increasing role of MRI lymphangiography in mapping lymphatic connections and dynamics. 2D echocardiography should be done to look for signs of right heart failure or obstruction of the major veins. Karyotype and genetic testing for RASopathies such as Noonan syndrome can be considered, especially if there are other dysmorphic features.

The initial management of chylothorax involves chest drainage. This is important for identification of the fluid as chyle, as well as to relieve respiratory distress in symptomatic effusions such as this. The mainstay of chylothorax management is dietary modification to reduce the flow of chyle through the thoracic duct and allow for healing. This patient was kept fully nil by mouth and started on total parenteral nutrition (TPN). Another option that may be better tolerated is a fat-free diet that includes medium-chain triglycerides (MCTs), which are absorbed directly into the portal vein without contributing to lymphatic flow. To address chyle losses, replacement of the drainage fluid with albumin, and correction of coagulopathy or low immunoglobulin levels should be guided by clinical condition and laboratory investigation. Treatment with somatostatin or octreotide (a somatostatin analogue) is thought to reduce lymphatic flow via vasoconstriction of the splanchnic circulation and reduction of intestinal blood flow. However, there is no consensus regarding the timing of introduction and starting dose of these medications. Initial intravenous dosage of octreotide ranges from 0.5 to 4 mcg/kg/hr and maximum dosages range between 6 and 12 mcg/kg/hr. Reduction of the lymphatic flow rate is usually seen within 3–6 days after starting octreotide, which can also be given subcutaneously.

Resch et al. (2022) reviewed 753 cases of neonatal chylothorax from studies published between 1990 and 2018. Of these, 29% had associated anomalies, with the most common being congenital pulmonary lymphangiectasia and pulmonary hypoplasia, and 16% had an associated genetic syndrome, with the most common being, in order, Down syndrome, Noonan syndrome, and Turner syndrome. Slightly over half (51%) required mechanical ventilation for a mean of 17 days, and most had a prolonged hospital stay (mean length of hospitalisation was 41 days). For medical interventions, 44% received TPN, 46% received a MCT-rich diet, 20% received octreotide, and 3% received somatostatin.

Initial fluid triglyceride level was 16.83 mmol/L, confirming the diagnosis of chylothorax. Fluid cholesterol level was 1.98 mmol/L. Analysis of the pleural fluid showed 250 white blood cells per microlitre, with 95% lymphocytes. Flow cytometry of these cells was negative for malignancy.

Bacterial, fungal, and acid-fast bacilli smears and cultures from the fluid were negative for any organism.

The patient was kept nil by mouth and started on TPN. Replacement of immunoglobulin and clotting factors was done as required. However, after 2 weeks of TPN, there was still daily drainage in excess of 10 mL/kg/day and he was started on continuous infusion of octreotide at a rate of 2 mcg/kg/hr. After starting octreotide, there was improvement in the rate of chest drainage over the next 1–2 days. Due to the prolonged duration of TPN, the patient developed cholestasis and liver injury, so MCT-rich feeds were started 4 days after commencing octreotide infusion and graded up as tolerated. However, after 1 month of these measures, there was still significant chest drainage resulting in reaccumulation of the effusion (Figure 6.4) and respiratory distress requiring non-invasive ventilation whenever the chest drain was blocked.

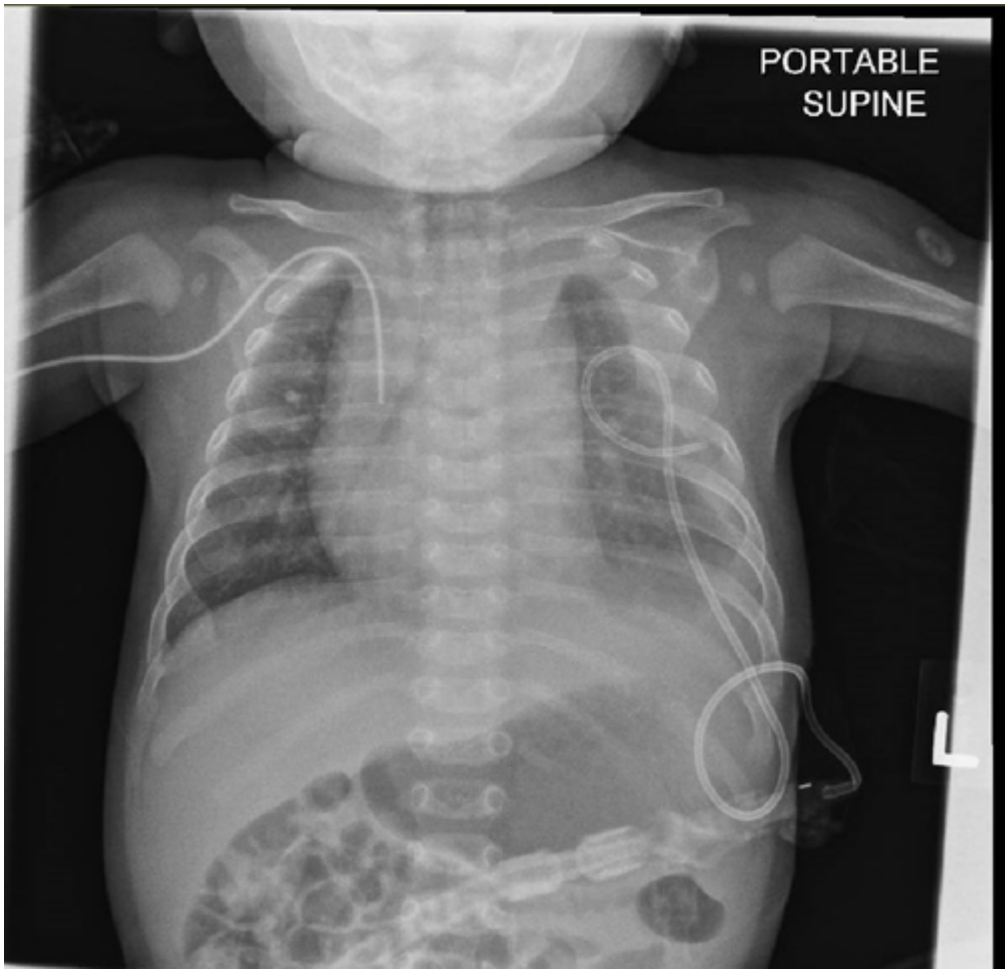

Figure 6.4 CXR showing reaccumulation of effusion with a left-sided pleural drain in place.⏎

Regarding the aetiology of the chylothorax, a neck and thorax MRI (Figure 6.5) and high-resolution CT thorax (Figure 6.6) were done. The CT and MRI did not show any features of pulmonary lymphangiectasia or focal masses. The 2D echocardiogram was normal except for a small atrial septal defect. Genetic testing was held off as there was no dysmorphism.

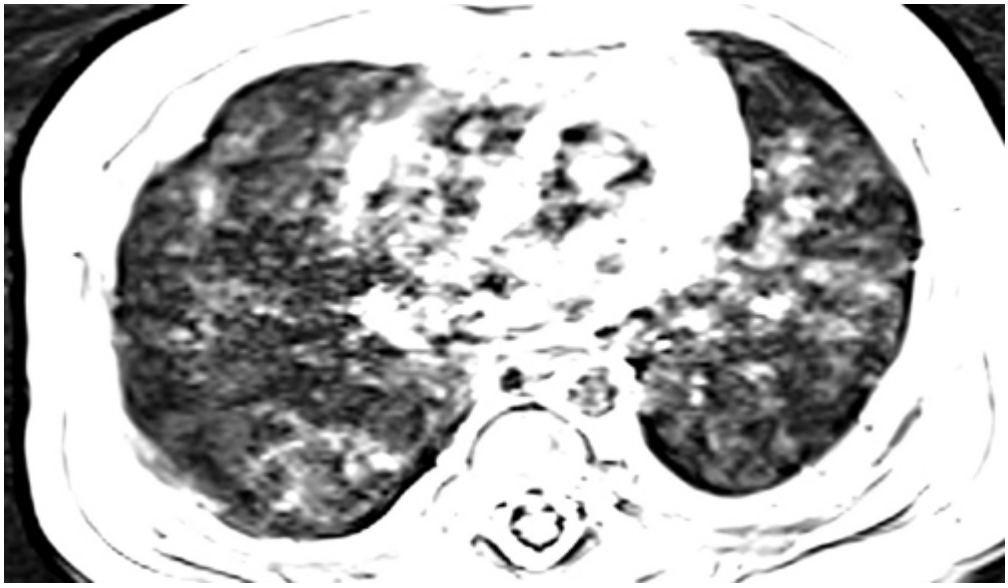

Figure 6.5 An MRI of the neck and thorax was done. There was no lymphatic malformation seen, but the interstitium of the lung was not well imaged on this window.⏎

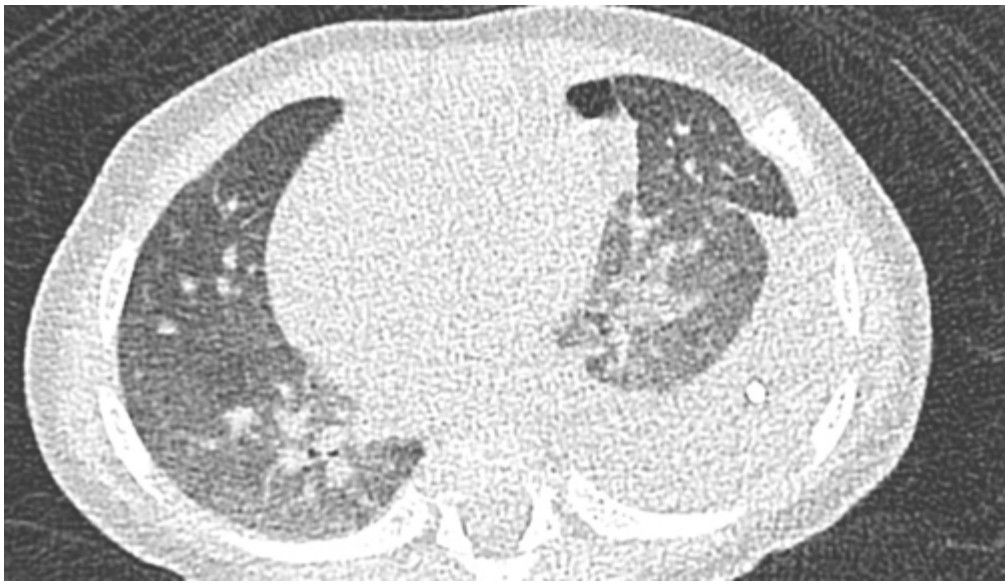

Figure 6.6 High-resolution CT. After the lung was re-expanded, there was no mass seen and there was no interstitial or interlobular septal thickening to suggest, e.g.,

pulmonary lymphangiectasia. The mediastinum had shifted back towards the left. (Note the drain in the left pleural space and the tiny anterior pneumothorax related to drain insertion.)⏎

QUESTION 3: *What is the treatment of chylothorax refractory to medical measures? What further investigation should be done for this patient?*

The response of chylothorax to medical measures such as dietary modification and somatostatin analogues can take many weeks. Most reviews have recommended at least a 3–4-week trial of medical therapy before considering surgical procedures unless there is a well-identified source of chyle leak, as more than 80% of chylothorax in children is amenable to non-operative management.

Surgical procedures for chylothorax include thoracic duct ligation, surgical or chemical pleurodesis, embolisation of the thoracic duct, or the insertion of a pleuroperitoneal shunt. In the review by Resch et al. (2022), 15% received chemical pleurodesis with a variety of agents, and 6% received various surgical procedures with the most common being surgical pleurodesis and ligation of the thoracic duct. For this patient, after 4 weeks of medical management, there was still significant drainage causing symptomatic reaccumulation of the effusion. Therefore, a lymphangiogram was done to look for any significant leak from the lymphatic system to facilitate planning for surgical treatment.

A lymphangiogram was done at 4 weeks post-chest drain insertion with lipiodol injected into the bilateral groin (Figures 6.7 and 6.8). This did not show any leak from the lymphatic system, and the lipiodol can have a therapeutic benefit, reducing lymphatic flow. It should, however, be avoided in cases of potential right to left shunt (atrial or ventricular septal defect, for example) as there is a risk of systemic oil embolisation and resultant stroke. Octreotide was stopped after the lymphangiogram (after a 2-week course of treatment) as there had been no further reduction in chest drainage after the initial improvement.

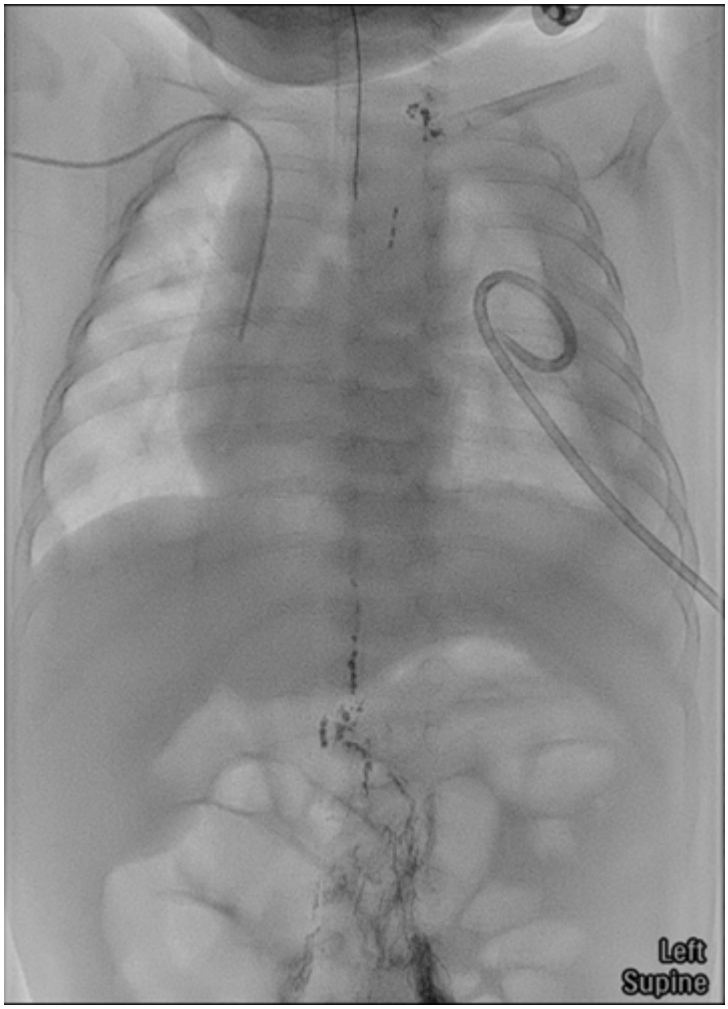

Figure 6.7 A lymphangiogram did not show any leak from the lymphatic system and has a therapeutic benefit in slowing central lymphatic flow.⏎

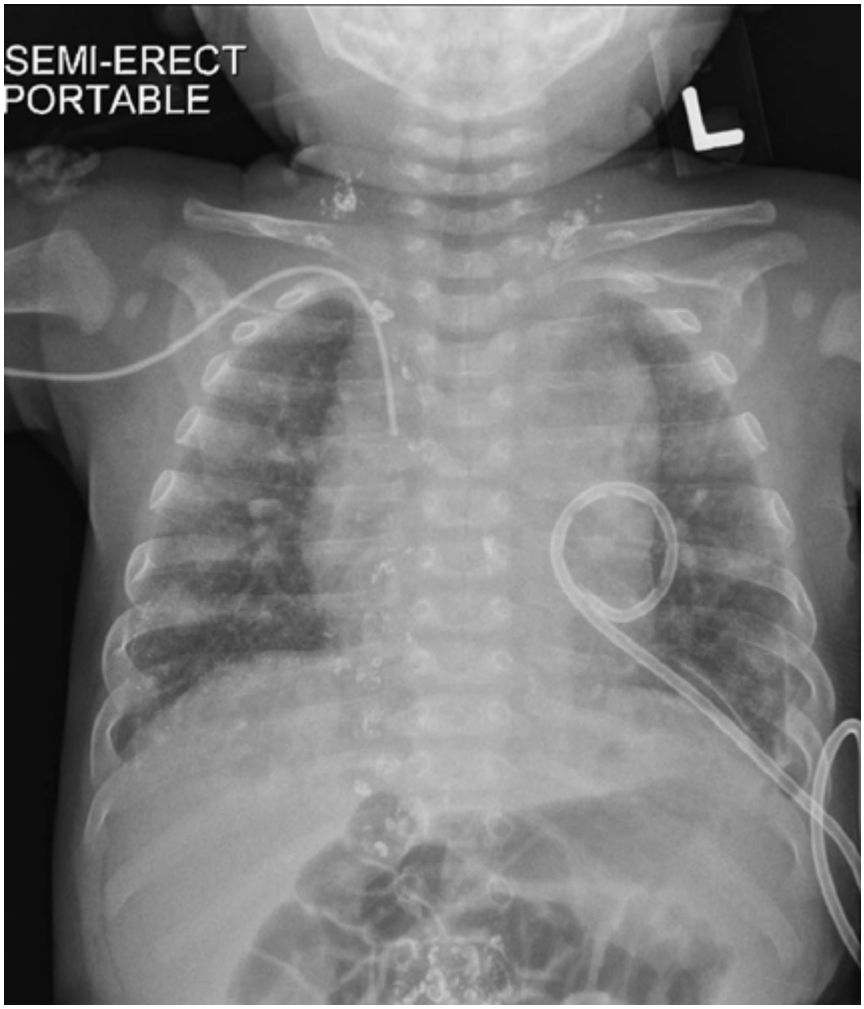

Figure 6.8 CXR done 12 hours after lymphangiogram showed bilateral patency of the lymphatic system and no delayed leak. Note the bright lipiodol in the supraclavicular nodes.

After the lymphangiogram, the patient developed a fever which lasted for 1 day. In retrospect, this was likely a side effect of the inflammatory effect of the lipiodol used in the lymphangiogram, as infective markers were not elevated, and blood and urine cultures returned negative. The chest drain output significantly decreased after the lymphangiogram, and the chest tube was able to be removed 1 week later.

QUESTION 4: *Does lymphangiography have a therapeutic effect in the management of chylothorax?*

The therapeutic effect of a lymphangiogram on chylothorax refractory to medical management has been previously reported. The mechanism is likely due to the inflammatory and sclerosing effect of lipiodol during its extravasation and has been noted to work better in patients with minor or no leak detected, as opposed to those with major leaks. Therefore, it can be considered as a minimally invasive treatment option for chylothorax refractory to medical management. The performance of the lymphangiogram in a small infant can be technically challenging, but Haga et al. (2020) reported the successful treatment of chylothorax in a premature infant weighing 800 g, illustrating that it can be a treatment option especially for patients in whom surgery is risky or technically difficult. It is also essential to have a detailed cardiac assessment to exclude potential intracardiac shunts prior to the procedure. If a shunt is present, there is a risk of a cerebrovascular accident occurring due to right to left shunting of lipiodol.

A follow-up CXR (Figure 6.9) at 1 month outpatient showed resolution of the chylothorax, and the patient has remained well and asymptomatic with no recurrence. This is likely to be an idiopathic neonatal chylothorax, as no underlying cause was identified.

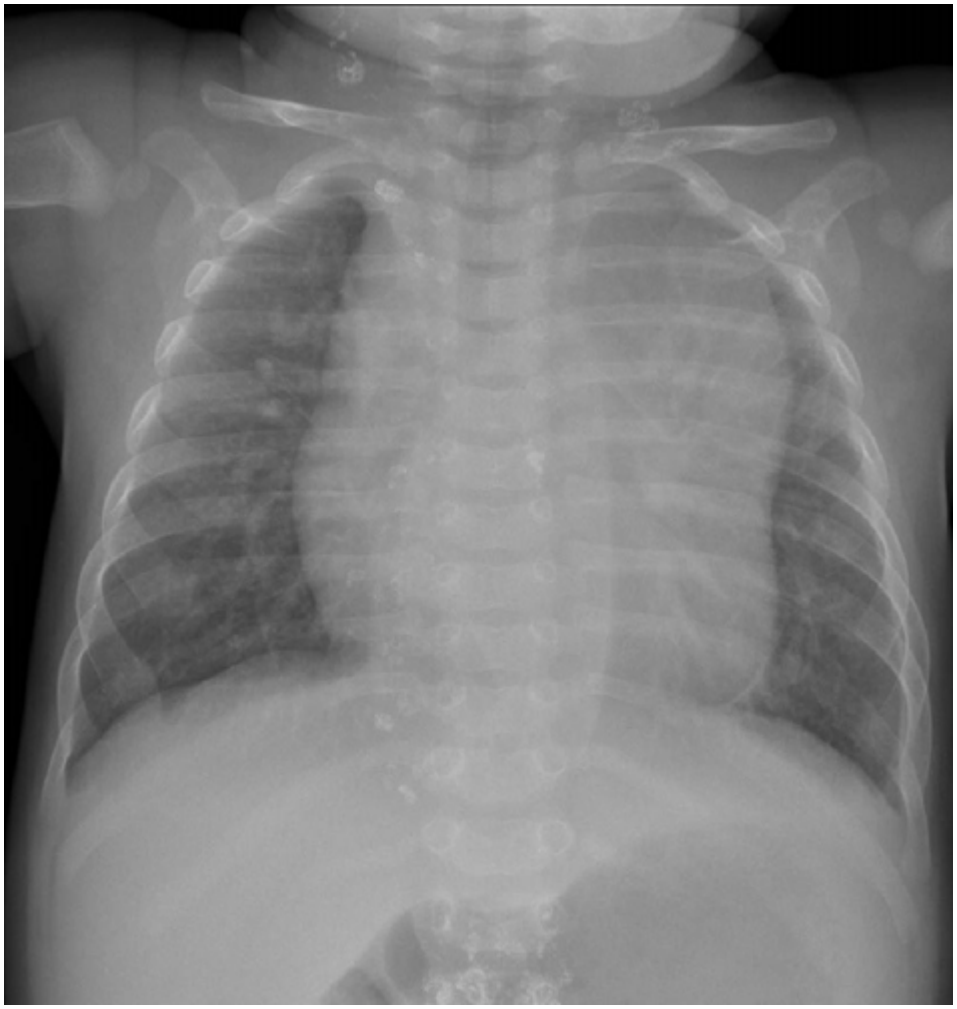

Figure 6.9 CXR showing resolution of chylothorax, return of the mediastinum to its normal location, and so-called thymic rebound.⏎

In the review by Resch et al. (2022), the overall mortality rate of neonatal chylothorax was 28%, but a number of these neonates had other life-limiting or serious congenital abnormalities. For those who survived, the long-term prognosis was generally good with no recurrence of the chylothorax on follow-up.

KEY LEARNING POINTS

The patient is a 3-month-old neonate with spontaneous chylothorax that was extensively investigated and treated with dietary restriction, total parenteral nutrition, and somatostatin analogues without success, but who ultimately responded after a lymphangiogram was done and has made a full recovery with no recurrence of the chylothorax on outpatient follow-up.

The important learning points from this case are:

- The investigation and management of a large pleural effusion in a previously well neonate.
- The treatment options for chylothorax, including medical and surgical management and anticipation of complications.
- The possible therapeutic effect of a diagnostic lymphangiogram, which can be considered as a minimally invasive treatment option for chylothorax refractory to medical management.

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CHAPTER 7 APPROACHES TO PREVENTING INFECTION AND OPTIMISING AIRWAY CLEARANCE IN A CHILD WITH CEREBRAL PALSY

R Dhandayuthapani and Don Urquhart

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INTRODUCTION

Children and young people with complex neurodisability, such as cerebral palsy, often have multiple comorbidities. Respiratory problems, specifically recurrent respiratory tract infection, are the leading cause of mortality in this cohort of children. Several interrelated factors predispose children with neurodisability to respiratory infection, namely dystonia, gastrointestinal dysmotility, swallowing problems, muscle weakness and spinal deformity, among others. The management of recurrent respiratory infections in children with complex needs warrants multidisciplinary assessment and discussion of treatment strategies. Such strategies include chest physiotherapy for airway clearance, prophylactic antibiotics, medications to control sialorrhoea and/or reflux, and surgical input, e.g. fundoplication. This case highlights some of the difficulties faced in managing a child with cerebral palsy with recurrent chest infections and frequent admissions to critical care. The case discusses commonly used intervention strategies and highlights that the needs of a child may evolve with time and age. The chapter discusses the emerging role of respiratory support as an adjunct to aid airway clearance, and the associated challenges and ethical

considerations for respiratory support and long-term ventilation in this patient group.

BACKGROUND

Baby Q was born at 35 weeks gestation by emergency caesarean section due to cord prolapse. Following delivery, he developed hypoxic-ischaemic encephalopathy, which subsequently evolved into dystonic cerebral palsy. Q had an unsafe swallow and was enterally fed via a nasogastric tube. He had a diagnosis of gastro-oesophageal reflux disease that was managed with omeprazole and domperidone. His variable tone was managed with nitrazepam and co-careldopa.

At the age of 6 months, Q presented to the emergency department with the sudden onset of increased work of breathing and peri-oral cyanosis. On review, Q was noted to be pale and mottled with cool peripheries. His observations at presentation showed a heart rate of 146 beats/min, respiratory rate of 44 breaths/min, SpO_2 of 100% on 2 L/min nasal cannula oxygen and a temperature of 37.5°C. An initial capillary blood gas showed severe respiratory acidosis (pH 7.15, pCO_2 10.2 kPa, HCO_3 20.7 mmol/L). His chest X-ray (CXR) on admission (Figure 7.1) showed a nodular infiltrate, right hilar adenopathy and subsegmental left lower lobe atelectasis. He was given a fluid bolus and commenced on intravenous antibiotics. A repeat blood gas was taken after chest physiotherapy had been performed, and this showed significant improvement (pH 7.36, pCO_2 6.10 kPa, HCO_3 24.4 mmol/L). He was admitted to the paediatric high-dependency unit for ongoing management.

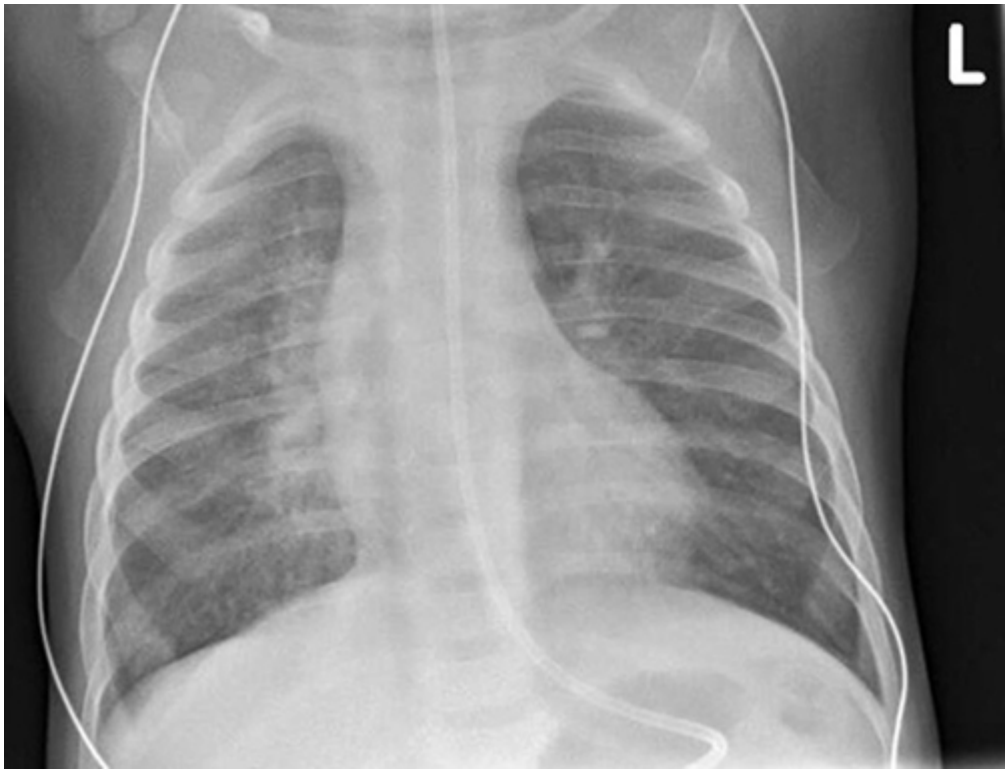

Figure 7.1 CXR taken during admission with bilateral peribronchial infiltrate, subsegmental left lower lobe atelectasis and presumed right hilar adenopathy.

Prior to this admission, Q had presented to hospital on six occasions, with similar respiratory symptoms, each warranting admission to high-dependency/critical care. He had been commenced on continuous positive airway pressure (CPAP) therapy for respiratory support during some of these admissions and required to be intubated and ventilated on one occasion. In view of his frequent and severe presentations, a consultation from the paediatric respiratory team was requested to help guide further management.

QUESTION 1: *What strategies could be employed to optimise the patient's respiratory health?*

In view of his recurrent presentations relating to lower respiratory tract infections, strategies were employed to (1) aid airway clearance and (2)

reduce the risk of infection. Q was commenced on prophylactic antibiotics (azithromycin at a dose of 10 mg/kg on 3 days per week), and he also started a regular, twice-daily airway clearance regime using a positive expiratory pressure (PEP) mask.

Children with complex neurodisability, such as cerebral palsy, may have inadequate coughs which prevent them from clearing secretions from the airway. This makes them prone to recurrent or chronic infections.

Strategies to augment airway clearance are employed to keep airways free of secretions and thus reduce the risk of infection. Airway clearance techniques used in children with cerebral palsy include positive pressure (PEP) devices, autogenic drainage (AD), and mechanical insufflation–exsufflation devices such as the cough assist. Such techniques have shown benefit in reducing admissions to hospital and reducing the duration of hospital admission.

In addition, nebulised hypertonic saline (3% or 7%) to aid expectoration is frequently used in this patient group with some evidence of a reduction in hospital admissions and antibiotic days as a result. DNase may also prove beneficial in aiding infectious atelectasis (in a small cohort study of children without cystic fibrosis), with clinical improvement and corresponding improvement of CXR changes during acute presentations. Neither of these is licensed for cerebral palsy, however, so parents must be informed they are being used off-label.

The setting of an acute lobar or subsegmental collapse may require more aggressive airway clearance using a combination of airway clearance physiotherapy and mucolytic (e.g. DNase) and mucoactive (e.g. hypertonic saline) agents. In this setting, adjuncts to airway clearance, e.g. cough assist device, intrapulmonary percussive ventilation (IPV) or the use of bi-level non-invasive ventilation prior to physiotherapy are commonly utilised. A bronchoscopy and bronchoalveolar lavage may also be indicated to clear mucus plugs obstructing large airways, with consideration of the instillation of DNase directly into the newly cleared bronchus at the end of such a procedure.

The use of prophylactic antibiotics, such as azithromycin, is common practice in children with neurodisability and recurrent lower respiratory tract infection. The practice is extrapolated from other disease models, e.g. cystic fibrosis, and a recent Cochrane review by Sanner and colleagues (2023) identified no currently published clinical trials to inform the usage of prophylactic antibiotics in children with neurodisability. A randomised clinical trial (PARROT study) of prophylactic azithromycin in this patient group was, unfortunately, prematurely terminated due to insufficient recruitment of eligible participants – primarily because many children were already on prophylactic azithromycin and their families and clinicians were not willing to consider stopping treatment for a randomised trial.

Q gradually improved and was discharged home once off oxygen. There was no clinical suspicion of sleep-disordered breathing. He continued on airway clearance physiotherapy and prophylactic azithromycin, with plans made for follow-up in the respiratory outpatient clinic.

Over the subsequent 4 months, Q unfortunately presented to hospital on a further five occasions, each time with symptoms and signs of lower respiratory tract infection. He was admitted to the high-dependency unit on each of these admissions with an escalation to respiratory support as CPAP or bi-level non-invasive ventilation (NIV) being required each time. He was reviewed again by the respiratory team as an inpatient for further input regarding management of his recurrent lower tract infections.

QUESTION 2: *What other management options can be considered now?*

Q had achieved ‘frequent flyer’ status, requiring regular and prolonged admissions for high-dependency care despite prophylactic antibiotics and a robust chest physiotherapy plan. The role of overnight respiratory support to further aid airway clearance was discussed with the parents, and a joint decision was made to trial CPAP with the aim of reducing the frequency of admissions related to respiratory infection. He was established on nocturnal CPAP at a fixed pressure of 8 cmH_2O.

The CPAP device was well tolerated initially, and pressures were optimised to 10 cmH_2O. He had a home cardiorespiratory sleep study (on CPAP) which showed satisfactory oxygenation and respiratory pattern as seen in Figure 7.2. The apnoea–hypopnea index was 0, with a mean SpO_2 of 97% and nadir of 93%.

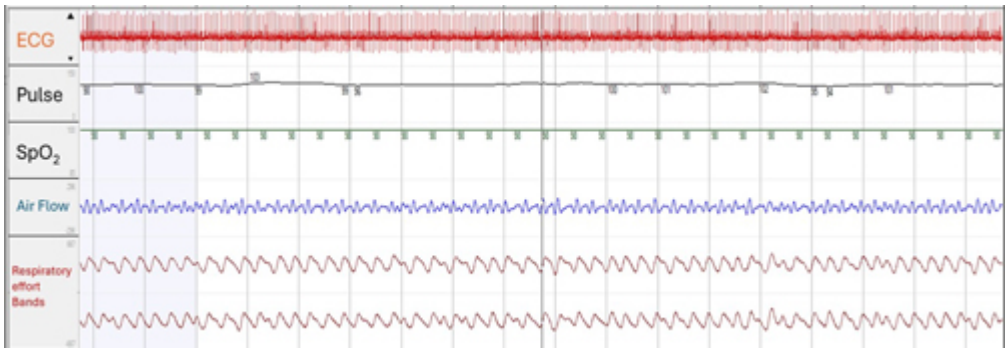

Figure 7.2 Cardiorespiratory study while on CPAP 10 cmH_2O shows regular respiration with normal airflow and synchronised chest and abdominal movements.⏎

Respiratory support is being increasingly used in clinical practice for children with complex needs, such as cerebral palsy, as an adjunct to airway clearance. Furthermore, such nocturnal respiratory support can offload respiratory muscles, improving energy levels during waking hours, as well as augmenting ventilation and cough. Data on the use of respiratory support in children with cerebral palsy are sparse and limited to case series. Whilst respiratory support has been shown to improve oxygenation and sleep breathing parameters, the impact on airway clearance and respiratory infections has, to date, not been demonstrated.

Q was discharged home to continue nocturnal CPAP, once parents were adequately trained and confident with the device. However, Q re-presented about a week after discharge with difficulty in breathing and was admitted to the high-dependency unit with his respiratory support escalated to bi-level NIV.

QUESTION 3: *What other investigations could be done to further investigate the patient's recurrent respiratory presentations?*

Given that Q has an unsafe swallow, we considered the possibility of gastro-oesophageal reflux disease (GORD)/aspiration contributing to recurrent lower respiratory infections. Q underwent an ENT assessment (to rule out a laryngeal cleft), as well as an upper gastrointestinal (GI) endoscopy, a flexible bronchoscopy and a pH-impedance study.

The upper GI endoscopy was normal in appearance, whilst oesophageal biopsies did not demonstrate any suggestion of reflux oesophagitis (though Q was on anti-reflux medications – omeprazole) at the time of endoscopy. ENT assessment (by suspension and microlaryngobronchoscopy) did not identify a laryngeal cleft.

Flexible bronchoscopy showed a structurally normal larynx and normal vocal cord movement. There was no evidence of airway malacia, erythema or swelling. The bronchoalveolar lavage, however, showed significant numbers of lipid-laden macrophages. The impedance study showed significant gastro-oesophageal reflux for age (reflux index 13.8%). In view of these findings, Q underwent a laparoscopic fundoplication to treat his reflux and insertion of a gastrostomy for long-term nutrition.

The predisposition to respiratory infection in children with complex needs is often multifactorial. Factors may include recurrent aspiration from above (e.g. uncoordinated swallow secondary to bulbar dysfunction) or from below (e.g. secondary to gastro-oesophageal reflux disease). Approaches to the investigation of aspiration include videofluoroscopy to assess swallow function, as well as 24-hour pH-impedance studies and upper gastrointestinal endoscopy to assess the severity of GORD. The management of GORD can involve, as in this case, a combination of anti-reflux medication, gastrostomy and fundoplication. There may, however, remain a risk of aspiration of saliva or upper airway secretions despite optimal GORD management. Hence an integrated approach to aspiration 'from above' and 'from below' should be undertaken, including the management of sialorrhoea with medical (hyoscine, glycopyrrolate or

botulinum toxin injection) or surgical (salivary gland resection) therapies. Use of antimuscarinics (e.g. hyoscine, glycopyrrolate) should be reviewed regularly to prevent excessively viscous secretions which may contribute to mucus plugging.

Q continued on his home nocturnal CPAP, prophylactic azithromycin and a regular airway clearance physiotherapy regimen. He was tolerating feeds well via his gastrostomy. Q tolerated the CPAP device well and achieved a period of stability for over a year from his chest perspective. The number of ED presentations and hospital admissions reduced over the next year to 8 (from 13 the year before). After joint discussion with his parents, Q was trialled off CPAP as an inpatient in line with parental wishes, and an oximetry done in air after discontinuing CPAP was satisfactory. However, over the course of the next few years, there was again a notable increase in the frequency and severity of respiratory infections with several admissions to hospital.

QUESTION 4: *What would be the most appropriate course of action now?*

Given that Q previously benefited from respiratory support in achieving a period of stability, the consideration of a re-introduction of CPAP was discussed with his parents during an acute admission. A joint decision was made to restart Q, now 4½ years old, on CPAP. He was commenced on nocturnal CPAP at a pressure of 10 mmH_2O. This again proved beneficial in reducing the number of presentations to the emergency department and hospital admissions, from six the year before to three the year after commencing respiratory support. The total duration of enteral and parenteral antibiotics used remained similar however (25 days the year before respiratory support to 22 days the year after). A cardiorespiratory study done before and after commencing nocturnal CPAP was unremarkable, with no evidence of sleep-disordered breathing.

As he grew older, Q began to become less tolerant of the CPAP device. He was averaging about 4–6 hours of CPAP use every night, with some nights being worse than others. This was starting to affect the sleep quality of his parents, due to a requirement for them to frequently reposition the mask

overnight. Furthermore, Q started to develop episodes of dystonia, which were often triggered by arousals that his family felt were related to the CPAP device.

QUESTION 5: *Should the patient still continue the nocturnal CPAP?*

The indications for long-term respiratory support in children with cerebral palsy may extend beyond the management of sleep-disordered breathing. These include the use of respiratory support as an adjunct to aid airway clearance in order to achieve a period of stability and reduce rates of hospitalisation. Hypothetically, CPAP can prevent alveolar de-recruitment during sleep. The use and tolerance of respiratory support (CPAP and NIV) in children can, however, be challenging with particularly high failure rates reported among children with complex needs.

Complex neurodisability, like cerebral palsy, can be a life-limiting condition for children and some may not survive into adulthood. Progressive deterioration of respiratory health, with repeated and prolonged hospital admissions, disrupts the time spent with their family at home. Hence, respiratory support may have a role in achieving a period of stability at home, though such benefits have to be weighed against the potential challenges with the ultimate aim of improving the quality of life of the child. This often involves a transparent and honest discussion with the family in setting realistic aims and potential complications of such interventions.

Furthermore, such open discussions need to be regularly maintained throughout the child's life course, which allows for the therapeutic relationship between parents and healthcare professionals to be optimised. Open discussions also aid early consideration of establishing ceilings of care when progressive respiratory failure is evident or developing anticipatory care pathways for acute presentations. Members of the multidisciplinary team are often engaged, with input from the lead clinical care team, palliative care team and those from the community. Early introduction of parallel palliative planning, concurrent to active medical management, allows for the psychological, social and spiritual needs of the

child and the wider family to be addressed as well. Such discussions should be frequently revisited and be flexible in meeting the evolving needs and wishes of the child and the family. Clear communication between the members of the multidisciplinary team of such evolving goals is also vital in coordinating the care provided for the child.

The benefits for Q were reducing the impact of respiratory infection (less hospitalisation) by augmenting airway clearance. The adherence to CPAP presented a challenge for Q and his parents, and poor tolerance of CPAP was having an increasingly negative impact on his sleep and quality of life as well as that of his family. Following extensive discussions with the family, Q's CPAP was discontinued when he was 7 years old.

KEY LEARNING POINTS

- The frequency and severity of respiratory infection in children with complex needs may be affected by a number of factors, including poor airway clearance, risk of aspiration and limited respiratory reserves.
- Assessment and management of respiratory problems in children with complex needs requires the input of a multidisciplinary team and is a journey that may evolve and change direction at different time points.
- The use of respiratory support (e.g. CPAP) in children with complex neurodisability extends beyond the role of managing sleep-disordered breathing, and this case highlights the utility of CPAP as an aid to airway clearance.
- Ultimately, the management of recurrent respiratory infection in children with complex needs is bespoke and requires individualisation, with the central aim being centred on the child's quality of life.

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CHAPTER 8 DID GOD DO IT OR DID THE DOCTOR DO IT?

A diagnostic conundrum

Helena Teresinha Mocelin and Gilberto Bueno Fischer

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INTRODUCTION

Children with complex diseases are frequently treated with multiple powerful medications, including monoclonal antibodies. It may sometimes be difficult to determine whether a new complication has arisen because of the underlying disease or as a complication of treatment. We report this case to illustrate this diagnostic dilemma.

CASE REPORT

A 5-year-old girl was admitted to the hospital with a history of persistent wheezing, which had exacerbated over the preceding 12 hours.

The patient's medical history included a diagnosis of Crohn's disease (CD) at the age of 1 year and 4 months. The initial symptoms were bloody stools and abdominal pain, and her Crohn's Disease Endoscopic Index of Severity (CDEIS-16) and Pediatric Crohn Disease Activity Index (PCDAI) revealed findings consistent with severe Crohn's disease. The patient was initially treated with azathioprine and prednisolone. At 1 year and 7 months, she was hospitalised due to a flare of Crohn's disease and also presented with

extraintestinal symptoms, including skin lesions. Infliximab (a monoclonal which binds circulating tumour necrosis factor [TNF]-α) was added to the treatment, and CD was controlled. Patients on biological response modifiers (BRMs), especially TNF-α inhibitors, have an increased risk of severe infections or reactivations, mainly from *Mycobacterium tuberculosis*. Her symptom screening was negative, she had had a BCG vaccine at birth, and the contact investigation for tuberculosis was unremarkable. Following current guidelines, the patient was tested for latent tuberculosis infection (LTBI) before starting treatment. The tuberculin skin test (TST) was negative, and the chest radiograph (CXR) revealed no abnormalities. Additionally, viral screening for herpes simplex, varicella zoster, Epstein–Barr, and hepatitis B returned negative results.

At 1 year and 10 months, she started to develop cough and wheezing. The CXR showed no abnormalities. She was treated with oral corticosteroids and rescue salbutamol, leading to partial improvement, followed by treatment with inhaled corticosteroids. At 2 years and 2 months, she was hospitalised due to fever and wheezing. Due to her persistent pulmonary symptoms, a fibreoptic bronchoscopy was performed, which showed hyperaemia and diffuse friability of the tracheal mucosa, with no narrowing of the airway. A bronchoalveolar lavage (BAL) revealed the presence of *Streptococcus pneumoniae* and *Pseudomonas aeruginosa.* She had a negative newborn screening for cystic fibrosis, and a sweat test with a chloride level of less than 29 mmol/L, making a diagnosis of cystic fibrosis unlikely.

At 2 years and 8 months of age, she presented with anaphylaxis to infliximab, which was discontinued, and she was switched to adalimumab, another monoclonal which binds circulating TNF-α.

At 3 years old, she was admitted for a wheezing exacerbation. Reviewing the clinical condition and notes, it was found that she had continuous symptoms of airflow obstruction. Even though the CXR was normal, it was decided to perform further investigation. A thoracic high-resolution computed tomography (HRCT) scan showed significant diffuse bronchial thickening and areas of parenchymal air trapping, particularly on the left

side. There was a moderate reduction, approximately 50%–60%, in the diameter of the left main bronchus, from its origin to the lobar bronchi. There was also infiltration of the peribronchial tissues, without luminal obstruction (Figure 8.1). She was maintained with an inhaled corticosteroid.

