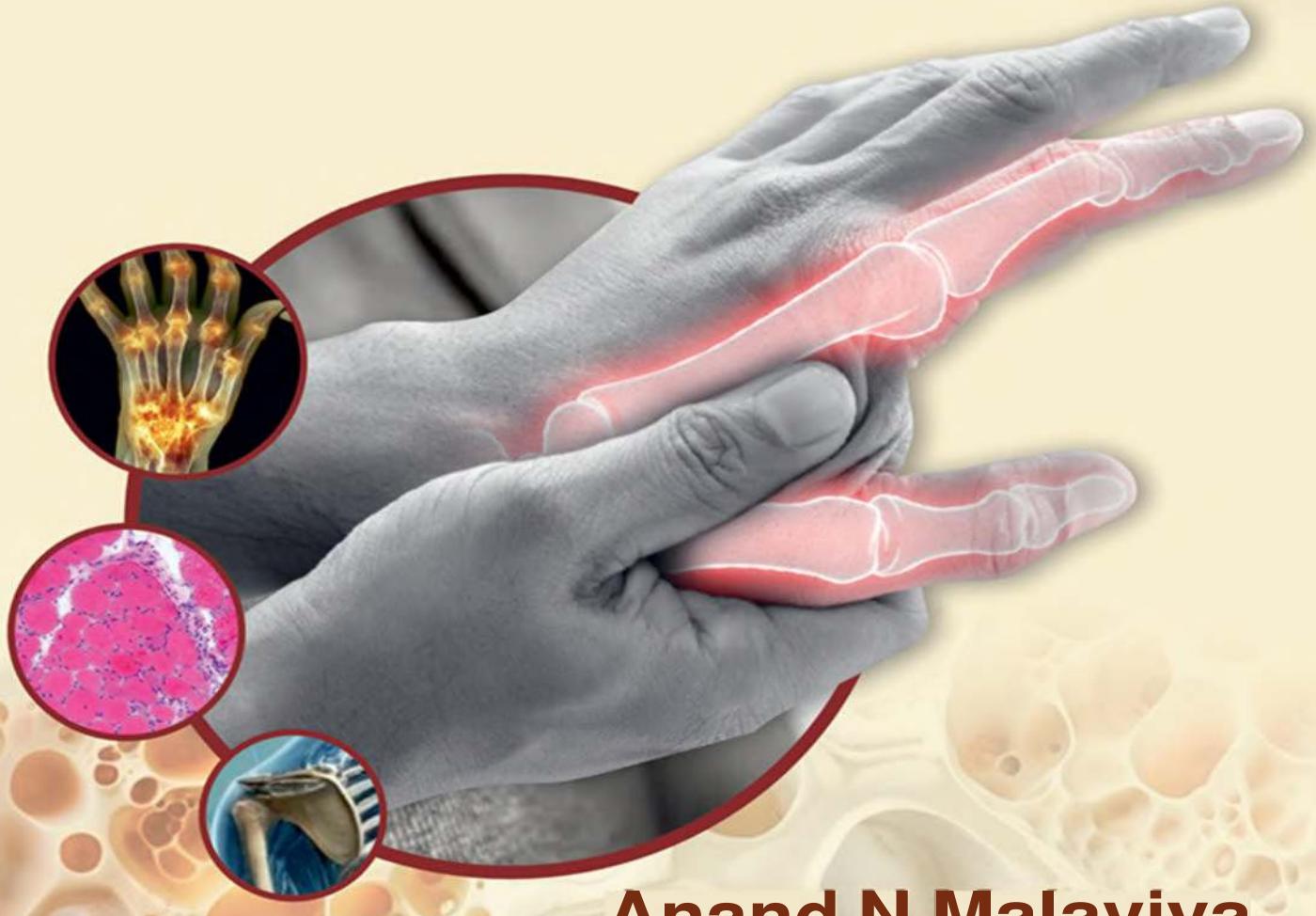
Rheumatology Essentials

A New Frontier for Aspiring Clinicians



Anand N Malaviya
Prashant Kaushik

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Dedication

I dedicate this book to the countless patients who have consulted me over the decades, journeying from across India, particularly from the hinterlands where access to proper medical care is scarce. Your trust and resilience have been my greatest teachers.

To my mother, from whom I inherited the habit of keen observation—a skill that has greatly enhanced my clinical acumen. To my father, who instilled in me the value of hard work, always quoting Thomas Edison: "Success is 10% inspiration and 90% perspiration." Your guidance and values have shaped my journey.

I wish to express my heartfelt gratitude to my beloved wife, Rekha, whose quiet understanding and unwavering support have been a source of strength during the writing of this book. Despite facing her own health challenges with courage and resilience, she never once complained about the attention I could not give her during this demanding journey. Her selflessness and love have been my guiding light, and this work would not have been possible without her steadfast patience and encouragement.

I also wish to acknowledge the invaluable role my brilliant students have played in making me the teacher I am today. Their insightful questions have constantly challenged me to convey complex concepts in the simplest way possible. This mutual learning experience has been instrumental in the creation of this book, where simplifying issues is at its core.

Last but certainly not least, I extend my heartfelt gratitude to my hardworking sons (Atin and Gaurav) and brilliant daughters-in-law (Tina and Sonali) for their unwavering encouragement and constant support in helping me stay abreast of the latest technologies shaping academia, as well as the evolving trends across science, music, and the arts. A special note of appreciation to my grandson, Nikhil, whose keen insight helped finalise the title of this book at a time when I found myself torn between five potential options, each vying to represent the essence of this work. And to Arihaan, who may never read or know his grandpa's writings—yet, in his quiet and beautiful way, inspires me beyond words.

Thank you all for your contributions to this endeavour.

Anand N Malaviya
New Delhi, India

Obeisance to the Teachers and the Teaching—I Pray to The Divinity in All!

First, in the form of birth-parents, who gave me a body, and, hence, a chance to fulfill my Dharma. Next, in the form of various teachers who imparted the worldly and Divine wisdom. In the Divine form of my wife, Richa who has been an incessant support, and has given two Divine daughters, Aadya and Aarya who are icons of kindness and success in life. Last but not the least, to all my students and patients who give me a chance to give back continuously, moving forward. One light, infinite lamps/bulbs!

Prashant Kaushik
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Foreword

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It gives me great pleasure to write the foreword for *Rheumatology Essentials: A New Frontier for Aspiring Clinicians*, a timely and thoughtfully structured book that addresses a critical area of medicine often under-recognized in general clinical training. Authored by a senior academician of national repute and a brilliant young clinician, this work represents a meaningful contribution to medical education, particularly in the field of musculoskeletal medicine and rheumatology.

The book is commendably divided into two comprehensive parts. The first lays a strong conceptual foundation, enabling readers to distinguish between immunoinflammatory disorders, mechanical–structural causes, and the increasingly recognized category of nociplastic or unexplained musculoskeletal pain. By offering a clear clinical framework supported by anatomical insights, symptom patterns, physical examination techniques, and essential investigations, this section empowers clinicians to make confident, accurate classifications—paving the way for appropriate specialist referrals.

The second part turns its focus on inflammatory rheumatic and musculoskeletal diseases (I-RMDs)—conditions that demand timely diagnosis and specialist care. Here, the authors provide concise yet clinically rich descriptions of prevalent rheumatic conditions, addressing key features, diagnostic principles, and evidence-informed management pathways. This clarity of purpose serves both students and practitioners alike.

Importantly, the book advocates for an integrated, multidisciplinary approach to musculoskeletal disorders—recognizing the distinct yet complementary roles of rheumatologists, physiatrists, pain specialists, and orthopaedic surgeons. By doing so, it avoids the common pitfall of therapeutic overreach and ensures patients receive care best suited to their condition and stage of disease.

This book is as much a practical guide as it is a call to broaden the clinical lens through which we view musculoskeletal ailments. I am confident that it will serve as a valuable resource for medical students, interns, generalists, and early-career specialists who seek clarity in this complex yet crucial area of clinical medicine.

Dr Vinod K Paul
MD, PhD, FAMS, FNASc, FASc, FNA

Preface

Welcome to the fascinating world of rheumatology, a relatively young subspecialty within general internal medicine that focuses on the ailments of the musculoskeletal system (MSK) called rheumatic and musculoskeletal diseases (RMDs). This book is intended for primary care physicians (PCPs) and postgraduate trainees in internal medicine or paediatrics. Additionally, senior undergraduate students preparing for their final exams may find useful insights that could aid them in their assessments.

In addition to enhancing clinical knowledge, this book aims to highlight the appeal of a career in rheumatology. Practitioners in this field often report high levels of job satisfaction and a balanced lifestyle, making it an attractive choice for those considering subspecialisation.