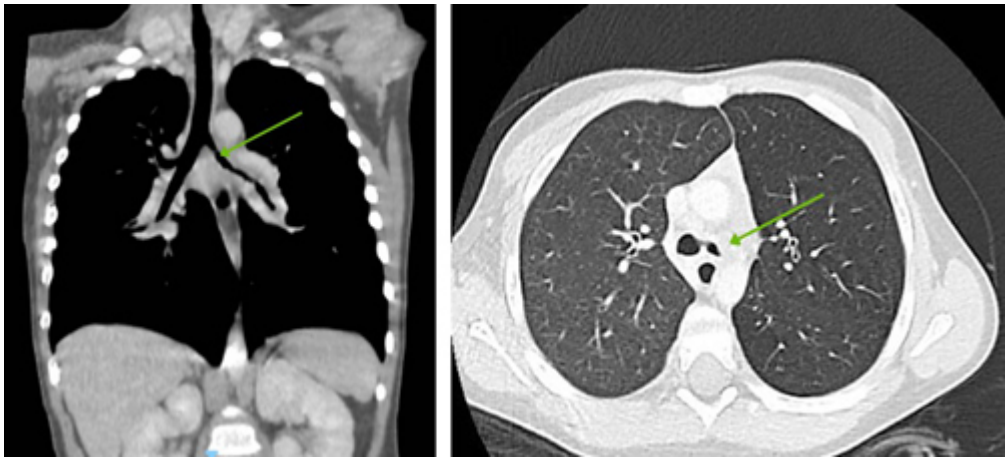

Figure 8.1 HRCT scan showed diffuse bronchial thickening with areas of parenchymal air trapping, particularly on the left side. There was a moderate reduction of approximately 50%–60% in the calibre of the left main bronchus from its tracheal origin to the lobar bronchi (arrow), with infiltration of the peribronchial tissues, without any obvious endoluminal lesion, but this cannot be confidently excluded on the CT scan alone.⏎

At 4 years and 7 months, impulse oscillometry revealed a severe increase in airway resistance, predominantly peripheral, and demonstrated a significant response to a bronchodilator (Figure 8.2). A long-acting beta 2-agonist was added to her inhaled corticosteroids.

		Pred	Linf	Lsup	Pré	%Pré	Pós	%Pós	Var(A
Date					23/10/		23/10		
Time					15:05:		15:24		
VT	[L]	0.17	0.10	0.25	0.25	141.7	0.26	147.4	-3.9
Z at 5 Hz	[cmH2O/(L/s)]	11.60	11.60	11.60	18.92	163.0	26.95	232.2	-29.8
R at 5 Hz	[cmH2O/(L/s)]	14.23	11.08	17.37	18.40	129.4	24.61	173.0	-25.2
R at 20 Hz	[cmH2O/(L/s)]	11.76	9.10	14.42	11.31	96.2	10.38	88.3	8.9
Delta R5-R20	[%]				38.55		57.80		-33.3
Diff R5-R20	[cmH2O/(L/s)]				7.10		14.22		-50.1
X at 5 Hz	[cmH2O/(L/s)]	-4.51	-6.02	-3.00	-4.38	97.1	-11.0	243.6	-60.1
Resonant frequency	[1/s]	21.53	21.53	21.53	34.54	160.4	30.65	142.4	12.7
AX	[cmH2O/L]	18.39	18.39	18.39	91.33	496.6	157.3	855.4	-41.9
Rcentral	[cmH2O/(L/s)]				5.87		0.67		777.1
Rperipheral	[cmH2O/(L/s)]				8.16		19.89		-59.0
CO at 5 Hz					0.4		0.6		-32.4

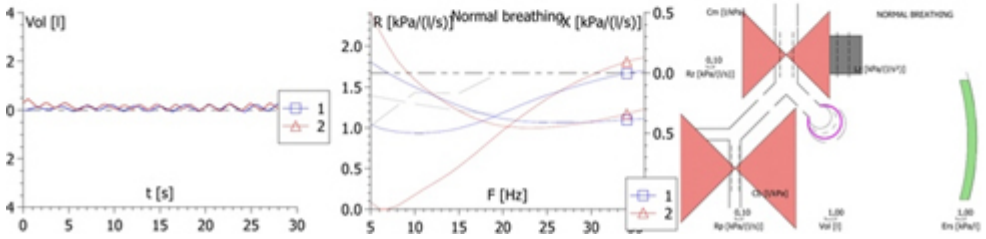

Figure 8.2 Impulse oscillometry at 4 years and 7 months showed a severe increase in airway resistance with peripheral predominance and a significant response to a bronchodilator.

At 5 years and 3 months, she was readmitted to the hospital due to worsening symptoms following discontinuation of adalimumab (3 months) due to a lack of medication supply by the health system. A chest x-ray showed hyperinflation of the right lung, with slightly more marked herniation of the contralateral right upper lobe through the anterior mediastinum. There was diffuse thickening of the bronchial walls and persistent leftward mediastinal shift and atelectasis of the left lower lobe (Figure 8.3).

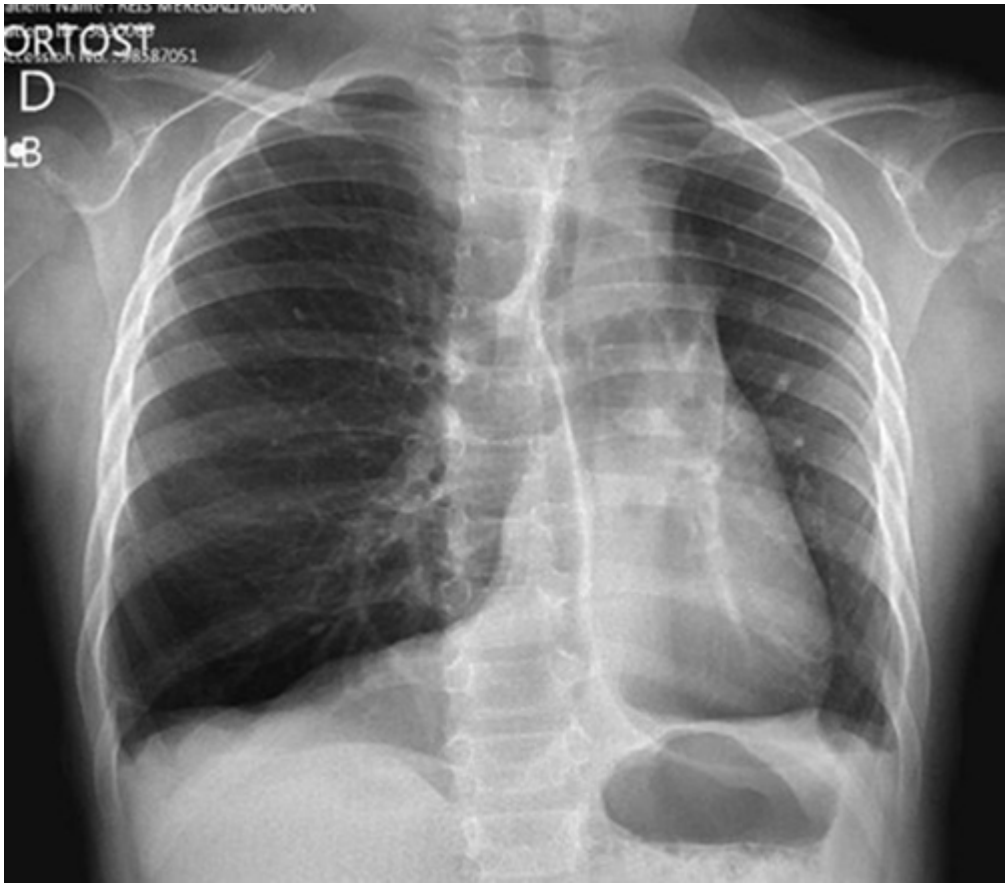

Figure 8.3 An X-ray at 5 years 3 months shows hyperexpansion of the right lung, with marked shifting of the right upper lobe into the left hemithorax (shifting of the anterior junction line), less marked displacement of the posterior junction line to the left and marked flattening of the right hemidiaphragm. There is diffuse thickening of the bronchial walls and persistent leftward mediastinal shift with complete atelectasis of the left lower lobe (seen behind the heart).⏎

A subsequent fibrobronchoscopy revealed a hyperaemic and friable trachea throughout its entire length, with a reduction in the calibre of the distal left main bronchus (Figure 8.4). A bronchial biopsy was performed, and the pathology examination revealed predominantly lymphocytic chronic inflammation (Figure 8.5). The result of BAL was as follows: leukocytes

400/µl; erythrocytes 760; neutrophils 94%; lymphocytes 5%; macrophages 1%. The culture from the BAL was positive for *Staphylococcus aureus*.

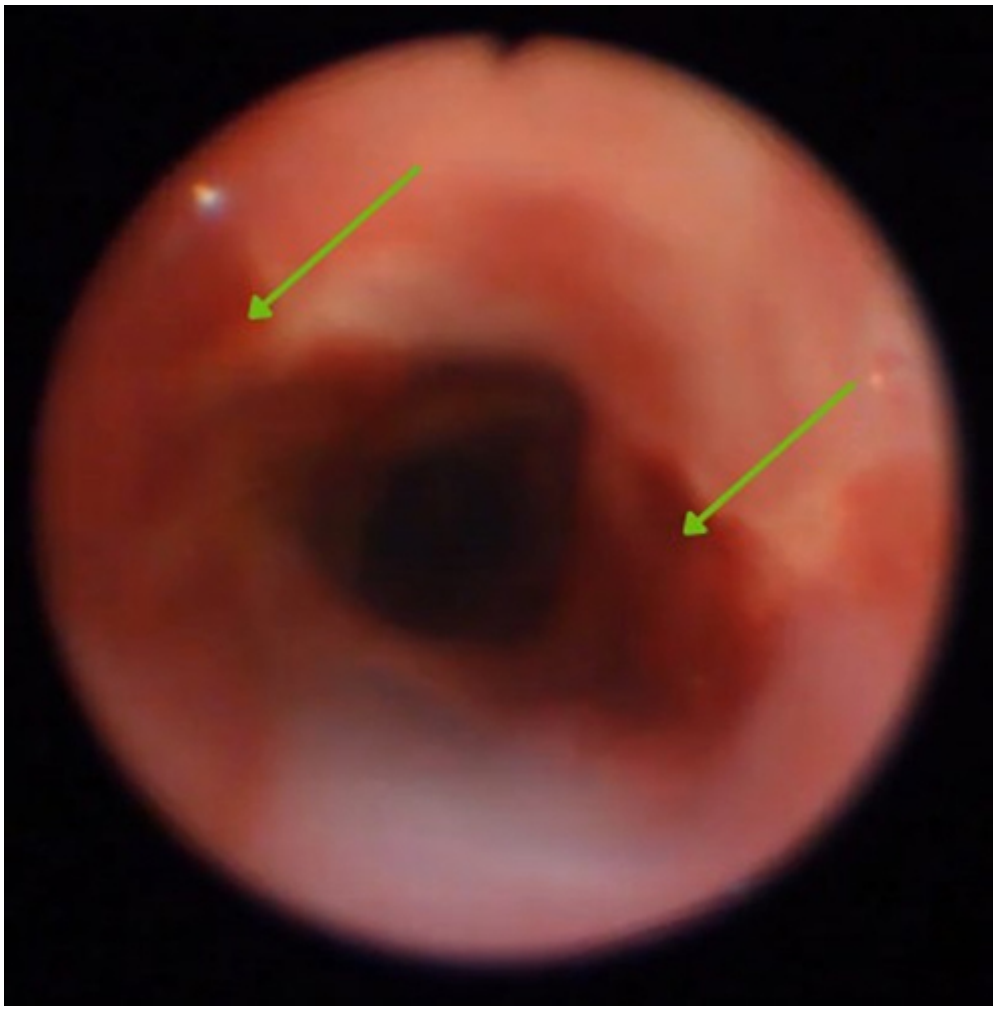

Figure 8.4 Fibrobronchoscopy at 5 years revealed a hyperaemic and friable trachea (arrows) throughout its length; reduction in the calibre of the distal left main bronchus.⏎

(Courtesy of Pediatric Thoracic Surgery Time.)

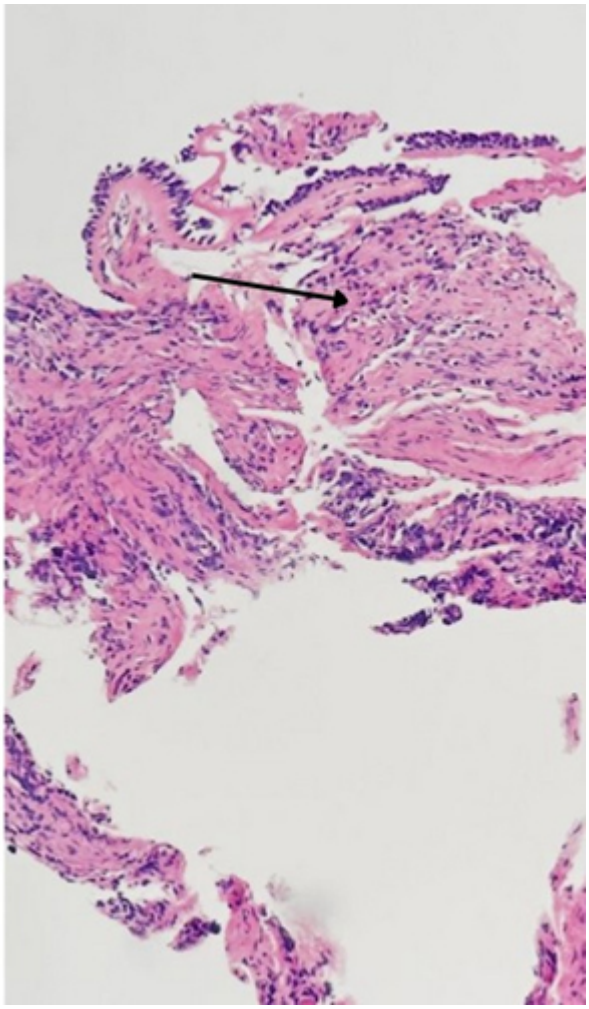

Figure 8.5 Pathological findings. Histopathological analysis of a biopsy specimen obtained from the trachea revealed chronic lymphocytic inflammation (black arrow).⏎

(Courtesy of Dr. Bianca Furlan.)

Microscopy with the Ziehl–Neelsen stain for detecting acid-fast bacilli, PCR GeneXpert® MTB/RIF Ultra (Cepheid) and culture for *M. tuberculosis* from bronchoalveolar lavage specimens were negative.

Further workup for infectious diseases, including fungal culture, was negative.

The second CT scan revealed a significant reduction in the diameter of the left main bronchus, with narrowing of up to 90% along its entire length, most notably in the distal segment. There was also a slight diffuse thickening of the walls of the intermediate bronchus, with a decrease in calibre of approximately 70% in the most distal segment. Additionally, there was complete atelectasis of the left lower lobe and hyperexpansion of the right lower lobe (Figure 8.6).

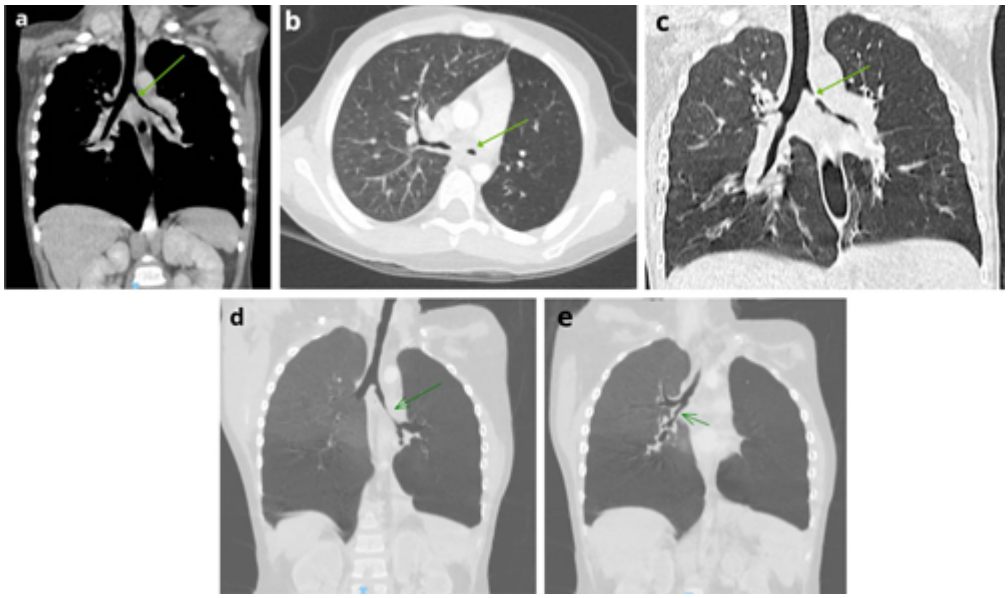

Figure 8.6 HRCT. (a–d) Significant reduction in the diameter of the right main bronchus, with narrowing of up to 90% along its entire length, most notably in the distal segment (arrow). (e) Diffuse thickening of the walls of the intermediate bronchus (arrow), with a decrease in calibre of approximately 70% in the most distal portion. There is complete atelectasis of the left lower lobe. The right lower lobe is expanded, presumed related to partial obstruction of the intermediate bronchus leading to air trapping, although a distal airway granulomatous component cannot be excluded.⏎

Adalimumab was able to be restarted. One month after the reinitiation of adalimumab, a new fibrobronchoscopy revealed a reduction in the volume of fibrin distributed throughout the respiratory tree; however, it remained friable during aspiration. There was also improvement in the calibre of the distal segment of the left main bronchus and the right basal bronchus.

QUESTION 1: *What are the potential causes of her respiratory symptoms?*

The differential diagnosis includes an unrelated condition such as asthma, a complication of her CD, and a complication of her anti-TNF-α therapy. However, the degree of the thickening would be very unusual for asthma.

In terms of an unrelated illness, the imaging findings make an asthma diagnosis implausible. Other chronic diseases such as cystic fibrosis, primary ciliary dyskinesia, and post-viral obliterative bronchiolitis were considered to be unlikely based on the clinical picture and imaging findings.

Inflammatory bowel diseases (IBD), which include Crohn's disease and ulcerative colitis (UC), are systemic illnesses that manifest not only in the gastrointestinal tract but also in other organs outside the intestine, known as extraintestinal manifestations (EIMs). Pulmonary manifestations of IBD in children are rare (3%–10%), while in adult patients they have been reported in 44% to 50% of cases.

Pulmonary involvement includes the upper and lower airways, lung parenchyma, and the pleura. The exact pathophysiology of pulmonary manifestations related to IBD remains unknown, but it is clearly inflammatory in nature. Respiratory symptoms may appear before, after, or simultaneously with the gastrointestinal presentation.

Clinically, the typical respiratory symptoms involving the lungs include a chronic, productive cough, tachypnoea, dyspnoea, and pleuritic pain. The main symptoms associated with airway involvement include cough, dyspnoea, stridor, and hoarseness. Furthermore, upper airway involvement

can lead to glottic or subglottic stenosis, inflammation, and tracheal stenosis.

The clinical spectrum ranges from asymptomatic (detected only through pulmonary function tests) to life-threatening respiratory problems, and the symptoms may be attributed to other causes or remain unrecognised by healthcare professionals. Pulmonary manifestations in children with inflammatory bowel disease typically remain asymptomatic and primarily involve the lung parenchyma, particularly the alveolar and interstitial regions, with organising pneumonia being the most commonly reported pathology. The majority of reported cases in children and adolescents are linked to CD rather than ulcerative colitis. The pulmonary lesions most commonly linked to CD are granulomatous diseases, which typically appear after gastrointestinal symptoms and often worsen during disease recurrences. These lesions can be detected both during active phases of the disease and during periods of remission.

A much commoner granulomatous respiratory disease in children is tuberculosis. The granuloma is a cellular organisation composed of T and B cells, macrophages, and dendritic cells capable of limiting the growth and spread of *M. tuberculosis.* This creates a dynamic balance between the pathogen and the host, leading to the latency of tuberculosis (TB) infection. Children infected with *M. tuberculosis* but who do not have active disease are classified as having latent pulmonary tuberculosis (LTBI) and are at risk of progression to active tuberculosis. Since airway Crohn's disease is most often a diagnosis of exclusion, it is essential to make every effort actively to exclude tuberculosis, as was done here.

TNF-α, a pro-inflammatory cytokine, is crucial for controlling mycobacterial infections. Its production plays a key role in the formation, organisation, and maintenance of granulomas. TNF-α enhances the phagocytosis and destruction of mycobacteria, promotes the apoptosis of ineffective macrophages, and prevents these cells from becoming reservoirs for the bacteria.

Thus, TNF inhibitors block cytokines that are crucial for host defence against various infections, including *M. tuberculosis.* The blockage of this cytokine impairs the immune system's ability to contain bacillary growth within protective granulomas. Adult patients receiving TNF-α inhibitors have an elevated risk of primary infections and a two- to fourfold increase in the risk of TB reactivation. Fortunately, unlike in adults, in children and adolescents, tuberculosis is a relatively uncommon complication of anti-TNF-α therapy if LTBI is screened for and treated before starting biologic treatment.

QUESTION 2: *What are the key differential diagnoses for pulmonary symptoms in patients with CD?*

Patients with Crohn's disease can develop respiratory illnesses due to various factors, including both infectious and non-infectious causes. Because many CD treatments can lead to immunosuppression, it is crucial to rule out infections, especially opportunistic ones such as tuberculosis, other mycobacterial infections, and fungi. Recognising pulmonary manifestations of inflammatory bowel disease is critical, as they can be mistaken for infections, potentially delaying appropriate treatment. Infection should be ruled out before treatment with a drug aimed at decreasing the underlying systemic inflammation, such as corticosteroids, immunomodulators, or biologics.

Side effects of medications used for the treatment of IBD may also cause pulmonary symptoms in patients with CD. The drug-related toxicities can have similar symptoms and pathology findings to IBD-related pulmonary manifestations. Drug-related lung injuries have been associated with the use of salicylates, azathioprine, 6-mercaptopurine (6-MP), methotrexate, mesalamine, sulfasalazine, and infliximab.

In this case, we did not consider that medications caused the large airways lesions because these medications, which are commonly used to treat IBD, primarily affect the lung parenchyma. Lung injuries related to infliximab can manifest as interstitial pneumonitis, alveolitis, and diffuse alveolar

haemorrhage. Typically, these injuries resolve upon discontinuation of the drug.

There is no gold standard for diagnosing LTBI and active tuberculosis in children, nor is there a universal diagnostic protocol. The TST and interferon-gamma release assay (IGRA) test for diagnosing latent tuberculosis infection have limited specificity and sensitivity. TST sensitivity is reduced in immunocompromised children, while IGRA shows low sensitivity in those under 5. Additionally, in children with inflammatory bowel disease, active disease may lead to indeterminate IGRA results.

Diagnosing active tuberculosis in children is challenging due to nonspecific symptoms that can be mimicked by other illnesses. Consequently, the diagnosis typically depends on a combination of epidemiological and clinical criteria, along with a nonspecific immunological test for tuberculosis infection and a chest image. The symptoms include weight loss, chronic cough, and fever, which are not always present. Other general signs and symptoms include anorexia, asthenia, night sweats, and lymphadenopathy. The most common form of pulmonary tuberculosis (PTB) is uncomplicated intrathoracic lymph node enlargement. On the other hand, children on anti-TNF-α therapy are prone to severe tuberculosis disease; symptoms tend to begin within the first 3 weeks of treatment initiation, and the most common presentation (78%) is miliary disease.

Culture remains the gold standard for the diagnosis of tuberculosis; however, microbiological tests are frequently negative because the number of bacilli in the lesions may be very low. The BAL specimens collected during bronchoscopy can be analysed using molecular assays and mycobacterial culture. The World Health Organization (WHO) recommends Xpert MTB/RIF (Xpert) and Xpert MTB/RIF Ultra (Xpert Ultra) as first-line diagnostic tests for pulmonary tuberculosis (PTB) and rifampicin resistance in children. Xpert Ultra is particularly effective for detecting tuberculosis in paediatric patients with paucibacillary TB, with a sensitivity of 95% and a specificity of 88.9%.

Bronchoscopy is the gold standard for evaluating airway compression and obstruction. Tracheobronchial tuberculosis (TBTB), which involves the trachea or bronchus, is typically diagnosed through tracheoscopy, with lymph node fistula being the most common type (approximately 96% of cases). Bronchial stenosis, a rare complication of endobronchial TB, occurs in 0.8% to 3% of cases. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a safe and effective method for diagnosing children suspected of having TB. This procedure provides real-time imaging and allows for the sampling of mediastinal and hilar lymph nodes. EBUS significantly increases the chances of obtaining tissue samples, which can be used for histological diagnosis, molecular testing, and microbiological confirmation. The procedure demonstrates high sensitivity and specificity, with culture positivity rates reaching up to 80%. This technique was not available to us.

Patients with immune-mediated diseases should be screened for LTBI at diagnosis before starting any immunosuppressive medications, especially if there is a possibility of future treatment with TNF-α inhibitors. This approach improves the accuracy of TB screening tests, as these tests may produce false-negative results in patients who have previously received immunosuppressive therapies. Patients with latent tuberculosis should be treated with isoniazid or a combination of anti-tuberculosis medications before starting anti-TNF therapy. It is essential to maintain a high level of suspicion for TB and to continuously monitor risk factors associated with TB acquisition.

In our patient, LTBI was ruled out before starting immunosuppressive therapy. A review of the medical history did not indicate any contact with *M. tuberculosis*, which could increase the risk of tuberculosis. Additionally, none of the tests performed identified the presence of *M. tuberculosis*, making the diagnosis of tuberculosis unlikely.

The final diagnosis was pulmonary manifestations of Crohn’s disease involving the large airways. The worsening obstruction of the trachea and bronchi following the discontinuation of adalimumab, along with the

notable, albeit incomplete, improvement observed after reintroducing the medication, supported this diagnosis.

QUESTION 3: *What investigations would you recommend for patients suspected of having pulmonary manifestations related to inflammatory bowel disease?*

Investigations are needed to exclude a coincidental intercurrent illness, to confirm the diagnosis of pulmonary complications of inflammatory bowel disease, and to exclude complications of treatment, especially tuberculosis.

Chest X-ray is usually normal or reveals nonspecific findings, such as bronchiectasis, pulmonary infiltrates, consolidation, nodules, and reticulonodular patterns. HRCT reveals bronchiectasis, localised concentric bronchial wall thickening, patchy asymmetric foci of consolidation in a peripheral or peribronchovascular distribution, and ground-glass opacities.

In children with airway CD manifestations, inflammation is predominantly in the small airways. In adults, a rare entity may involve the upper airways, pharynx, larynx, trachea, and main bronchi. In this situation, chest X-rays may show tracheal narrowing. In contrast, HRCT can identify clear circumferential or nodular thickening of the tracheobronchial wall and detect upper airway obstruction.

There is a very low prevalence of pulmonary changes on HRCT in children with IBD. This observation, along with the low incidence of abnormal pulmonary function tests, could suggest that pulmonary involvement in children with IBD is significantly less common than in adults. Therefore, performing routine HRCT would not be recommended in children unless there are respiratory symptoms. However, the differences in the pathological findings seen in HRCT scans between children and adults indicate a progressive nature of pulmonary involvement in IBD. While this progression often does not lead to clinical issues during childhood, it can substantially contribute to morbidity in adulthood.

Studies indicate that up to 94% of adult patients with active inflammatory bowel disease experience compromised lung function, particularly affecting the small airways, which are typically characterised by airflow obstruction without a significant reversibility to bronchodilators. In paediatric patients, spirometry and plethysmography yield inconsistent results, with lung function abnormalities typically being mild, predominantly obstructive patterns, and there is no correlation with IBD activity. A reduced diffusing capacity of the lung for carbon monoxide (DLCO) and the lung clearance index (LCI) may be significantly decreased. In children with Crohn's disease, there may be considerably reduced mid- and end-expiratory flow values, and 30% to 71% of asymptomatic patients exhibit bronchial hyperresponsiveness. Additionally, levels of fractional exhaled nitric oxide (FeNO) are elevated in children with IBD, compared to healthy individuals, regardless of disease activity. Only impulse oscillometry was performed in our patient because she had difficulty completing the manoeuvres required for spirometry and plethysmography, which is expected for this age group. Oscillometry demonstrated peripheral airway involvement in addition to the large airway involvement identified by fibreoptic bronchoscopy and HRCT. Other pulmonary function tests could not be performed due to unavailability at the site.

Bronchoscopy is a valuable diagnostic tool for evaluating large airways. This exam frequently reveals irregular, fragile, and haemorrhagic tissues, as it was found in our patient. Endoscopy may show small, patch-like (sub)-mucosal granulations in the large airways. The tracheal epithelium may be ulcerated and replaced by a thin layer of fibrin. Bronchoalveolar lavage can be performed to obtain specimens to identify infection and biopsies to identify the pattern of inflammation. A biopsy of mucosal granulations in the large airways may confirm that a granulomatous disease is present.

Non-infectious pulmonary disease in patients with Crohn's disease has variable histological appearances, including granulomatous inflammation and airway-centred disease. The most frequent pulmonary histology observed in children with CD includes non-caseating granulomatous parenchymal lesions. In one study of published cases of pulmonary manifestations in children with Crohn's disease, only 1 in 34 children

showed signs of tracheitis, as it was seen in our patient. In this reported case, a tracheal biopsy revealed granulomatous inflammation.

QUESTION 4: *What is the treatment for pulmonary manifestations of Crohn's disease?*

Once infectious and drug-related injury have been ruled out, treatment should be initiated. Standard therapy for the pulmonary manifestations of CD is not well described and is based on expert opinions. The therapy depends on the localisation and severity of the condition. An escalation of the current treatment for IBD should be considered, with an emphasis on the use of corticosteroids in the initial management. Corticosteroids can be administered either through inhalation or systemically, with the preferred route depending on the specific disease pattern. Parenchymal diseases and upper airway inflammation generally have better outcomes with systemic corticosteroids, whereas lower airway inflammation is more likely to improve with inhaled corticosteroids. For patients suffering from upper airway inflammation along with severe airway obstruction, such as subglottic stenosis, intravenous steroids (methylprednisolone) should be used. If the condition does not respond to steroid treatment, interventional bronchoscopy may be necessary, utilising techniques such as laser therapy, balloon dilation, or stent placement.

Most patients with pulmonary manifestations under standard treatment of IBD experience improvement in symptoms and imaging findings. In our patient, after restarting adalimumab therapy, her clinical symptoms and bronchoscopy findings showed significant improvement, which would not be expected were the child to be suffering from tuberculosis.

Most data on the pulmonary manifestations of inflammatory bowel disease in children come from case reports and case series with a small number of patients. The lung manifestations can differ widely and often create a complex diagnostic challenge. The relationship between IBD and pulmonary symptoms is not yet fully defined, highlighting the need for increased awareness and early identification of these associations. We are unaware of any guidelines recommending regular monitoring and treatment

of pulmonary manifestations in children with Crohn's disease. Clinicians should remain vigilant for pulmonary manifestations in patients with CD to ensure timely treatment, prevent complications, and reduce morbidity. Recognising these issues early allows for prompt intervention. Finally, as in any situation, the possibility that the doctor caused iatrogenic disease should never be forgotten.

KEY LEARNING POINTS

- Inflammatory bowel diseases (IBDs) are systemic illnesses that can present with pulmonary disease.
- These complications can affect the upper and lower airways, lung parenchyma, and pleura.
- The clinical manifestations can vary widely, ranging from asymptomatic cases to life-threatening respiratory problems.
- Treatment options for the larger airway manifestations of CD are not well established, highlighting the importance of corticosteroids and interventional bronchoscopy.
- In most patients, no symptoms and radiological findings improve with the standard treatment of IBD.
- Always consider the possibility of iatrogenic complications when caring for a child with a complex disease.

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CHAPTER 9 A RARE PAEDIATRIC CASE OF CHRONIC LUNG DISEASE AND IMMUNODEFICIENCY

To biopsy or not to biopsy?

Moria Be'er, Mika Rochman, Moran Lavie, and David Hagin

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INTRODUCTION

This case report presents a challenging and rare case involving a young girl with chronic lung disease, immunodeficiency, and a potential association with Kabuki syndrome. This chapter aims to detail the patient's clinical course, diagnostic challenges, and treatment outcomes.

CASE PRESENTATION

A 1.2-year-old girl, born at term as the second of twins, initially presented with recurrent and later persistent cough. She also had a cleft palate, which was surgically repaired, yet her respiratory symptoms persisted. The patient frequently presented with fever, cough, and persistent crackles on auscultation. Over time, her growth was impaired, and she developed digital clubbing.

QUESTION 1: *What initial diagnostic workup would you do?*

A thorough diagnostic evaluation was carried out, including:

1. Imaging
   - *Chest X-rays*: Initially showed peribronchial thickening and suspected left lower lobe infiltrates. Follow-up images showed persistent infiltrates and signs of chronic lung disease (Figure 9.1).
   - *Chest CT at 2 years*: Revealed a mosaic lung pattern, air trapping, and peribronchial thickening without bronchiectasis (Figure 9.2).
   - *Chest CT at 4 years*: Showed persistent large and small airways disease with more widespread bronchiectasis (Figure 9.3).
2. *Bronchoscopy and BAL*: Two bronchoscopies with bronchoalveolar lavage (BAL) were performed, revealing no anatomical issues. BAL and induced sputum cultures consistently identified *Haemophilus influenzae* as the primary pathogen. On one occasion, *Pseudomonas* was detected in a sputum culture and was successfully treated with oral ciprofloxacin to achieve eradication. Other positive cultures included *Moraxella catarrhalis* and *Streptococcus pneumoniae*. Fungal cultures were negative.
3. *Genetic testing*: Exome sequencing found a KMT2D missense mutation, classified as a variant of uncertain significance (VUS), associated with Kabuki syndrome. This variant was also present in her healthy father and sister. Kabuki syndrome

is a rare genetic disorder characterised by distinct facial features, developmental delay, congenital anomalies, and varying degrees of immunological dysfunction. It is most commonly associated with pathogenic variants in the KMT2D or KDM6A genes. Although our patient carried a KMT2D variant of uncertain significance, she exhibits some features seen in Kabuki syndrome, including cleft palate, recurrent infections, and immune dysregulation. However, she lacks the typical facial features and other major diagnostic criteria. Given this, the role of the KMT2D variant in her clinical presentation remains uncertain.

4. *Immunological testing*: The initial workup revealed low immunoglobulin levels, prompting further immunophenotyping. Testing showed abnormal B-cell maturation, with inadequate class switching and poor memory cell development (CD24highCD38low).
5. Additional laboratory tests

o *Sweat tests*: Normal results.

o *Cilia workup*: Nasal video microscopy conducted multiple times found no cilia, likely due to recurrent respiratory infections. Genetic testing revealed no primary ciliary dyskinesia-related mutations.

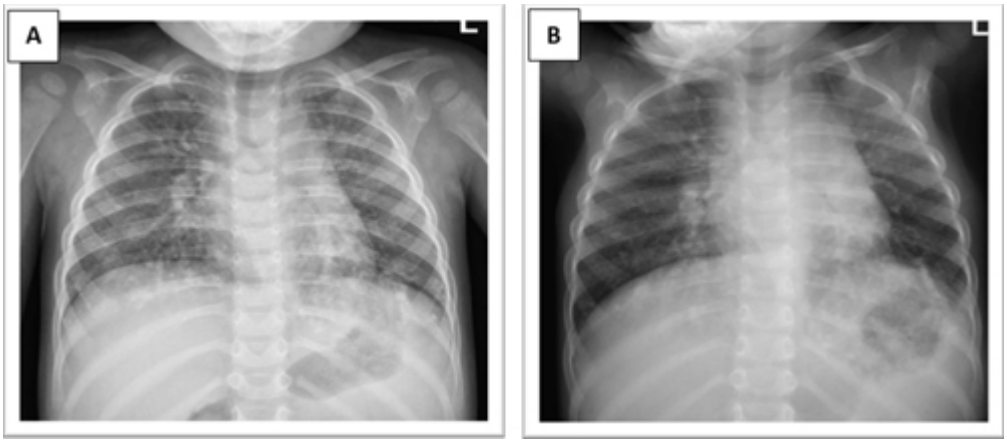

Figure 9.1 Initial chest X-rays.

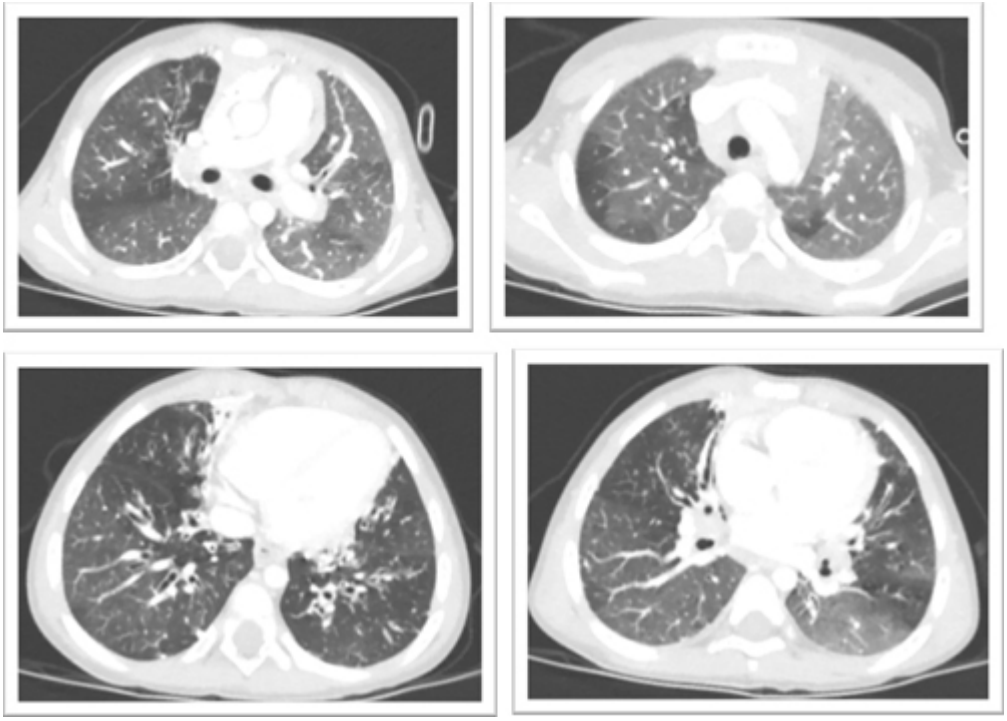

Figure 9.2 CT at age 2 years.

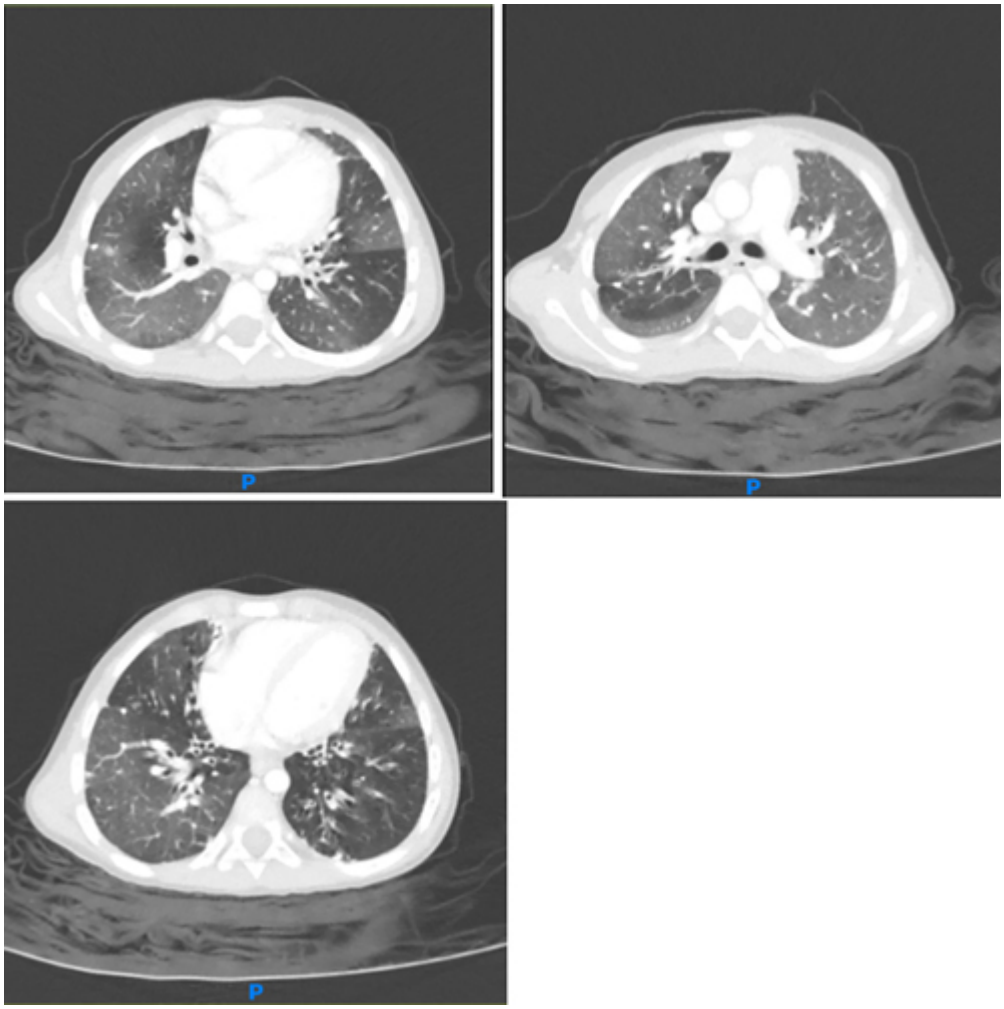

Figure 9.3 CT at age 4 years.⏎

Despite extensive diagnostic workup and treatment, including antibiotics, bronchodilators, inhaled corticosteroids (ICS), oral corticosteroids (OCS), and intravenous immunoglobulin (IVIG), the patient's condition deteriorated. Chest CT scans demonstrated worsening air trapping and the development of bronchiectasis.

QUESTION 2: *What test would you do next?*

Due to the lack of a definitive diagnosis and worsening symptoms, a lung biopsy was performed (Figure 9.4). Histological findings were consistent with granulomatous and lymphocytic interstitial lung disease (GLILD),

characterized by lymphoid infiltrates with germinal centres, non-necrotizing granulomas, and proliferation of CD20 cells.

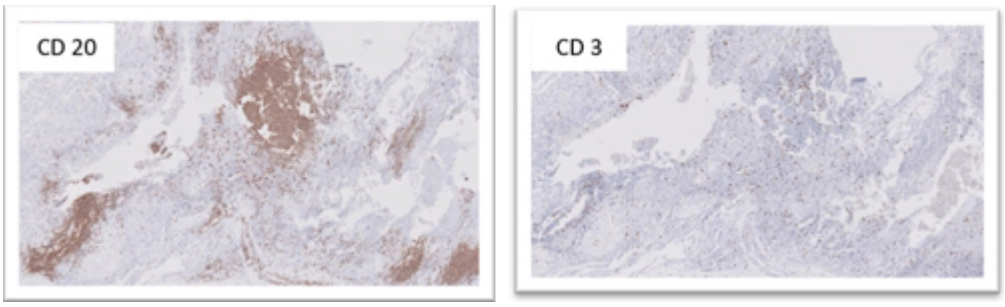

Figure 9.4 Lung biopsy.⏎

QUESTION 3: *What treatment would you advise now?*

Following the GLILD diagnosis, OCS were initially used as first-line therapy. However, the patient failed to respond adequately to OCS and experienced side effects. Consequently, rituximab therapy was initiated to manage the condition. Despite the introduction of rituximab, the patient subsequently experienced recurrent fever and intermittent cytopenias, which led to the discontinuation of the medication. Her condition did stabilize after discontinuation, but the management of her underlying immunodeficiency and chronic lung disease remains challenging.

KEY LEARNING POINTS AND DISCUSSION

This case highlights the complexity of diagnosing and managing a paediatric patient with GLILD in the context of underlying immunodeficiency and a genetic variant of uncertain significance. GLILD is a rare and challenging condition often associated with common variable immunodeficiency (CVID), though its occurrence in the context of Kabuki syndrome, as suggested by the KMT2D mutation found in this patient, adds another layer of complexity. GLILD is characterized by a combination of granulomatous inflammation and lymphoid hyperplasia, leading to progressive lung damage if not properly managed.

The treatment of GLILD is complex, particularly in paediatric patients, due to the heterogeneity of the disease and the potential for variable responses to therapy. In this case, oral corticosteroids were initially employed but were inadequate in controlling the disease and were associated with side effects. Given the suboptimal response, rituximab was introduced, targeting B cells to reduce lymphoid infiltration. However, the patient developed recurrent fever and cytopenias, which required discontinuation of the therapy. This illustrates the difficulties in balancing efficacy and safety in GLILD treatment.

The patient's clinical course was further complicated by recurrent respiratory infections and the early onset of bronchiectasis, which are significant risk factors for long-term morbidity in children with chronic lung diseases. The identification of a KMT2D missense mutation adds complexity to the case, as it is uncertain how this genetic finding contributes to the patient's respiratory and immunological manifestations. A further learning point is that more than one rare disease may coexist in the same child, and diagnostic efforts may need to continue after a single rare disease diagnosis.

Managing GLILD in such a young and complex patient requires a comprehensive multidisciplinary approach, involving close collaboration between paediatric pulmonologists, immunologists, geneticists, infectious disease specialists, and other healthcare providers. The challenges encountered in this case, including the inadequate response to standard therapies and the complications associated with biologic treatment, underscore the importance of integrating diverse expertise to tailor treatment plans, monitor disease progression, and address emerging complications effectively.

In summary, this case contributes to the understanding of GLILD in paediatric patients, especially those with underlying genetic and immunological complexities. The difficulties in diagnosis, treatment, and ongoing management underscore the need for careful, individualized care and a collaborative, multidisciplinary approach in such challenging cases. Additionally, this case highlights the importance of continued research into

the implications of genetic mutations, such as the KMT2D variant, in the context of chronic lung disease and immunodeficiency. There is also a pressing need to explore alternative therapeutic options for patients who cannot tolerate treatments like OCS and rituximab.

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CHAPTER 10 A BOY WITH HYDROPNEUMOTHORAX WHO DID NOT GET BETTER

Adelaide Ngina Masu

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BACKGROUND

Hydropneumothorax is a radiological finding of the presence of air and fluid in the pleural space. It is a rare manifestation of pleural disease in childhood. It is frequently reported as a manifestation of complicated pneumonia particularly due to streptococcus or staphylococcus. Necrotizing pneumonia with a ruptured pneumatoceles can lead to hydropneumothorax, and in certain regions of the world other infections like pulmonary TB are reported as a cause.

Hydropneumothorax condition can also occur secondary to chest procedures such as thoracentesis and transbronchial biopsy. Hydropneumothorax can be caused by chest trauma. Oesophageal and bronchopleural fistula can also lead to hydropneumothorax. Other conditions it has been reported to be secondary to are malignancy and rheumatological conditions, although these are rare in childhood.

The presentation is that of sudden onset of acute respiratory distress and unilateral pain. There is also asymmetrical expansion of the lungs with decreased air entry on the affected side. In a case where it causes a tension pneumothorax, cardiovascular collapse may be present.

A chest radiograph and a chest computed tomography scan are used for diagnosis. The radiological findings on chest radiograph reveal air and fluid

on the affected side with the absence of the meniscus sign seen in pleural effusion. Ultrasound can be used to identify a hydropneumothorax at the bedside, although this is not definitive.

The initial management of hydropneumothorax is to ensure that airway, breathing, and circulation are stable, with intervention where needed. A chest drain is inserted on the affected side to drain the fluid and air. The underlying cause needs to be treated to prevent recurrence.

Here we present a child with an apparently straightforward hydropneumothorax who did not improve despite multiple attempts at drainage of the pleural space. Further investigation revealed an unusual manifestation of a common diagnosis.

CASE PRESENTATION

A 10-year-old boy who was previously well presented to a referral hospital with symptoms of one day of exertional dyspnoea. A chest radiograph was performed (Figure 10.1).

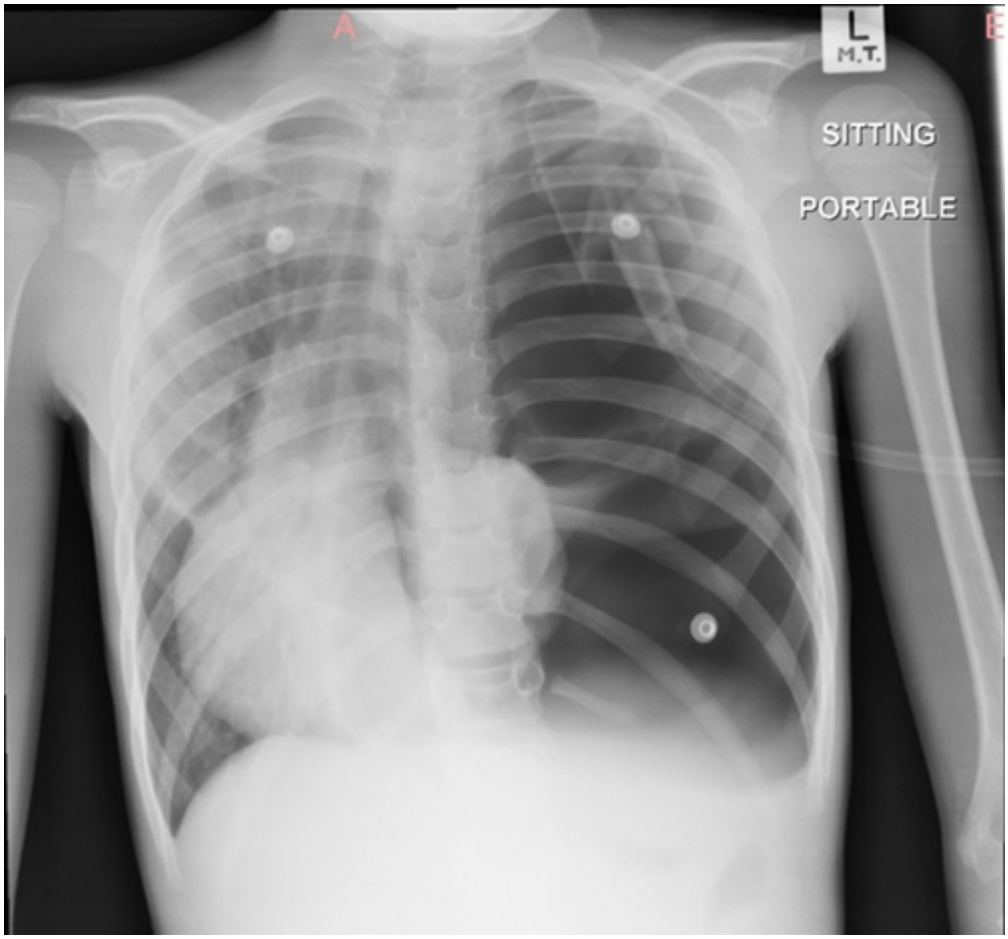

Figure 10.1 Chest X-ray taken during the first presentation at the referral centre.⏎

The radiograph showed a tension pneumothorax on the left side of the chest with marked mediastinal displacement. His past medical history was of recurrent chronic cough in early childhood which was attributed to a diagnosis of asthma, and this had improved with time. He had a positive family history of pulmonary tuberculosis.

He was referred to my institution, the Red Cross War Memorial Children's Hospital (RCWMCH), for further management of the pneumothorax, which persisted after three intercostal drain (ICD) insertions at the referring hospital. The first two drained nothing; the third drained purulent fluid. The pneumothorax persisted despite the first and second drains, although the pneumothorax was still under tension (Figure 10.2).

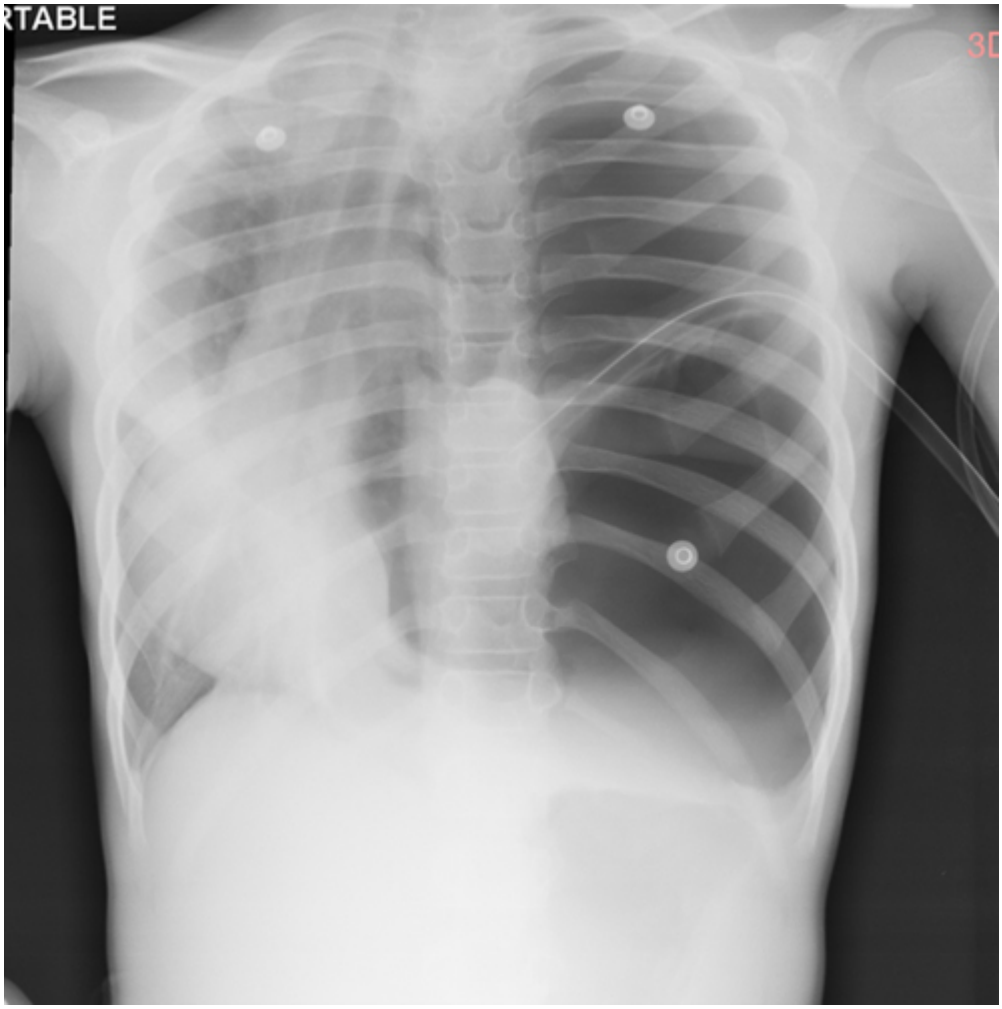

Figure 10.2 The new chest drain was inserted at the referral hospital. Despite the excellent position of the chest drain, the pneumothorax persists and remains under tension.⏎

On the third attempt, the ICD drained purulent fluid, and samples sent for analysis revealed an exudate (Table 10.1). A CT scan requested during admission was grossly abnormal (Figure 10.3). The boy was commenced on Augmentin 540 mg 8 hourly intravenously and was transferred to our institution.

Table 10.1 Initial investigations⏎

Investigation	Results

Investigation	Results
FBC	WCC 12.99, Hb 11.3, Plets 471
CRP	72 mg/L
HIV Elisa test	Negative
Sputum (2 samples)	GeneXpert PCR negative, AFB smear negative
Pleural fluid analysis	: Chemistry: Protein 64 g/dL, LDH ratio 5443 IU/L, Triglyceride 0.2 mg/dL Cells: 76 Polys, 4640 Lymphocytes TB GeneXpert: Negative, TB culture pending MCS: No microorganisms observed, culture pending *Exudate*

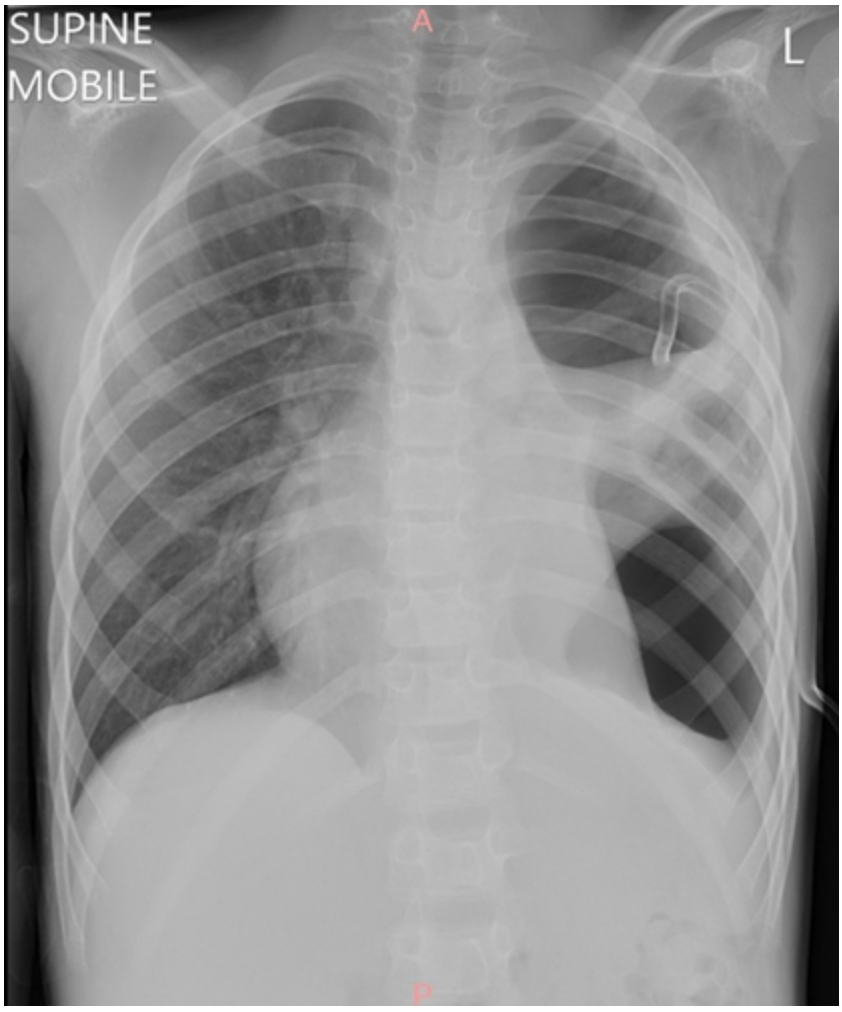

Figure 10.3 A chest drain reinserted at the RCWMCH. Despite an appropriately positioned intercostal drainage tube, the left-sided pneumothorax persists, with a new air-fluid level suggesting hydropneumothorax.⏎

The CT scan performed at the referring hospital demonstrated a gross hydropneumothorax on the left side causing collapse of the left lung and ongoing tension displacing the mediastinum to the right. Not shown on this scan was the deviation of the trachea and mediastinum towards the right side and flattening of the left diaphragm.

At presentation to the RCWMCH institution, physical examination revealed a child who was apyrexial with a respiratory rate of 25 breaths per minute, saturations of 98% in room air, heart rate of 94 beats per minute, and blood pressure of 132/79 mmHg. His respiratory examination showed him to be comfortable in room air and auscultation revealed decreased breath sounds in the left lung and crackles over the right lung. He had a normal abdominal examination. Investigations are summarized in Table 10.1.

QUESTION 1: *What is the differential diagnosis?*

A bacterial pneumonia can be complicated by hydropneumothorax. In support of this is purulent fluid on insertion of ICD and a pleural fluid exudate with elevated polymorphonuclear cells and elevated CRP in the blood. There were no microorganisms observed or cultured on the pleural fluid or the blood.

Pulmonary tuberculous effusion is another important consideration as it is endemic in the region and supported by the presence of an exudate with high protein levels. In addition to this, the boy had a positive family history of TB.

A malignant pleural effusion is another differential diagnosis; however, the exudate contained no blood and no masses were observed on imaging.

A secondary spontaneous pneumothorax with persistent air leak from, for example, a congenital thoracic malformation, is another possibility. However, it is not clear whether the lungs are normal on the side of the pneumothorax as the lung tissue is collapsed and the associated fluid is not classical.

QUESTION 2: *Was complicated pulmonary TB completely ruled out?*

The patient had now been on intravenous Augmentin (co-amoxiclav) for 7 days with no improvement, and there were continuing concerns of complicated pulmonary TB disease given the positive family history. The paediatricians proceeded to investigate further for pulmonary TB. A TB GeneXpert was repeated on more sputum and pleural fluid and was negative. A bronchoscopy was done which revealed purulent secretions in the left lower lobe of the left lung. The rest of the anatomy was normal. Bronchoalveolar lavage specimens were sent away for microscopy, culture, and sensitivity including TB GeneXpert and culture. A fourth chest drain was inserted by the surgeons in theatre and it drained 100 mL of purulent fluid. The results were negative pending cultures. A CT scan was repeated as seen in Figure 10.4.

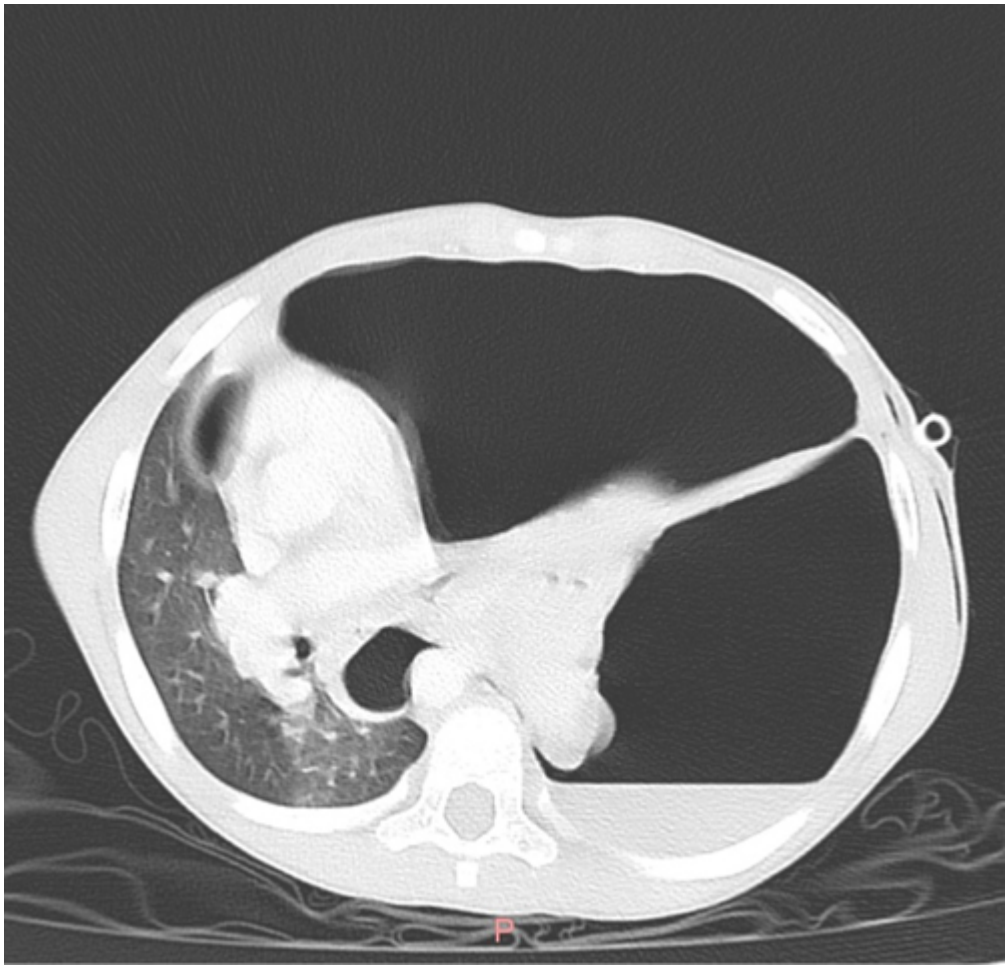

Figure 10.4 What abnormalities are seen on this CT?

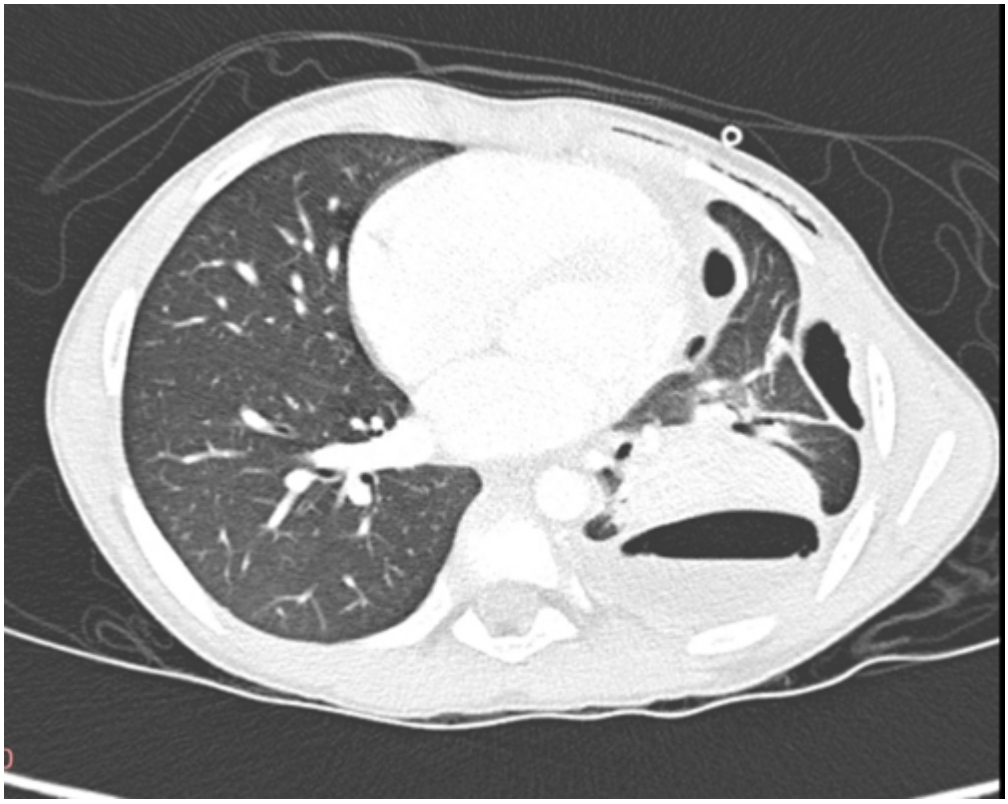

Figure 10.5 What are the appearances in the new chest CT scan?⏎

The chest CT scan now reveals a left hydropneumothorax with apical thoracostomy tube in situ with mild associated surgical emphysema. There is partial re-expansion of the left lower lobe which did not have an abnormal appearance as far as could be ascertained from the limited images and resolution of the prior tension with normal positioning of the mediastinum. The fistula is difficult to see, but the ongoing air leak means it is definitely present (Figure 10.5).

QUESTION 3: *What is the next step?*

The fevers continued with no improvement, and the child was now on TB treatment. The pneumothorax persisted with some expansion of the left lower lobe. The right lung was normal on the CT scan. Surgery was planned for a left-sided pleurodesis. At surgery, a left postero-lateral thoracotomy was performed. A hydatid cyst was found with an intact ectocystic wall and

some endocystic contents were present. The cyst was resected. The lung re-expanded and air leaks were closed. A postoperative chest X-ray showed marked improvement (Figure 10.6).

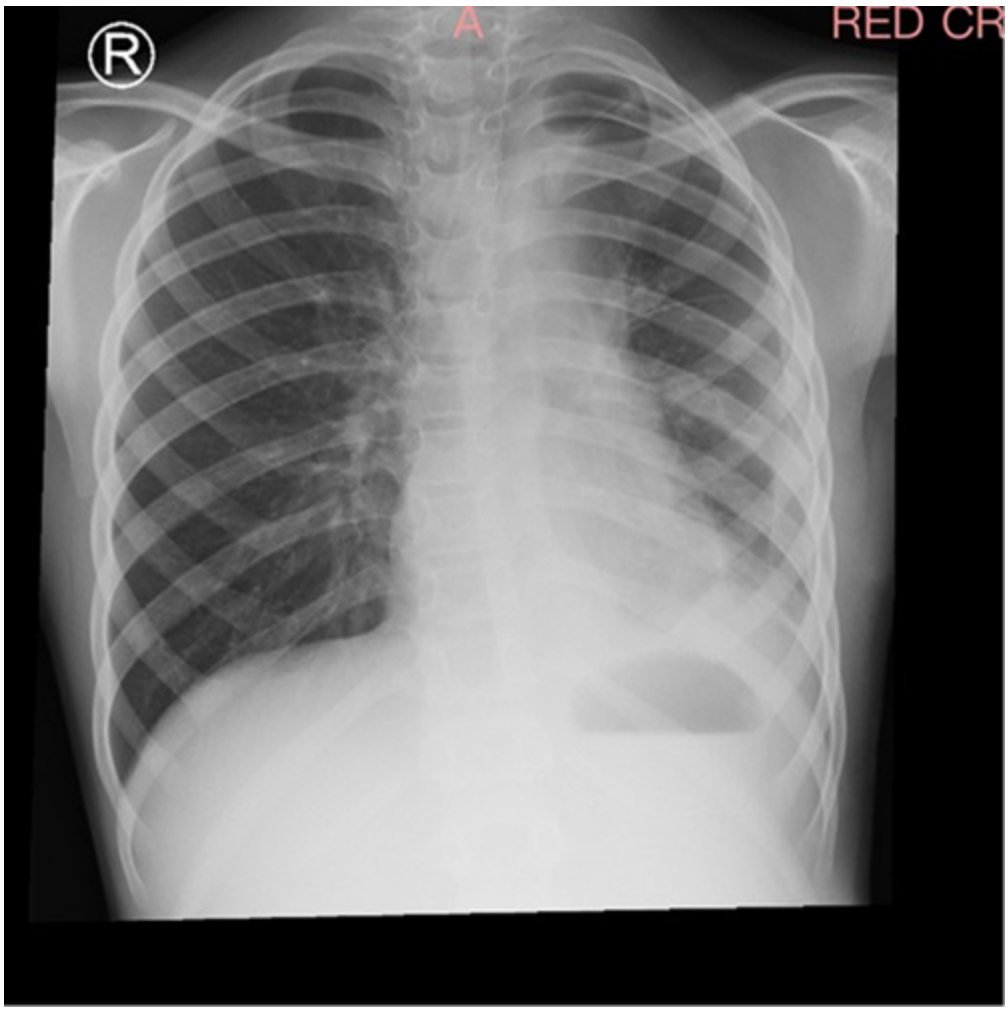

Figure 10.6 Postoperative chest radiograph showing marked re-expansion of the left lung.

The spirometry performed before discharge was normal. On re-examination of the chest CT scan, a fluid-filled cystic mass was noted on the right lobe of the liver (Figure 10.7). The child was started on praziquantel and albendazole (doses) for 6 weeks as the surgeons elected to manage the liver cyst without surgery. Subsequently, the echinococcus serology requested on admission to RCWMCH was positive (IgG 8.5 IU/L on ELISA test). At

follow-up in the clinic, the boy was well with no progression of his liver disease.

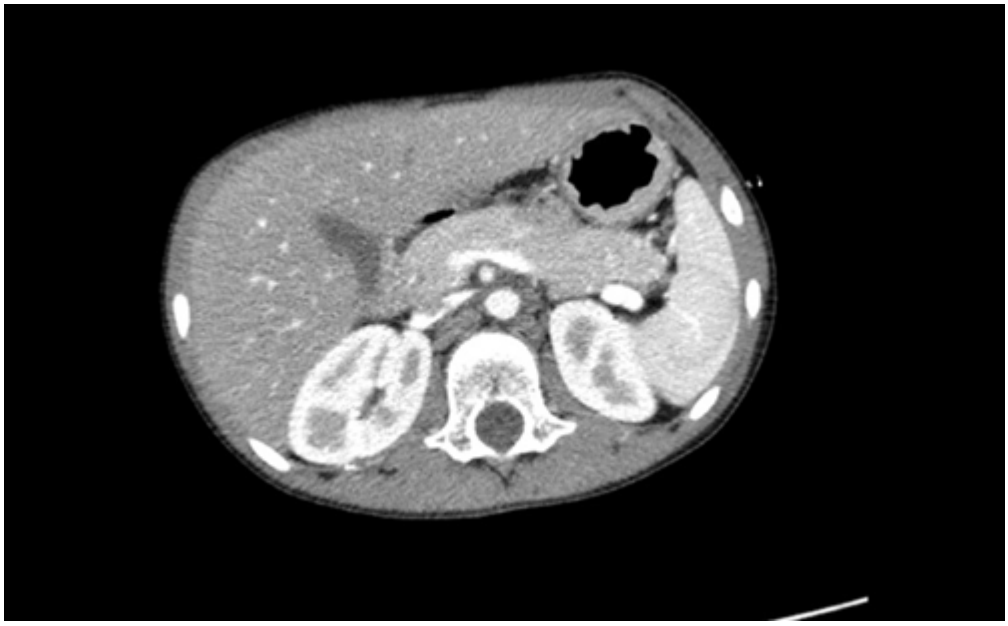

Figure 10.7 There was a hydatid cyst in the right lobe of the liver.⏎

DISCUSSION

This boy presented with what appeared to be a simple hydropneumothorax. When this failed to respond to medical treatment, investigations for an underlying cause were pursued appropriately, and the patient was referred for surgical management. This led to the underlying diagnosis of hydatid disease.

QUESTION 4: *How does hydatid disease present?*

A hydatid cyst presents as either pulmonary disease or hepatic disease, or both. In children, pulmonary disease predominates and presents as thin-walled cysts, either single or multiple cysts in either one or multiple lobes (Figure 10.8). The radiological presentation varies depending on the stage of development of the cyst and whether or not it is ruptured. An important

presentation of hydatid cystic lung disease is a pneumothorax, which is caused by the rupture of a cyst into the pleural space. This can be spontaneous or as a result of increased intrapulmonary pressure due to coughing or sneezing. Rupture of the contents of a hydatid cyst can either be direct, with both endocyst and pericyst spilling their contents into the pleural space, or a contained rupture where the endocyst ruptures and the pericyst remains intact. A bronchopleural fistula can also cause a pneumothorax that is refractory to treatment.

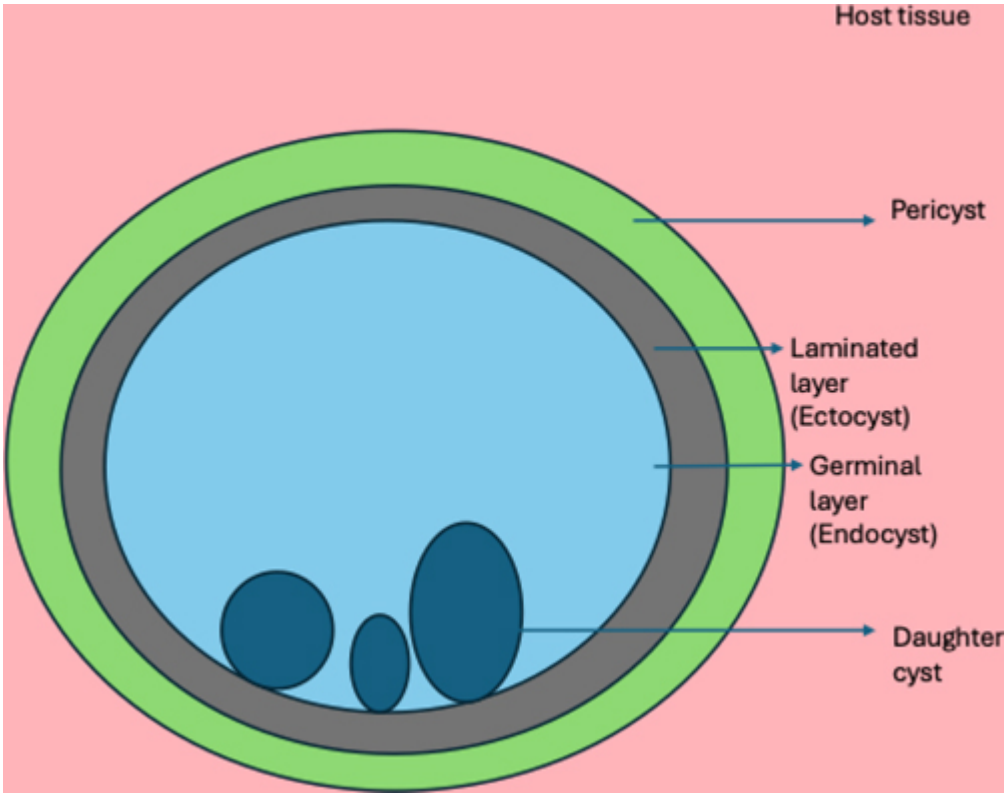

Figure 10.8 Picture of layers of hydatid cyst in host tissue.

QUESTION 5: *How is hydatid disease diagnosed?*

Hydatid pulmonary disease is diagnosed on chest radiology, chest CT scan, ultrasonography, or MRI scan by the presence of cysts in different states. Other supporting tests are available, like immunodiagnostics and

echinococcus serology; however, there is cross-reactivity with *Taenia* species. Polymerase chain reaction test is also available.

QUESTION 6: *How is it managed?*

The management of hydatid cysts differs in regions, with some advocating the excision of cysts whether they are complicated or not. The World Health Organization recommends medical management only for small or uncomplicated cysts. In the case of surgical excision of the cyst, parenchymal preserving methods are used, such as enucleation of the intact cyst or cystostomy. In some centres, treatment of the cysts with anthelminthics is used for specific indications such as inoperable liver cysts, multiorgan involvement, and prophylaxis against secondary echinococcus. The drugs of choice are albendazole and praziquantel, although some clinicians opt for monotherapy with albendazole.

In the case of hepatic cysts, percutaneous interventions can be performed instead of open surgery, and this has been demonstrated to have less adverse outcomes post-procedure, with a reduction in the length of stay in hospital. This technique is not routinely employed in the management of paediatric echinococcosis.

Complications from hydatid disease can be severe. The fluid contained in cysts is antigenic and toxic, and if cysts rupture into the peritoneum, anaphylaxis results. Spilling of the contents of hydatid cysts can even occur during surgery at the time of the removal of the cyst, also leading to anaphylaxis. A ruptured cyst can spread via the blood to different organs, causing daughter cysts to develop in other organs – an important extrathoracic clue to a thoracic diagnosis!

KEY LEARNING POINTS

- A clinical condition not amenable to therapy should raise the index of suspicion of wider possibilities of causes.

- In endemic areas, common conditions can present in unexpected ways.
- Hydatid pulmonary disease has a variety of presentations, some of which are rare and unusual.
- Pulmonary TB is not always the culprit of complicated pulmonary disease in high-burden areas.

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CHAPTER 11 UNEXPLAINED HYPOXAEMIA IN A TODDLER

A diagnostic journey

Brecht Van der Mast, Heidi Schaballie, Mariska De Lausnay, Petra Schelstraete, Bram De Wilde, Stijn Lambrecht, and Julie Willekens

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INTRODUCTION

A young patient presented with a seemingly straightforward case of bronchiolitis, characterized by respiratory distress and hypoxaemia. Despite appropriate treatment, the child's oxygen saturation failed to improve, presenting the treating team with a diagnostic challenge. As the case unfolded, a surprising diagnosis was made. This case gives an overview of the differential diagnosis of hypoxaemia and highlights the importance of careful interpretation of oximetry test results, even in the context of a common respiratory illness.

CASE PRESENTATION

A 14-month-old girl presented at the emergency department of a regional paediatric hospital with a 3-day history of fever, cough, dyspnoea, and anorexia. She had a history of viral-induced bronchial hyperreactivity, currently without maintenance treatment. The family history revealed sudden infant death of the father's sister. The mother suffered from asthma and pollen allergy. Both parents were active smokers.

Clinical examination showed a well-nourished child without dysmorphic features. The girl presented with tachypnoea (respiratory rate of 60/min), inter- and subcostal retractions, oxygen saturation (SpO_2) of 89%, and tachycardia (170/min). Lung auscultation was marked by bilateral wheezing and crackles. Mild splenomegaly was noted on abdominal palpation.

Peribronchial cuffing and infiltrative changes in the right perihilar and left infrahilar regions were visible on chest radiography (Figure 11.1). Biochemical workup revealed leukocytosis (WBC 22,600/µL) with neutrophilia, normal CRP, and mild normocytic anaemia (haemoglobin 9.3 g/dL [age-adjusted reference interval 11.0–14.0 g/dL]). Nasopharyngeal swab tested positive for respiratory syncytial virus and human rhinovirus.

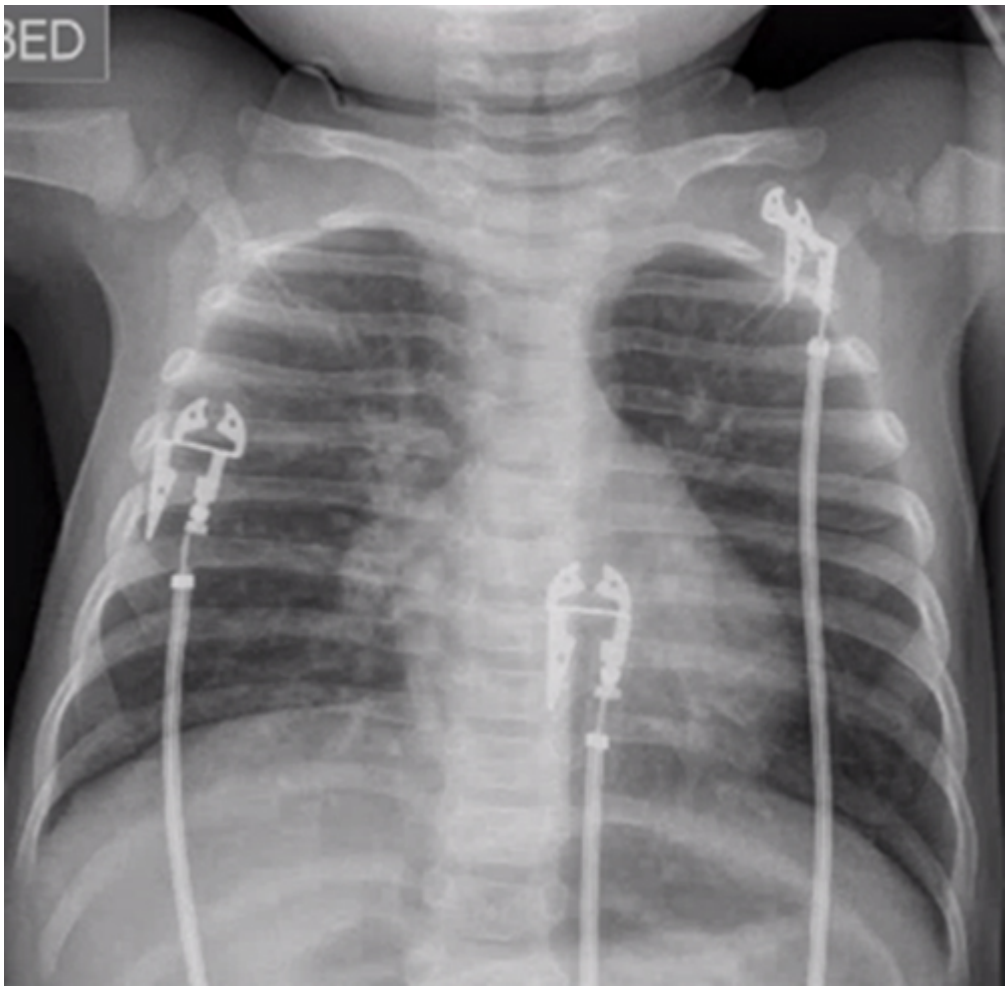

Figure 11.1 The initial chest X-ray shows peribronchial cuffing and infiltrative changes in the right perihilar and left infrahilar regions.⏎

QUESTION 1: *What is the most likely cause of this child's hypoxaemia?*

The presentation is compatible with viral bronchiolitis in a child with underlying bronchial hyperreactivity.

Treatment with salbutamol inhalations was started. However, due to progressive tachydyspnoea and persistently low SpO_2 despite supplemental oxygen, she was transferred to the paediatric intensive care unit. She was treated with high-flow nasal cannula oxygen therapy and corticosteroids. After 3 days, a marked clinical improvement was observed with normalized work of breathing and a borderline SpO_2 level of 92% with low-flow nasal cannula. She was transferred to the referring hospital for continued care. However, despite the clinical improvement and normalization of the lung auscultation, low SpO_2 persisted 4 days after transfer.

QUESTION 2: *What is your differential diagnosis for this persistent hypoxaemia?*

Hypoxaemia can be caused by different pathophysiologic mechanisms, as listed in Table 11.1.

Table 11.1 ⏎

Pathophysiologic mechanism	Examples	Diagnostic tests
Right-to-left shunt	Cyanotic congenital heart disease Intrapulmonary shunt Portosystemic shunt	Echocardiogram Bubble test Contrast-enhanced chest/abdominal CT Abdominal Doppler ultrasound Perfusion scan, obtaining counts over brain and kidneys to detect shunted contrast

Pathophysiologic mechanism	Examples	Diagnostic tests
V/Q mismatch	Obstructive airway disease Pulmonary thromboembolic disease	Chest CT Spirometry Contrast-enhanced chest CT
Hypoventilation	Congenital central hypoventilation syndrome Neuromuscular disease Medication-induced respiratory depression (narcotics)	Blood gas Sleep study Genetic analysis Creatine kinase
Reduced haemoglobin-carrying capacity	Methaemoglobinaemia Haemoglobinopathy	CO-oximetry or blood gas
Diffusion limitation	Interstitial lung disease	DLCO CT chest

A workup for chronic hypoxaemia was initiated. Chest radiography after 2 weeks showed no residual infiltrates. A contrast-enhanced chest CT was performed (Figure 11.2), showing no signs of interstitial lung disease, arteriovenous malformation, or intrapulmonary shunting.

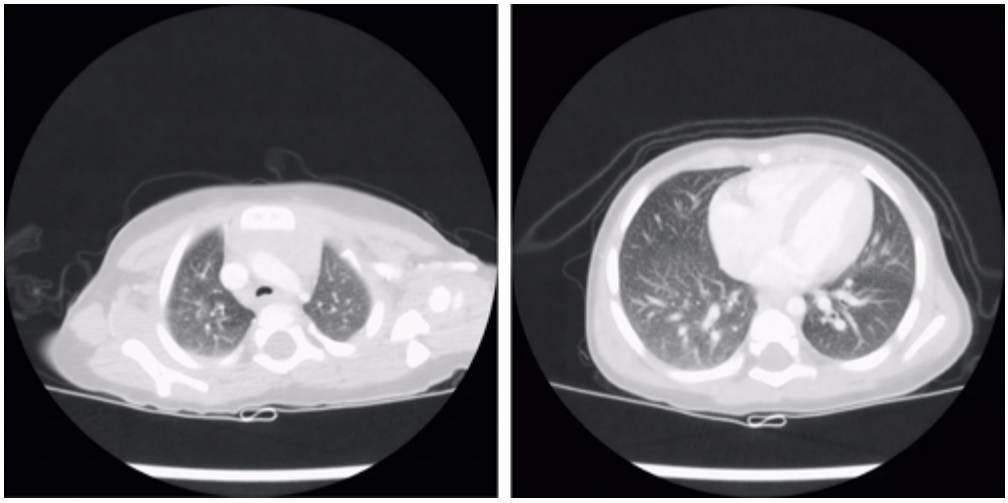

Figure 11.2 Chest CT images demonstrating mild mosaic attenuation thought to be too limited in extent to explain the clinical features.⏎

Laboratory tests demonstrated persistent normocytic anaemia, with a haemoglobin level of 7.8 g/L, mean corpuscular volume (MCV) of 93 fL (reference interval (RI) 70–86 fL), and haematocrit of 26.4% (RI 30–42%). Haemolysis workup revealed a significantly elevated reticulocyte count (168/1000), undetectable haptoglobin (<0.1 g/L), and markedly increased lactate dehydrogenase levels (995 U/L), consistent with haemolytic anaemia. Venous blood gas showed low levels of carboxyhaemoglobin and methaemoglobin.

Echocardiography showed no structural heart defects. A contrast-enhanced echocardiogram was negative, excluding an intrapulmonary or intracardiac shunt. Abdominal and liver Doppler ultrasound did not reveal any arteriovenous shunts. Splenomegaly was confirmed on the abdominal ultrasound. An overnight pulse oximetry and transcutaneous capnography revealed low SpO_2 (medium level of 89%–90%, rising to 93% with oxygen) with normal CO_2 values.

QUESTION 3: *What diagnostic test would you do next?*

An arterial blood gas was performed to confirm the hypoxaemia and showed a normal partial pressure of oxygen in the arterial blood (PaO_2), as well as a normal oxygen saturation (sO_2) measured by CO-oximetry. These results were in clear discrepancy with the pulse oximetry, which simultaneously showed a low SpO_2 of 89%. A congenital haemoglobinopathy was strongly suspected and haemoglobin electrophoresis was performed.

QUESTION 4: *How does pulse oximetry work and how can we be misled by it?*

Pulse oximetry is a non-invasive method used to measure the percentage of oxygenated haemoglobin relative to the total amount of haemoglobin, abbreviated to oxygen saturation (SpO_2). This technique relies on the differences in light absorption of oxyhaemoglobin and deoxyhaemoglobin. Each form has distinct optical absorption characteristics at different

wavelengths: oxyhaemoglobin absorbs mainly infrared (IR) light (~940 nm), whereas deoxyhaemoglobin absorbs mainly red light (~660 nm). The pulse oximeter consists of a light-emitting diode (LED) and a photodetector, which detect the pulsatile flow of arterial blood. The amount of absorbed light will change as the blood pulses; the device will calculate peripheral SpO_2 based on these absorption differences.