By the end of this book, readers will have a clearer understanding of rheumatology and its place in the broader medical landscape. PCPs will gain confidence in evaluating and triaging patients with RMDs, and aspiring specialists will have a better sense of whether rheumatology is the right path for them. For those interested in further specialisation, a list of hospitals and medical institutions in India offering DM, DNB, or Fellowship programs in rheumatology is provided.

Happy reading, and welcome to the enriching field of rheumatology!

Anand N Malaviya
Prashant Kaushik

Introduction

This book is thoughtfully divided into two parts, each designed to provide a comprehensive understanding of the musculoskeletal (MSK) system and its associated disorders, collectively termed 'rheumatic and musculoskeletal diseases' (RMDs).

PART I: Foundational Concepts

Part I focuses on categorising MSK ailments into three main classes

1. **Immunoinflammatory (immune-mediated) systemic rheumatic diseases**, also known as 'inflammatory rheumatic and musculoskeletal diseases' (I-RMDs).
2. **Mechanical–structural damage or, developmental abnormalities** leading to manifestations within the MSK system.
3. **Nociplastic pain, psychogenic pain, or pain amplification syndromes**, causing discomfort in various MSK regions without identifiable features of immunoinflammation or mechanical–structural damage.

In routine general clinical practice, approximately 20–25% of patients present with complaints related to RMDs. The majority of these patients fall into categories 2 and 3. These issues are explored in more detail in Chapters 2 to 6, with particular emphasis in Chapter 4.

The authors strongly believe that patients with non-inflammatory (category 2) RMDs due to mechanical–structural or developmental damage and deformities should primarily be managed by specialists in Physical Medicine and Rehabilitation ('Physiatry'). When physical and rehabilitative measures are insufficient due to advanced structural damage, orthopaedic surgeons should be consulted for further management, including surgical interventions. Similarly, patients in category 3, presenting with nociplastic pains, should be referred to 'pain management teams' for specialised care.

In contrast, patients with I-RMDs diseases (category 1) must always be diagnosed and treated under the direct supervision of a rheumatologist.

To establish a solid foundation, Part I begins with a chapter summarising the anatomical components of the MSK system relevant to understanding its disorders. Subsequent chapters focus on core symptoms, clinical approach for making a diagnosis, physical examination findings, minimal essential investigations as follows:

- **Core symptoms:** Highlights the characteristic symptoms differentiating I-RMDs, mechanical–structural issues, and unexplained pains or nociplastic pains.
- **Clinical approach to joint pain:** Provides a step by step guide to classify RMDs into inflammatory or noninflammatory categories, streamlining management plans.
- **Back pain and soft tissue diseases:** Offer practical approaches for quick classification of conditions as inflammatory or noninflammatory, aiding in appropriate specialist referrals.

- **Laboratory investigations:** Discusses the interpretation of test results in the context of clinical features, emphasising pre-test probability and likelihood ratios.
- **Imaging:** Explores the strengths and limitations of various imaging techniques in attributing findings to clinical symptoms.

The chapter on **Pain** is particularly noteworthy. Since 2016, there have been significant advances in understanding pain pathophysiology. A clear grasp of the types of pain and their relevance to specific diagnoses is crucial for devising effective management plans.

PART II: Inflammatory Rheumatic and Musculoskeletal Diseases

Part II delves into RMDs categorised as 'inflammatory' in nature—conditions for which rheumatologists must serve as primary caregivers. This section provides concise descriptions of commonly encountered diseases in this category. For each condition, the text summarizes their frequency in clinical practice, characteristic features, diagnostic approaches, and general management guidelines.

In contrast, noninflammatory MSK diseases (categories 2 and 3) encompass a wide range of conditions led by osteoarthritis and other 'wear-and-tear'-related ailments. These also include regional pain syndromes, typically caused by mechanical–structural stress, strain, or sprain. Such conditions should be promptly referred to specialists in Physical Medicine and Rehabilitation or Sports Injury Experts. When advanced structural damage is present, the expertise of orthopaedic surgeons—particularly in joint replacement surgery—is crucial.

It is vital that rheumatologists refrain from prolonging the treatment of such patients beyond a point where further damage reduces the likelihood of successful surgical outcomes, including joint replacements. By clearly delineating the responsibilities of various specialists and offering a structured approach to MSK disorders, this book aims to equip readers with the knowledge and confidence to address a wide spectrum of RMDs in their practice effectively.

Contents

Part I

Foundational Concepts

1. Musculoskeletal System and Organs Affected in Rheumatic and Musculoskeletal Diseases (RMDs)
2. Clinical History and Physical Examination of Patients with Rheumatic and Musculoskeletal Diseases (RMDs)
3. Clinical Approach to Diagnosing Joint Diseases
4. Triage of Patients RMDs: Differentiating Inflammatory from Non-Inflammatory Conditions
5. Back Pain
6. Soft Tissues and their Ailments
7. The Third Pain: "Pain other than the Nociceptive and Neuralgic Pain"
8. Laboratory Investigations in Rheumatic and Musculoskeletal Diseases (RMDs)
9. Imaging in Rheumatology

Introduction

In Part I of the book, a simplified overview of the musculoskeletal (MSK) system is presented. It summarises the specific organs of the MSK system and their functions and categorises the major groups of ailments that affect the MSK system, called 'rheumatic and musculoskeletal diseases' (RMDs). Based on these groups, the book clearly identifies the preferred specialists who should serve as the main caregiver for each category of RMDs, facilitating patient triage. The following chapters delve into specific clinical methods for evaluating the main symptoms of RMDs, including approaches to patients presenting with joint pain, back pain, soft tissue ailments, and generalised MSK pain. Part I concludes with a brief description of the appropriate requisition and interpretation of laboratory and imaging investigations, with an emphasis on the "Choosing Wisely" initiative.

CHAPTER 1

Musculoskeletal System and Organs Affected in Rheumatic and Musculoskeletal Diseases (RMDs)

The diseases that are included under the umbrella of 'rheumatic and musculoskeletal diseases' (RMDs) affecting the musculoskeletal (MSK) system, involve the following body parts/organs:

1. **Joints:** Although there are several types of joints in the body, for rheumatologists, '*diarthrodial (freely movable) cartilaginous joints*' are of main interest. An example of the same is provided in **Fig. 1.1**.

   Such joints are surrounded by a fibrous capsule, lined by a delicate bicellular membrane without basement membrane. This lining membrane of the joint capsule is called '*synovial membrane*'. The cavity created by the fibrous capsule is called 'the joint space'. It is filled by a clear transparent smooth sticky (honey-like) fluid called '*synovial fluid*'. It provides lubrication to the joints for facilitating their smooth range of movements over smooth glistening hyaline/articular cartilage that cap the end of the bones that makeup the joint. Any disease of the joints is called '*arthritis*'.

   a. **Articular cartilage:** Of the 3 types of cartilage in the body (fibrocartilage, hyaline cartilage, and elastic cartilage), the type that lines the joints and caps the ends of

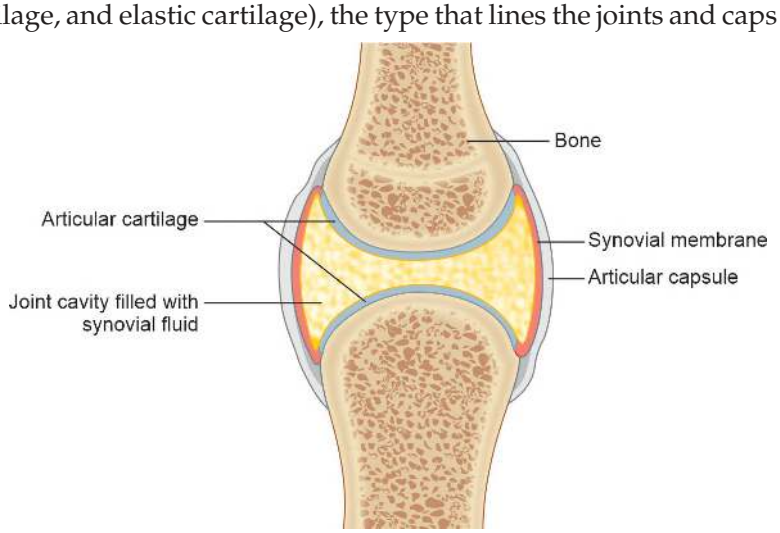


Fig. 1.1: A typical diarthrodial joint. (*Courtesy:* Miss Aashita Aggarwal)

the bones (e.g. distal surface of femur and proximal surface of tibia that make up the knee joint) is hyaline cartilage, which when part of the joint anatomy, is often called 'articular cartilage'. It is an avascular structure that gets its nutrition from the synovial fluid to which it is exposed continuously. Therefore, if the synovial fluid becomes unhealthy/abnormal it has a direct effect on the cartilage health and structure thus affecting the normal function of the joint. *Synovial membrane—involvement of the synovial membrane with any diseases is called 'synovitis':* In normal health synovium is a *sparsely cellular membrane* with 2 layers of loosely packed 1–2 cell-thick intimal layer without any basement membrane. The superficial layer (facing the joint cavity) contains type A cells, which produce synovial fluid for joint lubrication (*see* below). The second layer (away from the joint cavity) is relatively acellular containing scattered blood vessels, fat cells, and fibroblasts present in varying depth of the synovial sublining layer. These fibroblasts are called 'fibroblast-like synoviocytes' (FLS), the key cells involved in a major serious joint disease called '*rheumatoid arthritis*'. This synovial layer also contains a few lymphocytes and macrophages that are called 'macrophage-like synoviocytes' (MLS) that are part of the 'resident stromal cell network' similar to Kupffer cells in the liver. Understanding the histology of the synovium helps in recognizing the histopathological abnormalities in joint diseases, where *inflammation of the synovial membrane is referred to as 'synovitis'*.