Although pulse oximetry is a useful tool, certain conditions can lead to inaccurate SpO_2 readings due to the following mechanisms:

1. Inaccurate measurement of pulsatile arterial flow.

    - Poor peripheral perfusion including vasoconstriction: Difficulty detecting an accurate signal due to reduced blood flow (e.g., in hypovolemic shock, hypothermia, use of vasoconstrictive medication, poor cardiac output caused by cardiac failure or arrhythmia).
    - Motion artifacts, patient movement: Can lead to unstable readings.
    - In rare cases detection of venous pulsations (e.g., too tight placement of probe, or severe tricuspid regurgitation, or vasodilation in distributive shock) can lead to falsely low SpO_2.

2. Interference with light absorption.

    - Nail polish, artificial nails (especially black, red, or blue color): Interference with light absorption can lead to falsely low SpO_2 readings.
    - Carbon monoxide poisoning: Avidity of carbon monoxide for Hb is 240 times greater than that of oxygen. Pulse oximeters cannot distinguish between oxyhaemoglobin and carboxyhaemoglobin, leading to an overestimation of SpO_2.
    - Methaemoglobinaemia and sulfhaemoglobinaemia: Met- and sulfhaemoglobin interfere with light absorption, resulting in falsely low SpO_2 readings.

- Sickle cell disease: During vaso-occlusive crises, SpO_2 may overestimate the actual oxygen content due to increased carboxyhaemoglobin levels.
- Congenital haemoglobin variants: Some haemoglobin variants have reduced affinity for O_2, so changes in SpO_2 will be accurate. Other variants interfere with light absorption, leading to falsely low SpO_2 readings.
- Pigmented skin: Melanin in the skin can interfere with light absorption, leading to overestimation of SpO_2.
- Intravenous contrast fluids (e.g., methylene blue, indigo carmine) can result in falsely low readings of SpO_2 due to interference with light absorption.

Understanding these limitations is crucial for accurate clinical assessment and to avoid misdiagnosis.

OUTCOME OF THE CASE

Haemoglobin electrophoresis revealed an unstable haemoglobin variant, explaining the haemolytic anaemia, splenomegaly, and low SpO_2 with adequate sO_2. Genetic workup showed a c.275T>C (p.Leu92Pro) mutation in the HBβ gene, responsible for a rare unstable low oxygen affinity haemoglobinopathy called Hemoglobin Sabine. The patient was discharged without supplemental oxygen and will be followed up in the paediatric haematology clinic. The most recent laboratory workup showed persistent anaemia with markedly positive haemolysis parameters.

Haemoglobin is a tetramer composed of two alpha- and two beta-like globin subunits. To date, over 1800 variants have been described, caused by mutations affecting the globin genes. The interaction between globin chains and heme is crucial for both the oxygen-binding properties and structural stability of the molecule. Haemoglobin variants may alter these characteristics, leading either to molecular instability with associated haemolysis or to alteration in oxygen binding, resulting in high or low

oxygen affinity. High affinity haemoglobin variants have an increased ability to bind with oxygen in the lungs, resulting in normal SpO_2 levels but reduced oxygen release to the tissue, leading to tissue hypoxia. In contrast, low oxygen affinity variants release oxygen more readily to the tissues. At a normal pO_2 of 90 to 100 mmHg, most low affinity variants may be fully saturated. However, some low affinity haemoglobin variants may result in lower SpO_2 due to a right-shifted oxygen dissociation curve and a higher threshold to become fully saturated with oxygen. Moreover, a subset of haemoglobin variants can cause falsely low SpO_2 measurements due to abnormal light absorption by the pulse oximeter. In such cases – as in our case – the discrepancy can be resolved by comparing SpO_2 with SaO_2, obtained via arterial blood gas analysis (Figure 11.3).

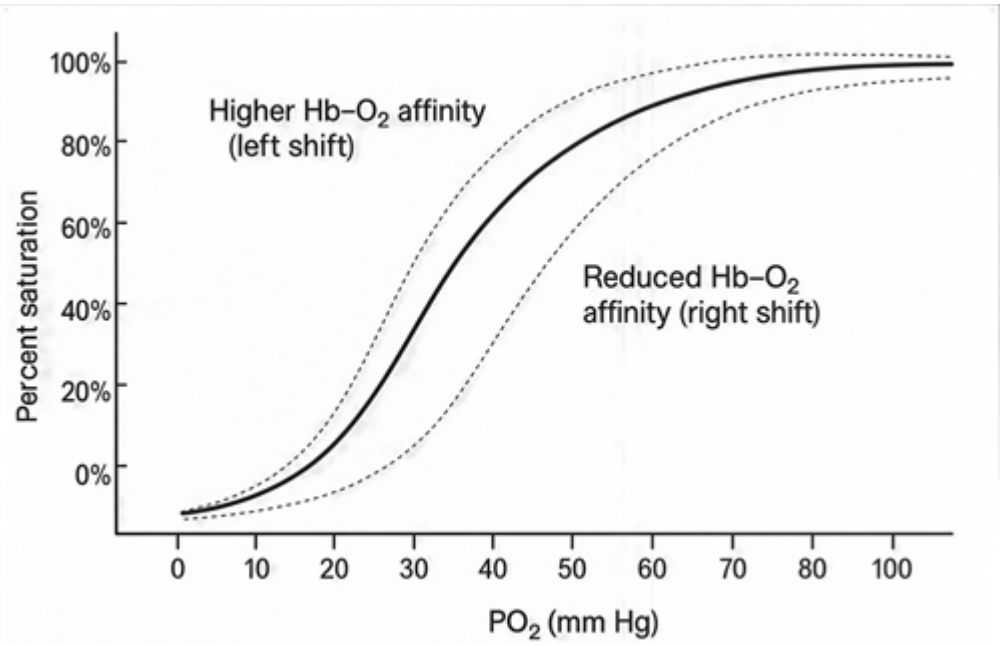

Figure 11.3 Haemoglobin dissociation curve. In haemoglobinopathies with reduced oxygen affinity, the oxygen dissociation curve shifts to the right, leading to decreased haemoglobin saturation at a given pO_2.

Since oxygen delivery remains adequate in low affinity haemoglobin variants, no medical intervention for low SpO_2 is required. The cornerstone

of management is patient and family education, enabling them to inform healthcare providers during future medical encounters and thereby avoiding unnecessary investigations. In the case of unstable haemoglobinopathies – such as in our patient – a mild haemolytic anaemia is typically present and should be monitored by a paediatric haematologist. Haemolytic crises may occur, particularly during infections or upon exposure to oxidant medications, similar to glucose-6-phosphate dehydrogenase (G6PD) deficiency. Common triggers include fluoroquinolones, nitrofurantoin, sulfonylureas, rasburicase, and methylene blue. However, no formal recommendations currently exist regarding specific medications that should be avoided for individual haemoglobin variants.

KEY LEARNING POINTS

Patients with unexpectedly low oxygen saturations on pulse oximetry often undergo extensive cardiopulmonary evaluation to identify the cause of hypoxaemia. However, in some cases, the reliability of the pulse oximetry measurement itself should be questioned, especially when clinical findings are not consistent with the degree of desaturation observed.

Pulse oximetry estimates oxygen saturation by measuring the differential absorption of infrared and red light by oxygenated and deoxygenated haemoglobin. While this method is non-invasive and widely used, it is susceptible to interference by abnormal haemoglobin variants, which can lead to falsely low or high SpO_2 readings.

The diagnostic challenge in this case was further compounded by the absence of a suggestive family history, which is often present in more common haemoglobinopathies (such as HbS or HbC). Here, the variant appeared to have arisen *de novo* – a phenomenon not uncommon in rare haemoglobinopathies and one that can further delay their recognition.

This case illustrates the importance of maintaining a broad differential diagnosis in cases of unexplained oxygen desaturation, and especially thinking about alternative or additional diagnoses in what appears to be a

common respiratory presentation like acute bronchiolitis. When SpO_2 values are inconsistent with the patient's clinical presentation, confirmatory arterial blood gas analysis is crucial to accurately assess oxygenation status and to avoid unnecessary and potentially invasive cardiopulmonary investigations. Capillary and venous blood gas measurements are insufficient for this purpose, as they do not provide reliable estimates of arterial pO_2 levels. In selected cases, arterialized capillary blood obtained from an earlobe may serve as an acceptable alternative to arterial sampling. However, this technique is not well validated in children and may yield inaccurate pO_2 measurements in this population.

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CHAPTER 12 A TEENAGER WHO COUGHED UP BLOOD

Tom Toin, Laurianne Coutier, and Philippe Reix

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INTRODUCTION

Paediatric diffuse alveolar haemorrhage (DAH) is a rare condition resulting from heterogeneous underlying diseases. This clinical case highlights the importance of a rigorous diagnostic approach based on a meticulous clinical examination and appropriate additional investigations.

CASE PRESENTATION

A 17-year-old male was admitted to the paediatric emergency ward for a first episode of moderate haemoptysis. He had a history of presumed dietary microcytic hypochromic anaemia treated by iron supplementation for 2 years. Familial history was unremarkable. There was no abnormal environmental exposure, nor recent travel abroad. The patient declared being a non-smoker and non-vaper.

At the paediatric emergency ward, the first clinical exam was normal. There were no signs of hypovolaemia or respiratory distress. A blood test and a chest X-ray were performed.

Moderate anaemia was observed, with a haemoglobin level of 10.5 g/L. Red blood cells were microcytic and hypochromic, with reticulocytes measured at 100 giga/L (N < 80 giga/L).

There was no evidence of any systemic inflammatory or other syndrome.

The chest X-ray revealed bilateral alveolar opacities, predominating in the lower lobes (peripherally on the left and projecting behind the diaphragm on the right) (Figure 12.1).

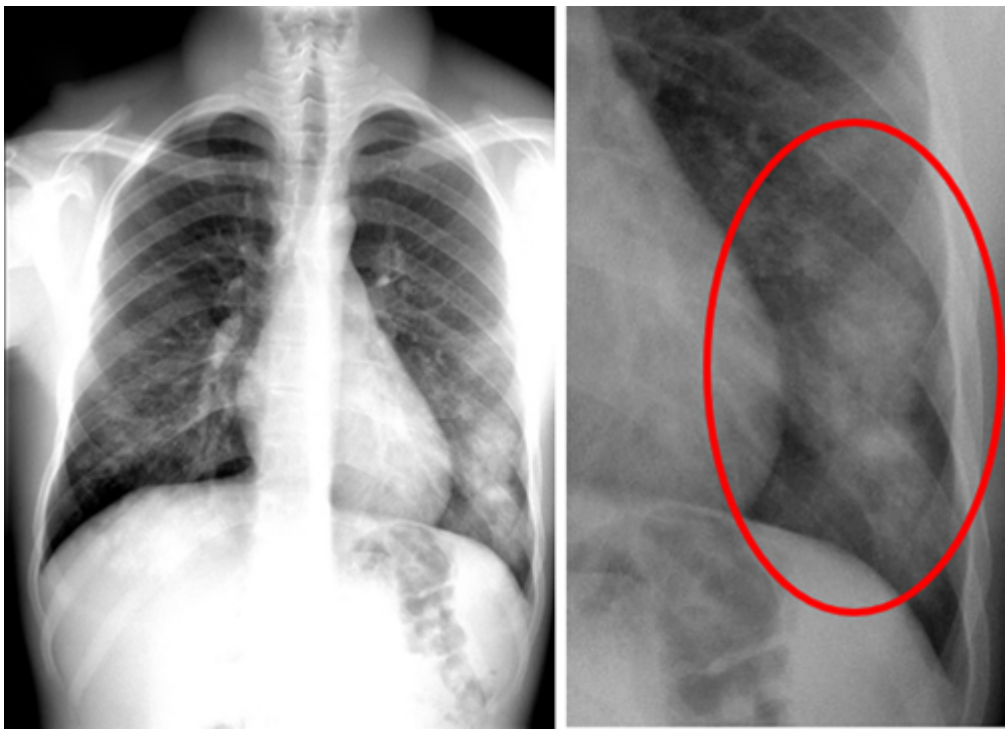

Figure 12.1 Chest X-ray at admission.

QUESTION 1: *What is the first diagnosis? What additional tests could you use to confirm your diagnostic hypothesis?*

The triad of haemoptysis, anaemia, and radiological pulmonary infiltrates should initially suggest the diagnosis of diffuse intra-alveolar haemorrhage (DAH).

A *contrast-enhanced chest computed tomography (CT) scan* should be done at this stage to (1) confirm lung bleeding, (2) investigate the extent of the disease, and (3) look for lung vascular abnormalities and any suggestions of an origin or cause (for example, pulmonary infarct, cavitating infection, hypertrophied bronchial arteries).

In our case, the CT scan showed bilateral peribronchovascular ground-glass opacification with subpleural sparing, involving both lower lobes and the posterior segments of the upper lobes.

There was also more dense consolidation in the left lower lobe, with air bronchograms. No vascular malformation was appreciable, and there was no interlobular septal thickening or parenchymal distortion to suggest established haemosiderosis (Figure 12.2).

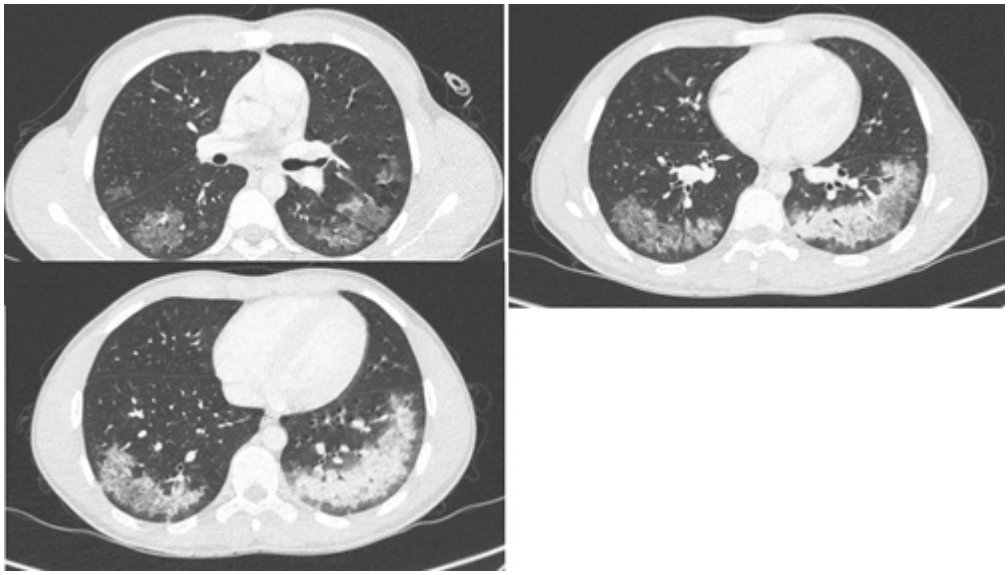

Figure 12.2 Initial CT scan performed at admission.⏎

QUESTION 2: *What is the next step in the investigations?*

A *bronchoscopy* and a *bronchoalveolar lavage* (BAL) are the next steps in this patient.

The procedure will help confirm the diagnosis of DAH by showing spontaneous diffuse bleeding or an increasingly bloody appearance of BAL after saline instillation. Bronchoscopy will also help evaluate the extent of bleeding.

DAH will be confirmed based on macroscopic and microscopic findings, namely the presence of siderophages. Siderophages are present as soon as 2

days after initial bleeding and may still be found a week later. A percentage of siderophages greater than 20% of the total macrophage count in the BAL is considered to support the diagnosis of DAH. The Golde score (Table 12.1) is a semi-quantitative assessment of haemosiderin-laden macrophages, which evaluates both the percentage of macrophages containing haemosiderin and the intensity of staining on a scale between 0 and 4. The result of this score may vary between 0 and 400. A score above 100 is highly indicative of DAH.

Table 12.1 Alveolar macrophage haemosiderin score grading system (the Golde score)

Grade	Description
0	Absence of blue colouration in the cystoplasm
1	Faint blue staining in the cytoplasm
2	Dense blue colour in a minor portion of the cytoplasm or medium colour intensity throughout the cell
3	Deep blue staining in most of the cytoplasm
4	Cell filled with haemosiderin, dark blue throughout the cytoplasm

A bronchoscopy was performed: the BAL fluid was frankly haemorrhagic. The proportion of siderophages was 36% and the Golde score was 156, confirming the diagnosis of intra-alveolar haemorrhage.

Respiratory function tests performed around acute bleeding may show an increased diffusion capacity of the lungs for carbon monoxide (DLCO), due to absorption of carbon monoxide (CO) by intra-alveolar red cells. A normal ventilatory pattern or a restrictive pattern may be observed.

QUESTION 3: *What aetiologies should be investigated? And how should they be investigated?*

The main causes of intra-alveolar haemorrhage can be divided into two categories:

- Intra-alveolar haemorrhage with non-immunological origin

- Intra-alveolar haemorrhage with immunological origin

Non-immunological causes include infectious causes, cardiovascular causes (heart disease with left heart obstruction, pulmonary hypertension), toxic and medicinal causes (anticoagulants, cocaine, vaping, for example), traumatic causes (asphyxia, suffocation), and haemostasis disorders.

Immunological causes include conditions associated with vasculitis (ANCA vasculitis, immune complex diseases such as anti-glomerular basement membrane disease, some systemic diseases such as systemic lupus erythematosus), coeliac disease, antiphospholipid syndrome or certain genetic causes responsible for auto-inflammatory diseases, for example, related to coatomer-associated protein subunit alpha gene mutations (*COPA*).

A complete clinical examination is strongly recommended to look for other organ involvement: lung, heart, skin, joints, digestive system, ENT, kidneys, eyes.

Additional examinations must be performed systematically:

- Detailed evaluation of BAL for infection
- Cardiac ultrasound
- Assessment of renal function (looking for proteinuria and urine examination for red cell casts)
- Coagulation tests
- Autoantibodies assessment (including anti-neutrophil cytoplasmic antibodies, anti-nuclear antibodies, antiphospholipid antibodies, and anti-transglutaminase antibodies)

When full investigations have failed to identify an aetiology, idiopathic pulmonary haemosiderosis (IPH) or pulmonary capillaritis should be considered. The only way to differentiate one from the other is to perform a lung biopsy to show neutrophilic alveolar wall inflammation in the case of capillaritis.

In our case, the clinical examination was normal, and there was no evidence of infection on BAL. Cardiac ultrasound was normal, as was the autoimmunity and auto-inflammatory workup.

However, the level of anti-transglutaminase and anti-endomysium antibodies were positive with, respectively, 13630 UA (N < 20) and 400 UA (N < 5).

Duodenal biopsies confirmed villous atrophy (Figure 12.3) and a final diagnosis of coeliac disease was made.

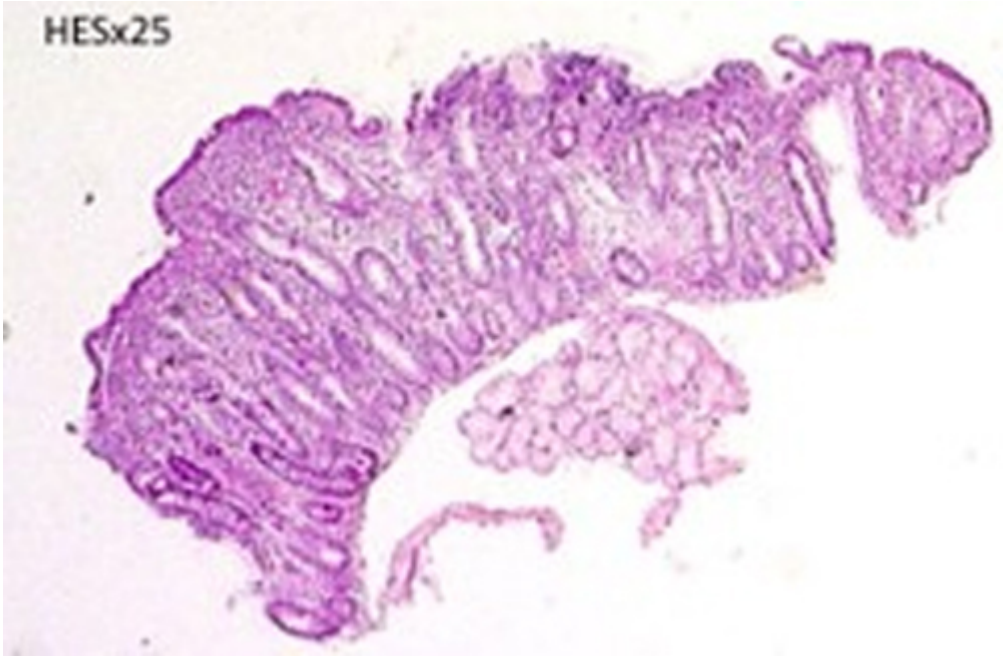

Figure 12.3 Duodenal biopsies showing total villous atrophy.⏎

(Photo provided by S Collardeau-Frachon.)

This association of coeliac disease and DAH is known as Lane–Hamilton syndrome.

A strict gluten-free diet was put in place, which was enough to stop lung bleeding and normalize the haemoglobin.

Table 12.2 Main causes of paediatric diffuse alveolar haemorrhage (DAH)⏎

DAH associated with dysimmune features	**ANCA vasculitis (granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis)Anti-glomerular basement membrane diseaseSystemic lupus erythematosusOther nonspecific autoimmune features with positive ANA, ANCA, SMA, or rheumatoid factorAntiphospholipid syndromeCoeliac disease = Lane–Hamilton syndrome**
DAH associated with immuno-allergic disorders	Pulmonary haemorrhage with cow's milk antibody (IgD) = Heiner syndrome
DAH in auto-inflammatory disease	COPA syndrome*
DAH secondary to other conditions	Infectious Cardiovascular diseases (including pulmonary arterial hypertension) Coagulopathy Lung damage due to exogenous toxicity Asphyxia, suffocation
Idiopathic pulmonary haemosiderosis **Pulmonary capillaritis**	

* COPA syndrome is a rare autosomal dominant monogenic auto-inflammatory disease caused by heterozygous mutations in the alpha protein of the coatomere subunit, which is part of the protein complex I (COPI).
Abbreviations: ANCA, anti-neutrophil cytoplasmic antibody; ANA, anti-nuclear antibody; SMA, smooth muscle antibody.

COPI performs an essential role in the signalling of the stimulator of interferon genes (STING), a key regulator of innate immunity, and the disease is classified in the group of interferonopathies.

It combines pulmonary, joint, and renal manifestations, which usually start in early childhood, before 5 years. It is characterized by variable expression and possible incomplete penetrance.

Most patients suffer from interstitial lung disease with recurrent episodes of DAH, which can be complicated by pulmonary fibrosis and terminal

respiratory failure. Another important interferonopathy is SAVI. Increasing numbers of presentations in teenagers and young adults are being described.

KEY LEARNING POINTS

- This case demonstrates the importance of thoroughly investigating any chronic iron deficiency anaemia that cannot be clearly explained. DAH can evolve insidiously over several months, and there may be no history of haemoptysis. It is important to thoroughly investigate these children to determine the underlying cause.
- There are specific treatments for some underlying causes of DAH, as in this case; hence a detailed workup is essential.
- The co-existence of coeliac disease and intra-alveolar haemorrhage is rare but known as Lane–Hamilton syndrome. The pathogenetic link between them is not fully understood, but coeliac disease should be excluded in patients with intra-alveolar haemorrhage of undetermined aetiology. A strict gluten-free diet should be implemented in these cases and is usually effective. However, additional immunosuppressive therapy is sometimes required.

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CHAPTER 13 THE ROLE OF FLEXIBLE BRONCHOSCOPY IN LOCALIZING LYMPHATIC LEAK

Kyndall Smith and Brooke Gustafson

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INTRODUCTION

This case highlights a unique use for the flexible bronchoscope in identifying an area of lymphatic leak in a paediatric patient with plastic bronchitis (PB). Patients with a history of the Fontan procedure are at risk for PB due to multiple physiologic factors. Elevated systemic venous pressures are required to drive cardiac output and pulmonary blood flow, which leads to interstitial fluid accumulation by the shift in Starling forces. Higher pressures also create endothelial dysfunction, further leading to capillary leak and lymphatic accumulation in the interstitial spaces.[1, 2] The thoracic duct and other lymphatic structures are at risk for direct injury during cardiothoracic surgery, which in turn leads to lymphatic abnormalities. When a lymphatic leak occurs in the bronchi, casts form and lead to cough, hypoxia, and airway obstruction. When the leak occurs into the pleura, chylothoraces occur. Management of lymphatic leak in this patient population is challenging, with minimal success in conservative, pharmacologic treatments. Imaging techniques such as dynamic contrast-enhanced magnetic resonance lymphangiography have been developed to assist with interventional procedures to embolize or ligate lymphatic channels.[2, 3] One of the challenges during these procedures is confirming which branch point leads to the channel causing the leak within the bronchus. The use of bronchoscopy to provide “eyes” inside the lung during dye injection has been shown to be helpful in confirming access and was successful in treating PB in the patient discussed herein (Figure 13.1).

A 4-year-old male with prenatally diagnosed pulmonary atresia presented to the emergency department with hypoxia and new onset wheezing 5 months following a fenestrated Fontan procedure. He appeared to be mildly ill with reduced breath sounds over the right chest and bilateral wheezing.

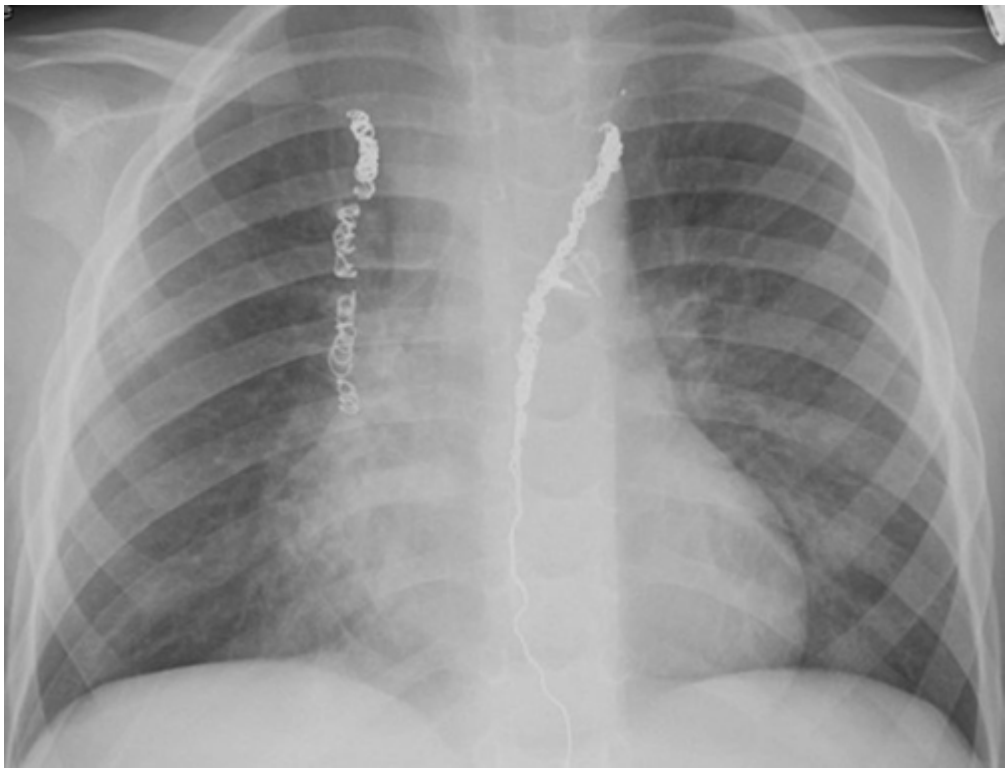

Figure 13.1 Chest radiograph with right middle lobe opacity.⏎

QUESTION 1: *What does the chest radiograph show?*

The chest X-ray shows an opacity in the right middle lobe, concerning for atelectasis or pneumonia. Embolization coils and vascular stents from previous procedures are noted, and the patient has a normal heart size.

He was treated with bronchodilator therapy, oxygen via nasal cannula, and admitted for further management. Initial lab

results were notable for positive viral testing for rhinovirus. Inflammatory markers and complete blood counts were normal.

His past cardiac history is notable for two perioperative periods complicated by chylous effusions that improved with chest tube placement, a low-fat diet, and pulmonary vasodilator therapy. He was initiated on systemic steroids after his third day of hospitalization due to some improvement with bronchodilator therapy but continued to have mild hypoxaemia, which was worse when asleep.

QUESTION 2: *What is the most likely diagnosis?*

Given his acute viral illness, the initial leading diagnosis was viral pneumonia. His clinical exam was notable for wheezing and thus a first-time asthma exacerbation was also considered as contributing to his illness. Given his persistent hypoxaemia and chest X-ray findings, antibiotics were given to cover for any superimposed bacterial pneumonia. Additional considerations as a reason for hypoxia included cardiac complications and sleep-disordered breathing.

On hospital day 4, he expectorated a large hyaline cast and was diagnosed with plastic bronchitis (PB). His respiratory status improved with diuretic therapy and airway clearance, and he was able to be weaned off supplemental oxygen over the next 48 hours.

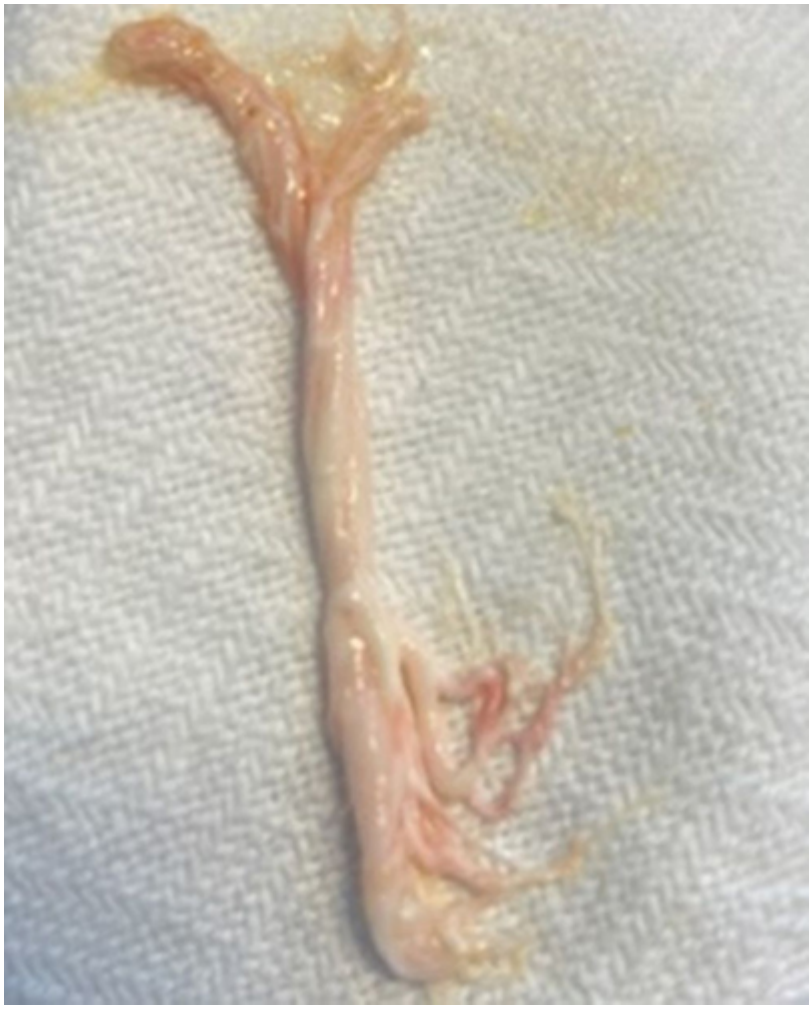

Figure 13.2 Expectorated airway cast.⏎

QUESTION 3: *What is plastic bronchitis and what are the initial steps in its management?*

The diagnosis of PB is made clinically when patients expectorate intrabronchial casts (Figure 13.2). These casts are generally acellular and may be secondary to infectious or inflammatory processes, acute chest syndrome, iatrogenic, primary lymphatic abnormalities, and/or following cardiac surgery. PB is rare and the true prevalence is unknown. Medical treatment of this condition is based on the aetiology of the cast formation and is unfortunately often not effective. Pharmacologic treatments including corticosteroids (systemic and inhaled), antibiotics, inhaled mucolytic

therapies, and plasminogen activators are often prescribed; however, they have not been shown to be consistently effective.[4] In patients with acute airway obstruction secondary to casts, flexible bronchoscopy is beneficial to remove occluding casts but does not prevent further casts from reaccumulating. Bronchoscopy is often performed at the time of diagnosis to evaluate cast burden and identify any focal areas of cast accumulation.

In patients with a history of cardiac surgery, casts are formed due to insufficient lymphatic drainage secondary to high pulmonary venous pressures. Cardiac catheterization is performed to evaluate pulmonary arterial and venous pressures to optimize pharmacologic therapy. Additionally, if the patient does not yet have a fenestrated Fontan, fenestration can be tried as an attempt to reduce pulmonary pressures.[4] Regardless of the aetiology, if medical management fails, interventional options to alter lymphatic drainage may be indicated and are further discussed next.

> *Outpatient cardiac catheterization was performed approximately 4 weeks after his hospitalization and demonstrated elevated Fontan pressures (mean pressures of 17–18 mmHg, normal range 2–6 mmHg) and transpulmonary gradient (12 mmHg, normal range 5–10 mmHg), with mild narrowing of his Glenn anastomosis that improved with angioplasty. Airway evaluation with rigid and flexible bronchoscopies was unremarkable without visualization of any airway casts. Following this procedure, the patient continued to have intermittent expectoration of casts at home and the pulmonary vasodilator regimen was adjusted without significant improvement.*

QUESTION 4: *What imaging studies and/or procedures may be needed to treat patients with PB?*

After failed medical management, further information on the patient's lymphatic system should be obtained, generally by performing magnetic resonance lymphangiogram (MRL).[5] Based on results of this imaging, lymphatic embolization, stenting, and thoracic duct ligation may be pursued. In paediatric patients, lymphatic channels may be difficult to access given their small size; thus, some of these interventions may not be successful. Incorporating bronchoscopy as a tool to confirm placement in the leaking lymphatic channel may improve outcomes and lead to more long-term resolution of PB.[5] In patients with a failing Fontan and ongoing cast expectoration, cardiac transplant may be indicated to definitively correct the underlying cardiac abnormalities once all other treatment options have been exhausted.[6]

QUESTION 5: *How was the patient managed and what transpired?*

The patient underwent an MRL which demonstrated abnormal contrast reflux into right pulmonary hilar lymphatics off two parallel channels emanating from the subcarinal thoracic duct. Given imaging results and failure of medical management, a decision was made to perform selective lymphatic embolization of the refluxing channels if able to be accessed.

Interventional radiology performed selective injection of dilute isosulfan blue dye (diluted with normal saline) into the sub-selected refluxing right pulmonary lymphatic channel. Concurrent flexible bronchoscopy prior to and following dye administration demonstrated accumulation of dye within the proximal right upper lobe, medial aspect of the bronchus intermedius, and entirety of the right middle lobe following dye administration, confirming correct placement of the catheter (Figure 13.3).

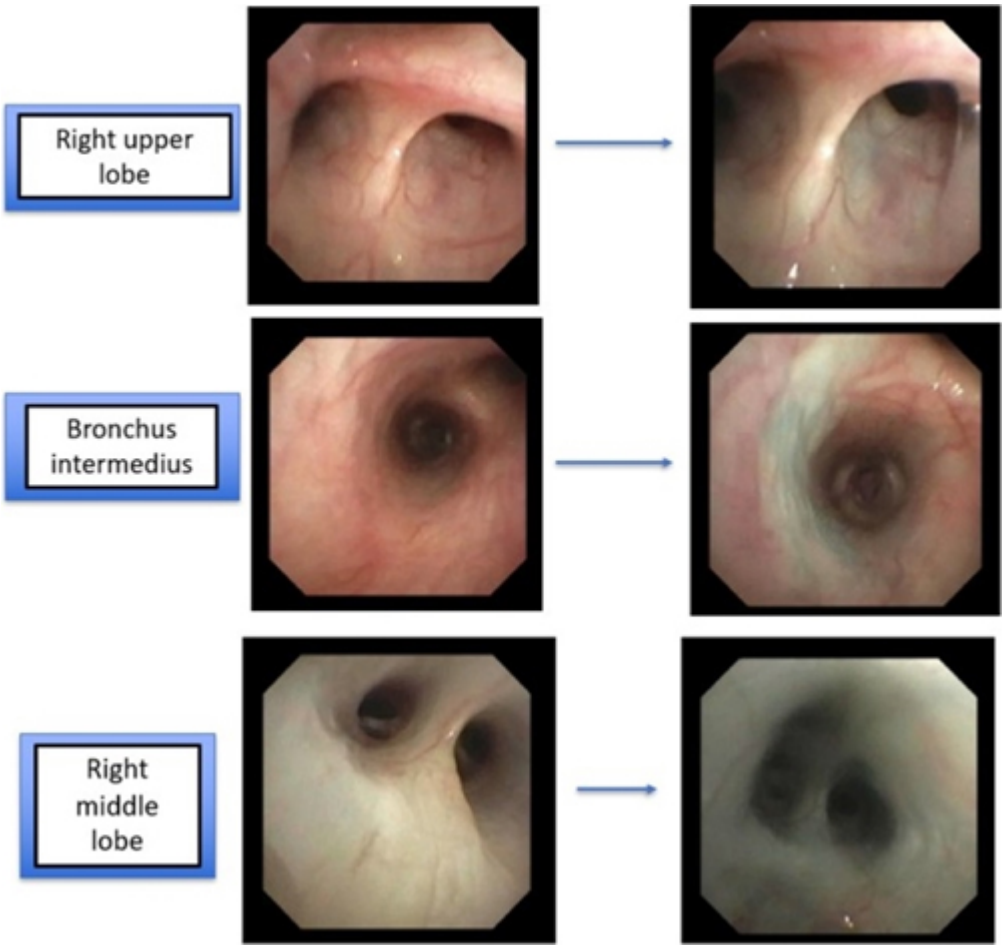

Figure 13.3 Images captured during flexible bronchoscopy.

This channel was successfully embolized with a glue cast (Figure 13.4) and no further flow was seen with contrast injection on repeat lymphangiogram. The patient has not had recurrent cast formation following this procedure, and his pulmonary symptoms have resolved.

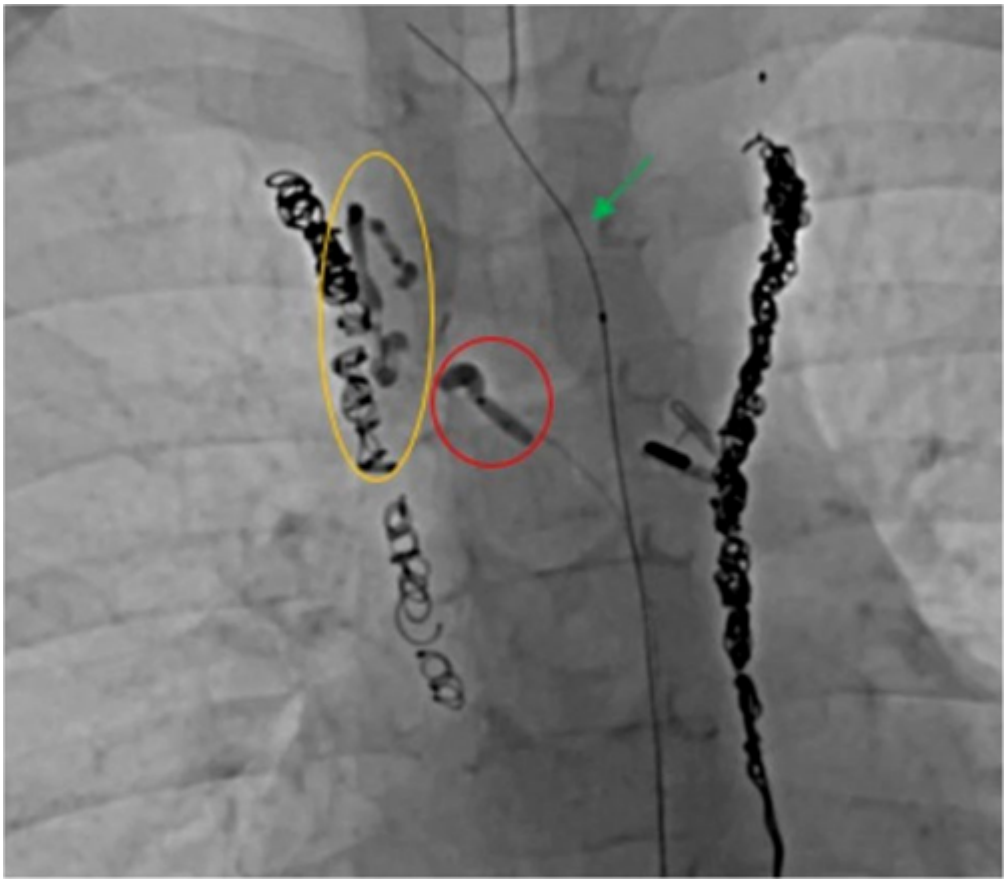

Figure 13.4 Yellow: Area of lymphatic reflux identified with dye infusion. Green arrow: Catheter in place temporarily occluding thoracic duct. Red: Area of glue cast being instilled into appropriate lymphatic channel via catheter guided off the thoracic duct branch point.⏎

KEY LEARNING POINTS

- Plastic bronchitis should be considered as a cause of hypoxia and chronic cough in patients with a history of cardiac surgery.
- Medical management of plastic bronchitis has limited, if any, effectiveness. Interventional procedures hold promise in palliating and correcting lymphatic leak in certain patient populations and may avoid the need for cardiac transplant.

- Utilization of flexible bronchoscopy during advanced imaging to confirm lymphatic channel involvement prior to embolization may lead to improved patient outcomes, and further studies are needed.

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CHAPTER 14 RESPIRATORY DISTRESS IN AN INFANT BORN TO A MOTHER WITH TUBERCULOSIS IN CAPE TOWN

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INTRODUCTION

Over a million children (<15 years) develop tuberculosis (TB) each year globally, with a quarter of them dying from the disease. The diagnosis and treatment of child TB are made more complex when the child has disease caused by *Mycobacterium tuberculosis* (*Mtb*) that is resistant to first-line TB drugs.

CASE PRESENTATION

A 4-month male infant presented to a hospital in Cape Town, South Africa, with symptoms and signs of lower respiratory tract infection. He had a 5-day history of cough, elevated respiratory rate, a low-grade fever and had crackles on auscultation in the right lower region posteriorly.

The mother had started treatment for drug-susceptible TB 6 months earlier. This was 7 months into her pregnancy and 2 months prior to delivery. She had been diagnosed with TB based on a sputum sample that was positive for *Mtb* on Xpert MTB/RIF Ultra with no mutations suggestive of rifampicin resistance. Adherence to her treatment was uncertain, and she had stopped treatment a few weeks before the baby was brought to the

hospital. She had been treated for TB on two occasions prior to this most recent episode, 3 years and 6 years previously.

The infant had been born at term, was exclusively breastfed, and a good weight gain trajectory was seen on his growth chart (weight at 4 months was 7 kg; 50th percentile). Given that his mother had been diagnosed with TB during pregnancy, he had been evaluated for TB at birth with a chest radiograph; blood tests to look for abnormal blood counts, inflammation or deranged liver function; and a lumbar puncture. All were normal. His mother was HIV negative at antenatal booking. The boy was not vaccinated with Bacillus Calmette–Guérin (BCG) and did not receive any TB preventive treatment (TPT).

Two induced sputum samples were obtained from the infant; a chest radiograph was largely normal; and a full blood count demonstrated haemoglobin 10.1 g/dL, mean corpuscular volume 78.5 fL, total white cell count 17.9×10^9/L and platelets 629×10^9/L. He had a negative HIV rapid test. The boy was discharged on a course of amoxicillin, with follow-up planned a couple of weeks later. However, the child was not brought to that appointment, and the results of the induced sputum test were not checked by the hospital team.

The child re-presented 6 weeks later with a 3-day history of cough and fast breathing, but no fever. The child continued to be growing well (weight 7.5 kg; 50th percentile), but a chest radiograph taken at that time demonstrated that the child had enlarged hilar lymph nodes with large airways compression and resultant hyperinflation of both lungs (Figure 14.1). The induced sputum sample taken at the initial presentation had been Xpert Ultra trace positive (a result which demonstrates the presence of low quantities of *Mtb* DNA but does not permit ascertainment of mutations associated with rifampicin resistance), and a sample sent for liquid culture had grown *Mtb* after 30 days with resistance demonstrated to isoniazid, rifampicin and ethionamide, but with susceptibility to fluoroquinolones, bedaquiline and linezolid.