b. **Synovial fluid:** This complex lubricating fluid is produced by the ultrafiltration of plasma (of the blood). It consists of substances that make it smooth and viscous, primarily composed of hyaluronan and lubricin that provide its lubricating property. There are several additional components in the synovial fluid that are in small/trace amounts needed to maintain normal healthy synovial fluid. In any type of joint disease, synovial fluid becomes abnormal, losing its transparency (becomes turbid due to the presence of inflammatory cells) and loses its lubricating property. This as well as the property of synovial fluid to provide nutrition to the hyaline cartilage on the surface of which the joints move, leads to cartilage damage (that can be seen on plain radiographs as 'erosions') and loss of joint function. A simple procedure of joint aspiration for obtaining synovial fluid and its analysis goes a long way in confirming diagnosis in specific clinical situations (discussed in Part I, Chapter 8).

2. **Enthesis (plural is 'entheses') and enthesitis (a disease in enthesis/entheses):** Enthesis is an organ in the musculoskeletal system that does not get that much importance in the undergraduate curriculum of anatomy when compared to bones, muscles, or joints. Yet, in the field of RMD, the importance of enthesis is next only to the joints. Understanding anatomy, physiology and its pathology is pivotal for understanding the 2nd most common form of arthritis called 'spondyloarthritis'. Therefore, understanding entheses are possibly more important for understanding RMDs than bones or muscles. In the MSK system, tendons are the tissues that attach muscles to bones. Similarly, ligaments attach bones to one another. The anatomical site where a tendon or ligament attaches to the bone, is called an enthesis (plural is entheses). Any disease of enthesis is called '*enthesitis*'. **Figure 1.2** shows an example of enthesitis.

   There are clinical conditions where the disease/damage/pathology is entirely localised to enthesis. On the other hand, there are several diseases under the

The area where the fibres of the Achilles tendon attach to the periosteum on the posterior surface of the calcaneus is a common site for inflammation, known as 'enthesitis'. This condition frequently occurs in spondyloarthritis, particularly psoriatic arthritis.
In this photograph, the site circled in red on the left side highlights swelling. In contrast, the site circled in green on the right side appears normal.

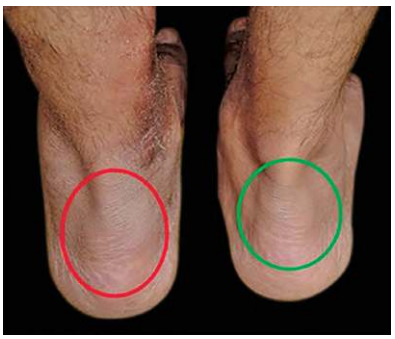


Fig. 1.2: Enthesitis at the insertion of Achilles tendon on the posterior surface of calcaneus

category of RMD where the pathology may not be localised to one enthesis but be more widespread affecting entheses in several parts in the musculoskeletal system. Moreover, in certain diseases the pathology may start at entheses but spread to involve other parts of the joints, including synovium (classic example is synovitis in psoriatic arthritis). Despite obvious synovitis in such patients, they still remain classified as 'enthesitis-related' because that was the site of the initiation of its pathology e.g. 'enthesitis-related arthritis' (ERA) in paediatric patients who are labelled 'spondyloarthritis' on reaching adulthood.

3. **'Back' and 'spine':** The spine is the largest structure in the musculoskeletal system and the most important one. It is said that the phenotype of vertebrates mainly depends on the anatomy of their spine. Thus, humans have a particular phenotype because our spine supports standing on 2 legs (bipeds) as against quadrupeds who cannot stand on 2 legs mainly because of the differences in the structure of their spine. It is also a fact that *Homo sapiens* have a particular body shape, which is largely due to the specific anatomical structure of our spine. Moreover, the spine shows a certain glaring paradox. It is very strong to be able to bear the body weight while standing upright yet, it is flexible to allow bending/twisting and move about freely with flexibility. Despite such flexibility, it is designed to protect a delicate vital structure, namely the spinal cord and its major nerves that connect the brain with the rest of your body making it possible to control the body movements. Therefore, it becomes important to understand its anatomy that provides such strength in the face of remarkable flexibility. The strong muscles, bones, and cartilage with flexible ligaments and muscles in the spine make the spine such an ingenious structure. This complexity of its anatomy and physiology makes it susceptible to sprain, strain, injury, and certain diseases that are characterised with back pain, the most common symptoms in the field of RMDs. It is not the aim of this chapter to describe the detailed anatomy, mechanics, and the physiology of the spine except to name some of the important structures that should be kept in mind with reference to spinal complaints/diseases.
   a. **The vertebrae:** The spine consists of 33 vertebrae stacked over each other with 'cushion-like' spongy vertebral disks (*see* below). The spine has 5 distinct areas:

i. The cervical spine with 7 vertebrae in the neck that support the head.
ii. The thoracic (or dorsal) spine with 12 vertebrae.
iii. The lumbar spine consists of 5 vertebrae, a main component of 'lower back'.
iv. The sacrum consists of 5 fused (in adults) sacral vertebrae; and
v. Coccyx that (usually) consists of 4 fused (in adults) coccygeal vertebrae (the number of coccygeal vertebrae can vary from 3 to 5). The different segments of spine are depicted in **Fig. 1.3**.

b. **Intervertebral disks:** The intervertebral disks are made of an external ring-like structure that consists of fibrous cartilage, a highly resilient structure that can withstand high physical forces and act as shock absorbers. It is lined by the annulus fibrosus that encases a gelatinous core called the nucleus pulposus.

c. **Spinal ligaments:** These are robust fibrous bands that hold the vertebrae in proper alignment, stabilize the spine, and shield the disks. There are 4 major ligaments of the spine. These are:
i. Anterior and the posterior longitudinal ligaments (ALL and PLL) that join and hold the vertebral bodies. These are the 2 primary spine stabilizer ligaments.
ii. The supraspinous ligament connects the tips of the vertebral spine.
iii. Interspinous ligament is a thin and short structure that attaches to another ligament called the ligamentum flavum.
iv. Ligamentum flavum connects the laminae (thin plate of bone that makes the roof of the vertebral canal) of adjacent vertebrae. It is the strongest ligament in the spine traversing the length of the spine from the base of the skull to the pelvis. Its main role is the protection of the spinal cord and nerves. Posteriorly, it touches the facet joint capsules.

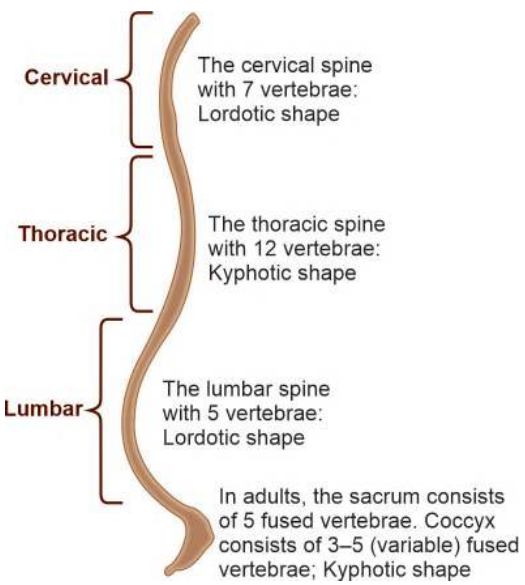
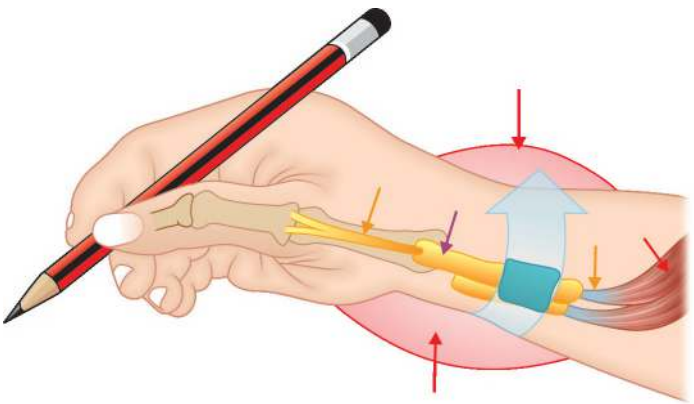


Fig. 1.3: A diagrammatic representation of the spine (wavy dark brown line): The spinal curvatures, segments and the number of vertebrae in each segment

d. **Muscles:** There are several muscles that help the spinal movements. The muscles are covered with fascia that taper off making tendons that attach to the bone. In the thoracic region the spinal muscles are:
   i. *Longissimus thoracis* that helps thoracic spinal extension and lateral flexion as well as rib rotation.
   ii. *Iliocostalis thoracis* that aids to the function of longissimus thoracis.
   iii. *Spinalis thoracis* is the main muscle for extending the thoracic spine, in the lumbar region.
   iv. *Psoas major* flexes the spine at lumbar and lower levels and at the hip joint.
   v. *Quadratus lumborum* causes lateral flexion of the spine.
   vi. *Multifidus* is the strongest muscle in the spine consisting of short triangular muscles that make the deep back muscle in the transversospinalis group on either side of the vertebral column from the cervical to the lumbar spine.

e. **Lumbar zygapophyseal joints:** These are the only synovial joints in the spine that form part of the posterior element of the spinal deeply involved in load transmission at the vertebrae. These are small joints present at the postero-lateral articulation between vertebrae with capacity of ~1–2 ml of fluid they comprise. Being involved in load transmission, they are prone to degenerative (osteoarthritic) joint disease. Involvement in inflammatory joint diseases or other types of inflammatory arthritis including crystal arthropathies is not well described.

4. **Soft tissue:** Tissues between bone and dermis are called 'soft tissue'. Soft tissue makes up the bulk of MSK. Its components include:
   a. **Striated muscles:** The organ that moves the joints.
   b. **Tendons**
      i. *The fibro-collagenous components:* The thread/ropes that transmit the muscle force to the bones for the movement of the joints.
      ii. *The tendon sheaths:* Delicate covers of the tendons on which they glide smoothly when muscles contract helping normal joint movements.
   c. **Ligaments:** Fibro-collagenous tissues with extremely high tensile strength that keep the bones joined together yet permitting their movements at the joints. **Figure 1.4** depicts some of the soft tissues mentioned above.
   d. **Panniculus:** This term is used differently by the rheumatologists and the rest of the medical community. Generally, it refers to obesity and its grading, often used by bariatric surgeons. In contrast, rheumatologists identify panniculus as the subcutaneous tissue that covers most of the body excluding certain areas of the head-face and parts distal to wrist and ankle. It consists of fat lobules separated by septae. Septae support arterioles, venules and superficial nerves reaching the skin (dermis, epidermis). As an organ, there could be involvement of the panniculus that can then be classified as 'lobular panniculitis', 'septal panniculitis'; either of them with or without vasculitis. Thus, there are several varieties of RMDs involving/affecting panniculus. Understanding panniculitis, especially with their histopathological



Arrows of different colours represent different soft tissues as follows: *Red:* Muscles; *Dark yellow:* Tendons; *Purple:* Tendon sheath; *Light yellow:* Retinaculum (ligaments are similar soft tissues, not shown in the diagram)

Fig. 1.4: Soft tissues in the musculoskeletal system (*Courtesy:* Miss Aashita Aggarwal)

examination, helps the diagnosis of both 'primary' panniculitides as well as panniculitides seen in other RMS, thus aiding the diagnosis of the primary RMD (e.g. *lupus profundus*, a specific type of panniculitis seen in patients with systemic lupus erythematosus (SLE)). **Figure 1.5** gives a diagrammatic representation of the anatomy of panniculus.

Inflammation which primarily involves septa without affecting the vessels is called 'septal panniculitis'; erythema nodosum being its prototype. In contrast, inflammation in lobules is called 'lobular panniculitis' the prototype of that being 'erythema induratum of Bazin' (supposed to be due to sensitivity to tubercle bacilli). If the septal blood vessels also show inflammation, then the term is *panniculitis with vasculitis* (e.g. leukocytoclastic vasculitis, cutaneous polyarteritis nodosa).

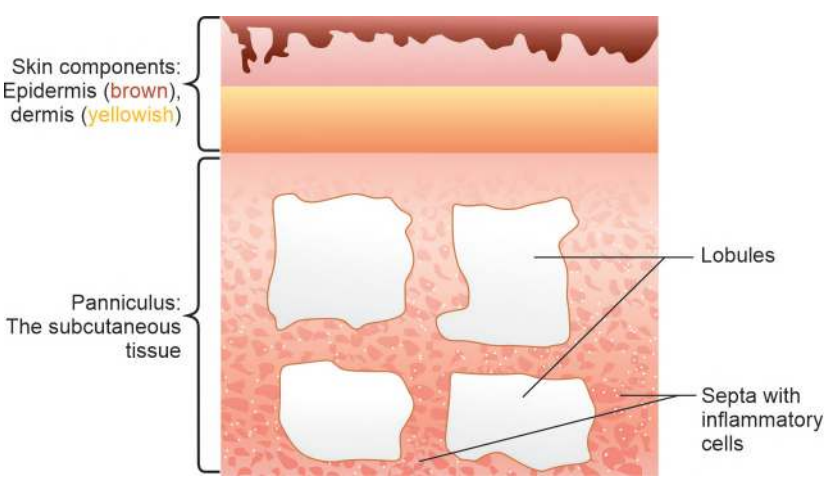


Fig. 1.5: Line diagram showing cross-section of panniculus. Lobules (containing lobular adipose cells) are encased in septa (consisting of fibrous tissue that partitions the lobules and supports the arterioles, venules and the nerves that traverse from deeper tissues to the dermis)

e. **Bursae:** Bursa (plural is bursae) is a sack-like structure in the MSK system that cushions the bones, tendons and muscles in the vicinity of joints. It absorbs sudden pressures that may be fall any region of the MSK system. Several, relatively big bursae are seen around the 4 main large joints of the body, namely shoulders, elbows, hips, and the knees. Bursae in and around ankles are also important. Disease of bursae are called '*bursitis*'. A common clinical feature that brings the patients to rheumatologists. **Figure 1.6** gives examples of bursae present around the knee.

f. **Fascia:** A connective tissue sheath that surrounds every organ of the body is called fascia. The fascia covering the MSK organs may get involved in certain diseases, called '*fasciitis*'. There could be some RMDs where fasciitis is a prominent feature, e.g. '*eosinophilic fasciitis*'.

5. **Diseases without borders' but immunoinflammatory in nature, often with autoantibodies:** This group has diseases that are not limited to a particular organ, e.g. blood vessels. Thus, *systemic vasculitides*, although not part of the musculoskeletal system, make one of the most serious groups of diseases that are managed by rheumatologists. The main reason that rheumatologists are the treating specialists for systemic vasculitides is that their treatment involves immunomodulatory/immunosuppressive drugs, an area of expertise in which rheumatologists are at the forefront. Similarly, there is one disease with a group of autoantibodies called 'antiphospholipid antibodies' in which thromboembolism can affect any size and any type of blood vessels (veins/arteries) in any organ of the body. This disease is called 'antiphospholipid syndrome (APS)'. Interestingly, one of the antibodies seen in this disease (called anti-β_2-glycoprotein 1) directly 'attacks' the decidual tissue causing pregnancy loss, pregnancy complications, foetal growth retardation and foetal death. In recent years a large number of similar multisystem inflammatory diseases are being discovered under an umbrella term 'autoinflammatory syndromes' that

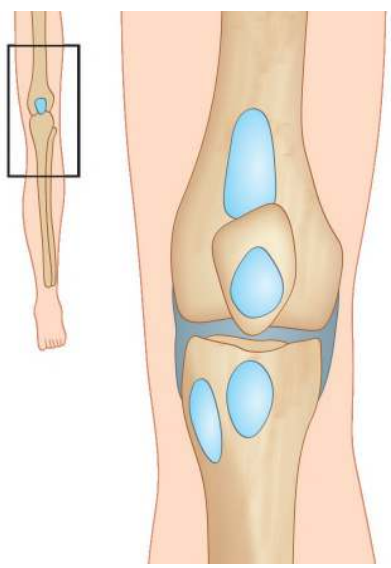


Fig. 1.6: Common bursae around the knee *shown in light blue colour* (*Courtesy:* Miss Ashita Aggarwal)

are due to uncommon/rare genetic mutations. Quite often, rheumatologists are consulted for such diseases.