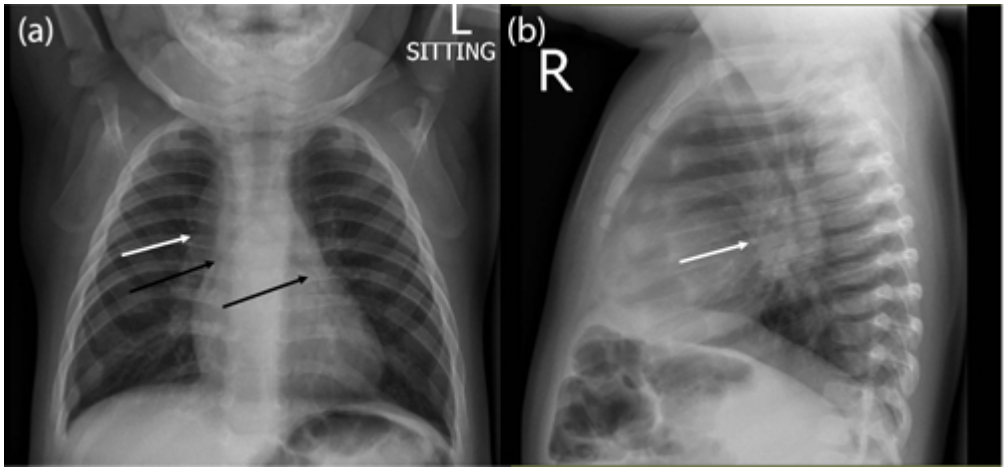

Figure 14.1 (a) Anteroposterior and (b) lateral chest radiographs on treatment initiation showing enlarged right hilar and subcarinal nodes (white arrows) with bilateral compression of main bronchi (black arrows) and resultant hyperinflation of both lungs.⏎

QUESTION 1: *What is the optimal treatment regimen for this child and what evaluations are required prior to starting treatment?*

In 2022, the World Health Organization (WHO) revised its guidance around the use of both bedaquiline and delamanid for children, suggesting that both drugs could be used from birth in all children (Table 14.1). Previously, these drugs were only recommended for children older than 6 years (bedaquiline) or 3 years (delamanid). Several clinical trials in adults with multidrug-resistant (MDR)-TB (i.e., TB disease caused by *Mtb* strains resistant to at least isoniazid and rifampicin) have been completed, which used fully oral regimens, including combinations of bedaquiline, pretomanid, linezolid and moxifloxacin for 6–9 months. These trials demonstrated excellent efficacy of these regimens, but these are only available for older children (≥14 years) due to pre-clinical testicular toxicity of pretomanid to juvenile animals. The Beat-Tuberculosis and the End TB trials have subsequently demonstrated good efficacy of fully oral 6-to-9–month regimens including bedaquiline, delamanid, levofloxacin (or moxifloxacin), linezolid, clofazimine and pyrazinamide. As all of these drugs are approved for use in

children, efficacy data from these trials can be applied to all age groups. Several groups have summarised these results and provide evidence-based guidance for the construction of MDR-TB regimens for children and the WHO has now updated its guidance. Prior to starting treatment, it is important to exclude anaemia, evaluate liver function and check for any congenital conductive cardiac conditions.

Table 14.1 Summary of drugs used to treat drug-resistant tuberculosis in children with possible adverse events and suggested monitoring required

Drug	Adverse events	Monitoring
Bedaquiline	Headache, nausea, liver dysfunction, QT-interval prolongation	• Clinical • If given with other QT-prolonging drugs, for ECG at baseline and then monthly
Levofloxacin/Moxifloxacin	GI disturbance, arthralgia/arthritis, sleep disturbance, raised intracranial pressure QT-prolongation (moxifloxacin has greater QT-prolongation effects than levofloxacin)	• Clinical • If given with other QT-prolonging drugs, for ECG at baseline and then monthly
Linezolid	GI disturbance, headache, myelosuppression, peripheral neuropathy, optic neuritis, lactic acidosis, pancreatitis	• Clinical • Visual acuity testing when possible • Baseline and then 2-weekly FBC and differential WCC for first month, then monthly

Drug	Adverse events	Monitoring
Clofazimine	Abdominal pain, Skin discoloration, ichthyosis, QT-prolongation	• Clinical • If given with other QT-prolonging drugs for ECG baseline and then monthly
Terizidone/Cycloserine	Behavioural changes, depression, sleep disturbances, headache, seizures	• Clinical
Delamanid	GI disturbance, dizziness, paraesthesia, anxiety, hallucinations, QT-prolongation	• Clinical • If given with other QT-prolonging drugs, for ECG at baseline and then monthly
Pretomanid*	GI disturbance, peripheral neuropathy, acne, skin rash, pruritus, anaemia, liver dysfunction, headache	• Clinical • Visual acuity testing when possible

* Only recommended in adolescents 14 years and older due to the lack of data in children.
Abbreviations: ECG, electrocardiogram; FBC, full blood count; GI, gastrointestinal; WCC, white cell count.

The child had an electrocardiogram (ECG) that demonstrated a Fridericia-corrected QT interval of 371 milliseconds and had bloods taken which showed a haemoglobin of 10.5 g/dL and an alanine transferase of 16 IU/L. He was started on bedaquiline (80 mg once daily for 14 days, followed by 40 mg three times a week), levofloxacin (150 mg once daily), linezolid (150 mg once daily), terizidone (similar to cycloserine; 125 mg once daily) and clofazimine (25 mg once daily). He was prescribed vitamin B6 (6.5 mg daily; terizidone/cycloserine interferes with vitamin B6–dependent pathways in the central nervous system) and vitamin D (400 international units daily; given as found to be deficient), and given the airways compression seen on the chest radiograph, he was also started on

prednisolone 15 mg once daily, with a plan to treat at full dose for a month, to be followed by a 2-week taper to stop. Given concerns about the care given to him by his parents, the social services were involved, and he was admitted to a specialist TB hospital for ongoing care, pending social care evaluation and management.

QUESTION 2: *What ongoing follow-up is indicated, and what investigations are suggested during follow-up?*

Follow-up is required for three main reasons. First, to evaluate treatment response and identify potential treatment failure early. Second, to promote adherence and provide medical and social support, as well as education about the disease and infection control. Finally, to identify adverse events related to the drug therapy prescribed earlier (Table 14.1). In this situation, it would be important to monitor symptom resolution, weight gain, improvement in chest radiology and elimination of *Mtb* from the sputum to confirm that the child is responding well to treatment and there is no recurrence of disease. In addition, he should have regular ECG monitoring (as he is receiving >1 QT-prolonging drug; for this child, these include bedaquiline, clofazimine and, to a lesser extent, levofloxacin), as well as monitoring of full blood counts including differential white cell count and liver function (to monitor for potential bone marrow suppression from linezolid and hepatotoxicity from bedaquiline). At every follow-up, opportunities should be taken to reinforce the importance of adherence to therapy and enquire about any social support needed.

After 2 months on treatment, he developed acute respiratory distress with wheeze and stridor and required supplementary oxygen therapy.

QUESTION 3: *What are the differential diagnoses for these new-onset symptoms and signs?*

There are several differential diagnoses for these symptoms and signs. First, it would be important to evaluate whether the child had worsening of his TB disease, due to either incorrect treatment or poor adherence. It would also be important to consider whether the child has developed an immune

reconstitution inflammatory syndrome (IRIS). It is not uncommon, even in children who are HIV-negative, to develop an inflammatory response some weeks, or even months, into treatment as the immune system reactivates and reacts to *Mtb* antigens. This can manifest with fever, enlarging lymph nodes, hepatosplenomegaly, weight loss, worsening chest radiographic findings and elevated inflammatory markers. If intrathoracic lymph nodes enlarge, they can compress large airways causing a ball-valve effect, leading to hyperinflation, wheeze, and ultimately airways obstruction, collapse and consolidation. It can be challenging to distinguish IRIS from worsening TB/failure of TB treatment. This situation is commonly managed with steroids and continuation of TB therapy. Other differentials would include new infection with a non-*Mtb* pathogen, an inhaled foreign body or other coincident respiratory illness. However, a foreign body would be unusual but not unheard of in a child of this age; babies who are too young to put things in their mouth may be fed potential foreign bodies by an older child trying to be helpful.

Repeat chest radiography demonstrated improvement in airway compression and decreased hilar node enlargement, but there were some new right middle lobe infiltrates with no evidence of foreign body inhalation (Figure 14.2). A nasopharyngeal sample tested positive for adenovirus, and he was given supportive care for adenovirus bronchiolitis, with supplementary oxygen and nasogastric feeding. He recovered from this episode and continued to improve. However, 6 weeks later he became increasingly pale and lethargic. His heart rate and respiratory rate increased. A full blood count demonstrated that he had a haemoglobin of 6.1 g/dL, with normal white cell count and platelets.

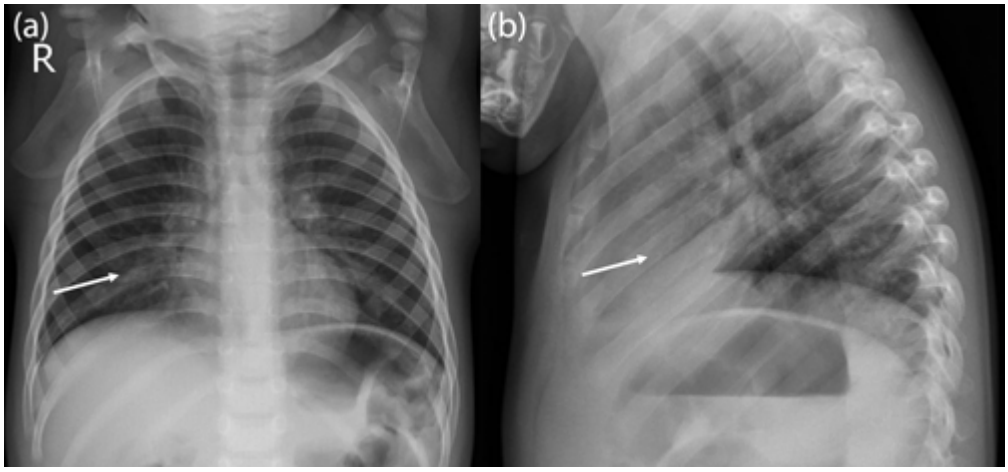

Figure 14.2 (a) Anteroposterior and (b) lateral chest radiographs taken at 2 months on treatment following acute respiratory deterioration, showing bilateral perihilar infiltrates and improving right hilar/subcarinal nodes with new right middle lobe infiltrates (arrows), clinically suspected to be due to superimposed viral infection.

QUESTION 4: *What are the possible causes of his anaemia, and what is the most appropriate management?*

Differential diagnoses would include iron-deficiency anaemia due to inadequate iron in the diet. This is not uncommon in a child being exclusively breast fed at this age (9 months of age), but the onset is very sudden and the degree of anaemia is severe. He could have a hereditary blood dyscrasia such as sickle cell anaemia or beta-thalassaemia major, conditions which can present at this age when fetal haemoglobin is replaced. The infant may have a bleeding disorder or a chronic infection (worsening of TB or other infection). Parvovirus B19 can cause symptoms of acute anaemia in an otherwise well child. However, the most likely reason for his anaemia is an adverse effect from the linezolid. The child should be investigated for other causes of anaemia, but the linezolid should be stopped and held until his haemoglobin rises to the lower limit of normal. If he is compromised from a cardiovascular perspective, a red cell transfusion could be considered. If linezolid is essential to the drug regimen

and other drug options are not available, a rechallenge with linezolid could be considered at two-thirds the original dose (10 mg/kg instead of 15 mg/kg at his age and weight) when the haemoglobin has normalised. However, in most instances, other drugs are used, or the regimen continues without linezolid.

As the child had already received linezolid for 3.5 months, it was stopped and the other drugs (bedaquiline, levofloxacin, terizidone and clofazimine) continued without the addition of any other agent. Bedaquiline was stopped after 6 months, and he continued the other three drugs for a further 6 months to a total therapy duration of 12 months. He was growing well (weight 10.5 kg at age 17 months; 50th percentile), and his chest radiograph had improved. He was discharged home into the care of his aunt, due to social care concerns of neglect from his parents.

KEY LEARNING POINTS

- The management of babies born to women who had TB during pregnancy can be complex. Initial screening for congenital TB is indicated, but once TB has been excluded in the infant, the baby should receive BCG.
- The mother had experienced three episodes of TB. This should be a red flag for an immunodeficiency or repeated poor adherence.
- The possibility of an infection with both a drug-resistant and drug-susceptible strain of *Mtb* should always be considered in a situation such as this, with the susceptible strain isolated on culture but the resistant strain untreated by antibiotic therapy and able to both replicate and infect others.
- This case demonstrates the importance of obtaining respiratory samples from a child for microbiological analysis. In this instance, the child had a strain with a different drug-susceptibility pattern to the one that the mother had at the start of her TB episode.
- The interpretation of an Xpert MTB/RIF Ultra “trace” result can be challenging, as it has reduced specificity for TB compared to a positive result. It also does not provide any information on the drug

susceptibility of the organism, as is additionally provided with a positive result.

- The drug regimens used to treat MDR-TB in children have changed dramatically in the last 10 years. Other than pretomanid, almost all other drugs that are used in adults can be used in children of all ages, and lessons learnt from adult drug-resistant TB trials can inform the management of child drug-resistant TB.
- It is critically important to understand the possible adverse events that can be caused by each TB drug and monitor for these closely.

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CHAPTER 15 BIG HEAD, STUBBORN LUNG

A quirky case of ventriculomegaly and collapsed lung

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INTRODUCTION

Respiratory disease in children can manifest in other organ systems, and there may be blurring of the boundaries between what were once thought to be discrete entities. This case illustrates this in a child with a neurological presentation of what was once thought to be a pure respiratory disease. The case emphasizes the need to look beyond the respiratory tract even if no extrapulmonary manifestations of what is thought to be the diagnosis have been described.

CASE REPORT

Baby M, the second baby of consanguineous parents, was found to have bilateral dilated ventricles in a routine antenatal ultrasound scan. Fetal magnetic resonance imaging (MRI) confirmed bilateral ventriculomegaly and normal third and fourth ventricles. The antenatal period was otherwise uneventful, and she was born at term via caesarean section (CS), the indication being previous CS. Her birth weight was 3.540 kg and head circumference was 35.5 cm. She passed meconium and urine immediately. In light of abnormal antenatal scans, a postnatal MRI of the brain was done at 6 hours of life; it revealed bilateral colpocephaly with dangling choroid plexus and a retrocerebellar cerebrospinal fluid (CSF) high intensity area suggestive of a prominent Cisterna Magna or arachnoid (Blake's pouch) cyst for which

conservative management was planned. In the MRI scan, fluid intensity was also noted in the middle ear and mastoid antrum bilaterally (Figure 15.1).

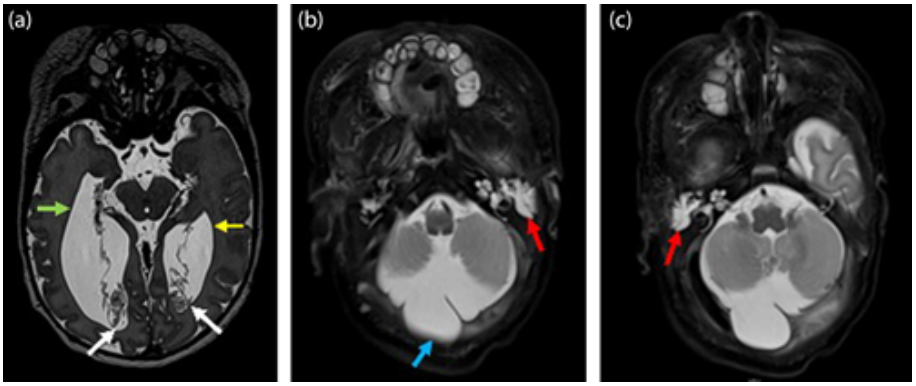

Figure 15.1 (a) MRI brain (DRIVE images) showing bilaterally dilated lateral ventricles with frontal horn width on right (green arrow; 6 mm) and left (yellow arrow; 6.7 mm). Occipital horns are dilated out of proportion to frontal horns suggestive of colpocephaly. Dangling choroid plexus (white arrows) can be seen in the lateral ventricles. (b) Prominent retrocerebellar CSF space with septations within suggestive of a prominent cisterna magna or arachnoid cyst (blue arrow) was seen on the T2W sequence with no mass effect on the cerebellar parenchyma. (c) Fluid signal intensity was seen in the middle ear and mastoid antrum bilaterally in T2W sequence (red arrows in (b) [left ear] and (c) [right ear]).

At 12 hours of life, she developed oxygen desaturation requiring low-flow oxygen administration. A radiograph of the chest showed a collapsed right upper lobe (RUL). Sepsis screen was negative. A small patent ductus arteriosus with bidirectional shunting was seen on echocardiogram. Low-flow oxygen was successfully discontinued by day 8 of life; however, the right upper lobe collapse remained unresolved. Newborn hearing screen, using automated auditory brainstem response (AABR) at birth, suggested hearing loss and the baby was referred for a further hearing screening at 6 weeks of age.

During a vaccination clinic visit at 4.5 months, the child was found to have adequate weight gain and was achieving milestones, albeit with a mild motor

developmental delay. There were no referrals made to the paediatric respirology services at this point.

At 5.5 months of life, the child was brought to the emergency room with increased cough, fast breathing and retractions noted over the preceding 2 days. Her mother had also noted a wet cough on most days in the preceding months. There was no history of rhinitis or ear discharge. The child was afebrile with a heart rate of 170/min, respiratory rate of 68/min, blood pressure of 90/54 mmHg, and SpO_2 of 97% in room air. She had intercostal and subcostal retractions. Her weight was 7.2 kg (50th centile), length 66 cm (50th to 85th centile), and head circumference 44 cm (85th to 97th centile). Sunset eye sign was noted, and the anterior fontanelle measured 3.5 × 3.5 cm. On examination of the respiratory system, there were reduced breath sounds heard over the right supraclavicular and infraclavicular areas. A chest radiograph revealed persistence of the RUL collapse (Figure 15.2). During a 6-day hospital stay, she improved with high-flow oxygen, antibiotics, and other supportive care.

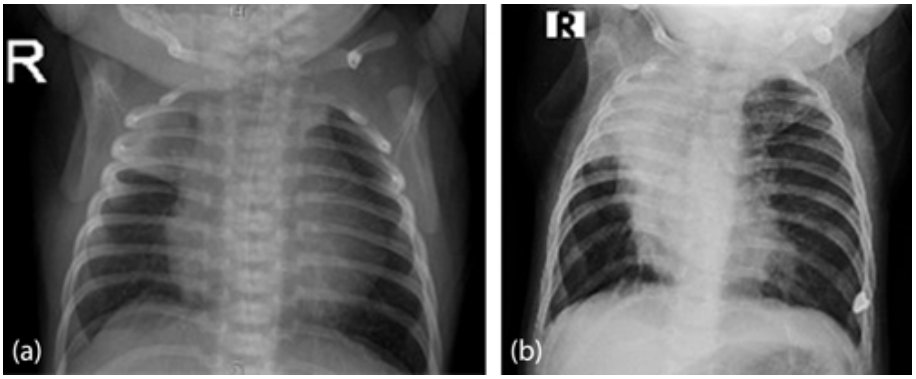

Figure 15.2 (a) Chest radiograph showing right upper lobe opacification and partial collapse at 12 hours of life. (b) Worsening of the right upper lobe collapse at 5.5 months of life with new hyperinflation of the aerated right and left lungs.⏎

QUESTION 1: *What are the most likely differential diagnoses at this point, and what investigations would you do next?*

The differential diagnoses in Table 15.1 should be considered at this point, along with the investigations conducted to support or rule them out.

In keeping with the differential diagnoses, cross-sectional imaging of the thorax was planned followed by bronchoscopy to look for anatomical and intramural anomalies.

Table 15.1 Differential diagnoses for Baby M

Disorders	Points for	Points against
	Parenchymal Lung Disease	
Lobar pneumonia	Clinical presentation	Persistence of chest radiograph findings from the neonatal period may indicate an aetiology beyond perinatally/community-acquired infection
	Airway Obstruction	
Intrinsic causes Mucous plugging Oblitrative bronchiolitis *Intramural causes* Tracheomalacia Bronchomalacia *Extrinsic causes* Vascular rings and slings Enlarged pulmonary vessels Hilar lymphadenopathy secondary to infection/pulmonary tuberculosis	Early presentation persistence of the RUL collapse Pulmonary tuberculosis can cause persistent lung collapses	Not yet confirmed at bronchoscopy or imaging No stridor or suprasternal retractions No history of contact; Xpert TB PCR and MGIT cultures on gastric aspirates ruled out pulmonary tuberculosis
	Impaired Airway Clearance	
Neuromuscular causes Respiratory muscle weakness Impaired cough reflex *Disorders of mucociliary clearance* Cystic Fibrosis (CF) Primary Ciliary Dyskinesia (PCD)	Possible due to presence of a central cause in the context of an abnormal MRI brain Respiratory distress in a term neonate followed by daily wet cough and persistent RUL collapse Hearing loss	No clinical signs of hypotonia or impaired cough reflex Sweat chloride level was normal Rarity of PCD itself

Disorders	Points for	Points against
	Gastro-Intestinal Causes	
Gastro-oesophageal reflux disease	GERD can cause recurrent/persistent respiratory symptoms/findings	No clinical features of GERD like arching, feeding difficulties, poor weight gain Barium swallow was negative for GERD
	Chronic Aspiration	
Neurological cause Structural airway anomalies such as laryngeal cleft or H-type fistula	Presence of a posterior fossa anomaly Persistent RUL collapse	Normal clinical swallow assessment and nasopharyngolaryngoscopy Bronchoscopy pending
Inborn errors of immunity	Recurrent/persistent pneumonia	Normal full blood counts, good growth, and absence of other infections Screening immunoglobulin levels were normal

At 6 months, a CT scan of the thorax showed right upper lobe collapse with extensive air bronchograms (Figure 15.3a, b) with subsegmental atelectatic areas in the left lingula and anteromedial segment of the left lower lobe. A flexible bronchoscopy with bronchoalveolar lavage (BAL) was done at 8 months of life and revealed a tracheal origin of the right upper lobe bronchus (Figure 15.3c), without any obstruction or mucous plugging. BAL fluid (BALF) showed a significant growth of *Streptococcus pneumoniae*. Galactomannan ELISA on BALF was >6 units (positive). At this point, serum Galactomannan ELISA was negative. Fungal and mycobacterial cultures of BALF were negative and the Xpert TB PCR test was negative as well. The child was treated with oral antibiotics (amoxicillin–clavulanate) for 2 weeks and oral antifungal (voriconazole) for 16 weeks.

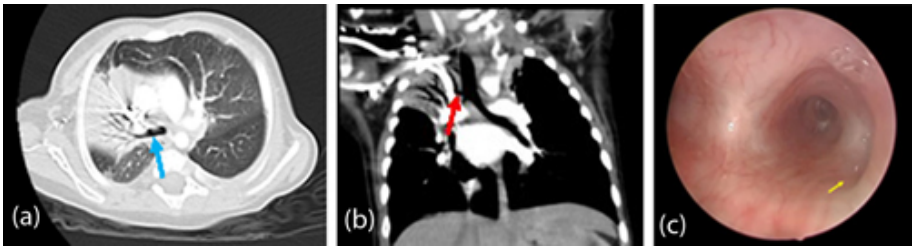

Figure 15.3 (a) Axial section on cross-sectional imaging of the thorax (blue arrow) showing the tracheal origin of the right upper lobe bronchus and collapse and consolidation of the right upper lobe with extensive air bronchograms. (b) Corresponding coronal

section on cross-sectional imaging of the thorax (red arrow). The tracheal bronchus can be seen very clearly. (c) Right upper lobe bronchus dividing just above the level of the carina (yellow arrow).⏎

For further clarification of the aetiology, next-generation sequencing for a panel of genes for the differential diagnoses including immunodeficiency, PCD, and CF revealed the presence of a homozygous pathogenic variant of c.441C>A in the MCIDAS gene suggestive of primary ciliary dyskinesia.

QUESTION 2: *What are the manifestations of primary ciliary dyskinesia (PCD) in the neonatal period?*

The clinical manifestations observed during the neonatal period should raise a suspicion of PCD prompting further evaluation (Table 15.2).

Table 15.2 Manifestations of PCD in neonates⏎

Symptoms and signs	Remarks and specifics in PCD
Neonatal respiratory distress (NRD), especially in a term baby	Up to 80% of term neonates with PCD experience respiratory distress (RD), often misattributed to common conditions like transient tachypnoea of newborn (TTN), respiratory distress syndrome (RDS), or neonatal pneumonia. In PCD, respiratory distress typically begins within 12 hours of life in 50% of cases and within 24 hours in 80%, though some may present later.
Prolonged requirement of supplemental oxygen	The median duration of supplemental O_2 requirement is 5 days but can extend to as long as a few weeks.
Nasal congestion from birth	Neonatal rhinitis (up to 32% cases) is one of the earliest symptoms of PCD and usually persists for a lifetime.
Lobar atelectasis	Lobar atelectasis affects 70% of term PCD infants with respiratory distress, typically in the upper and middle lobes.
Prolonged hospitalization at birth	The median neonatal length of stay can be as long as 9 days.
Middle ear effusions and referred hearing at birth	Individuals with PCD frequently experience middle ear effusions, leading to conductive hearing loss and subsequent speech delays during infancy.
Congenital heart defects	Neonates with PCD can have congenital heart malformations, from simple (3.5%–6%) to complex (2.6%).

Symptoms and signs	Remarks and specifics in PCD
Situs anomalies	Presence of situs inversus totalis (more than 40% cases) and situs ambiguus (12%–24% cases) are known to occur in PCD. In the background of neonatal RD, even a single organ defect like dextrocardia or polysplenia should alert the clinician to consider PCD.
Prenatal ventriculomegaly and hydrocephalus	PCD-related genes CCNO, MCIDAS, and FOXJ1 are associated with hydrocephalus and prenatal ventriculomegaly.

QUESTION 3: *What are the types of cilia; and list the rare manifestations of ciliopathies?*

Cilia are classified into three distinct types based on microtubular structure and function: nodal, sensory, and motile cilia. Defects in any category can give rise to a group of disorders known as ciliopathies.

Present transiently in the ventral node of the gastrula during embryogenesis, the ultrastructure of embryonic nodal cilia shares several characteristics with epithelial motile cilia, such as the circular configuration of nine microtubule doublets, complete with both inner and outer dynein arms. However, unlike typical motile cilia, nodal cilia lack a central pair of microtubules, thereby adopting a nine outer doublet with no central pair (9+0 configuration). The motility of nodal cilia determines situs in the developing fetus.

Motile cilia demonstrate a nine outer doublet configuration with a central pair (9+2 configuration) and are typically found as multiple cilia (multicilia), whereas sensory cilia demonstrate both 9+0 (primary) as well as 9+2 (kinocilia in the inner ear as well as olfactory cilia) configurations and exist as monocilia on the cell surface. Motile cilia are primarily located on multiciliated cells that constitute the epithelial lining of the respiratory tract, the ependymal cells of the ventricles of the brain, and the luminal walls of the fallopian tubes. They are also responsible for the motility of *Chlamydomonas*, one of the unicellular algae.

Primary cilia, with sensory and signaling roles, are found on almost all human cells; thus, these primary cilia syndromes (non-motile ciliopathies) manifest as a constellation of numerous defects, such as skeletal anomalies, sensory impairments (blindness and deafness), neural tube defects, renal cysts, and developmental and cognitive abnormalities. We also now know that there can be significant overlap between motile and non-motile ciliopathies. Retinitis pigmentosa is also a feature of ciliopathies.

Rare manifestations associated with motile and non-motile ciliopathies are listed in Table 15.3.

Table 15.3 Uncommon manifestations of motile and non-motile ciliopathies⏎

Rare manifestations	Comments
Motile Ciliopathies	
Very severe and early onset of chronic destructive lung disease	PCD associated with RGMC caused by disease-causing variants in CCNO, MCIDAS, and FOXJ1 can result in severe lung disease with early presentation.
Antenatally detectable ventriculomegaly and hydrocephalus	Can be seen associated with disease-causing variants in CCNO and MCIDAS; usually non-obstructed and does not require neurosurgical shunt placement. *De novo* loss-of-function variants in FOXJ1 and autosomal recessive pathogenic variants in TP73 are associated with severe obstructive hydrocephalus and aqueductal stenosis, often necessitating neurosurgical shunting to alleviate intracranial pressure.
Increased choroid plexus size with or without arachnoid cysts	Can be seen in patients with PCD due to pathogenic variants in MCIDAS, as seen in Baby M. Antenatal detection is possible.
Lissencephaly	It may manifest in individuals harbouring pathogenic TP73 variants.
Polysplenia and asplenia	Can occur as part of situs ambiguous (respectively left and right isomerism).
Probable higher frequency of ectopic pregnancies	A higher incidence of ectopic pregnancies in females with PCD have been reported in case reports and small series.
Male infertility without morphological abnormality of sperm	Mutations in PCD-associated genes encoding preassembly factors, including DNAAF2 (KTU) and DNAAF6 (PIH1D3), cause sperm immotility with preserved normal morphology. However, up to 50% of males with PCD are fertile.
Non-Motile and Syndromal Ciliopathies	
Alström syndrome (AS)	Mutations in ALMS1 cause AS characterized by sensorineural hearing loss, retinal degeneration, cardiomyopathy, obesity, hypertriglyceridemia, insulin-resistant diabetes, and hepatorenal disease. There may be recurrent oto-sino-pulmonary infections showing clinical overlap with PCD.
X-linked recessive mental retardation syndrome (XLMR)	Allelic to oral–facial–digital type I syndrome, XLMR is characterized by intellectual disability, macrocephaly, and ciliary dyskinesia.
Simpson–Golabi–Behmel syndrome type 2 (SGBS2)	Allelic to oral–facial–digital type I syndrome, SGBS2 is an X-linked recessive disorder characterized by severely impaired intellectual development, macrocephaly, and ciliary dyskinesia.
Retinitis pigmentosa	Mutations in retinitis pigmentosa GTPase regulator (RPGR) cause retinitis pigmentosa, and some individuals have typical PCD symptoms.

Rare manifestations	Comments
Leber congenital amaurosis	Mutations in CEP290 lead to complete or partial blindness with no visible ocular defect along with respiratory symptoms in some individuals.
Jeune syndrome	Caused by DYNC2H1 mutations, Jeune syndrome is characterized by a narrow thorax with short ribs, trident acetabulum, cone-shaped epiphyses, polydactyly, and recurrent lung infections associated with ciliopathy.
Joubert syndrome	A ciliopathy which presents predominantly with neonatal respiratory abnormalities such as hyperpnoea, apnoea, and rarely respiratory distress.
Various malformations or dysfunction of other organ systems such as the face, ears, liver, kidneys, skeleton, or haematopoiesis	Rare syndromal PCD variants are result of dysfunction of associated gene products in both multiple motile cilia and non-motile cilia.

QUESTION 4: *What is the approach to diagnosing PCD?*

PCD, a rare but increasingly recognized disease, usually manifests in the neonatal period. Given the diverse defects in ciliary biogenesis, structure, function, and organization underlying PCD, there is no single gold-standard diagnostic test. Certain mutations may present with a classical phenotype despite normal electron microscopy (EM) ultrastructure or normal nitric oxide levels. Thus, PCD diagnosis necessitates a panel of tests rather than a single modality, with the probability of a definitive diagnosis increasing with the number of positive tests. Test selection and the diagnostic algorithm depend on patient age, test availability, and the expertise of the performing centre.

Once an appropriate clinical phenotype of PCD is recognized, the panel of tests in Table 15.4 can be used to diagnose PCD.

Table 15.4 Diagnostics in clinically suspected PCD patients⏎

Diagnostics	Requirements	Results	Comments

Diagnostics	Requirements	Results	Comments
Nasal NO (nNO) level	• ≥5 years old and cooperative • Requires pre-existent heath status without an ongoing viral infection for at least 2 weeks prior to test • NO analyzers using chemiluminescence technology and well-trained operators using standard operating protocols • CF must be excluded (30% can have low nNO)	• Consider PCD if <77 nL/min by exhalation against resistor manoeuvre on at least two separate occasions with sensitivity and specificity of 98% and >99%, respectively (healthy controls have values >300 nl/min)	• Sensitive, rapid, non-invasive, and results are immediately available • False-negative results can occur with genotypes including RSPH1 and CCDC103 • Cystic fibrosis, diffuse panbronchiolitis, non-atopic sinusitis, HIV, etc. may produce false positive results • Tidal breathing measurements are less sensitive and specific than breath-hold manoeuvres

Diagnostics	Requirements	Results	Comments
Gene mutation analysis	• Done at any age • Choice of specific test depends on gene coverage, ethnicity, and performing centre	• Two* pathogenic or likely pathogenic variants in trans within one autosomal recessive PCD-causing gene	• May be none detected in 20%–30% cases • Intronic variants in DNAH11 and CCDC39 are missed in next-generation sequencing panels • More than 50 genes have been identified so far • Inheritance is autosomal recessive except for X-linked syndromic genes and FOXJ1 and TUBB4B, which are autosomal dominant

Diagnostics	Requirements	Results	Comments
Respiratory ciliary transmission electron microscopy (TEM)	• Done at any age • Requires pre-existent good heath status without an ongoing viral infection for at least 2 weeks prior to test • Requires examination of a minimum of 20–50 clear ciliary cross-sections with abnormalities being consistently present across cross-sections of multiple cilia • Laboratory with extensive experience in ciliary pathology	• Presence of class 1 ultrastructural defects confirm diagnosis of PCD: ◦ Outer dynein arm defect ◦ Outer and inner dynein arm defect ◦ Absent inner dynein arm with microtubule disorganization, radial spokes, or central apparatus	• Normal ultrastructure or subtle anomalies unrecognized by TEM are present in 30% of PCD • Changes apart from class 1 defects are nondiagnostic • TEM fails to detect PCD caused due to RGMC or oligociliary defects, for instance, genotypes CCNO and MCIDAS

Diagnostics	Requirements	Results	Comments
High-speed video microscopy (HSVM) with functional ciliary beat/waveform analysis	• Done at any age • Requires pre-existent heath status without an ongoing viral infection for at least 2 weeks prior to test • To minimize secondary damage, it may be necessary to analyze multiple separate ciliary biopsies taken on different visits; alternatively, culturing a single biopsy of ciliated respiratory epithelial cells at an air–liquid interface can exclude secondary ciliary dyskinesia • Should be done only in centres with immense experience in this modality	• Abnormal ciliary beat pattern • Specific beat patterns, such as completely immotile, immotile with occasional residual movement, reduced bend, and reduced beat amplitude, hyperfrequent with reduced beat amplitude, or with a circular motion when viewed from above, or a mixed pattern may occur • Sensitivity and specificity in diagnosing PCD are 100% and 96%, respectively, as per ERS guidelines, and 96% and 91% when compared with diagnostic outcomes	• Some PCD phenotypes may have normal or near-normal ciliary beating (like RSPH1, CCDC103, DNAH9) • Non-standardization of beat-pattern interpretation may lead to interobserver variability • Abnormal ciliary beat pattern may be seen in secondary insults like viral infections, environmental exposures, or poor quality/inadequately processed biopsy specimens
Immunofluorescence (IF) testing for ciliary proteins	• Done at any age • Requires pre-existent heath status without an ongoing viral infection for at least 2 weeks prior to test	• PCD is diagnosed in the absence of fluorescence of ciliary proteins in specific axonemal components	• Limited to a few experienced centres • PCD caused by DNAH11 and HYDIN variants may be missed • Not suitable for PCD resulting from RGMC or oligociliary defects, like CCNO and MCIDAS

Diagnostics	Requirements	Results	Comments
EM ciliary tomography	• Done at any age • Requires pre-existent heath status without an ongoing viral infection for at least 2 weeks prior to test	• Subtle morphological abnormalities detected	• Limited to a few experienced centres • Not needed if a previous obvious EM abnormality detected

* In PCD linked to RPGR, OFD1, PIH1D3 (X-linked), and FOXJ1 and TUBB4B (autosomal dominant), a single pathogenic or likely pathogenic variant suffices for diagnosis.

QUESTION 5: *What is the aetiopathology of persisting upper lobe collapse in the patient?*

A persistent collapse of the right upper lobe in Baby M is likely attributable to a combination of PCD as the underlying primary lung condition with concomitant fungal colonization and presence of anomalous branching of the right upper lobe bronchus, which could have impaired optimal drainage of the lobe, thereby perpetuating persistent atelectasis. However, at bronchoscopy, the airways were patent with air bronchograms on CT.

Furthermore, neonates with PCD demonstrate a predisposition to atelectasis, alongside lobar collapses at birth, both of which may persist over time. Lobar collapse in term neonates is, in fact, a rare occurrence and should prompt the treating physician to consider PCD as a differential diagnosis, especially when faced with unexplained neonatal respiratory distress, situs anomalies, persistent oxygen dependence, or any confluence of these clinical features.

Significant galactomannan level in the bronchoalveolar lavage fluid of this child probably suggests fungal colonization of the diseased right upper lobe, which, in conjunction with other factors, may contribute to the persistent non-resolution of the collapse. However, this was not confirmed by positive cultures.

In general, the pathophysiology underlying upper lobe collapse in PCD remains unclear, with potential mechanisms including compression of the upper lobes due to differential gas trapping and hyperinflation in the lower lobes, as well as the infant being in a supine position for the majority of the time. Impaired mucociliary clearance is possible in the supine position, potentially resulting in mucus

accumulation and lobar collapse, particularly in the dependent lobes, which are the upper or middle lobes when the infant is lying on their back.

QUESTION 6: *Is surgical removal of the right upper lobe warranted?*

Baby M is currently 2 years and 4 months old and is being managed conservatively with the initiation of daily airway clearance therapy and azithromycin prophylaxis. She has gained weight (50th centile) and height (50th to 85th centile) appropriately for age, and does not have bronchiectasis or ear infections. Hearing is normal. She maintains a baseline respiratory rate of 34/min, with a SpO_2 of 100% on room air. Breath sounds are reduced over the right upper lobe, and her chest radiograph reveals persistence of the right upper lobe collapse. She has been vaccinated against respiratory viruses. She has not required neurosurgical intervention for ventriculomegaly, and no further neuroimaging has been performed to date.

Given the progressive nature of PCD and the high likelihood of future multi-lobar involvement, our approach prioritizes non-surgical management. Notably, bronchial tree anomalies are not typically associated with the spectrum of PCD. The only other case documented in the literature describes a child who underwent a lobectomy for persistent right upper lobe collapse and was subsequently diagnosed with PCD, attributed to CCDC40 gene variants, when symptoms persisted despite surgical intervention. While surgery is generally reserved for localized disease unresponsive to standard PCD treatments, the presence of anomalous bronchial anatomy in our patient may necessitate resection to mitigate potential complications. However, overall, non-surgical management is preferred.

QUESTION 7: *What are the characteristic features of MCIDAS-associated RGMC, with an emphasis on its structural brain manifestations?*

Mutations in the MCIDAS gene result in a mucociliary clearance disorder characterized by a reduced number of motile cilia. The few remaining cilia exhibit severe axonemal defects due to the absence of essential motor proteins, rendering them immotile and thereby meeting the definition of PCD.

Individuals with MCIDAS mutations present with neonatal respiratory symptoms, typically lack situs anomalies, and often develop early-onset severe lung disease. Diagnostic evaluations reveal low nNO levels, absence of cilia on TEM, as well as HSVM. These findings support the diagnosis prior to confirmation through genetic analysis.

Neurologically, these patients may exhibit hydrocephalus, diffuse choroid plexus hyperplasia, arachnoid cysts, and a patent aqueduct. However, these children typically do not exhibit neurological deficits or developmental delay. This could be likely due to the early onset of hydrocephalus, during a period when the brain's structural compliance allows compensation for elevated cerebrospinal fluid pressure. Consequently, the decision to perform a ventriculoperitoneal shunt in these children should be approached with caution and individualized.

Baby M's development is age appropriate except for mild motor delay of about 4 months. Her head circumference is 52.5 cm (>97th centile) with normal tone and deep tendon reflexes. Currently, she has no neurological deficits and is under strict clinical follow-up.

KEY LEARNING POINTS

- It is imperative for paediatricians and neonatologists to recognize the earliest subtle manifestations of PCD, such as unexplained respiratory distress in term newborns (all such babies should be screened for PCD), persistent atelectasis, migratory collapses, and ventriculomegaly to facilitate timely and appropriate referrals.
- In term neonates with unexplained respiratory distress, PCD should be excluded; in the absence of the ability to test for this diagnosis, diligent follow-up is critical.
- There is a spectrum of ciliopathies, and PCD is no longer a discrete entity as once thought. Patients with PCD may have retinitis pigmentosa and complex congenital heart disease, and patients with motile ciliopathies may have a PCD-like phenotype including increased likelihood of neonatal respiratory distress and sinopulmonary disease.
- When seeing non-respiratory patients, always ask yourself if the patient could have a ciliopathy. The child with congenital heart disease and a cough or rhinitis could have underlying PCD and be at risk of respiratory complications if unrecognized!

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CHAPTER 16 A CASE OF PULMONARY HYPERTENSION

A challenge in LMICs

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INTRODUCTION

We are presenting this case because it represents a significant diagnostic challenge due to the patient's nonspecific and minimalistic clinical presentation. The potential of such a presentation to mimic more common childhood conditions underscores the risk of delayed diagnosis of pulmonary hypertension (PH). We therefore highlight the critical importance of including pulmonary hypertension in the differential diagnosis and illustrate the systematic workup required for its classification and staging. While treatment may fall to paediatric cardiologists in some centres, the common referral pattern of "it's not the heart" for patients without overt cardiac disease means that paediatric pulmonologists must be vigilant, as we often are the ones who, in many settings, end up managing these children.

CASE PRESENTATION

A 9-year-old girl, with a previously unremarkable medical history, presented with two distinct episodes of syncope whilst playing in recess, these episodes occurring over the preceding year. During the evaluation, she reported experiencing dyspnoea upon exertion. The patient denied the presence of recurrent respiratory symptoms, wheezing, cyanosis, chest pain, or snoring. There was no family history of pulmonary hypertension, congenital anomalies, or early unexplained deaths. The birth history was unremarkable. There was no significant history of previous diseases or illnesses, nor any relevant medication history including exposure to high altitudes, toxic cooking oils, or travel.

On examination, the patient exhibited normal heart and respiratory rates. Oxygen saturation levels were recorded at 90%–91% on room air but improved to 97% with supplemental oxygen at a flow rate of 0.5 l/min. The patient appeared well-nourished and non-cyanotic, displaying a normal respiratory pattern without any signs of distress. She had no nasal discharge or polyps. Chest palpation was described as showing a normal apex beat, cardiac auscultation identified a grade II systolic heart murmur, a not particularly loud S2, indistinguishable P2, and no prominent jugular veins. Lung auscultation was normal. No signs of digital clubbing, oedema, or skin lesions were present. The patient did exhibit hepatomegaly, with the liver border palpated near the umbilicus.

QUESTION 1: *(Workup)*

Given the patient's presentation of syncope, exertional dyspnoea, and the findings of a grade II systolic heart murmur, what investigations would you prioritize to further elucidate the underlying causes of her symptoms?

Summary of investigations

The initial laboratory investigations showed normal complete blood count, coagulation profile (including testing for the Leiden V factor), electrolytes, renal function tests, liver function tests, thyroid function tests, haemoglobin

electrophoresis, and HIV screening. Biomarkers for ventricular function, specifically NT-proBNP, were measured both at baseline and during follow-up. This patient had an elevated NT-proBNP at 15,815.3 pg/mL. The echocardiogram revealed moderate pulmonary arterial hypertension, with a pulmonary artery systolic pressure (PASP) of 40 mmHg. Additionally, there was severe dilation of the right heart chambers; however, no structural cardiac abnormalities were identified (Figures 16.1 and 16.2).

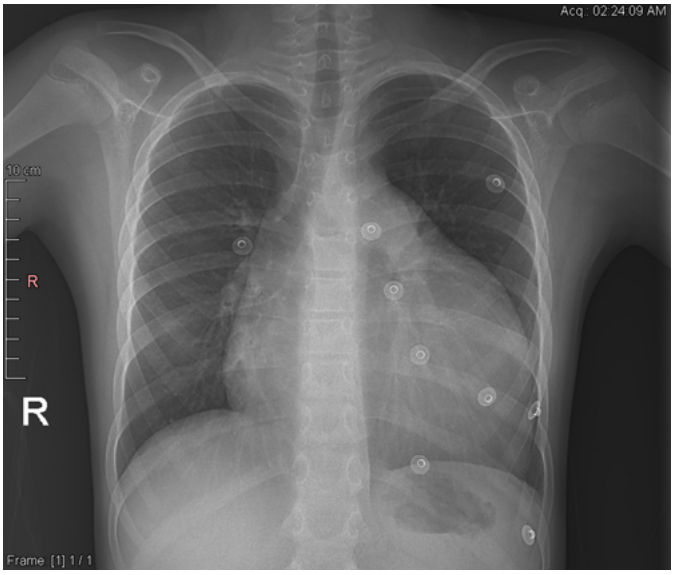


Figure 16.1 Chest X-ray showing cardiomegaly with marked dilation of the pulmonary arterial trunk, with no evident airway nor parenchymal disease.