6. **Organs that may get affected in RMDs:** Theoretically, any organ in the body can get involved in some of the systemic RMDs, However, a few of them get involved so often that rheumatologists should have good grounding in the anatomy and physiology of those organs. The most important and often involved organ is skin, kidney, gastrointestinal tract, lung, and nervous system. Of course, haematological changes are common in most systemic diseases and that also includes RMDs. An area that is also important for rheumatologists concerns conception, pregnancy, puerperium and foetal health. Although direct involvement of heart is not a common feature of the most of the common RMDs, indirect effect of decreased mobility (lack of physical activity and regular exercise causing metabolic syndrome) and generalised inflammation increase the risk of atherosclerotic cardiovascular disease (ASCVD) that may be ~1.5 times more than the general population and may rise almost equal to that of diabetes mellitus. Among endocrine diseases, hypothyroidism is one of the commonest multimorbidity seen with RMDs.

   The above description provides the commonly affected musculoskeletal organs and regions that are involved in diseases with the main symptoms being pain and inability to perform movement-related body functions. In contrast, some diseases have multisystem manifestations that test the clinical acumen of the physicians. It is not uncommon that rheumatologists are consulted in such cases who, with their experience of dealing with most such diseases, can make a diagnosis without difficulty.

CHAPTER **2**

Clinical History and Physical Examination of Patients with Rheumatic and Musculoskeletal Diseases (RMDs)

The cornerstone of diagnosing and managing rheumatic and musculoskeletal diseases (RMDs) is a thorough and meticulous clinical history. Unlike many other medical specialties, *rheumatology heavily depends on detailed history-taking and physical examination*. While a few basic laboratory tests can be valuable, they often provide supportive rather than definitive findings. However, indiscriminate use of advanced immunological tests—such as autoantibody panels and other immune markers—can be misleading, creating diagnostic confusion rather than clarity. This approach is akin to "casting a wide net into the ocean in hopes of catching something valuable." Consequently, there is a well-known saying: "*Rheumatology is the last bastion of clinical medicine*."

A group of experts in diseases of musculoskeletal (MSK) system from different parts of the world have developed recommendations for an undergraduate curriculum to improve the teaching of the rheumatic and musculoskeletal diseases (RMDs) in medical schools. Besides several goals of this curriculum for teaching RMDs, its primary emphasis is on inculcating skills in the clinical assessment of MSK system to classify patients into:

- *Structural/mechanical* MSK problems (the "**Green flag**" RMDs) including:
  - Regional pain syndromes
- *Systemic inflammatory* RMDs affecting the MSK system (the "**Red flag**" RMDs)
- *Pain amplification* syndrome (the "**Yellow flag**" MSK diseases)

In addition to the above 3 classes of RMDs a 4th category has been added to the group of RMDs, namely '***Back Pain***' due to its high prevalence in the community surpassing the 3 types of RMDs (mentioned above). Whether back pain should be considered as a 4th category, however, remains debatable. The authors of this book believe that back pain can also be classified under the above-mentioned 3 categories, namely '**Red flag**', '**Green flag**', '**Yellow flag**' back pain. The only minor point with back pain is a 4th category that the authors would like to identify as '**Sinister Back Pain**' (discussed in detail in Part I, Chapter 5).

This chapter focuses on the clinical assessment skills needed to evaluate the MSK system. It aims to help classify a patient's RMD within the appropriate category of the MSK disease classification framework, providing a structured approach to understanding its components **(Fig. 2.1)**.

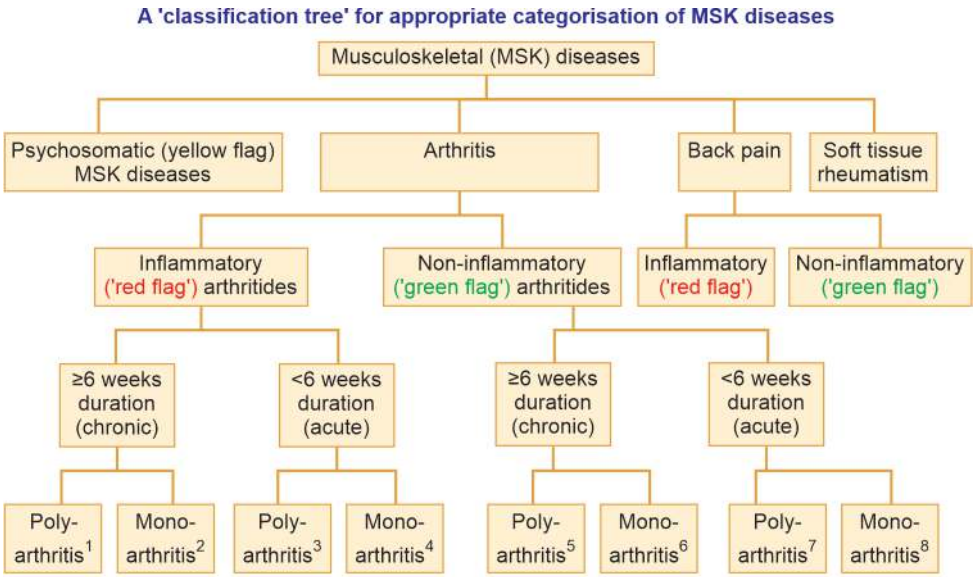


Fig. 2.1: A classification tree for organizing the RMDs in the appropriate class within the musculoskeletal (MSK) system

Clinical Skills in History Taking for MSK Diseases

Assessment of any organ system uses the 3 time-honoured tools of clinical medicine, namely appropriate *clinical history*, *physical examination* and focused *investigations*. The MSK system is no exception; it also uses the same methodology to reach a diagnosis. In this part of the chapter salient points in MSK history taking, a quick '*screening physical examination*' of MSK system, i.e. the now-famous 'GALS' (gait, arms, legs and spine) system, and focused investigations (based upon the provisional diagnosis), are described.

Understanding the Patient's Story

Patients with common RMDs often present with a range of symptoms. Some of the *most common complaints* include:

1. **Pain in one or more joints:** It is the most common symptom that prompts patients to seek a rheumatologist. In everyday language, any joint-related ailment is often referred to as "arthritis," creating the misconception that it is a single, well-defined condition. Similarly, the Hindi term "gathia-baye" is commonly used with the same connotation. However, in modern medicine, arthritis is not a specific disease but a broad term encompassing various joint disorders without identifying a particular aetiology, pathology or diagnosis. Therefore, using the term arthritis without proper qualifiers can be misleading. To ensure clarity in communication and accuracy in diagnosis, it is essential to describe arthritis with appropriate descriptors, as detailed in this chapter.
2. **Early morning stiffness (EMS)** that is a highly specific feature indicative of *inflammatory nature* of the joint disease, often called '**red-flag arthritis**', e.g. rheumatoid

arthritis (RA), systemic lupus erythematosus (SLE), and spondyloarthritis (SpA), including psoriatic arthritis (PsA). Presence of significant EMS distinguishes inflammatory joint diseases from the other 2 classes of RMD, namely mechanical–structural damage-related joint pain or, psychogenic pain (as already *discussed above* (i.e. **green flag** or **yellow flag** joint pains, respectively). Clinically significant EMS lasts at least 30–60 minutes and gradually improves with gentle movement, such as showering or performing daily activities. It is important to distinguish EMS from the *gelling phenomenon*, which occurs in non-inflammatory arthritis like osteoarthritis (OA). Gelling happens after periods of immobility and resolves within minutes of movement, such as knee stiffness after prolonged sitting. Unlike RA, SLE, SpA or PsA, OA is not a systemic inflammatory disease.

3. **Swelling and redness of joints:** Common in inflammatory arthritis, including RA, gout, and PsA, others.
4. **Muscle pain and weakness:** Found in conditions such as idiopathic inflammatory muscle diseases (IIM, e.g. dermatomyositis); may be seen in fibromyalgia.
5. **Limited range of motion:** Often associated with joint pathology that could be mechanical/structural in nature (e.g. OA), or inflammatory in nature (e.g. RA), or regional pain syndromes (e.g. frozen shoulder), mostly occupational mechanical/structural in nature.
6. **Back pain:** Most commonly it indicates simple mechanical stress/strain-related lower back pain, or psychogenic back pain. Less commonly, the cause of back pain could be due to inflammatory etiopathology. This group of diseases causing back pain are called '*spondyloarthritis*' (SpA).
7. **Constitutional symptoms–Fatigue, loss of weight and appetite, feverish feeling/fever:** These are prevalent symptoms in RMDs; indicative of and associated with systemic inflammatory RMDs like SLE, systemic vasculitides, and only occasionally with other inflammatory arthritides.
8. **Skin rashes:** Present in diseases like SLE (malar rash), dermatomyositis (heliotrope rash), psoriatic arthritis and a few others.
9. **Raynaud's phenomenon:** A symptom of systemic sclerosis (SSc), SLE, and other systemic connective tissue disease (e.g. Sjögren's disease, mixed or undifferentiated connective tissue diseases), where fingers turn white → blue → finally turn red in response to cold (often called 'French tricolour'!). There is a similar condition called '*Primary Raynaud's disease*' that is not due to any disease, seen in ~30% of women, more often in countries with cold climate.
10. **Numbness or tingling:** Although mainly seen in neurological diseases that do not belonging to the field of rheumatology, entrapment of certain peripheral nerves due to swelling/inflammation in certain regions of MSK do belong to RMDs, e.g. carpal tunnel/tarsal tunnel syndromes, or peripheral neuropathy secondary to some of the RMDs, e.g. systemic vasculitides.

Pain in the Joint(s)—'*Arthritis*'

Among all the symptoms listed above, pain is the main symptom in the majority of patients presenting with RMDs. Therefore, a good understanding of pain

pathophysiology along with its clinical aspects, comes handy for a rheumatologist while analysing the clinical history. With this in mind, a separate chapter on 'pain' (Part I Chapter 7), has been provided in this book. However, some basic general features of pain that help in its quick classification, are provided here to understand patient's story related to presenting complaint of pain. The main clinical points related to pain due to joint pathology are as follows:

- The most common type of pain we experience in daily life, whether from minor or major injuries that cause tissue damage, is called ***nociceptive pain***. This pain is typically felt at the site of injury and, to some extent, in the surrounding area. In the context of RMDs, joint diseases of any type cause pain in the joint. In patients with joint pathology, *both active and passive joint movements cause pain*. In contrast, *when the surrounding tissues (e.g. tendons, bursae, muscles) are affected, passive movements typically cause less pain*.
  - A subset of such pain is called *referred pain*. Such a pain may be felt away from the exact seat of pathology (e.g. shoulder pathology may be felt at the outer middle-lower part of the upper arm). Such pain is called 'referred pain'. The cause of *referred pain* is due to the common nerve supply of these anatomical regions (for details see Part I, Chapter 7).
- In contrast to nociceptive pain, ***neuralgic pain*** has very different characteristics (for details see Part I, Chapter 7). An important feature of distinction of nociceptive pain arising in the joints from neuralgic pains is that the latter shows *longitudinal spread*, running through the length of the arm or leg (the path of the affected nerve). On the other hand, pain due to a joint pathology does not show longitudinal spread but rather, remains localised to the joint or, when multiple joints are affected (e.g. several metacarpo- or inter-phalangeal joints), the pain is felt in a *horizontal line* (as against longitudinally as in neuralgic pains). This is pictorially depicted in **Fig. 2.2**.
- In addition to these 2 types of pains, there is a type of pain called ***nociplastic pain*** (also identified as ***'3rd pain'***). There are patients with psychogenic pains which, in contrast to the pain localised to joint(s), more diffuse crossing the anatomical borders and is associated with *biopsychosocial issues*. This category of pain is described in more detail in Part I, Chapter 7.

Stiffness

The feeling of *'joint(s)/body getting stiff' after a period of rest'* is common even in normal persons. However, *prolonged early morning stiffness* (including any prolonged immobility during daytime) that starts to improve with gentle movements (e.g. walking up to the washroom in the morning, carrying our self-hygiene, undressing-shower-dressing, and grooming, making breakfast, etc.), is *common in inflammatory RMDs*. Although it is not essential for making the diagnosis of an inflammatory joint disease, *stiffness that start relaxing by ≥1 hr after getting up in the mornings is usually suggestive of an inflammatory RMDs*. The exact cause of significant stiffness in inflamed joints is not known. Recent studies indicate that morning stiffness may be related to impaired fibrinolysis of neutrophil enmeshed fibrin deposits along the synovial membrane.

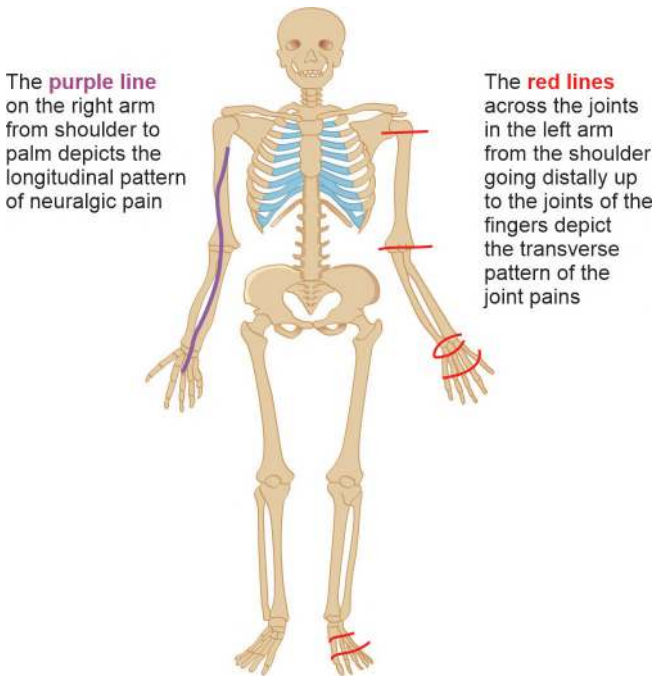


Fig. 2.2: This illustration depicts the nature of neuralgic pain radiating longitudinally through the right arm (**purple line**). In contrast, pain due to arthritis in various joints of the arm (**red line**) follows a transverse pattern of occurrence

Swelling of the Joints

Joint swelling is the third most common symptom of joint disease and is often associated with pain. However, some patients may notice swelling with little or no pain. Swollen joints may appear enlarged, puffy, or boggy due to fluid accumulation (joint effusion), inflammation, or soft tissue thickening. Normally, the anatomical contours of a joint—such as pits, troughs, grooves, and bony prominences—along with natural skin creases, help define its shape. However, swelling can obscure these features and they appear 'bland'. In inflammatory conditions, the skin over the joint may appear red and feel warm. In non-inflammatory causes, swelling is usually more localized and firmer. In individuals with lighter skin tones, redness is more noticeable, whereas in darker skin, it may present as a subtle darkish hue.

Inflammatory swelling occurs when immune cells and cytokines leak from postcapillary venules into surrounding tissues, leading to pain and fluid accumulation. If a nearby anatomical space, such as a joint cavity or bursa, is involved, it fills with inflammatory fluid, resulting in joint effusion. Effusion can be detected through various clinical maneuvers, and joint aspiration with fluid analysis (for cells, crystals, or infectious agents) is a key diagnostic procedure in rheumatology.

Loss of Function of the Joints

Inability to perform normal daily chores is the most bothersome symptom of almost all the ailments of the musculoskeletal system. Even selfcare, e.g. self-hygiene, taking

a shower, undressing-dressing and taking food, may become difficult. Simple body mobility required to carry out daily chores, may get affected requiring round-the-clock help. Such dependency on others brings frustration and depression which is a common multimorbidity in chronic RMDs. This physical and mental state often leads to so-called 'pain-sensitisation' which is now recognised as the leading cause of nociplastic pains. Loss of function is considered a paramount issue from the standpoint of the patient with an RMD. With increasing recognition and the importance of improving and ameliorating 'patient reported outcome' of any ailment, rheumatologists now use a widely validated 'tool' to 'measure' the degree of loss of function in any RMD. This tool is called 'The Health Assessment Questionnaire' (HAQ). It was originally developed in 1978 by a famous American rheumatologist James F. Fries, and colleagues at Stanford University, California. It was one of the first self-reported disability measure. Since then, it has been translated and modified in several countries around the world but continues to remain at the core for assessing disability, especially in RMDs. HAQ (or its modified versions) are now mandated outcome measure for day-to-day clinical assessment and clinical trials in rheumatoid arthritis and some other MSK diseases (e.g. bath ankylosing spondylitis functional index {BASFI}). Therefore, in rheumatology practise, improving the disability index of the patient under treatment is one of the main treatment goals.

Constitutional symptoms: A good clinical history for constitutional symptoms that include fatigue, feverish feeling/fever, loss of weight and appetite, are important clinical features. Constitutional symptoms clearly distinguish the 'inflammatory' category of RMDs from the other 2 categories, namely RMDs related to 'mechanical–structural-developmental' issues (e.g. OA); and RMDs caused by 'biopsychosocial issues' (e.g. fibromyalgia).