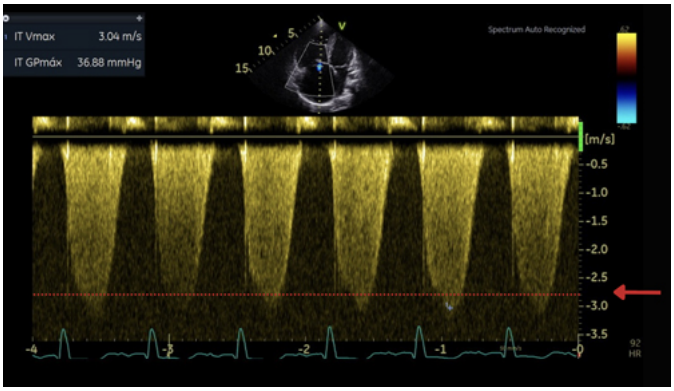


Figure 16.2 Echocardiogram with pulmonary hypertension. Increased systolic peak tricuspid regurgitant velocity (3.04 m/s). This velocity, along with an estimated PASP of ~40 mmHg, is consistent with pulmonary hypertension. For reference, a systolic peak tricuspid regurgitant velocity >2.8 m/s (red dotted line) is suggestive of an elevated mPAP (>20 mmHg).

According to the REVEAL registry, dyspnoea on exertion is reported as the most common symptom of PH, being present in 53% of cases. Syncope is noted as the second most prevalent symptom in 36% of cases, while chest pain occurs in 16% of cases. Nevertheless, all of these remain very non-specific. Additional symptoms may include hemoptysis (secondary to pulmonary infarcts related to pulmonary arterial thrombosis or embolic occlusion), failure to thrive, irritability, feeding intolerance, pedal oedema, and signs of malabsorption. Clinical manifestations associated with heart failure such as tachycardia, tachypnoea, oedema, and hepatomegaly may also be present.

Furthermore, skin and joint issues may arise if PH is a manifestation of a systemic condition, such as scleroderma or lupus. Associations with various genetic syndromes including trisomies, coloboma, congenital heart defects, atresia or stenosis of the choanae, genitourinary anomalies, CHARGE syndrome, Duane syndrome, glycogen storage diseases, and metabolic disorders have been described.

In our patient's case, she only manifested dyspnoea on exertion and episodes of syncope along with hepatomegaly at presentation.

A chest CT was performed to evaluate lung disease and vascular lesions, including angiography to assess for aortopulmonary collaterals, pulmonary vein stenosis, peripheral pulmonary artery stenosis, occlusion, or thrombus. The patient's chest CT demonstrated no signs of pulmonary veno-occlusive disease and showed normal lung parenchyma (no septal lines, centrilobular ground-glass opacities or nodules, or enlargement of the mediastinal lymph nodes). Notably, there was evidence of contrast medium reflux towards the dilated suprahepatic veins. This is, however, increasingly seen outside the setting of pulmonary hypertension with the use of high-power pump injectors so is of variable importance as an imaging finding from between centres.

Cardiac catheterization is considered the gold standard for diagnosing pulmonary arterial hypertension (PAH), as it confirms the diagnosis, assesses severity, rules out left-sided heart disease, and evaluates response to vasodilators through acute vasoreactivity testing (AVT). Right heart catheterization indicated no significant response to supplemental oxygen or inhaled nitric oxide (iNO) (Figure 16.3).

Pulmonary function tests, 6-minute walk test (6MWT), and cardiopulmonary exercise testing were performed to evaluate exercise tolerance and functional capacity (done at baseline and to monitor changes in functional status).

Finally, an abdominal ultrasound was performed to exclude porto-pulmonary hypertension. The ultrasound revealed hepatomegaly with diffuse dilation of the suprahepatic veins, while the portal vein was of normal calibre without evidence of thrombosis or focal liver lesions, and no porto-pulmonary hypertension.

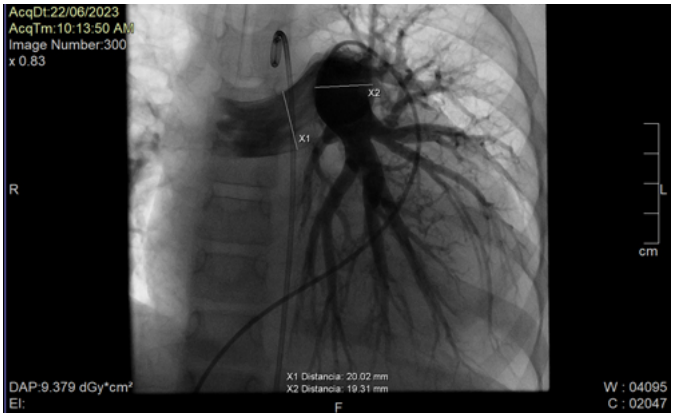


Figure 16.3 Right heart catheterization showing aberrant pulmonary vascularization with marked dilation of the main pulmonary artery and rapid tapering with "pruning" of the peripheral vasculature, reflecting elevated pulmonary vascular resistance.

Consultations with haematology, immunology, and hepatology yielded no evidence of underlying diseases. Genetic testing is currently pending.

QUESTION 2: *(Differential diagnosis and staging)*

What possible diagnoses should be considered, and how would you stratify the risk associated with these conditions?

Presumptive diagnosis and management

Idiopathic pulmonary arterial hypertension (IPAH) was deemed the most likely aetiology and based on the clinical findings the patient was classified as AVT negative, high-risk PAH. Determinants of PAH risk are shown in Table 16.1 and differential diagnosis in Table 16.2.

Table 16.1 Determinants of paediatric pulmonary idiopathic arterial hypertension risk

Low risk	Determinant	High risk
Normal	**Growth**	FTT
No	**Clinical RV failure**	Yes
I, II	**WHO functional class**	III, IV
No	**Symptom progression**	Yes
Minimally elevated	**NT Pro BNP**	Markedly elevated or rising
>350 m	**6MWT (>6 yo)**	<350 m
No	**Echocardiography**	RA/RV enlargement Reduced LV size Increased RV/LV ratio Reduced TAPSE Low RV FAC Pericardial effusion
Systemic CI >3.0 $L \cdot min^{-1} \cdot m^{-2}$ Systemic venous saturation >65% AVT +	**Haemodynamics**	Systemic CI <2.5 $L \cdot min^{-1} \cdot m^{-2}$ mRAP >10 mmHg PVRI >20 $WU \cdot m^2$ Systemic venous saturation <60% PACI <0.85 $mL \cdot mmHg^{-1} \cdot m^{-2}$

Source:Adapted from Rosenzweig EB, et al., Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management, *Eur Respir J,* 2019 Jan;53(1):1801916.

Table 16.2 Differential diagnosis and clinical classification of pulmonary hypertension

Type IPAH	Type IILeft heart disease	Type IIILung diseases/hypoxia	Type IVPulmonary artery obstructions	Type VUnclear or multifactorial

Type IPAH	Type IILeft heart disease	Type IIILung diseases/hypoxia	Type IVPulmonary artery obstructions	Type VUnclear or multifactorial

• Idiopathic
  ◦ Long-term responders to CCB
• Heritable
• Drug/toxin-induced
• Associated
  ◦ Connective tissue
  ◦ HIV
  ◦ Portal hypertension
  ◦ Congenital heart disease
  ◦ Schistosomiasis
• Venous/capillaries involvement (PVOD/PCH)
• Persistent PH of the newborn
	• Heart failure
	  ◦ Preserved LVEF
	  ◦ Reduced or mildly reduced LVEF
	  ◦ Other cardiomyopathies
	• Valvular heart disease
	  ◦ Aortic valve
	  ◦ Mitral valve
	  ◦ Mixed
	• Congenital/acquired cardiovascular conditions leading to post-capillary PH
		• COPD/emphysema
		• Interstitial lung disease
		• Combined pulmonary fibrosis and emphysema
		• Other parenchymal lung diseases (not in type V)
		• Nonparenchymal restrictive diseases
		  ◦ Hypoventilation syndromes
		  ◦ Pneumonectomy
		• Hypoxia without lung disease (altitude)
		• Developmental lung disorders
			• Chronic thromboembolic PH
			• Other pulmonary artery obstructions
			  ◦ Sarcomas
			  ◦ Malignant tumours
			• Nonmalignant tumours
			  ◦ Arteritis without connective tissue disease
			  ◦ Congenital pulmonary artery stenosis
			  ◦ Hydatidosis
				• Haematological disorders
				• Systemic and metabolic
				  ◦ Sarcoidosis
				  ◦ Pulmonary Langerhans cell histiocytosis
				  ◦ Neurofibromatos I
				• Metabolic disorders
				  ◦ Glycogen storag
				  ◦ Gaucher disease
				• Chronic renal failure with or without haemodialysis
				• Pulmonary tumour thrombotic microangiopathy
				• Fibrosing mediastinitis
				• Complex congenital heart disease

Source: Adapted from Kovacs G, et al. Definition, classification and diagnosis of pulmonary hypertension, *Eur Respir J,* 2024 Oct;64(4):2401324.
Abbreviations: PAH, pulmonary arterial hypertension; PVOD, pulmonary veno-occlusive disease; PCH, pulmonary capillary haemangiomatosis; LVEF, left ventricular ejection fraction.

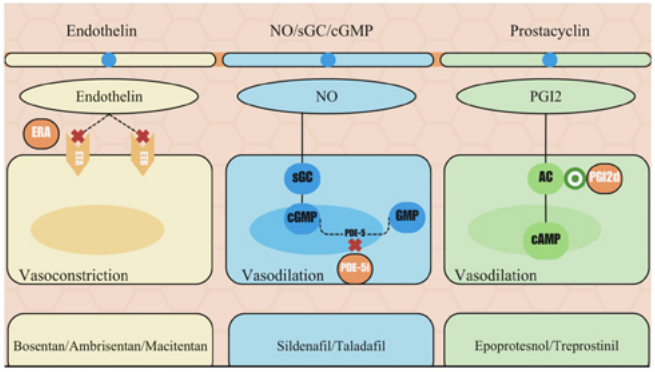
In addition to the previously mentioned laboratory evaluations, it is advisable to conduct comprehensive genetic testing for mutations in the following genes: BMPR2, ALK1, ENG, SMAD, KCNK3, ELF2AK4, Cav1, and TBX4. This genetic testing is particularly important as over 35% of paediatric cases of pulmonary arterial hypertension are associated with gene mutations. We are still looking at the possibility of how we can obtain these tests in our country.

Currently, there is no cure for pulmonary hypertension, and no single medication can uniformly manage the condition. Vaccination against influenza and pneumococcal infections is recommended. It is important to manage fever to minimize the consequences of increased metabolic demands. Patients should avoid decongestants and pseudoephedrine, and constipation should be treated to prevent Valsalva manoeuvers.

Domiciliary oxygen may be prescribed for emergency use or continuous use in cases of chronic hypoxemia, including treatment for upper respiratory tract infections. Anticoagulation therapy should be considered on a case-by-case basis and is not routinely indicated.

Treatment should be guided by risk stratification and vasoreactivity testing according to established algorithms. If AVT is positive, calcium channel blockers should be initiated. In cases where AVT is negative, further risk stratification is necessary. For patients classified as low risk, monotherapy with either an endothelin receptor antagonist (such as bosentan or ambrisentan) or a phosphodiesterase 5 inhibitor (such as sildenafil or tadalafil) is recommended. If there is clinical deterioration, early combination therapy should be considered.

For patients identified as high risk, the use of epoprostenol or treprostinil should be strongly considered. Early combination therapy with an endothelin receptor antagonist or phosphodiesterase 5 inhibitor may also be appropriate in these cases (pathways targeted in said therapies are illustrated in Figure 16.4).



AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; ET, endothelin; ETx, endothelin receptor; GMP, guanosine monophosphate; NO, nitric oxide; PDE-5, phosphodiesterase-5; PGI2, prostacyclin also called prostaglandin I2; sGC, soluble guanylyl cyclase.
Adapted from Tsai H, et al. Recent advances in the management of pulmonary arterial hypertension. F1000Res. 2016 Nov 24

Figure 16.4 Comparison of pharmacodynamic effects of pulmonary arterial hypertension therapies.

In select situations, early lung transplantation or palliative interventions such as atrial septostomy may be warranted.

Timely follow-up appointments are essential, with recommendations for assessments every 3 to 6 months to monitor disease progression and treatment efficacy.

The initial treatment regimen for our patient included supplemental oxygen therapy and sildenafil. Additionally, bosentan was requested. Further efforts are underway to obtain treprostinil through legal channels within the country.

At a 2-month follow-up appointment, the patient demonstrated clinical stability. Notably, there were no new episodes of syncope reported, and the patient experienced a reduction in dyspnoea during exertion. Furthermore, oxygen saturation levels showed improvement. No episodes of hemoptysis were described.

Despite these positive developments, NT-proBNP levels remained elevated at 11,054 pg/mL, but there was a 30% fall from the first measurement. The echocardiogram performed during this follow-up showed no change compared to the initial measurement (pulmonary artery pressure remaining at 40 mmHg).

KEY LEARNING POINTS

- The nature of the presentation of PH is very nonspecific, which underscores the critical need for clinicians to actively consider this diagnosis; without such awareness, it may easily be overlooked.
- Pulmonary hypertension in children is predominantly caused by lung disease, followed by cardiac diseases. It rarely manifests as a primary diagnosis (10% of cases). Global incidence remains unknown, but there are reports indicating an incidence of 0.48 cases per million children annually.
- A complete family history and physical examination are key for diagnosis, with emphasis on exertional dyspnoea, syncope episodes, chest pain, hemoptysis, and the presence of either heart murmurs or signs of heart failure. Be aware of associations with genetic syndromes.
- As for diagnostic workup: echocardiography and cardiac catheterization remain fundamental for diagnosis and assessment of AVT and severity. Baseline and follow-up NT-proBNP levels should be attained. Genetic testing, if available, is important as 35% of PH have genetic contributing factors. Search for underlying aetiologies and comorbidities with contrast chest CT and abdominal Doppler ultrasound. Pulmonary function tests (PFT) for detailing functional status.
- There is no single curative medication. Treat according to AVT. If AVT is positive, start with a calcium channel blocker. If AVT is negative, assess risk: low-risk ERA/PDE5i or high-risk epoprostenol/treprostinil.

For any, consider early combination therapy, especially if there is disease progression. Ensure timely follow-up every 3–6 months.

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CHAPTER 17 A TODDLER WITH PERSISTENT PRODUCTIVE COUGH AND CHEST X-RAY CHANGES

Duo-Tong Cheng, Chun Yi Ting, and Justin Liang Yi Wee

DOI: 10.1201/9781003588955-17

INTRODUCTION

Chronic cough in children is a common reason for healthcare visits. While repeated viral infections are typically the leading cause, it is crucial to recognize warning signs that may require additional investigation and treatment.

CASE PRESENTATION

H is a 3-year-old Chinese boy who visited the respiratory clinic for a follow-up 1 month after an episode of pneumonia. He had been hospitalized for bronchopneumonia following a week of mild fever and 11 days of a chesty cough, without any signs of shortness of breath. Infectious markers were not elevated, and tests for respiratory viruses via PCR, mycoplasma serology, and blood cultures all returned negative (Figure 17.1). He received a course of amoxicillin and remained clinically stable during his hospital stay, without requiring oxygen support.

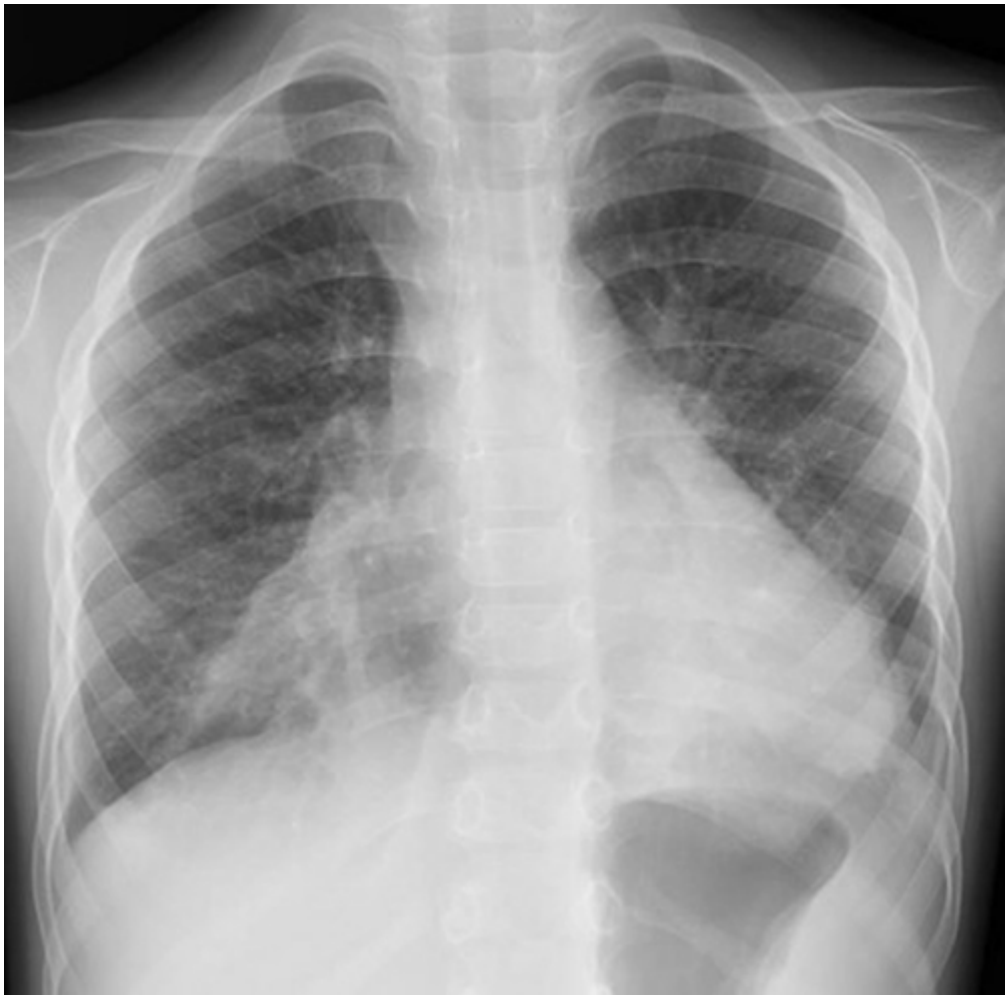

Figure 17.1 Initial chest X-ray showed bronchopneumonia involving right middle to lower lung and retrocardiac changes. No pleural effusions were seen.⏎

During the clinic visit, H's parents mentioned that his cough persisted even after completing the prescribed course of antibiotics. While the cough had greatly improved since his hospitalization, it remained persistent and occasionally productive. His mother also mentioned that he may have had another episode of fever with flu-like symptoms a week before the clinic visit. He has no prior history of pneumonia or wheezing, and there were no signs of weight loss or history of hemoptysis. There were no known contacts with individuals suffering from tuberculosis or chronic cough. He

has a personal history of allergic rhinitis but is not on medication, and there is no family history of atopy. Additionally, he is under follow-up care with the cardiothoracic surgeons for pectus excavatum, and a baseline chest CT was performed a year ago, prior to the onset of any symptoms.

Upon examination, H appeared comfortable with no signs of respiratory distress. He was growing according to his weight percentiles. Although he had a few episodes of productive coughing during the clinic visit, his lungs were clear upon auscultation. His pectus excavatum was noted, becoming more pronounced when he cried. There were no signs of digital clubbing (Figure 17.2).

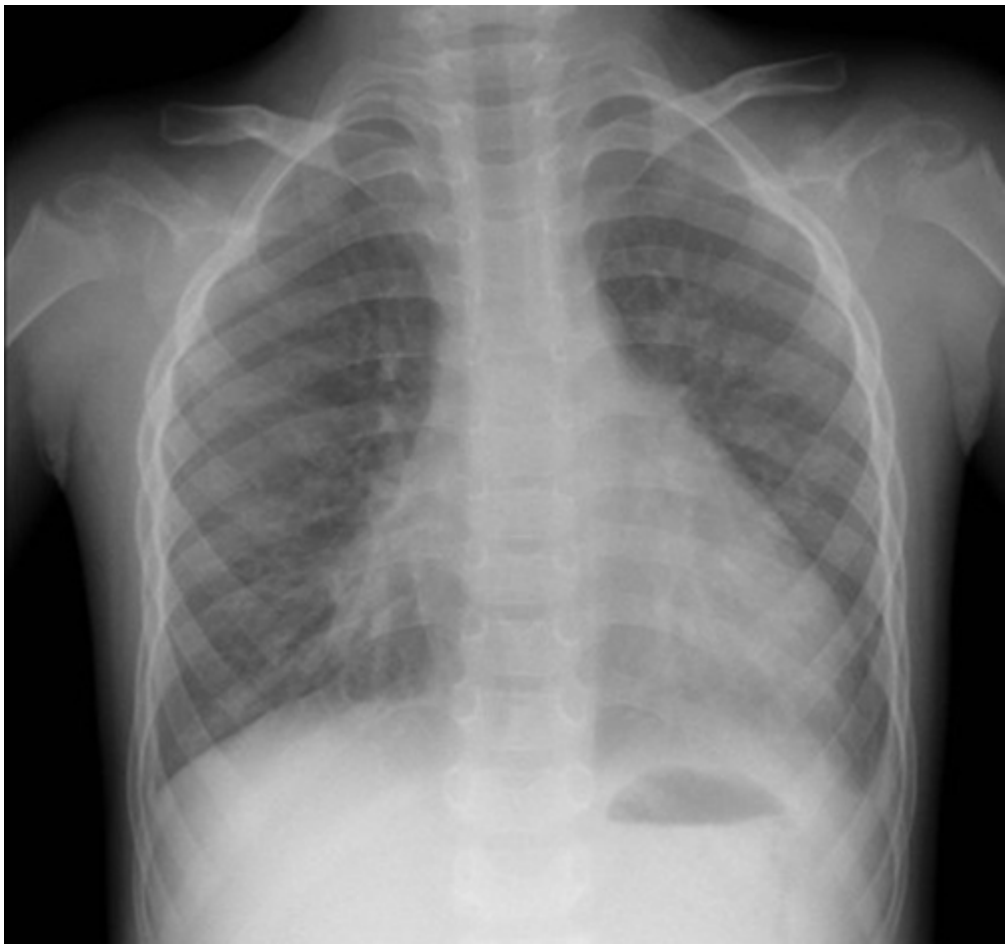

Figure 17.2 Repeat chest X-rays in clinic showed some improvement in airspace changes bilaterally.

QUESTION 1: *What are the most likely diagnoses at this point?*

Given his age and relatively short history of improving productive cough, the following diagnoses should be considered:

1. Recurrent respiratory infections (due to the recent onset of fever and flu-like symptoms)
2. Foreign body aspiration (although there is no history of choking, foreign body aspiration should remain a high consideration in this age group)
3. Bronchiectasis (possible post-infectious complications, particularly given the abnormal repeat chest X-ray)
4. Less likely, a congenital airway or pulmonary lesion (given normal CT thorax prior to onset of illness)

QUESTION 2: *How would you further evaluate this patient?*

A review of the previous CT thorax revealed areas of focal hyperinflation in the posterior-medial left upper lobe, as well as scattered regions in the left lower lobe. These findings raised concern for air trapping due to airway compression (Figure 17.3).

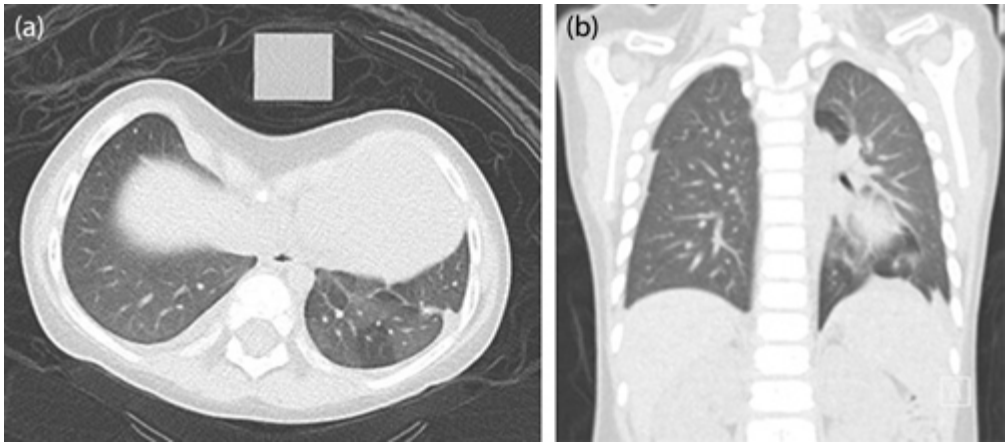

Figure 17.3 (a and b) Patchy areas of pulmonary overinflation within the left lower lobe. Mild bilateral pleural thickening is seen. The left lung appears smaller with the left diaphragm positioned higher than the right.

Given his clinical improvement after the antibiotic course, H was prescribed a 10-day course of oral clarithromycin and started on treatment for allergic rhinitis.

He returned for a follow-up appointment 6 weeks later and reported some improvement in his symptoms. However, the cough never completely resolved and had worsened in the past week. This worsening was not associated with any fever or new infectious symptoms. His weight was static.

On examination, he was mildly tachypnoeic with a persistent productive cough. Auscultation of his lungs revealed occasional expiratory wheeze and bilateral crackles (Figure 17.4).

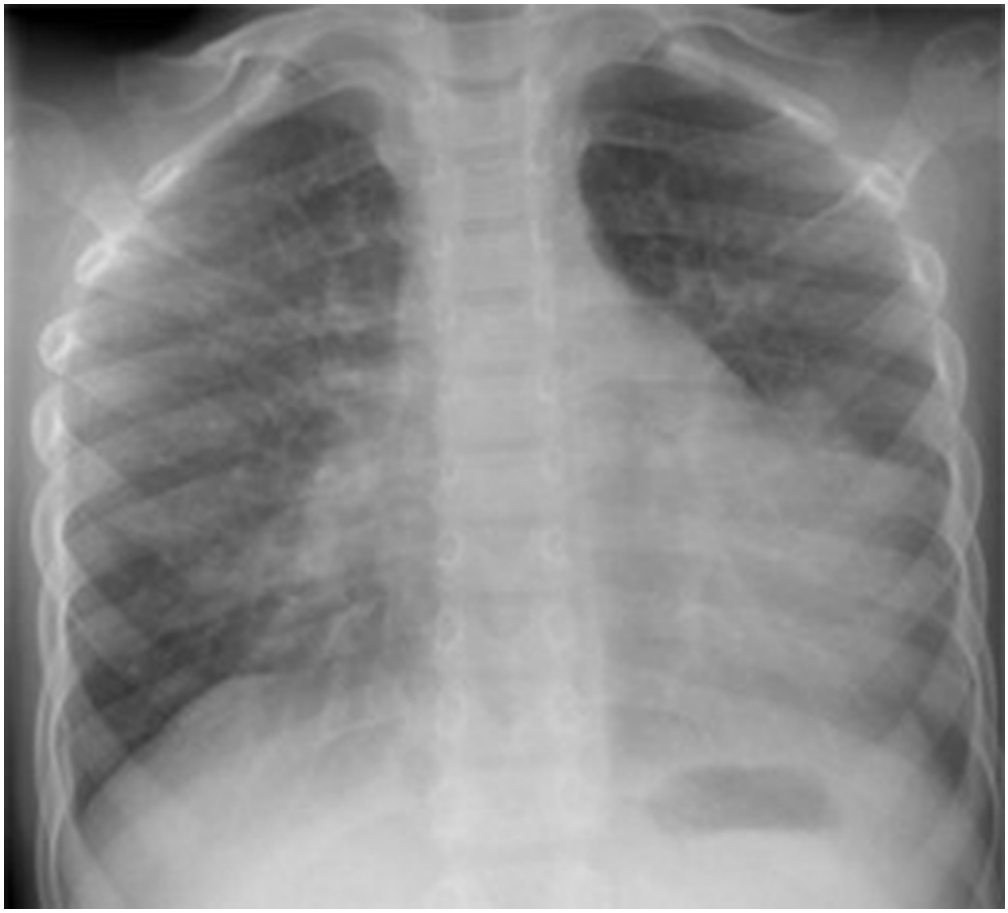

Figure 17.4 A repeat chest X-ray shows worsening bilateral consolidation with no pleural effusions.

QUESTION 3: *How would you manage this case now?*

H was admitted from the clinic for initiation of intravenous antibiotics and planned for further workup in view of persistent (worsening) chest X-ray changes as well as symptoms. He was given a regular salbutamol metered-dose inhaler (MDI) in view of wheeze heard with some response.

To investigate concerns of airway compression or malacia, given the persistent symptoms and evidence of pulmonary overinflation on the previous CT thorax, he underwent flexible bronchoscopy and bronchoalveolar lavage (BAL). The bronchoscopy revealed thick mucopurulent secretions throughout the bilateral segmental bronchi in the

lower lobes. While the right main bronchus appeared normal, the left main bronchus was narrow up to the opening of the left upper and lower lobes, with difficulty manoeuvring the scope into the left lower lobe. No foreign body was seen.

The infective workup from the BAL sample was positive for human coronavirus, rhinovirus/enterovirus, and *Aspergillus niger* complex, as well as *Penicillium* species from the fungal culture (which returned a few months later). All other microbiological tests, including those for tuberculosis and bacteria, returned negative.

Immunology investigations, including IgGAME, immunoglobulin subclasses, and specific antibodies to vaccines, were unremarkable. A swallowing assessment revealed no signs of pharyngeal dysphagia, and the sweat test was negative. The parents declined genetic testing for primary ciliary dyskinesia and cystic fibrosis.

CASE OUTCOME

His symptoms gradually improved after a week of intravenous ceftriaxone, followed by 2 weeks of oral cefuroxime and daily chest physiotherapy. A repeat CT thorax was performed, which did not show typical signs of *Aspergillus* invasion. A decision was made in conjunction with the infectious disease specialist to hold off treatment for aspergillosis as his cough had improved.

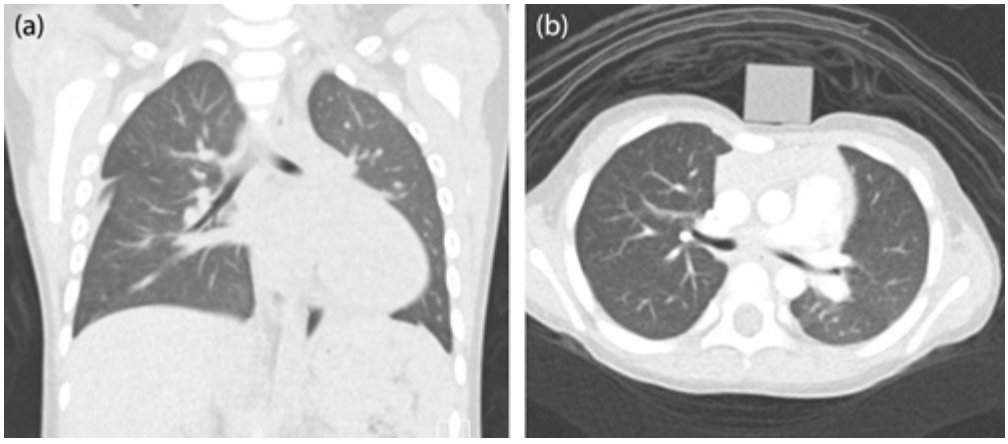

Figure 17.5 (a and b) Repeat CT thorax shows worsening Haller index with mild compression of the right atrium and ventricle with slight heart displacement to the left. The left main bronchus appears compressed with patchy areas of segmental pulmonary overinflation.

During his clinic review, H's parents reported the complete resolution of his cough, with no reduction in effort tolerance. However, they expressed concern about the worsening pectus excavatum, as indicated by an increased Haller index on the repeated CT thorax. He was evaluated by both cardiothoracic and plastic surgeons and was advised to undergo vacuum bell therapy.

Ultimately, his parents decided to take him to China, where he underwent Nuss bar insertion. He remained clinically well after the surgery (Figure 17.6).

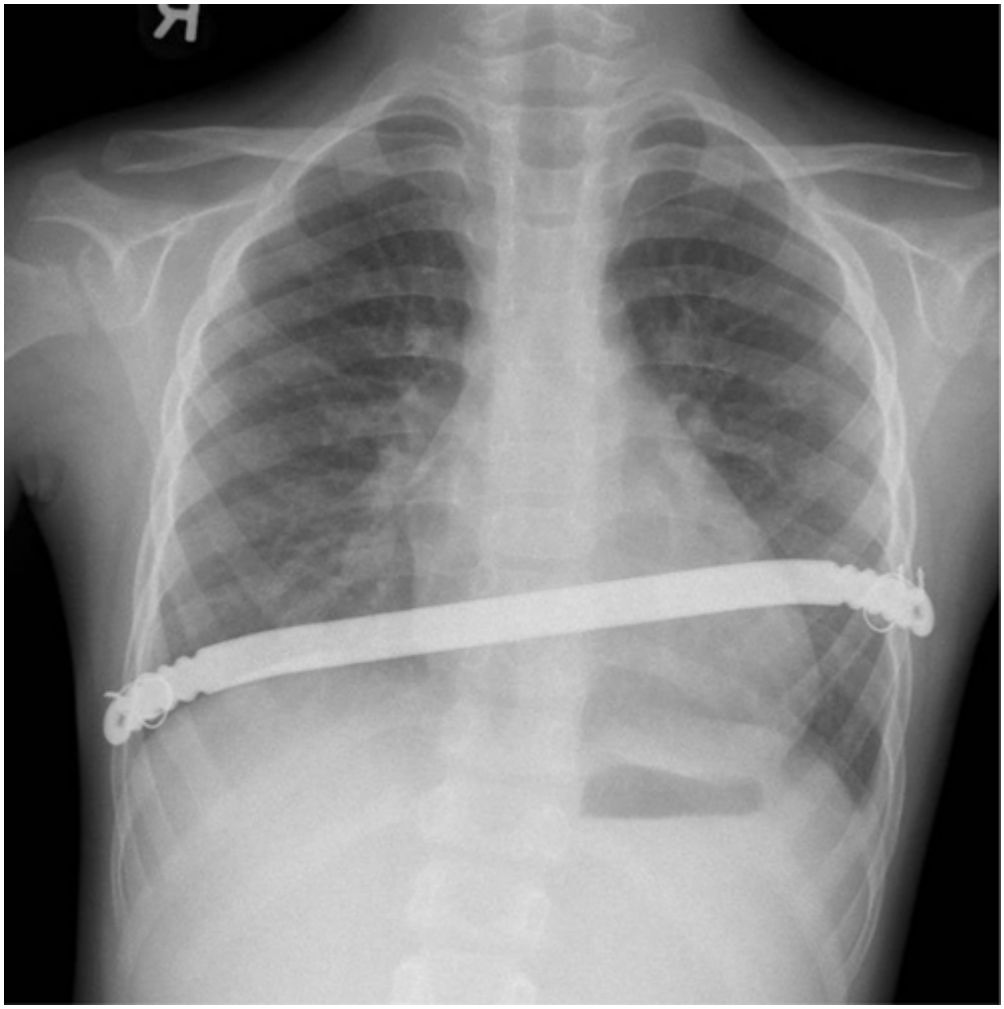

Figure 17.6 Chest X-ray revealed optimal position of Nuss bar with improved airway changes.

KEY LEARNING POINTS

Persistent pneumonia is defined as the continuation of symptoms and radiological changes for 4 weeks or longer, despite treatment [1]. Unresolved pneumonia, despite appropriate antibiotic treatment, requires further investigation. Once it is confirmed that the patient has completed the appropriate course of antibiotics, potential causes of unresolved pneumonia should be considered, including [2]:

1. Reactive airway disease or asthma

2. Aspiration pneumonia or gastro-oesophageal reflux disease
3. Foreign body aspiration
4. Complications from pneumonia, such as bronchiectasis and post-infectious bronchiolitis obliterans
5. Airway abnormalities, such as bronchomalacia (congenital or extrinsic compression)
6. Cystic fibrosis
7. Primary ciliary dyskinesia
8. Immunocompromised state
9. Tuberculosis (TB)

History	What do they imply
Young age of onset	May indicate congenital malformation or a hereditary disorder
Cough with diurnal variation	May be suggestive of bronchial asthma, but further confirmatory tests are needed
Cough related to feeds or swallowing	May be suggestive of foreign body inhalation if sudden onset May also be due to gastro-oesophageal reflux, swallowing dysfunction, or simply a poor feeding technique
Past history of recurrent skin or ear infection Poor weight gain	Suggestive of immunodeficiency Frequent pneumonia and ear infections or sinusitis may also be indicative of primary ciliary dyskinesia
Frequent loose and offensive bowel motions with failure to thrive	Suggestive of cystic fibrosis, especially in Caucasian children
History of exposure to chronic cough or TB	To rule out pulmonary TB

Recurrent pneumonia affecting the same lobe raises suspicion for a localized disease, which could include [3]:

1. Narrowed airways

    a. Extrinsic compression from lymph nodes, tumours, or a vascular ring
    b. Bronchial wall abnormalities like bronchomalacia, laryngeal web, or stricture
    c. Endobronchial causes such as TB, foreign body, or tumours

2. Congenital lung lesions, benign lung cyst, emphysema, or sequestered lobe
3. Focal bronchiectasis

While pectus excavatum does not directly cause pneumonia, it can contribute to conditions that increase the risk of pneumonia, especially in children [4, 5, 6].

1. Restrictive lung disease [7]

    a. The sunken chest wall can restrict the expansion of the lungs, reducing lung capacity for expansion.
    b. If the lungs cannot fully expand, the air exchange is less efficient. This can result in impaired ventilation where bacteria and viruses are more likely to grow, potentially leading to pneumonia.

2. Increased risk of respiratory infections with impaired immune response

    a. The restricted chest wall decreased the patient's ability to clear secretions as well as weakened cough reflex.

Accumulation of secretions increases the risk of pneumonia.

3. Altered heart function

    a. In severe cases of pectus excavatum, the abnormal position of the sternum can exert pressure on the heart, affecting circulation and oxygen delivery, which in turn affects lung health and immune function.

The optimal age for the repair of pectus excavatum remains controversial. There has been concern with open repair during childhood including recurrence risk, risk of impaired thoracic growth, and possible restrictive pulmonary impairment post-surgery [8]. In recent years, studies have shown better outcomes in preserving chest wall integrity and enhancing patients' growth with surgery done using minimally invasive techniques in patients older than 3 years of age [9]. Ultimately, surgical chest wall reconstruction should be considered for young patients with a severe pectus excavatum deformity and associated physiologic impairment.

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CHAPTER 18 AN INFANT WITH INTERMITTENT WHEEZE

Chun Yi Ting, Duo-Tong Cheng, Justin Liang Yi Wee, and Arun Kumar Pugalenthi

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INTRODUCTION

This is a 4-month-old infant who had presented with a 1-month history of intermittent wheezing episodes, without any obvious intercurrent respiratory infections. This case illustrates the approach and evaluation for intermittent wheezing in an infant.

CASE PRESENTATION

Q is a 4-month-old Malay infant who had presented with intermittent episodes of wheezing since 3 months of age. These episodes were typically more pronounced after feeding, with the parents reporting hearing wheezing for about 30 minutes post-feeding. The wheezing tended to improve after she calmed down or when she was positioned laterally with the right side up. There would also be brief wheezing episodes on agitation that resolved spontaneously. No wheezing was heard when she was asleep, and there was no history of stridor. Over the last month, Q had remained afebrile with no cough or runny nose symptoms.

Q was born at 38^{+6} weeks gestation via normal vaginal delivery, with a birth weight of 2632 g. There were no significant antenatal concerns, and antenatal scans were normal. She had remained clinically well during the neonatal period.

Q first presented to our hospital at 4 months of age with a 3-day history of cough and increasing breathlessness. She was treated for acute bronchiolitis with nebulized adrenaline, and the wheezing resolved prior to discharge. Five days later, she reattended with worsening tachypnoea and wheezing. However, on examination, no wheeze was heard. A chest X-ray (Figure 18.1) performed revealed peribronchial thickening at the right perihilar region with right-sided airspace opacities. Of note, bilateral mainstem bronchi appeared reduced in calibre.

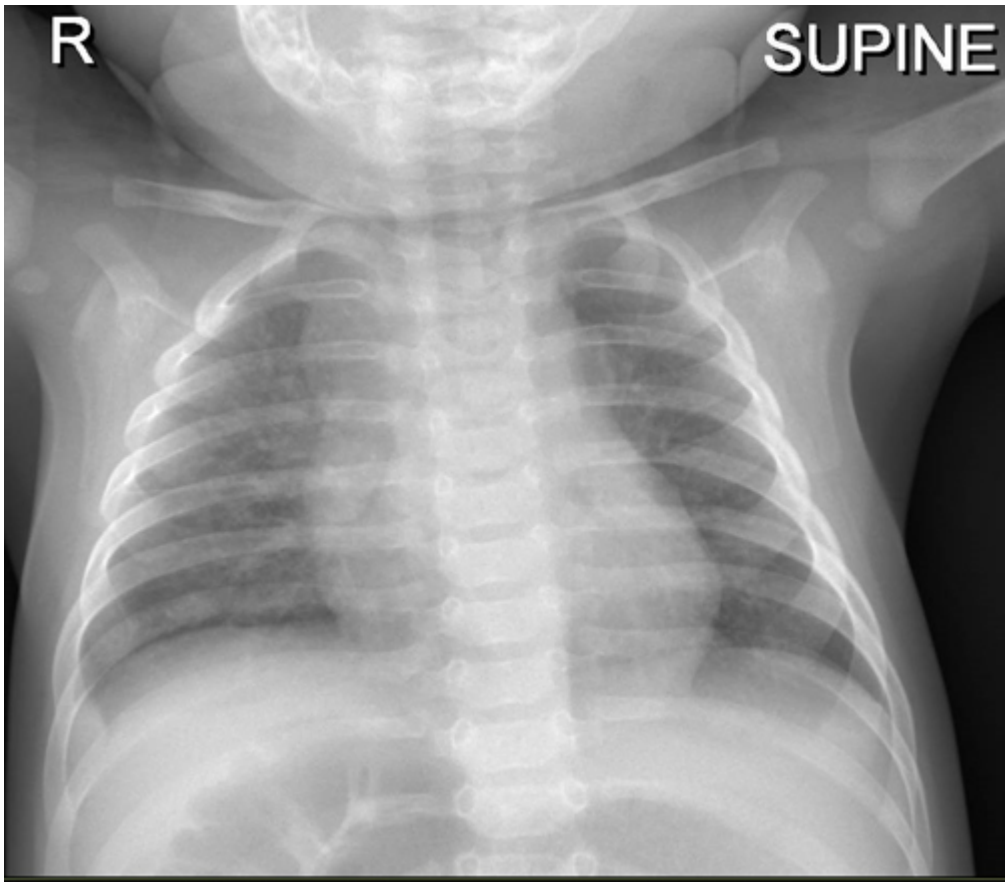

Figure 18.1 Chest X-ray showing right perihilar peribronchial thickening and airspace opacities, as well as reduced calibre of bilateral mainstem bronchi.⏎

Q has a family history of atopy in which her father and paternal uncle have asthma and are currently on inhaled corticosteroids. There is no personal history of eczema.

QUESTION 1: *What are the most likely diagnoses at this point?*

Given the intermittent nature of the wheezing episodes over a month without respiratory infections, the following diagnoses should be considered:

1. Tracheomalacia or bronchomalacia
2. Extrinsic lower airway compression including:
    a. Congenital vascular anomalies (e.g., vascular sling, vascular rings, innominate artery compression)
    b. Masses (e.g., bronchogenic cyst, lymphoma, teratomas)
    c. Lymphadenopathy (e.g., tuberculosis)
    d. Enlargement of cardiac structures
3. Tracheo-oesophageal fistula (given episodes occurring after feeds)

QUESTION 2: *What subsequent evaluations would you consider?*

On admission, Q's full blood count showed mild normocytic, normochromic anaemia (Hb 10.3 g/DL) and C-reactive protein was mildly elevated at 24.4 mg/L. A nasopharyngeal swab for respiratory viruses was negative. Renal panel was normal.

Q underwent a CT thorax (Figure 18.2) that revealed enlarged lymph nodes in the supraclavicular, mediastinal, and both hilar regions, with consequent narrowing of the airways, oesophageal compression, and vascular encasement. There was also ground-glass opacification of the right upper lobe. Given the CT findings, concerns for tuberculosis (TB) and lymphoma were raised.