Other Symptoms in Patients with RMDs

It is to be noted that out of all the diseases under the category of RMDs, most of them that make up the bulk of routine patients in daily rheumatology practise, are *multisystem diseases*. Therefore, besides complaints related to musculoskeletal system, such patients often present with complaints primarily related to other systems of the body. It is quite common that a patient with any RMD doing well in the follow-up of a rheumatologist develops certain symptom(s) related to other systems of the body that may have become more prominent in the course of the disease. For example, a patient with inflammatory polyarthritis diagnosed as 'seronegative rheumatoid arthritis' (SNRA), after months of follow-up, may present with skin lesions that are typical of psoriasis. At that stage the diagnosis changes from 'SNRA' to 'psoriatic arthritis' (PsA). There are innumerable such examples where the *diagnostic 'course-correction'* is required on the appearance of a new symptom related to any other body system. Also, a detailed history including careful *'system review'* and a detailed *family history* may reveal complaints related to some other system of the body that may reveal the real nature of the RMD needing a revision in the original diagnosis. Therefore, eliciting history, often asking 'direct questions' related to these additional symptoms, help in narrowing down the diagnostic possibilities. Such detailed clinical history taking also helps the American College of Rheumatology's (ACR's) principle of 'Choosing wisely' campaign, which recommends preparing a

short list of most relevant investigations that could be requisitioned to aid reaching the correct diagnosis. Some more common symptoms related to the other organ systems but often associated with certain RMDs are given below.

Dermatology: Skin-mucosal involvement is quite common in several RMDs. Therefore, a detailed history of any type of skin-mucosal related complaint needs utmost attention of the rheumatologist. If in doubt, opinion of dermatologist must be taken. The list of skin-mucosal involvement in RMD is rather long but some typical diagnostic lesions include the following:

- *Photosensitive rash* and 'butterfly rash' in patients with systemic lupus erythematosus (SLE). Its differentiation with rosacea may require help of a dermatologist.
- *Heliotrope rash* that is pathognomonic of dermatomyositis, along with Gottron's papules, Gottron's sign, 'mechanic's hands, 'shawl sign', 'V-neck' sign and 'holster sign'.
- *Hardening* of the skin in systemic sclerosis
- Dependent *'palpable purpura (like)'* lower leg lesions appearing on prolonged standing in Sjögren's disease.
- Colour changes (pale white → bluish → red) in the fingers on exposure to cold temperature that is typical of *'Raynaud's phenomenon'* and *'Raynaud's disease'*.

Additional commonly seen dermatological lesions in RMDs may include the full spectrum of skin lesions including macules, papules, pustules, acneiform lesions, different form of panniculitides-related subcutaneous lesions/nodules (erythema nodosum, erythema induratum, lupus profundus), 'lupus pernio' of sarcoidosis, various types of ulcers including vasculitic ulcers, pyoderma gangrenosusm, etc. The list is rather long, and it is not the aim to cover all of them in this book. Suffice it will be to emphasize that close cooperation with dermatology is essential for satisfactory management of a variety of patients under the speciality of rheumatology.

Ophthalmology: Eye is important to rheumatologists for two reasons. First, eyes are often involved in common RMDs. For example, patients with spondyloarthritis (SpA), the second most common inflammatory arthritis, frequently show acute anterior uveitis (AAU) as their first symptom of the disease. Such patients are often referred to rheumatologists for appropriate rheumatological diagnosis and treatment. Conversely, patients with SpA under rheumatology follow-up may develop eye-related complaints that will require an expert opinion of an ophthalmologist. Another common symptom in RMD patients is 'sicca', i.e. dryness in the eyes and mouth. Objective confirmation of 'dry eye' also requires help of ophthalmologists. Second reason for a close cooperation of rheumatologists with ophthalmologists is because of the prolonged use of the drug hydroxychloroquine, which is the mainstay of treatment of several RMDs. Regular retinal examination by an ophthalmologist is essential in patients who are on prolonged treatment with this drug. Eyes are involved in many of the common RMDs including RA, SLE, systemic vasculitides, others that would require help from an ophthalmologist.

Complains Related to other Organ Systems of the Body

Besides these two major specialities, RMD patients may have complaints related to almost all the other body systems. *Neurological symptoms* are frequently seen in SLE, systemic

vasculitides, Behcet's syndrome. *Lung and heart related symptoms*, mainly dyspnoea on exertion and dry cough, are common in some of the RMDs due to the complication of pulmonary arterial hypertension and chronic interstitial pneumonitis, besides other often seen complication of pleuritis and pericarditis. *Gastrointestinal symptoms*, starting from oesophageal symptoms to gastric complaints (reflux symptoms in systemic sclerosis), going down to small bowel (pseudo-obstruction in SLE and SSc) and large bowel-rectum involvement as seen in SpA secondary to ulcerative colitis and Crohn's disease. 'Anticipatory adverse effects' related to one the most used drug in rheumatology, namely low-dose methotrexate (LD-MTX) are mainly felt in the gastrointestinal tract (nausea, vomiting, bloating, abdominal discomfort, hyperacidity, etc.). Although *liver-related complaints* are not common in the field of rheumatology, widespread problem of metabolic (dysfunction)-associated steatotic liver disease (MASLD; old name NAFLD), affects treatment of RMDs. LD-MTX being one of the commonest drugs used in the field of rheumatology, often causes borderline transaminitis due to underlying MASLD. Haematological issues are usually not the complaints of the patients with RMDs but, *haematological multimorbidity* is quite common in RMDs. Anaemia of chronic inflammation, often associated with iron deficiency anaemia, thrombocytopenia (often seen in anti-phospholipid syndrome, SLE) or thrombocytosis (as a reflection of severe systemic inflammation, most common in systemic vasculitides), leucopoenia (especially lymphopenia) in SLE and leucocytosis mainly due to systemic inflammation) in systemic vasculitides is often seen in RMDs. *Thyroid* autoimmune diseases (especially hypothyroidism) are a common multimorbidity in RMDs. *Renal diseases*, although not the presenting complaint in RMDs, are some of the most serious multimorbidities in RMDs especially SLE and systemic vasculitides. *Renal diseases* are mostly symptomless in early stages, when only urinalysis and kidney function tests may be abnormal. On the other hand, *reproduction-related complaints are common* in some of the RMDs, namely SLE and anti-phospholipid syndrome (APS). Thus, miscarriages, foetal loss, foetal growth retardation, premature birth, preeclampsia-eclampsia and the so-called HELLP-syndrome (haemolysis, elevated liver enzymes, and low platelets) are common in APS.

Drug-related complaints/issues in RMDs: Unlike other fields of medicine, several drugs commonly prescribed in RMDs are not well understood even by non-rheumatologist physicians/surgeons; classic example being methotrexate. Most non-rheumatologists are not aware of the 2 types of methotrexate dosing, namely the 'low-dose' (LD-MTX) and the 'high-dose' (HD-MTX) with 2 log-order difference in these 2 doses, making them 2 entirely different drugs with no commonality. While HD-MTX is a cytotoxic drug used for the treatment of cancer, LD-MTX is an immunomodulatory drug (possibly acting through adenosine release and modulating some of the inflammatory cytokines) without any cytotoxicity. It is not uncommon for the patients and their treating physicians to complain about '*methotrexate toxicity*' that is not related to methotrexate but to the misunderstanding about it. Similarly, *hydroxychloroquine* which was widely misused around the world during COVID-19 pandemic leading to myocarditis, is often blamed for some or the other issues in RMDs. Extensive studies have established the safety of HCQ at the dose used in RMDs. Patients often need to be reassured in the context of any of the several issues discussed above.

With the above discussion, it would be obvious that eliciting a detailed clinical history is crucial to identifying patterns suggestive of the 3 main aetiopathological categories of RMDs, namely:

1. **Mechanical–structural damage-related pain** (often called degenerative conditions), mostly seen in older patients, or developmental defects in the musculoskeletal (MSK) system causing symptoms, mainly in the paediatric age-group.
2. **Immunoinflammatory** (autoinflammatory or autoimmune inflammatory) conditions, which make up the majority of the patients in a rheumatology clinic, prototype being rheumatoid arthritis.
3. **Nociplastic pain**; a type of chronic (more than 3 months) generalised or localised, shifting pain in MSK crossing the anatomical boundaries without any discernible cause; frequently present with complex, multifaceted symptoms that develop insidiously over time and explained on the basis of biopsychosocial model of pain perception.

Examination of the musculoskeletal system: *Making it a part of the general physical examination*

The human musculoskeletal (MSK) system contains approximately **360 joints**, though the exact number may vary slightly due to anatomical definitions and individual differences. These joints are classified into three main types:

- **Synovial joints (~250):** Freely movable joints found in the spine, hips, shoulders, knees, elbows, ankles, wrists, feet, palms, toes, and fingers. These joints allow for a wide range of motion.
- **Cartilaginous joints (~70):** Partially movable joints located in the spine (intervertebral disks) and rib-sternum connections, providing limited movement and stability.
- **Fibrous joints (~40):** Immobile joints found in the skull (sutures) and between certain bones, such as the tibia and fibula. These joints primarily offer strength and structural support.