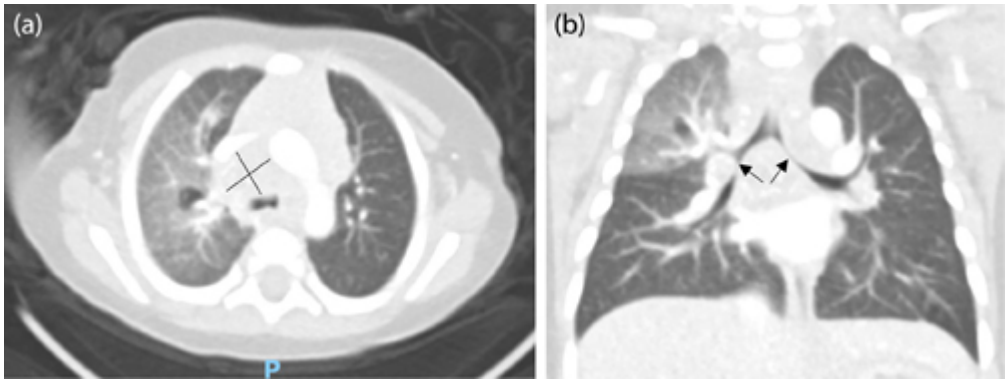

Figure 18.2 (a) CT thorax showing enlarged lymph nodes, especially at the right paratracheal region, measuring approximately 2.1 × 1.6 cm. (b) CT thorax showing narrowing of the bilateral main bronchi secondary to compression from enlarged lymph nodes, more on the left.

Further history then revealed that Q's grandmother from Indonesia, who had TB many years previously and had completed treatment, visited Q and cared for her for 3 weeks during her neonatal period. During her stay, Q's grandmother had an intermittent cough and soon after returning to Indonesia, she was again diagnosed with TB and had restarted treatment.

Q had no constitutional symptoms and was feeding well with good weight gain. There was also no significant family history of malignancy.

QUESTION 3: *How would you manage this patient?*

Q was isolated with airborne precautions and a Mantoux test was done, which subsequently returned positive with a wheal of 15 mm at 16 hours. Further TB workup was performed including sending gastric aspirates for AFB (acid-fast bacilli) smears, AFB culture, and TB PCR. She was also referred to infectious diseases to advise on further microbiological investigations as well as oncology due to concerns for possible lymphoma. Her abdominal ultrasound was normal, and a neck ultrasound showed a few enlarged supraclavicular lymph nodes. Peripheral blood film, lactate

dehydrogenase, uric acid, alpha-fetoprotein, and beta-hCG all returned normal.

Q subsequently underwent a supraclavicular excisional lymph node biopsy, along with flexible bronchoscopy at the same setting. Bronchoscopy findings included a narrow left bronchial opening and bronchus intermedius, through which a size 2.8 mm flexible bronchoscope was easily passed and the airway calibre appeared otherwise normal after the initial narrowing bilaterally. The mucosa was mildly inflamed, but no mucosal lesions were seen.

Her microbiological workup returned positive for cytomegalovirus (CMV) PCR in the urine, blood (log 5.1), and bronchoalveolar lavage (BAL). Hence, she was started on IV ganciclovir. As respiratory viruses polymerase chain reaction (PCR) testing from the BAL returned positive for influenza B, *Mycoplasma pneumoniae*, and respiratory syncytial virus (RSV), she was also treated with oral oseltamivir for 5 days and oral azithromycin for 3 days. In view of the fever that had developed inpatient on day 5 of admission, she was cultured and covered with IV Augmentin, and this was stopped after the bacterial cultures from the bronchoalveolar lavage returned negative.

Thereafter, AFB smears from gastric aspirates, bronchoalveolar lavage as well as cerebrospinal fluid were negative. TB PCR from the blood, BAL, cerebrospinal fluid, and the lymph node were also negative. Histopathology of the biopsied lymph node showed necrotizing granulomatous lymphadenitis with a large zone of caseating necrosis, with presence of acid-fast bacilli. There were no features of malignancy (Figure 18.3).

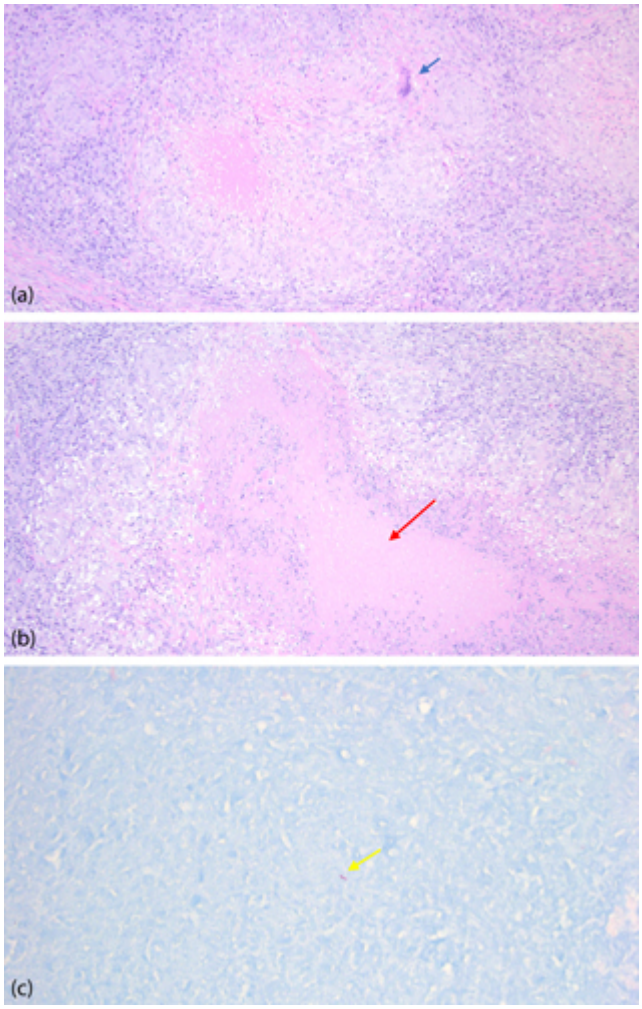

Figure 18.3 (a) Slide showing a necrotizing granuloma with a closely associated Langhans giant cell (blue arrow). (b) Presence of large zones of caseating necrosis (red arrow) surrounded by histiocytes, i.e., necrotizing granuloma. (c) An acid-fast bacillus is present among the necrotizing granulomas (yellow arrow).

Therefore, she was initiated on TB treatment with PO rifampicin, isoniazid, ethambutol, and pyrazinamide (RHZE) as well as PO prednisolone. Q clinically improved while inpatient and was discharged clinically well on room air.

CASE OUTCOME

A month later, the AFB culture sent from the lymph node biopsy subsequently was reported as positive for *Mycobacterium tuberculosis* complex, whereas the AFB cultures from gastric aspirates and BAL were negative. Q completed TB treatment with 2 months of RHZE, followed by 4 months of RH treatment. After 2 weeks of oral prednisolone at 2 mg/kg/day, the steroid was gradually weaned over the next month. With regard to her postnatal CMV viraemia and pneumonitis, she completed 4 weeks of treatment with intravenous ganciclovir followed by oral valganciclovir. She tolerated the treatment well, and her intermittent wheezing episodes resolved within 2 months of treatment.

Given the multiple lymphadenopathy with CMV viraemia and a positive Mantoux test, she was also referred to immunology for concerns of immunodeficiency. Subsequent workup showed mild B-cell lymphopenia with slightly low anti-CD3 and anti-CD28 proliferation. As she had otherwise remained clinically well with no further significant infections, tolerated live vaccines well and has normal growth, this is not likely to be clinically significant, and she is on continued follow-up with immunology.

Q has since remained well, with no other respiratory symptoms or concerns. A repeat CT thorax (Figure 18.4) 2 years later showed interval resolution of the mediastinal and hilar lymph nodes and the ground-glass opacification, as well as normal calibre and patent trachea and bronchus. Therefore, bronchoscopic evaluation was not repeated.

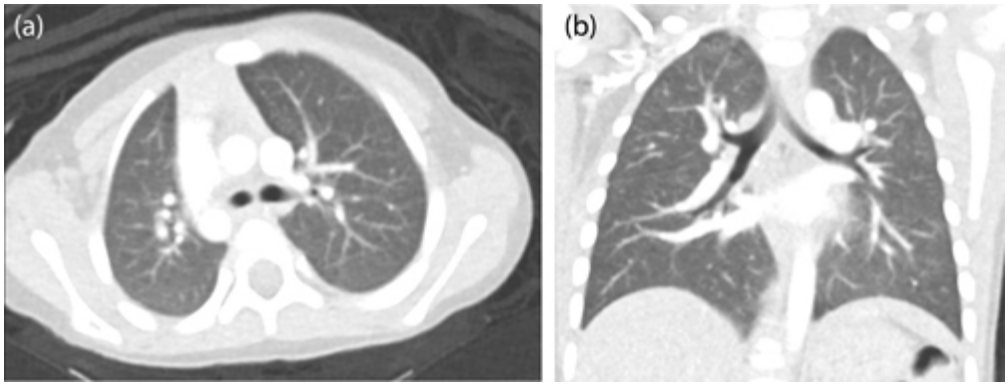

Figure 18.4 (a) CT thorax showing interval resolution of the right paratracheal lymphadenopathy with normal calibre of bilateral main bronchi. (b) CT thorax showing normal calibre of bilateral main bronchi and bronchus intermedius.⏎

KEY LEARNING POINTS

Recurrent wheezing due to structural airway abnormalities

Structural airway abnormalities may present with recurrent wheezing in infants, and should be considered as a differential if the clinical presentation is not suggestive of bronchiolitis or asthma.

Wheezing is a common presentation in infancy and early childhood, with approximately 30% of children presenting with wheezing before the age of 3 years [1]. The presence of wheezing suggests airway obstruction, and the character of the wheeze provides clues to the location of the pathology. A high-pitched polyphonic wheeze heard mainly during expiration is usually heard in bronchiolitis or asthma, whereas a low-pitched monophonic wheeze is suggestive of a fixed large or central airway obstruction, such as tracheomalacia [1].

While the most common causes of recurrent wheezing in infancy are due to respiratory infections in a child with underlying bronchial hyperreactivity or infantile asthma, in a child with persistent wheezing that presents early in life and is not responsive to asthma treatment, structural airway abnormalities should be considered. Recurrent episodes of wheezing that are not triggered by respiratory infections but are instead triggered by changes in position or feeding should raise suspicion for underlying structural or anatomic causes, and further evaluation is warranted.

A study performed by Saglani et al. on children aged between 3 months and 5 years with severe recurrent wheezing found that 13 out of 37 patients (36%) had a structural airway abnormality [2].

Some of the structural airway abnormalities that may present with recurrent wheeze include [1,3]:

1. Anomalies of the tracheobronchial tree.

    a.Congenital tracheomalacia or bronchomalacia – Wheezing may be noticed at birth but usually becomes more obvious after 2 to 3 months of age. Depending on the degree of malacia, symptoms may range from mild noisy breathing to severe respiratory distress.
    b.Congenital vascular anomalies (e.g., vascular rings or slings) – These can also cause biphasic stridor.
    c.Fistulas between the tracheobronchial tree and other anatomical structures – These usually present with recurrent pneumonias and/or chronic cough.

2. Mediastinal masses including tumours, teratomas, bronchogenic cysts, enlarged lymph nodes causing compression of trachea or bronchi (as seen in this case).
3. Foreign body aspiration – This may present with either acute (more commonly) or chronic wheezing (if the diagnosis is missed and the foreign body is retained).
4. Cardiovascular disease.

    a.Dilated cardiovascular structures causing airway compression, such as cardiac conditions resulting in left atrial enlargement or dilated pulmonary arteries.
    b.In patients with heart failure and poor left ventricular function, pulmonary venous congestion may cause wheezing due to lymphatic and bronchial vessel engorgement that results in bronchiolar obstruction and oedema.

In infants suspected of having an underlying structural cause of wheezing, investigations would include a chest X-ray (if not already performed), CT thorax, flexible bronchoscopy, and/or echocardiography.

Lymphobronchial tuberculosis in infants and children

In infants and children, primary TB may manifest as hilar or mediastinal lymphadenopathy, and lymphadenopathy is considered the hallmark of radiological diagnosis of TB in children [4]. Lymphobronchial TB (LBTB) refers to tuberculous lymphadenopathy that affects the airways and includes a spectrum of airway involvement including extrinsic compression, intra-luminal airway obstruction by inflammation, or protrusion of caseating lymph nodes into the airway [4]. While regional lymphadenopathy is a very common presentation of TB in children, airway compression by enlarged lymph nodes (i.e., LBTB) is only seen in 38% of patients based on CT scans [5].

Younger children and infants are more likely to develop TB after infection with *M. tuberculosis* and are more prone to developing lymphadenopathy as well due to their immature immune systems [4]. Their airways are also narrower and more pliable due to less supportive cartilage, making them more susceptible to compression by the enlarged lymph nodes [6]. Tuberculous mediastinal lymphadenopathy may cause tracheal compression, whereas hilar lymphadenopathy may compress the bronchus intermedius and left main bronchus [6]. A retrospective study that reviewed CT scans of children with lymphobronchial TB found that the commonest site of lymphadenopathy was the subcarinal mediastinum (97%), and the bronchus intermedius was the most frequent site of airway compression (28%) [4].

Clinical presentation and symptoms will depend on the degree of airway obstruction and range from being asymptomatic to chronic cough, recurrent wheeze, stridor, respiratory distress, and recurrent pneumonias [7]. Partial airway obstruction may cause hyperinflation due to air trapping from a ball valve effect, while complete airway obstruction may result in lobar collapse [5].

In cases of airway compression secondary to LBTB, corticosteroids can be considered as an adjunct therapy. However, the role of corticosteroids in LBTB is controversial. Corticosteroids suppress inflammation in the lymph

nodes and airways; hence, they may prevent bronchial compression due to erosion of the lymph nodes into the bronchial lumen [8]. In two prospective, randomized, placebo-controlled studies examining the use of systemic steroids in children with LBTB, the group that was treated with steroids showed significant improvement in endobronchial obstruction [9]. However, not all studies show a clear benefit of corticosteroids, and further studies are required.

In addition, bronchoscopic and/or surgical intervention may be required to restore airway patency. As such, it is important that timely identification and diagnosis are made, as delayed diagnosis and treatment may cause the distal lung parenchyma to be affected and lead to irreversible lung damage.

Contact tracing in children diagnosed with tuberculosis

When a child is diagnosed with tuberculosis, it is important to screen all who may be close contacts of the child, in addition to parents. All household contacts as well as others who had spent prolonged periods of time in the same enclosed space (for instance, grandparents, relatives, teachers) should be screened as well. Other non-household contacts who have spent significant time with the infected person, especially in an indoor setting, during the infectious period should also be screened. The infectious period is defined as either 3 months before the first positive sputum sample or from the onset of cough to the initiation of TB treatment, whichever is longer [10].

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CHAPTER 19 PERSISTENT SEVERE WHEEZING IN A YOUNG CHILD FROM AN LMIC

Pierre Goussard and Ernst Eber

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INTRODUCTION

Preschool wheezing has many causes, and it is always important to determine if there is an underlying diagnosis to be made. In a low- and middle-income country (LMIC), infectious causes such as tuberculosis (TB) must also be considered. TB can cause bilateral as well as unilateral wheezing. The chest X-ray should be evaluated carefully as both mediastinal lymph nodes and airway narrowing may be present. It is important to confirm the TB diagnosis, and determine the drug sensitivities and severity of airway compression. We present this case to illustrate the range of diagnostic procedures available via fibreoptic bronchoscopy, which can be used to confirm that TB is the underlying diagnosis, thus facilitating proper and early treatment.

CASE PRESENTATION

A 12-month-old boy presented with a 2-week history of cough, tachypnoea and difficult breathing. There was no significant previous medical history, apart from that he was born at 33 weeks with a weight of 2.1 kg. His mother was HIV positive and on antiretroviral therapy (ARVs), but he was confirmed HIV PCR negative on two occasions. On examination, he was pale, and exhibited tachypnoea and bilateral wheeze. The wheezing was louder on the right side. He was started on nasal prong oxygen and IV

Augmentin and bronchodilators. The boy was referred as he did not respond to treatment and the wheezing was severe.

INVESTIGATIONS

The chest X-ray is shown in Figure 19.1. Significant hyperinflation was visible bilaterally, but there is very little parenchymal disease. Large airway pathology was present with displacement of the trachea to the left, and significant narrowing of the bronchus intermedius (BI) as well as the left main bronchus (LMB). The right paratracheal, and right and left hilar lymph nodes (LNs) were present, as well as significant subcarinal LNs. The visible signs of subcarinal LNs are the presence of fullness and increased density/opacification below the carina and the shifting of the para-oesophageal line. The LNs were confirmed on the lateral chest X-ray with the doughnut or hamburger sign present.

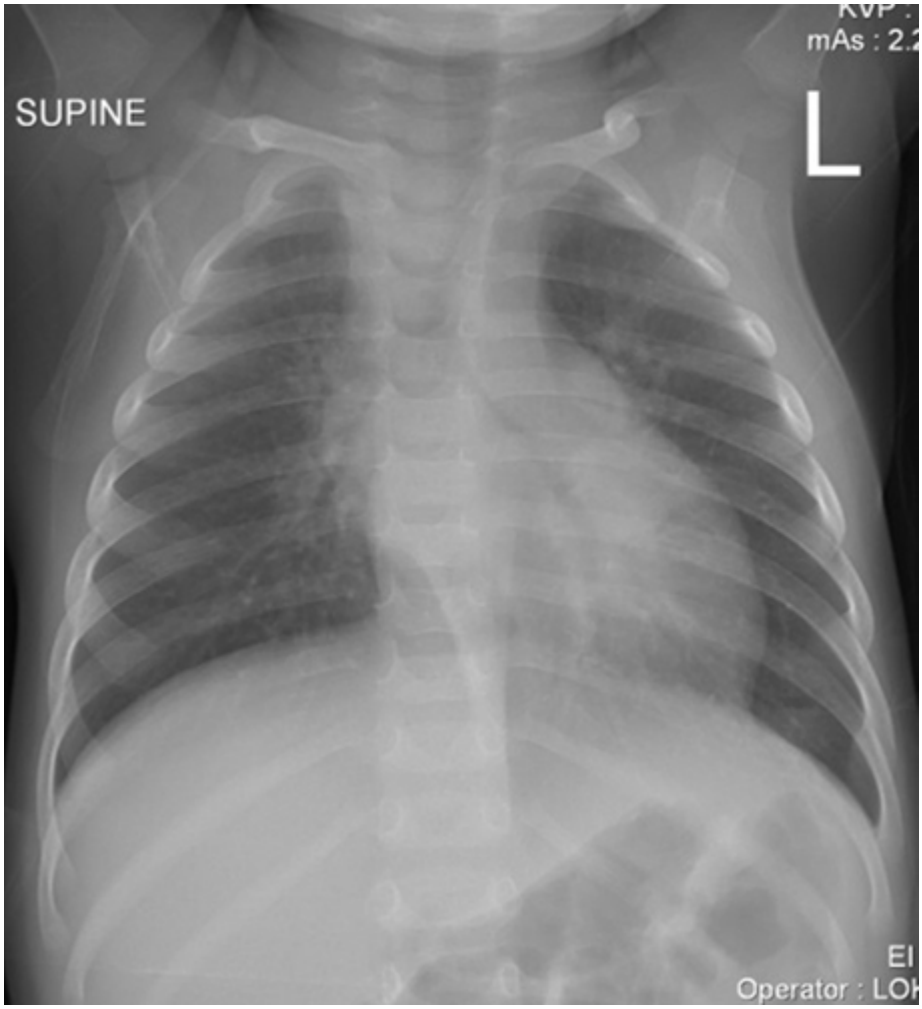

Figure 19.1 AP chest X-ray. Significant hyperinflation was visible bilaterally but very little parenchymal disease. There is a large airway obstruction with displacement of the trachea to the left, narrowing of the BI as well as the LMB. The right paratracheal, and right and left hilum lymph nodes (LNs) are present as well as significant subcarinal LNs.⏎

QUESTION 1: *What is the differential diagnosis?*

Acute viral infection in ex premature baby, congenital airway abnormality, foreign body aspiration (less likely due to bilateral signs), and tuberculosis

(TB) are much more likely than the other diagnoses given the degree of lymphadenopathy.

The radiological picture is very suggestive of complicated pulmonary tuberculosis (PTB) with significant airway compression (Figures 19.1 and 19.2). The diagnosis needs to be positively confirmed even though the patient is from a very high incidence area.

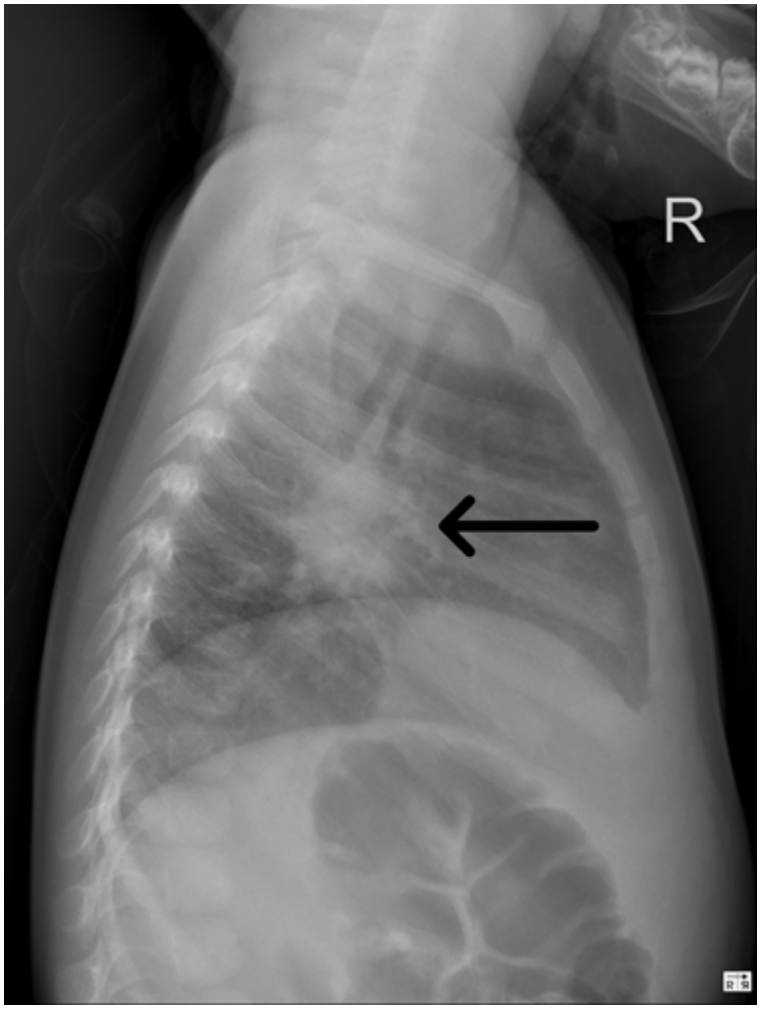

Figure 19.2 Lateral chest X-ray. LNs confirmed with the doughnut or hamburger sign present (arrow).

Due to the chest X-ray findings and the severity of airway obstruction, a four-drug TB treatment (rifampicin [RIF], isoniazid [INH], pyrazinamide [PZA], and ethambutol [EMB]) was started. Methylprednisolone 2 mg/kg 8

hourly was added for the first 48 hours due to the severity of airway obstruction and the clinical distress. The child improved, and methylprednisolone was changed to oral prednisone 2 mg/kg daily.

QUESTION 2: *Why does the TB diagnosis need to be positively confirmed?*

A response to high-dose steroids is not specific and although the diagnosis is likely, it needs to be confirmed for three important reasons: (1) otherwise it would just remain suspected TB and another diagnosis such as lymphoma could be missed; (2) to obtain samples for microbiological testing to determine drug sensitivity; and (3) to institute contact tracing – if this child has TB it will have been acquired from a likely undiagnosed adult in the child's family circle.

QUESTION 3: *What challenges were faced in making the diagnosis in this patient?*

There was no known adult TB contact, the mother's X-ray was normal, a Mantoux skin test was negative, and two gastric washings were Xpert MTB/RIF negative.

QUESTION 4: *What are the invasive methods that can be used to find the organism?*

A bronchoscopy was performed with a 4.0 mm video bronchoscope with a 2.0 mm working channel. There was 50% tracheal compression from the right, broad carina, the BI 90% narrowed, and the LMB 75% narrowed (Figures 19.3 and 19.4), but no endobronchial lesions which could be sampled. The bronchoscopy picture was very suggestive of TB, but Xpert MTB/RIF remained negative on bronchoalveolar lavage (BAL).

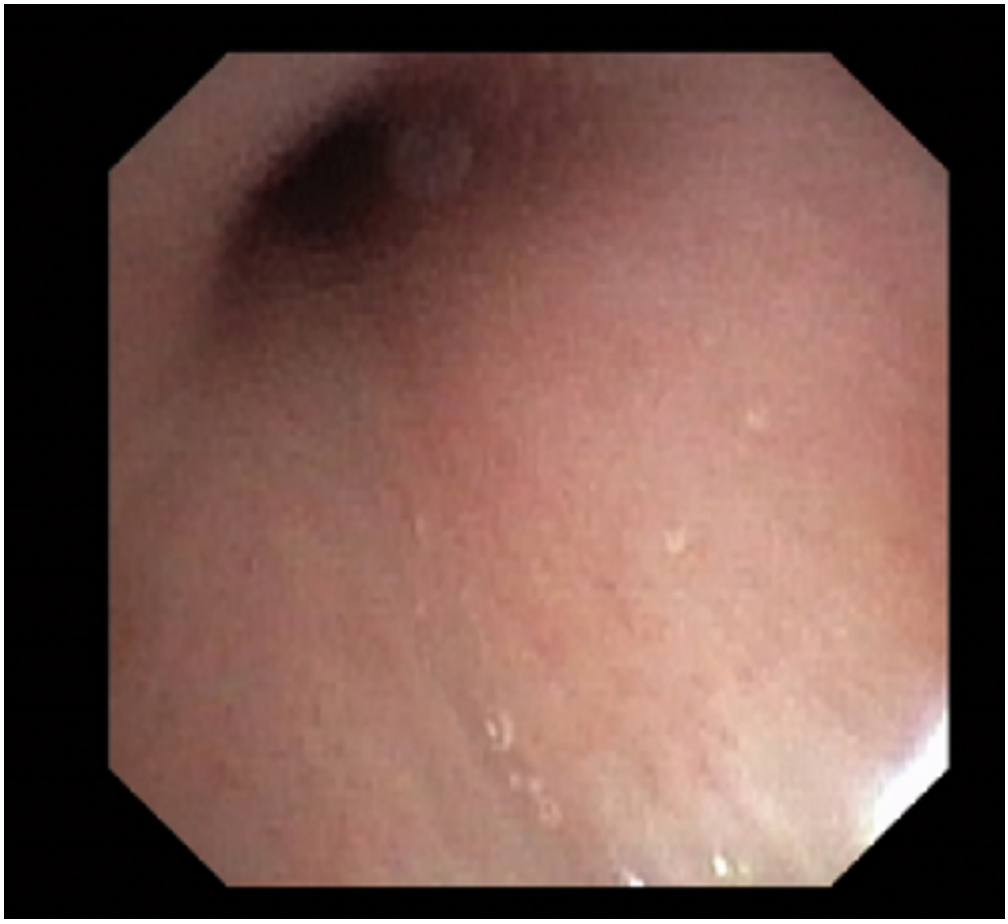

Figure 19.3 Bronchoscopy image demonstrating narrowing of the LMB.⏎

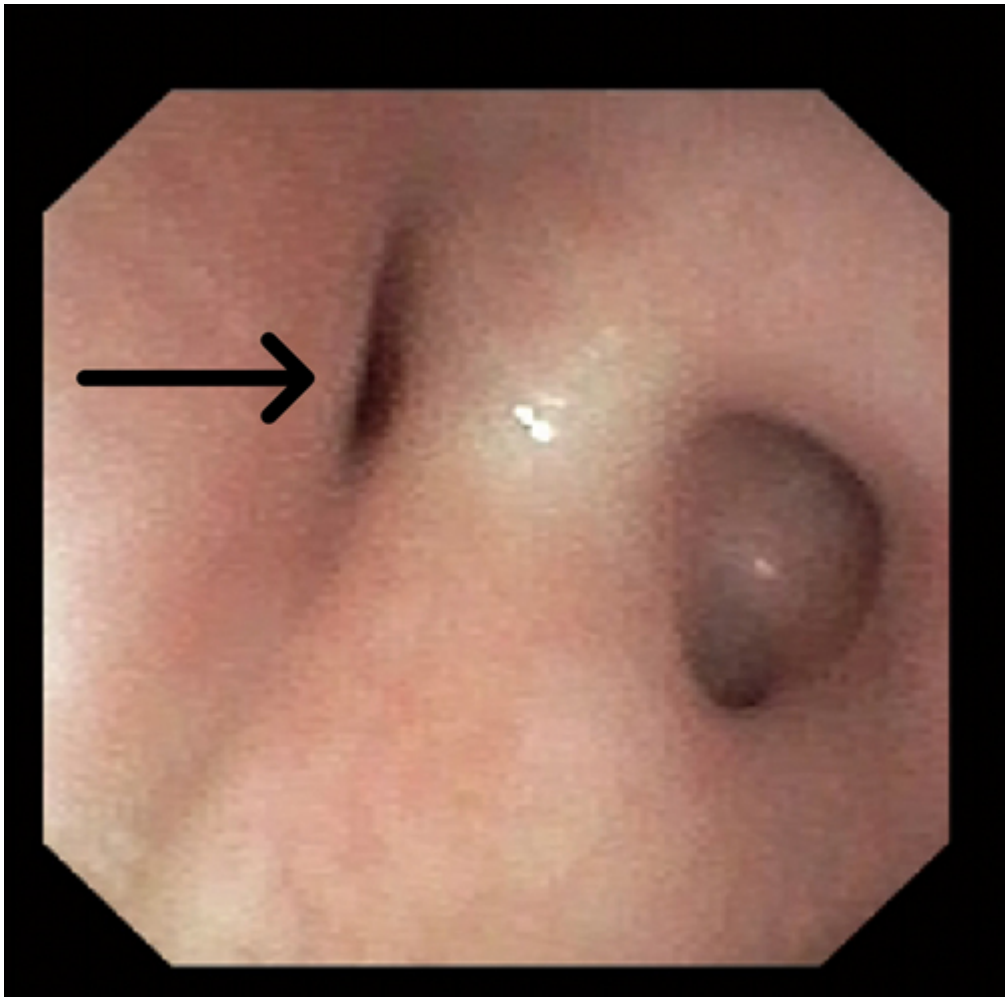

Figure 19.4 Bronchoscopy image demonstrating narrowing of the BI.

QUESTION 5: *How can advanced imaging be combined with interventional bronchoscopy?*

A contrast CT scan was performed to identify possible LNs for biopsy with interventional bronchoscopy. The enlarged mediastinal LNs were confirmed; these included the bilateral paratracheal, bilateral hilar, and subcarinal LNs. The subcarinal LN was large with areas of necrosis. This creates a very splayed carina that would make transbronchial needle aspiration (TBNA) possible. Because the repeat gastric washing remained negative, a follow-up bronchoscopy was performed one week after the

original bronchoscopy. There was improvement in the degree of airway compression, with BI improving to 75% and LMB to 50% compression. A radial endobronchial ultrasound (EBUS) probe was used through the 2.0 mm working channel of the 4.0 mm video bronchoscope. Enlarged right paratracheal and subcarinal LNs were demonstrated with the radial EBUS probe. The largest area visible was from the right side of the carina. TBNA was performed with a 2.0 mm Wang needle. This was repeated with three samples for Xpert MTB/RIF and culture and two samples for histological confirmation. On-site cytology did confirm the sample was Ziehl–Neelsen positive. TB was confirmed on the tissue obtained from TBNA, which was Xpert/MTB RIF positive. There were no complications related to TBNA except for self-limiting minimal bleeding from the biopsy site. This area was watched for a couple of minutes to confirm no further active bleeding. The time duration for the bronchoscopy was 9 minutes, which included inspection, BAL, radial EBUS, and TBNA (Figures 19.5–19.11).

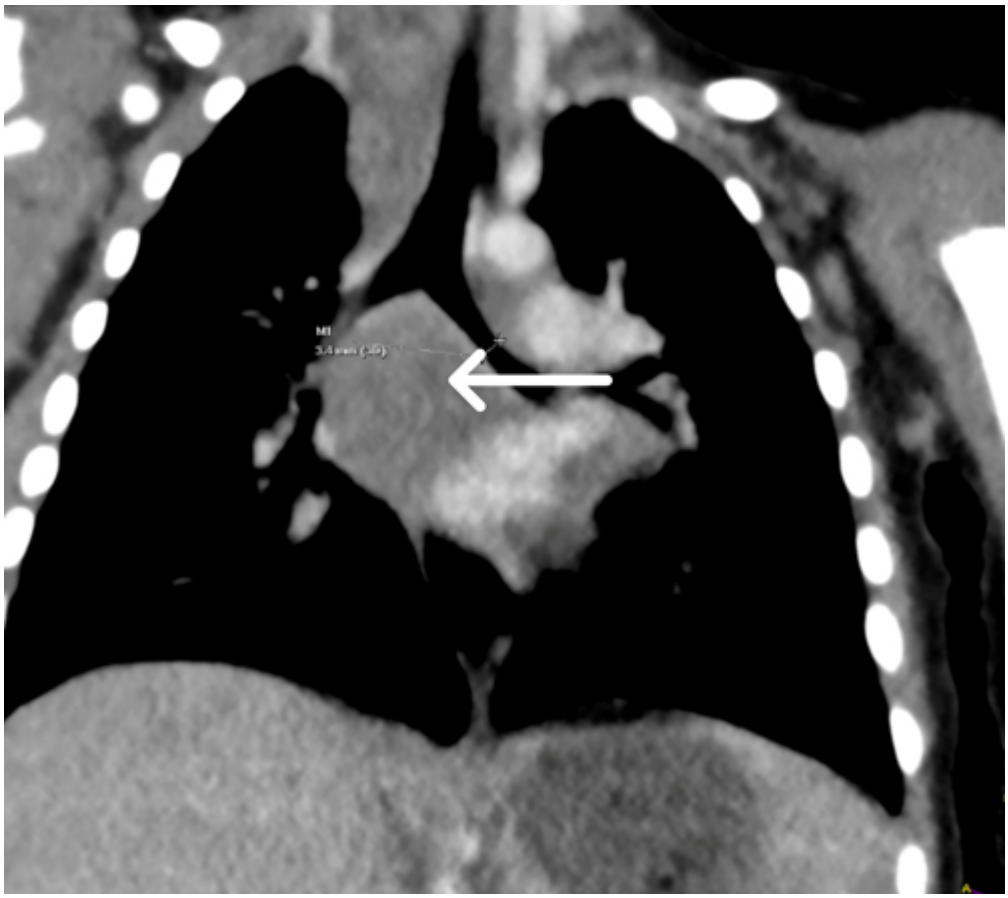

Figure 19.5 Coronal reconstruction of CT scan showing a very large subcarinal LN with necrosis and near-complete occlusion of the BI.

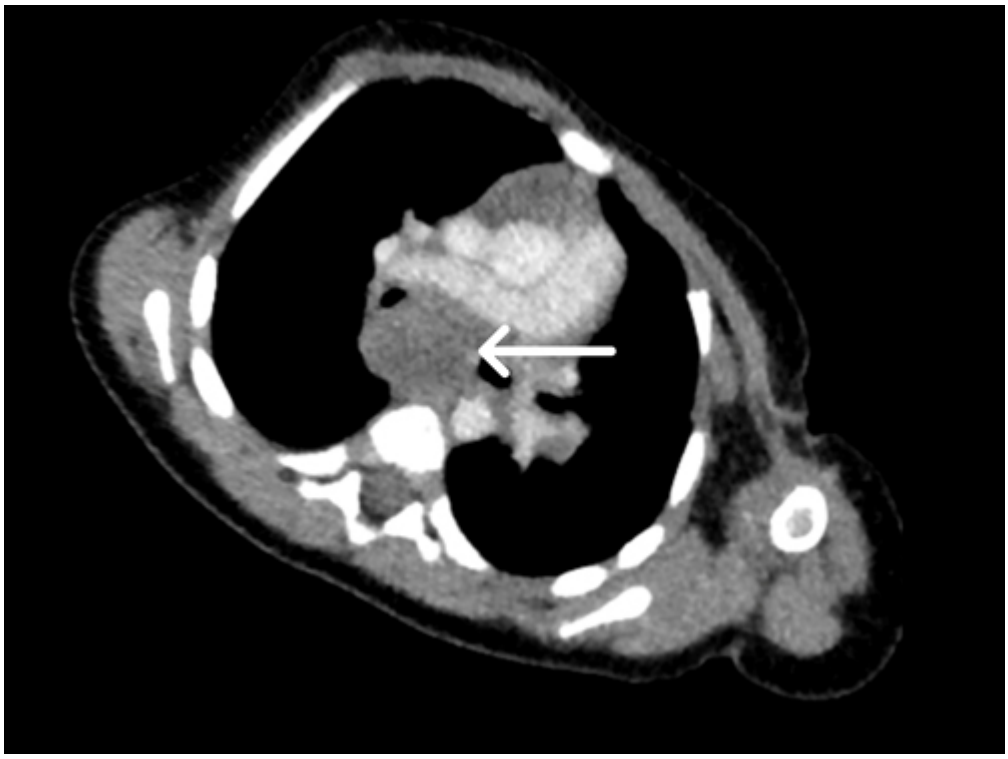

Figure 19.6 Chest CT scan image at the level of the carina demonstrating a large subcarinal LN.

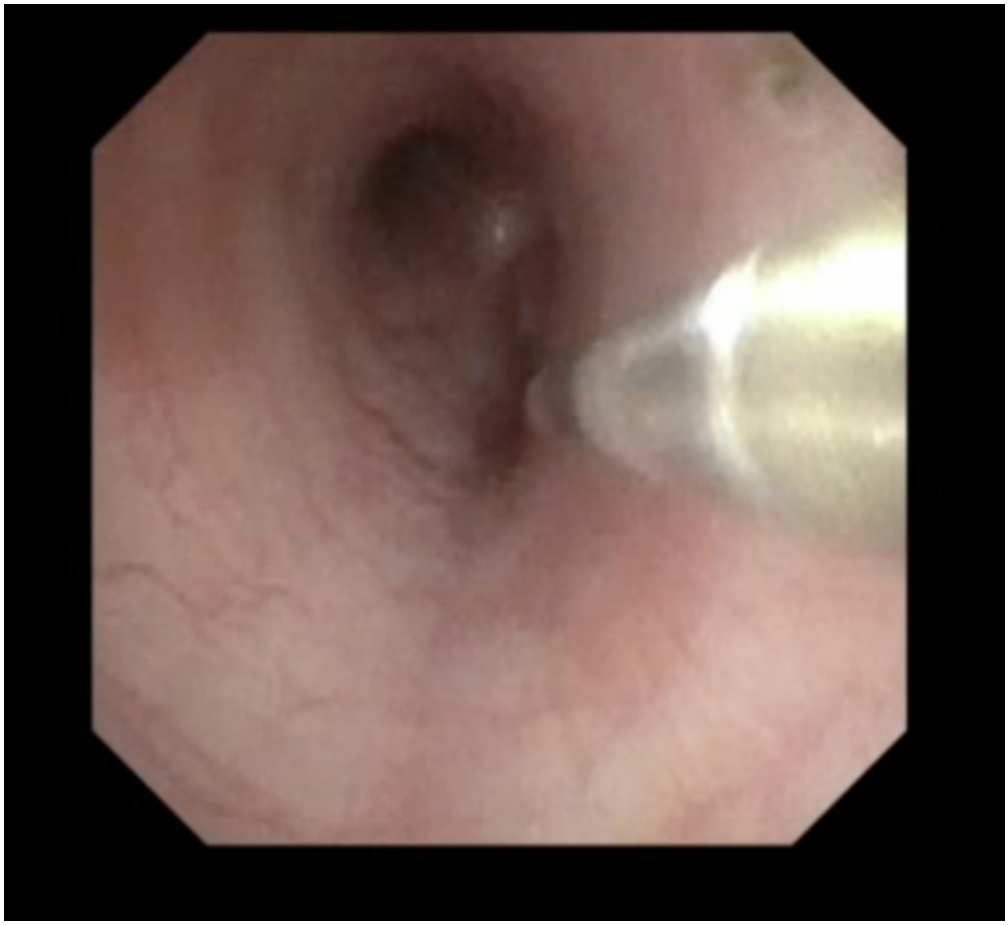

Figure 19.7 Radial EBUS probe visible in the trachea at the position of the right paratracheal area.

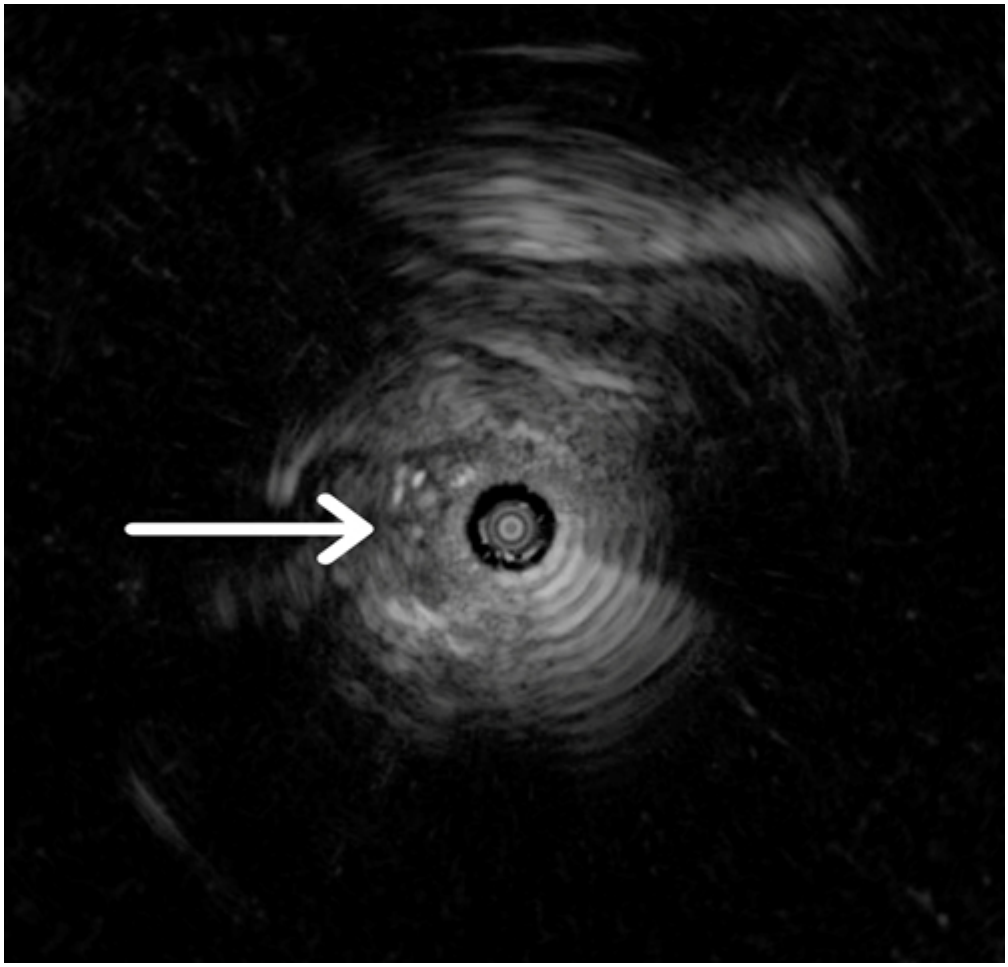

Figure 19.8 Radial EBUS image identifying the subcarinal LN.

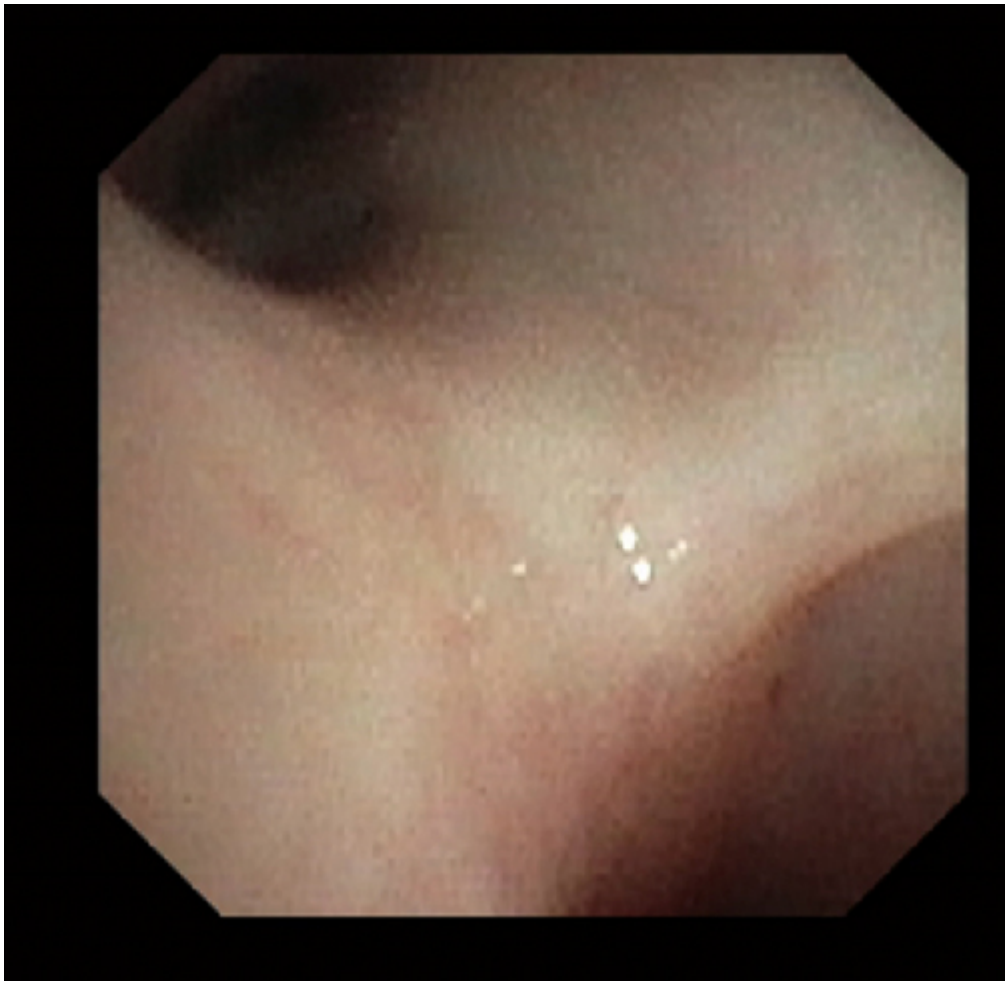

Figure 19.9 Bronchoscopy image of the broad carina, which makes it suitable for TBNA.

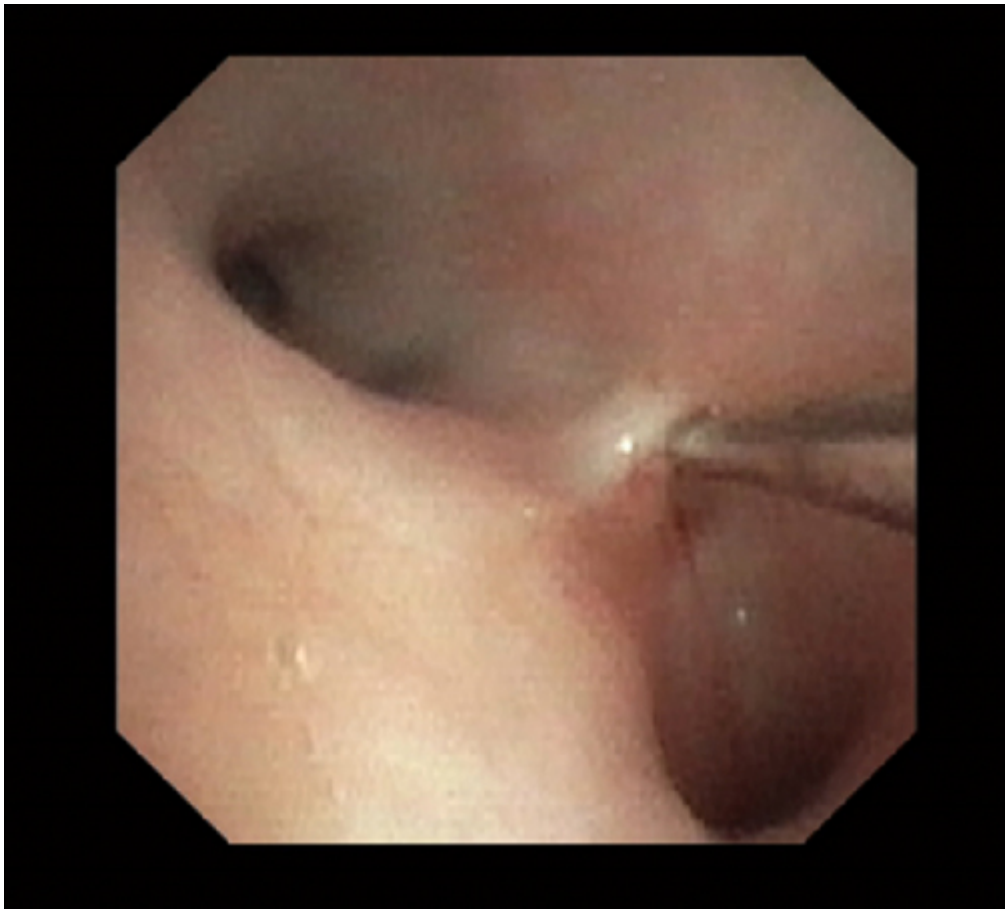

Figure 19.10 Wang needle inserted into the subcarinal LN.

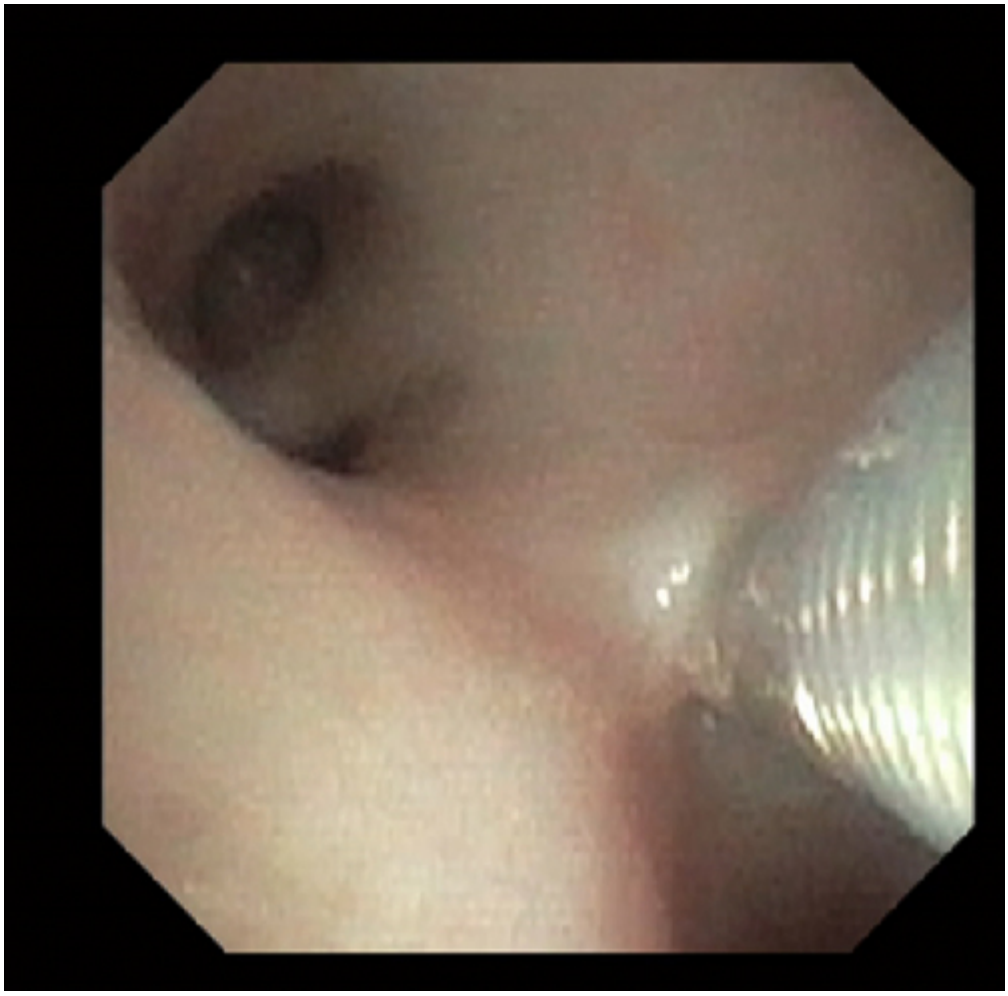

Figure 19.11 Subcarinal LN aspirated with multiple passes.

FOLLOW-UP

A bronchoscopy will be repeated after one month of TB treatment and corticosteroids to determine response to treatment. If there is no further improvement in the severity of airway compression, open decompression of mediastinal LNs will need to be performed. This would be through a right-sided thoracotomy in an attempt to drain the right paratracheal and the large subcarinal LNs.

The mother has two other children who screened negative for TB.

DISCUSSION

This case illustrates that confirming the diagnosis of TB in young children may be difficult because they do not expectorate sputum and often they are paucibacillary. It demonstrates how interventional fibreoptic bronchoscopy may be diagnostic in such children.

Lymphobronchial tuberculosis (LBTB) is defined as tuberculous lymphadenopathy affecting the airways because the enlarged lymph nodes can cause compression of the large airways. LBTB is most commonly seen in younger children. The caseating mediastinal LNs can herniate into the airway and result in bronchogenic and haematogenous spread which can lead to obstruction and occlusion of the airways. Complicated intrathoracic lymph node disease is defined as the presence of nodal large airway compression with the spectrum of endobronchial or “lymphobronchial” TB, including extrinsic bronchial compression, an actively caseating lesion, granuloma formation, a polypoid mass lesion, and LN protrusion through mucosal erosion with ulceration.

Severe airway obstruction due to PTB is more often seen in children younger than 24 months, but this can also occur in much older children. The young child’s airways are especially vulnerable for the following reasons: (1) the small size of the airway, (2) airway wall malacia, (3) the close relationship between the mediastinal LNs and the large airways, as well as (4) concurrent viral infection, which may reduce the airway calibre even more. Airway obstruction can also be the result of both external compression and LNs that have herniated into the airways. The LNs can also enlarge due to immune reconstitutions after TB treatment has been started. It is important to identify and confirm airway obstruction due to TB because airway compression is classified as severe PTB requiring 6 months of treatment, whereas minimal disease in the absence of airway compression requires only 4 months of therapy [6].

The clinical and radiological picture of LBTB depends on the degree of luminal obstruction and on whether a node has eroded into the lumen of the airway. Parenchymal complications of TB airway obstruction include

collapse, ball valve effect leading to local areas of hyperinflation, expansile pneumonia, necrotizing pneumonia, and cavitation. When airway obstruction is complete, the affected segment or lobe will show collapse as air is removed from the segment by resorption; this is not a common presentation, and other pathologies should be considered in these cases. When the tuberculous LN ulcerates through the bronchial wall, the caseous contents of the node can be aspirated into the lung segment or lobe supplied by that bronchus. The initial reaction is of a hypersensitivity nature, but as the airway obstruction becomes complete, the reaction changes to an immune reaction and can lead to expansile pneumonia, caseation, and liquefaction of the lung parenchyma [7].

Airway compression can be identified on good quality chest X-rays even in very young children. Airway compression is either directly visible or secondary due to the effect of airway compression leading to a ball valve effect or lobar collapse. Bronchoscopy is the gold standard for confirming airway compression due to TB. Not only can bronchoscopy confirm airway compression but also determine the severity and nature of obstruction and allow endoscopic interventions to manage airway obstruction. Diagnostic sample collection is the main indication for bronchoscopy in children with PTB. Although bronchoscopy is not routinely indicated for sample collection, it is an attractive option for simultaneous visualization of the airways, confirming the presence of caseating LNs and determining complications. Children are frequently started on treatment without bacteriological confirmation.

In resource-rich settings, bronchoscopy is mostly used to collect diagnostic samples, whereas in resource-limited settings, its value mainly lies in the management of complicated airway disease. Compared to cultures, the Xpert MTB/RIF assay gives rapid microbiological confirmation of TB including rifampicin sensitivity and thus reduces the time to appropriate treatment. The Xpert MTB/RIF assay detects mycobacterial deoxyribonucleic acid (DNA) from live and dead organisms and may remain positive for some time after treatment initiation. Bronchoscopy may also result in TB being excluded as a diagnosis and thereby may allow timely diagnosis and definitive treatment of other pathologies such as

malignancy. Radiological features such as pneumonia, expansile pneumonia, and airway compression may be associated with bacteriological confirmation on BAL fluid, but only the visualization of LNs in the airway during bronchoscopy can predict bacteriological confirmation on BAL fluid. When intramural lesions are present, endoscopic sampling can be performed with either forceps or cryobiopsy. Samples are sent both for histology and microbiological testing for TB.

TBNA routinely used in adults to diagnose malignancies in areas adjacent to the trachea or central bronchi can also be used to biopsy the subcarinal or other LNs depending on their size. In younger children, subcarinal LNs may be the only nodes amenable to sampling and are the most commonly involved mediastinal LNs with a reported diagnostic yield of 50%. Complications of TBNA in children are rare and restricted to self-limiting bleeding visible at the biopsy site. Additionally, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a well-established tool in investigating mediastinal and hilar lymphadenopathy in adults and is also suitable for older children.

There is limited information on EBUS-TBNA in paediatric practice, but one study suggested 92% adequate samples in 55 children, with diagnostic material in 57%, a 78% positive culture rate, and no major complications. The larger bronchoscope sizes required for EBUS-TBNA limit its use in younger children, but newer devices are smaller. Unfortunately, this investigation method remains costly in LMICs.

A radial probe EBUS uses a flexible catheter housing a rotating ultrasound transducer that produces a 360-degree (“radial”) ultrasound image and was first used to guide transbronchial biopsy by Herth et al. [13].

The radial probes are compatible with channel diameters from 2.0 to 2.8 mm and can be inserted directly through the working channel or used with a guide sheath.

The radial probe EBUS is suitable for localization and sampling of peripheral lesions including pulmonary nodules. This is done by passing a

1.4 mm diameter EBUS probe with a 1.9 mm outer plastic guide sheath through the working channel of the bronchoscope. The EBUS is advanced into subsegments until the pathological area is identified. The probe is withdrawn, leaving the sheath in place, through which the biopsy forceps or brush is then passed to take samples [8]. Fluoroscopy-guided biopsy is then performed at the identified location. The 4.0 mm bronchoscope is the smallest suitable bronchoscope for use of the radial probe EBUS. Radial probe EBUS has been used to diagnose lung cancer and other conditions causing peripheral lung nodules, including mycobacterial infection. In children, the radial probe EBUS has the advantage over convex probe (linear) EBUS that it can be used in much younger children and with less airway compromise, with precise real-time confirmation of the lesion location and a 360-degree view. Another possible approach is searching for extra thoracic lymph nodes to sample via ultrasound guidance (cervical or supraclavicular being common targets). This is particularly useful where there is no access to paediatric-sized EBUS probes and expertise or where the child is older and could be sampled without general anesthesia.

There is limited data on its use in children, and most existing data is on its use in peripheral lung lesions. Bouso et al. [14] described the use of radial EBUS in immunocompromised children with pulmonary nodules or focal opacities. They were able to identify lesions in 84% of cases, and radial EBUS increased the detection rate of clinically significant pathogens by 62% compared with BAL, with no major complications occurring.

KEY LEARNING POINTS

- Young infants with PTB can present with severe wheezing due to bilateral airway compression.
- Bronchoscopy can be used to determine the cause of airway obstruction and to collect samples for microbiological confirmation.
- Interventional bronchoscopy can be used to sample mediastinal LNs.
- There is limited data to support the use of radial EBUS to identify mediastinal lymph nodes for possible biopsy in children who are too young to use convex probe EBUS.

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CHAPTER 20 RECURRENT PNEUMONIA AND A MEDIASTINAL MASS

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The diagnosis of a mediastinal mass is complex, with many different possibilities. We present this child to illustrate the clinical approach to a mediastinal mass which was a surprise finding in a child thought to have a simple pneumonia, to illustrate the principle that 'simple' pneumonia needs careful evaluation.

CASE REPORT

We present the case of a female patient aged 10 years with a history of intermittent chest pain localized to the right pectoral region. The symptoms first appeared in November 2023 and worsened in February 2024, prompting her presentation to the emergency department of the Children's Emergency Hospital St. John in Galați, Romania, on 26 February 2024. After a history and clinical examination, a chest radiograph was performed which revealed a large opacity projected over the right lung base, effacing the right heart border and associated with a large predominantly subpulmonic effusion, along with moderate cardiomegaly and accentuated hilar markings (Figure 20.1). Based on these findings, the patient was admitted for further investigations and specialized treatment.

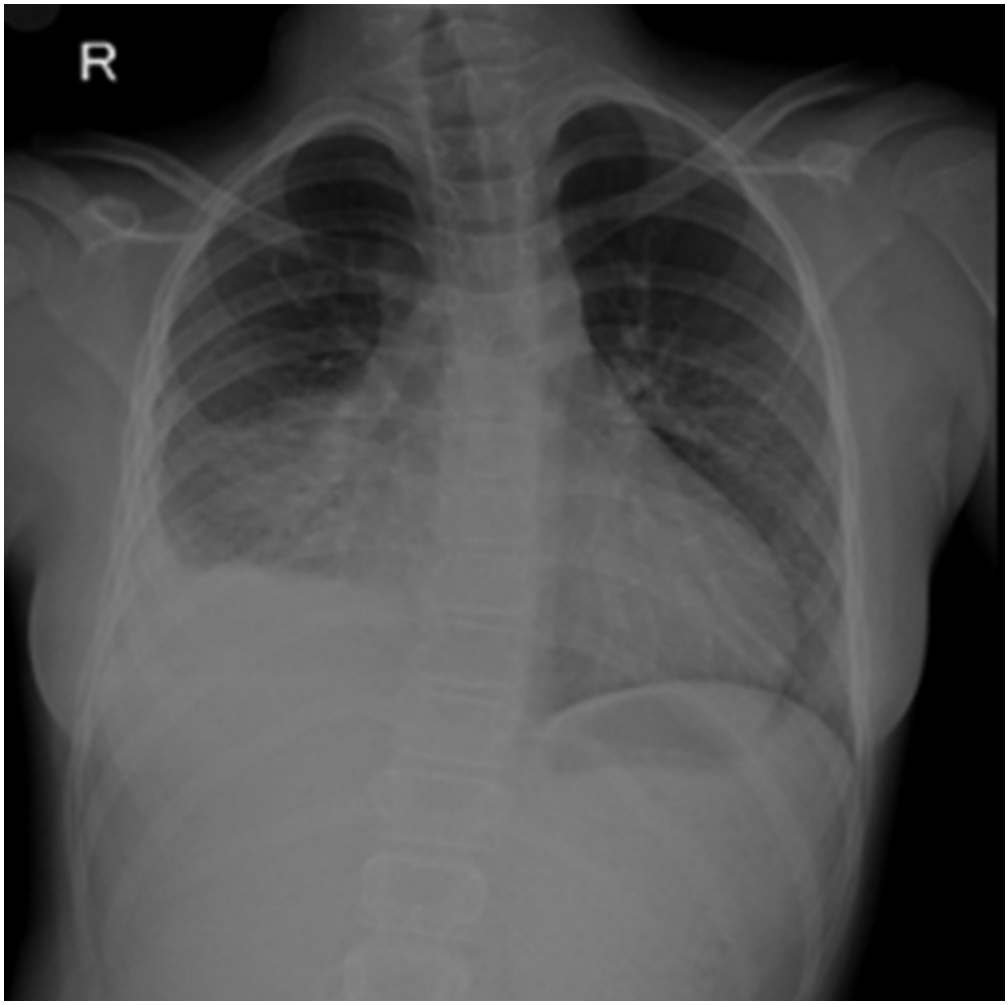

Figure 20.1 Chest radiograph from 26 February 2024 showing a large opacity projected over the right lung base, effacing the right heart border and associated with a large predominantly subpulmonic effusion. No hilar adenopathy is evident.⏎

On admission, the patient was pale with a hyperaemic pharynx and tonsils, and the tonsils were enlarged (grade I–II). Pulmonary auscultation revealed normal bilateral breath sounds but with a markedly decreased intensity over the right hemithorax, predominantly in the basal region. Oxygen saturation (SpO_2) was 98% on ambient air.

Initial investigations were as follows. Complete blood count (CBC) revealed leukocytosis, neutrophilia, and thrombocytosis: leukocytes, 16.4 × 10^3/μL (4–10.5 × 10^3/μL); neutrophils, 10 × 10^3/μL (1.8–8 × 10^3/μL); platelets, 520 × 10^3/μL (150–450 × 10^3/μL). The C-reactive protein was elevated (CRP: 3.2 mg/dL, normal 0–0.5 mg/dL) as were the erythrocyte sedimentation rate (ESR: 90 mm/h; normal 2–12 mm/h) and fibrinogen levels (567 mg/dL; normal 150–400 mg/dL). Immunological testing indicated hypergammaglobulinaemia, with increased IgG levels (IgG: 2834 mg/dL, normal 600–1300 mg/dL). Pharyngeal and nasopharyngeal exudates were sterile, and the respiratory bacteria panel was negative. However, viral testing detected the presence of human rhinovirus.

Laryngotracheal secretion aspiration was collected for bacterial culture, which yielded a positive result for macrolide-sensitive, aminoglycoside-sensitive, and penicillin G-resistant *Staphylococcus aureus* (MSSA). The diagnosis of pulmonary tuberculosis was considered and a PCR test for *Mycobacterium tuberculosis* was performed returning a negative result. Additionally, the tuberculin skin test (IDR 5UI PPD) was negative at 72 hours. The QuantiFERON test was also negative, effectively ruling out the diagnosis of tuberculosis. On 4 March 2024, a further chest radiograph revealed bilateral perihilar interstitial thickening and accentuated hilar markings, improved from the previous radiograph. However, from a biological standpoint, the CBC had normalized, and the inflammatory markers exhibited a downward trend, indicating clinical, biological, and radiological improvement.

Given the apparently favourable evolution, the patient was discharged with instructions to continue azithromycin therapy at home, guided by the antibiotic sensitivity results from the laryngotracheal secretion culture (azithromycin, clarithromycin, clindamycin, gentamicin, oxacillin).

Follow-up and readmission

On 15 March 2024, the patient presented to her paediatrician with a 3-day history of productive cough and nasal secretions. At the time, she was still completing the previously prescribed antibiotic treatment at home.

The chest radiograph at the Pneumophthiology Hospital of Galați revealed an opacity in the right middle lobe. Given these findings, hospital readmission was recommended, and the patient was referred to the Children's Emergency Hospital St. John Galați for further evaluation and management.

Clinical examination on admission revealed that the child was pale and in a febrile state (T = 38°C). Once again, examination of the oropharynx revealed a hyperaemic pharynx and enlarged tonsils.

Pulmonary auscultation showed bilateral symmetrical breath sounds. Additionally, scattered, intermittent crackles were detected in the right hemithorax. Despite these findings, there was no evidence of functional respiratory impairment. The patient exhibited a productive cough and nasal secretion with an oxygen saturation (SpO_2) of 98% on ambient air.

Laboratory tests revealed hypochromic anaemia, with haemoglobin (Hb) 10.89 g/dL and a haematocrit of 32.9%; the white cell count was normal. The CRP was 3 mg/dL, ESR was 105 mm/h, and fibrinogen levels were 402 mg/dL. Additionally, alpha-fetoprotein (AFP) was 2.38 ng/mL (reference range: 0.8–34.8 ng/mL), and total beta-hCG was <1.2 mIU/mL. Both pharyngeal and nasopharyngeal exudates were obtained and no pathogens were isolated.

Despite the initiation of antibiotic treatment based on the culture and sensitivities of the laryngotracheal secretions from the previous hospitalization, and the apparently favourable evolution of the clinical and laboratory parameters, a chest radiograph 10 days post-hospitalization revealed an ill-defined, inhomogeneous opacity of medium density, located in the lower half of the right lung field, which obscured the right cardiac silhouette. This opacity appeared reduced in size compared to the previous examination but contained abnormally dense foci suspicious for calcification. Additionally, bilateral increased interstitial markings were noted, particularly in the peri- and infrahilar regions (Figure 20.2). The previously demonstrated pleural effusion had completely resolved.

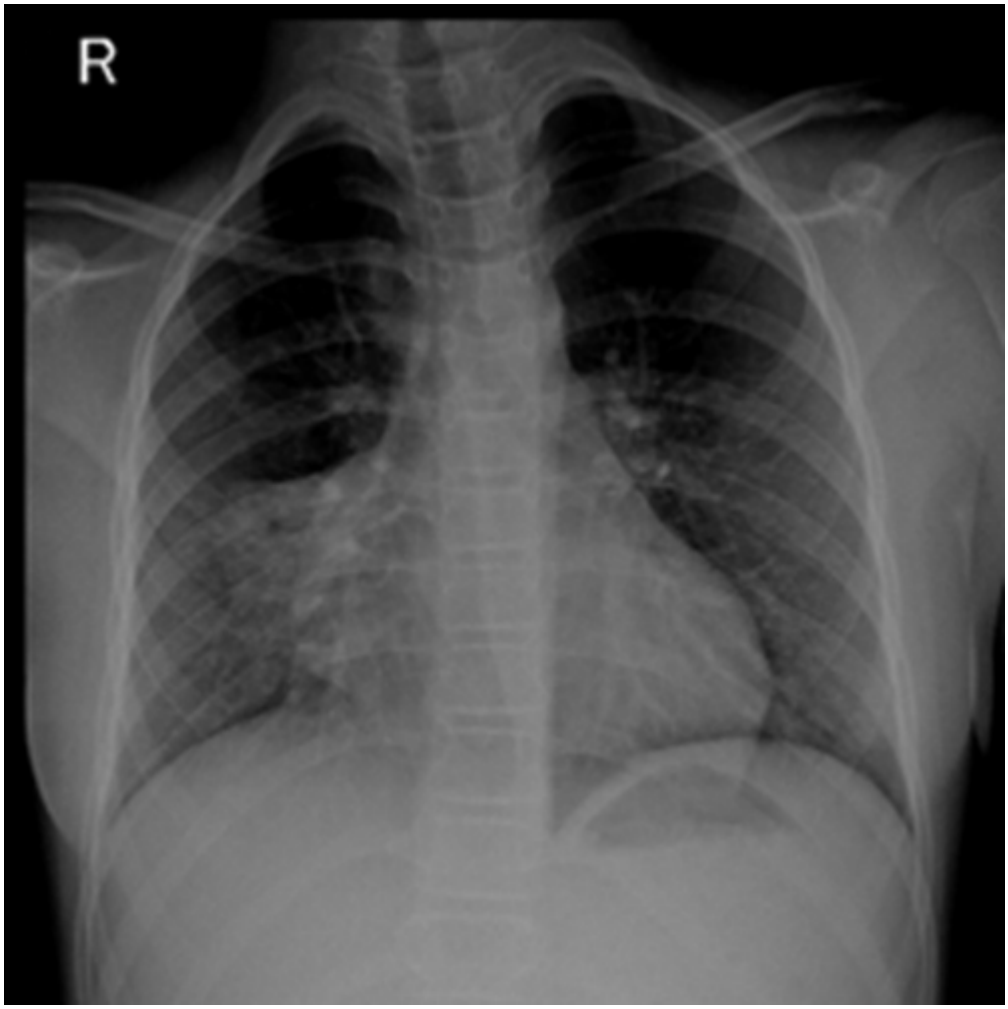

Figure 20.2 Chest X-ray from 24 March 2024 showing an inhomogeneous opacity located in the lower half of the right hemithorax, which obscured the right cardiac silhouette, with resolution of the previous pleural effusion.⏎

Given these findings, a chest CT scan was recommended for further evaluation.

Chest CT findings

The chest CT scan revealed a well-demarcated, round-oval, multiseptate, space-occupying lesion with an inhomogeneous structure (Figure 20.3).

This lesion exhibited areas of contrast-enhancing parenchymal tissue, adipose tissue, and coarse calcifications. Additionally, bilateral axillary lymphadenopathy was noted, with the largest lymph nodes located on the left side, which may be within the normal range; given the final diagnosis, they are unlikely to be pathological. The left upper lobe showed signs of an incidental congenital thoracic malformation, possibly bronchial atresia (Figure 20.4). Furthermore, hyperdense lesions were observed in the gallbladder, initially thought to be gallstones.

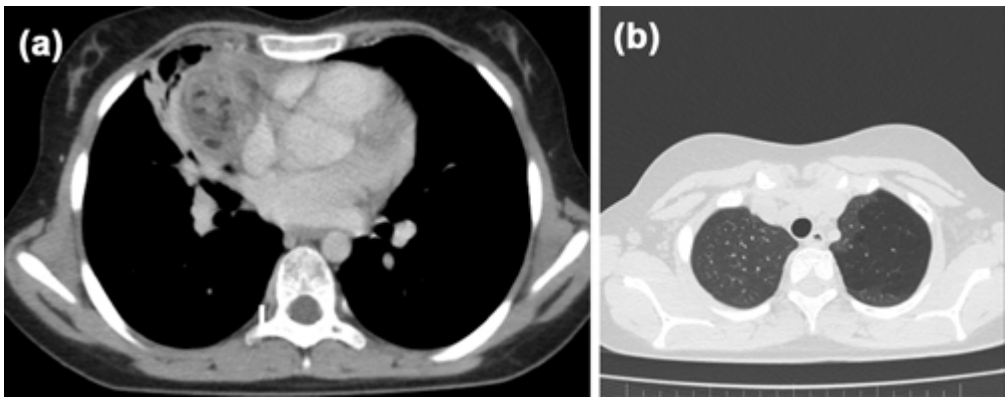

Figure 20.3 (a and b) CT pulmonary showing a well-demarcated, round-oval, multiseptate, space-occupying lesion with an inhomogeneous structure. This lesion exhibited areas of contrast-enhancing tissue, adipose tissue, and coarse calcifications.⏎

These findings raised the suspicion of a space-occupying lesion located in the anterior mediastinum, warranting further diagnostic evaluation.

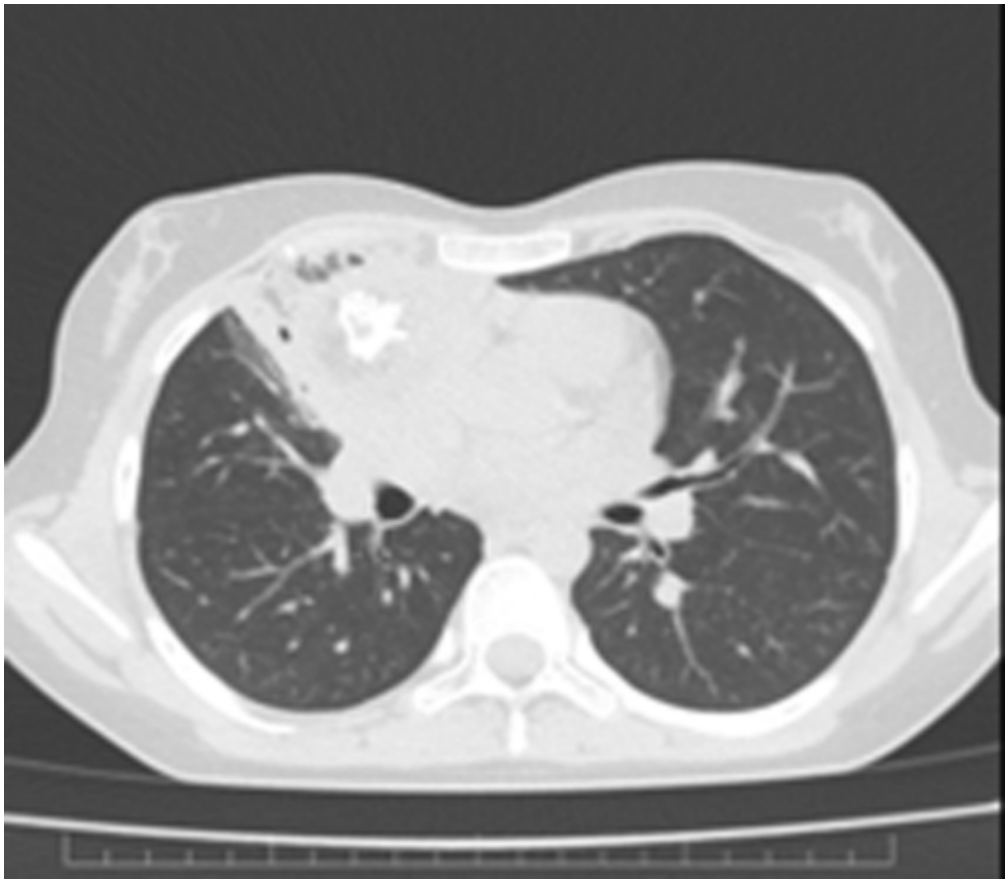

Figure 20.4 Chest CT. The left upper lobe is hypodense, in keeping with a small, incidental focus of bronchial atresia.⏎

Abdominal ultrasonography findings

The abdominal ultrasound revealed a normal-sized liver with homogeneous structure and echogenicity. The gallbladder was distended, thin-walled, and fluid-filled, without evidence of cholelithiasis. This last finding was surprising, given that it is very unusual to see gallbladder pathology on CT that cannot be seen on ultrasound; normally it is the other way around, with ultrasound being the more sensitive test. The portal vein had a normal calibre and was patent. The pancreas exhibited a homogeneous structure without signs of ductal dilatation. The spleen was of normal size for the patient's age, with a homogeneous structure, and the kidneys were of normal size with no pelvicaliceal distension or evidence of calculi,

displaying a homogeneous parenchyma. No free fluid was detected in the peritoneal cavity.

Echocardiography findings

Echocardiography demonstrated a hyperechoic, bullous-appearing mass in the paracardiac region, but without signs of haemodynamic disturbance.

Management and surgical intervention

Given the results of the CT examination, the patient was referred to the Pediatric Surgery Department of Sf. Maria Hospital in Iași, where an exploratory thoracoscopy was performed. Initially, pleural adhesions were divided, and the right anterior mediastinal mass was excised, with haemostasis being secured. The procedure also included pleural space lavage and chest drain placement, and a central venous catheter (CVC) was positioned in the right internal jugular vein under ultrasound guidance. A thoracoscopy was performed (Figure 20.5).

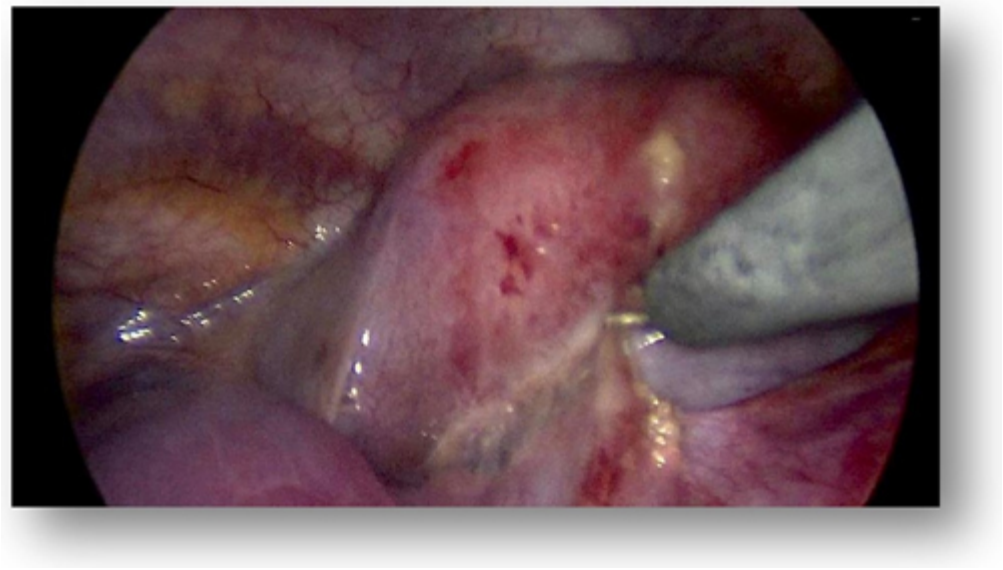

Figure 20.5 Thoracoscopy revealed tumour formation.⏎

On the third postoperative day, the chest drainage tube was removed, and on the fourth day, the CVC was removed.

The patient was discharged on the seventh postoperative day in satisfactory general condition. A follow-up clinical re-evaluation and chest radiograph was recommended 2 weeks post-discharge.

Microbiological examination

The microbiological examination of the closed purulent collection revealed the presence of rare polymorphonuclear cells and numerous red blood cells. Both microscopy and culture results were negative at 48 hours and 5 days postoperatively, respectively.

Histopathological examination

The histopathological examination revealed stratified squamous epithelium with keratinization, along with cutaneous adnexa and adipose tissue, as well as other mature elements, including pseudostratified respiratory epithelium, cartilaginous tissue, bone tissue, and nerve ganglia. Within the cyst, rods were observed in an amorphous mass of keratin debris. Additionally, there were areas of ulceration, granulation tissue, fibrin, foreign body reaction, and haemorrhage (Figure 20.6). The pathological diagnosis was a benign teratoma.

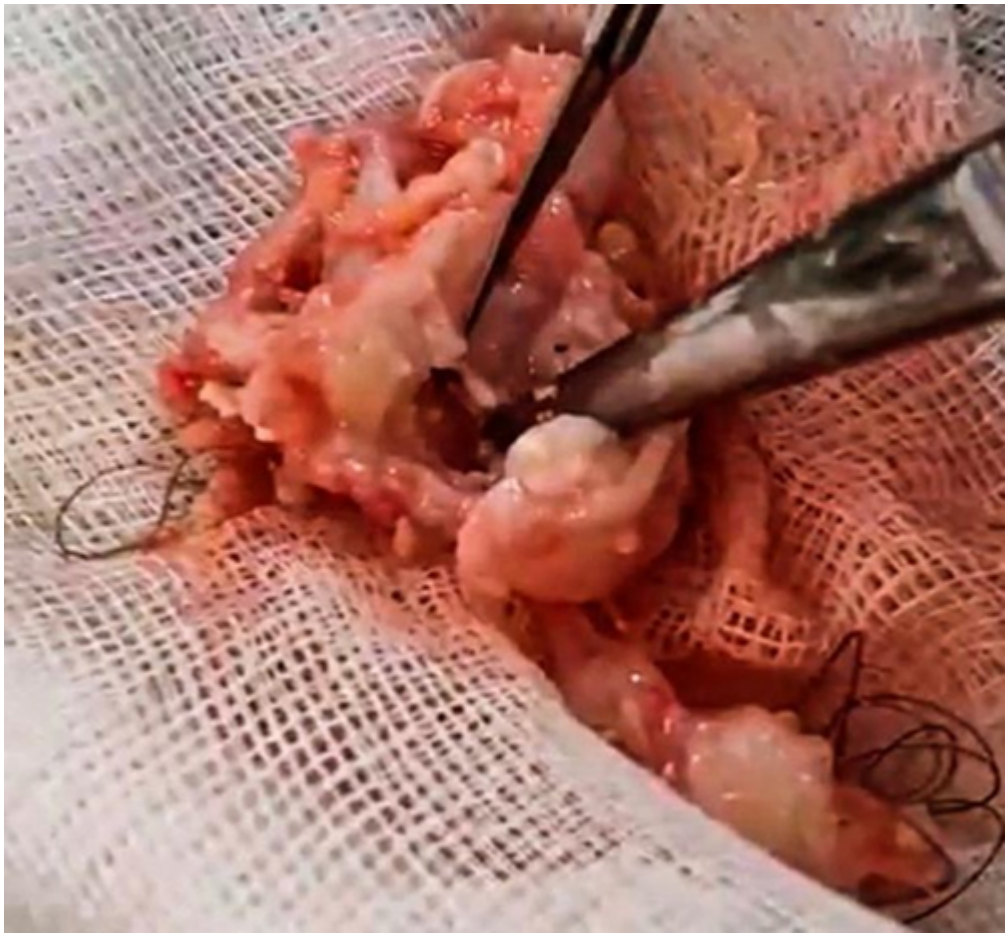

Figure 20.6 The macroscopic appearance of the tumour.⏎

The postoperative course was favourable, and the 6-month CT re-evaluation revealed an unchanged area of bronchial atresia in the left upper lobe, but otherwise, the lungs and airways appeared normal, with no evidence of pleurisy, pericarditis, or mediastinal masses.

In light of the most recent CT examination, an imaging re-evaluation was recommended 1 year later to assess the progression of pulmonary emphysema. Regarding the mediastinal teratoma, an oncologic re-evaluation is advised every 3 months or as needed depending on any new clinical features.

DISCUSSION

The mediastinum is the most common primary extragonadal site for germ cell tumours, which are a rare and heterogeneous group of neoplasms. Although histologically similar to their gonadal counterparts, they differ considerably in clinical features, biological behaviour, and prognostic outcomes.

The anterior mediastinum, a virtual space containing lymphoid structures, the thymus, blood vessels, and nerves surrounded by mesenchymal tissue, represents the most frequent location of thoracic teratomas. These tumours account for 7%–10% of all teratomas, with 80%–88% classified as mature, making them the most common benign tumours of embryonal origin. Mediastinal teratomas can be diagnosed at any stage, from the fetal period through adolescence and even into adulthood. While the majority are located in the anterior mediastinum, a small number have been reported in the posterior mediastinum. In paediatric cases, mediastinal teratomas are typically benign with a favourable prognosis; however, the presence of germ cells may alter the prognosis and necessitate adjuvant treatment following surgical excision.

Approximately 60% of patients with mediastinal teratomas are asymptomatic, with the diagnosis often being made incidentally on a chest radiograph performed for unrelated reasons. However, mediastinal tumours may also present with nonspecific symptoms, primarily due to the mass effect exerted on adjacent structures. Symptoms such as chest pain, cough, dyspnoea, dysphagia, or respiratory failure are typically associated with tumour progression and compression of mediastinal structures. Chest radiography serves as a key diagnostic tool for identifying mediastinal abnormalities and conventionally, CT is the imaging modality of choice for evaluating teratomas. However, recent studies have indicated that thoracic MRI offers superior accuracy compared to lung CT, particularly in identifying tumour invasion of the capsule and adjacent structures.

These tumours typically present as anterior mediastinal masses with components of soft tissue, calcifications, and fat. A definitive diagnosis can only be established after excision of the mass. Surgical excision remains the primary treatment approach, with histological findings playing a crucial

role in assessing tissue composition and guiding subsequent therapeutic management. Histologically, the presence of immature tissue does not affect the prognosis in children under 15 years of age. However, for patients over the age of 15, mediastinal teratomas have a high incidence of malignant behaviour, which is typically indicated by elevated levels of AFP or beta-hCG. These serum tumour markers are crucial for the diagnosis and monitoring of mediastinal germ cell tumours. It is well established that patients with benign teratomas do not present with elevated tumour markers.

Repeated respiratory infections, especially in the same location and when slow to resolve despite extended antibiotic therapy, should serve as a red flag for the attending physician. Such cases may indicate an underlying pathology. Repeated infections in different locations may be a sign of an immune problem such as cystic fibrosis, primary ciliary dyskinesia, and immune deficiency, whereas recurrent localized infections suggest bronchial obstruction or a parenchymal lesion such as a congenital thoracic malformation.

Even when benign in nature, mediastinal teratomas can cause significant mechanical complications due to their location. As such, treatment can be particularly challenging, as the mass may become adherent to major organs and vessels, including the heart, nerves, and lung blood vessels, complicating the surgical approach. Adhesions often result from recurrent respiratory infections. Large tumours require excision through median sternotomy or thoracotomy, while smaller tumours may be approached via anterior mediastinoscopy or thoracoscopy.

As anterior mediastinal masses are relatively rare in children, the differential diagnosis for such conditions can be quite challenging. Potential diagnoses include thymoma, lymphoma, thymic cyst, lymphangioma, neurogenic tumours, germ cell tumours, and mesenchymal tumours. Each of these conditions presents with distinct features, but their overlap can make it difficult to accurately distinguish between them, especially in cases involving complex or less common pathologies.

Such a child requires a comprehensive, multidisciplinary approach to ensure accurate diagnosis and effective management. The team should consist of:

- Paediatricians to oversee the patient's clinical condition and initial evaluation.
- Radiologists to interpret imaging studies, particularly CT scans or MRIs, which can reveal the presence, size, and location of the teratoma and assess its relation to surrounding structures.
- Surgeons to determine the optimal surgical approach, whether it requires thoracotomy, sternotomy, or less invasive techniques like thoracoscopy.
- Anatomic pathologists to perform histopathological examination post-surgery and provide further insight into the tumour's nature, guiding treatment decisions.
- Oncologists for postoperative follow-up if malignancy is suspected.

This sort of comprehensive evaluation should lead to timely surgical intervention and follow-up, improving the prognosis for patients with mediastinal teratomas.

KEY LEARNING POINTS

- When a child presents with relapsing pneumonias and an atypical clinical course despite appropriate antibiotic treatment, it is important to consider further investigations, especially when initial clinical and radiographic findings are nonspecific.
- Repeated chest radiographs showing opacification that does not clear completely should prompt a more in-depth imaging approach including CT scanning. This is crucial to detect underlying issues that might not be apparent on routine X-rays, such as masses, structural anomalies, or complications such as infections, tumours, or other pathologies requiring more specific treatment.
- Mediastinal teratomas, both benign and malignant, can cause significant compression of surrounding structures, including the lungs,

leading to recurrent pneumonias or other respiratory issues.
- This underscores the importance of including mediastinal tumours in the differential diagnosis of recurrent respiratory symptoms or persistent pneumonia, especially in cases that fail to respond well to standard antibiotic treatment.

Also, with the pulmonary CT scan performed to establish the definite diagnosis of right lung lobe opacity, our patient was also incidentally diagnosed with a small congenital thoracic malformation for which no treatment is planned (Figure 20.4).

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