Given the number and complexity of joints, a comprehensive musculoskeletal (MSK) examination may seem daunting, especially to beginners. However, rheumatologists have streamlined the MSK assessment, integrating it into the general physical examination without compromising its diagnostic value. This chapter describes MSK examination as a part of the general physical examination.

The GALS System of Screening Examination of the Musculoskeletal (MSK) System

This system was developed by rheumatologist in United Kingdom that has been adopted worldwide since the year 2004. A video demonstration of how to perform GALS examination is available at the following link: https://www.youtube.com/watch?v=-uBZk4gKXBY

Its components are as follows:

GALS Examination Breakdown

1. **Gait (walking pattern)**
   - Observe the patient walking across the room, turning, and walking back.
   - Assess for **symmetry, smoothness, stride length, and balance**.
   - Look for **limping, instability, stiffness, or asymmetry** (e.g. antalgic gait in arthritis, waddling gait in muscle disorders).

The 2 important points to be observed in 'walking pattern' are:

- *Type or appearance of gait:* Abnormal appearance of gait is indicative of neurological diseases, e.g. hemiplegic gait—typically seen in patents with hemiplegia, shuffling gait—is a walking pattern where you drag your feet along the ground instead of lifting them fully. It can be caused by a number of conditions, including Parkinson's disease, injuries, and other health issues, "festinant gait", typically seen parkinsonism.
- *Rhythm of gait:* The rhythm of a normal gait is 'dot', 'dot', 'dot' ... . In patients with musculoskeletal problems in the legs start to 'favour' the affected side leading to 'dash-dot', 'dash-dot' pattern. Therefore, an abnormal rhythm of the patient's gait is indicative of an RMD involving a leg.

2. **Arms (upper limb assessment)**
   - **Posture and inspection:** Observe resting position and any visible deformities or swelling.
   - **Active movements:** Ask the patient to:
     – Place hands behind their head (assessing shoulder and elbow function).
     – Extend their arms forward and turn their palms up (checking wrist and forearm rotation).
     – Make a fist and then fully extend the fingers (assessing fine motor function and hand joints).
   - **Grip strength and function:** Ask the patient to squeeze your fingers and perform tasks like buttoning a shirt.
3. **Legs (lower limb assessment)**
   - **Posture and inspection:** Look for joint swelling, deformities, or muscle wasting.
   - **Active movements:** Ask the patient to:
     – Perform a knee flexion and extension (while lying down or sitting).
     – Internally and externally rotate the hip while lying down.
   - **Function tests**
     – Observe heel-to-toe walking for balance.
     – Perform the "sit-to-stand" test to assess lower limb strength and joint function.
4. **Spine (posture and mobility)**
   - **Inspection:** Observe from the front, side, and back for any abnormal curvature (e.g. scoliosis, kyphosis).
   - **Cervical spine (neck movement):** Ask the patient to:
     – Touch their chin to their chest (flexion) and look up (extension).
     – Turn their head side to side (rotation) and tilt ear to shoulder (lateral flexion).
   - **Thoracic and lumbar spine**
     – Ask the patient to bend forward and try to touch their toes (lumbar flexion).
     – Observe for smooth, even movement and any signs of pain or restriction.

Key Features of GALS Examination

- **Quick and systematic:** Takes only a few minutes to perform.
- **Designed for screening:** Helps identify patients needing further musculoskeletal evaluation.
- **Widely used:** Ideal for general practitioners, rheumatologists, and medical students.

Individual Joint Examination

Based upon GALS screening of the MSK, the main affected joints (often called *actively inflamed joints*) can be gauged. Accordingly, those joints can then be examined in more detail as follows:

For the examination of joints, a simple method to remember is:

'Look', 'Feel', 'Move' and 'Move the Joint while Feeling it'

1. **Look at the joints (inspect the joints):** By *looking at the joints* one would be able to recognise the normal anatomical contour that is lost if the joint is abnormal. Normal 'pits', 'grooves', 'gutters' and bony prominences in and around the joints are noted for any anatomical abnormalities. For example, swelling of the knee joint is easily recognised by the obliteration of the normal pits and grooves that are visible around a normal knee. Fullness of the normally seen semilunar groove just proximal (above) to the upper border of patella (suprapatellar pouch) is a clear indication of joint effusion. Para-olecranon groove seen on the posterolateral aspect of the elbow joint, the 'floor' of which is made up of the articulation between lateral epicondyle and head of radius, is normally a groove in a fully extended elbow. If there is effusion in elbow joint this groove gets obliterated and if the joint effusion is large, it will show a vertical oblong bulge. Any visible deformities, subluxations and abnormalities in weight-bearing axis (for weight-bearing joints) should be noted.
2. **Palpate the joint:** The next step is to *feel the joint*. It is to elicit joint-line tenderness and to confirm swelling if any and the type of selling; is it bony swelling, soft spongy swelling of synovial proliferation or is it due to joint effusion? Using the back of the hand skin temperature over the joint can be ascertained and compared with the other side; if the other side is also affected then with the skin temperature in the region proximal (above) to the affected joint can be used for comparison. A warm joint indicates an inflammatory pathology. While feeling the joint one can use special manoeuvres to elicit joint effusion in specific joints. For example, '*patellar tap*' is a sign where the suprapatellar bursa is squeezed fully by gripping the lower anterior thigh firmly to drain all excess fluid if any, into the joint space. Then patella is forced towards the lower end of femur producing a click as the fluid is displaced and the patella hits femur. A positive patellar tap sign indicates the presence of moderate amount of knee effusion. '*Fluid wave sign*' is the other test that detects even smaller amounts joint fluid in the knee. For this test message the knee on its medial side moving the hand upwards and pressing laterally to push the joint fluid in the suprapatellar bursa. This manoeuvre accentuates the depression on the medial side between patella and lower medial side of the femur. Then, take the hand on the upper lateral side of the knee and 'milk' the joint fluid pushing the hand medially and downwards. This manoeuvre will push the joint fluid from the suprapatellar bursa back in the joint space that will again obliterate the normal depression seen between the medial upper end of patella and lower medial end of femur. Similarly, the effusion in the elbow joint is easily palpated when the elbow is fully extended. In the presence of joint effusion, the paraolecranon groove would show fullness and if the fluid is in large amount, there would be a bulge instead

of the groove. Fluctuation may be elicited on this bulge confirming the presence of elbow effusion. A simple way of eliciting joint tenderness in a group of joints, e.g. metacarpophalangeal or metatarsophalangeal or mid-foot joints is to *squeeze/compress* those joints using your grip **(Fig. 2.3A and B)**. The test should be performed very gently as patients may have severe tenderness in these joints for example in patients with rheumatoid arthritis.

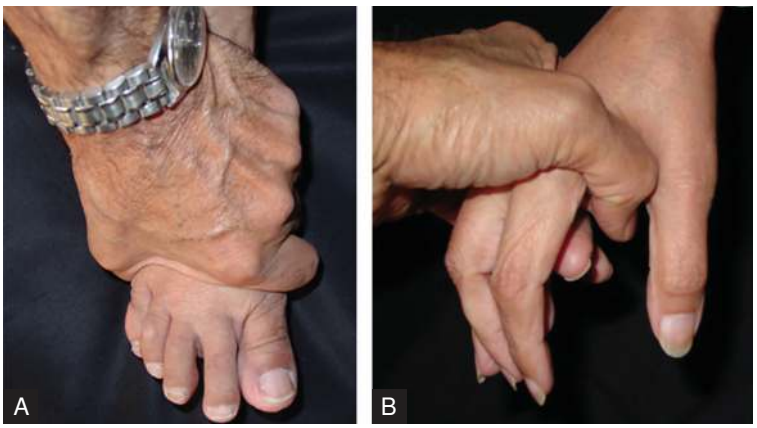


Fig. 2.3A and B: A simple clinical screening test to elicit tenderness in the metatarsophalangeal joint (A) and metacarpophalangeal joint (B) by gently squeezing these joints

3. **Test the range of movement of the joint:** Moving a normal joint would elicit the normal range of movement (ROM) for that joint. In joint disease the ROM may be reduced due to pain, swelling, fibrous contractures or actual bony ankylosis. Moving the joint may also detect laxity of the ligaments or if the joint has become completely flail.
4. **Moving the joint while feeling it** elicits crepitations in the joint, clicks in the joint, tendon rubs around the joints. It is useful to further narrowing down the possible aetiopathology of the joint involvement.

Synthesizing Clinical History and Physical Examination to Reach a Provisional Diagnosis of the Joint Disease

Based upon the clinical history and physical examination of MSK, answers to the following 4 questions help reach a provisional diagnosis as follows:

1. **Number of affected joints**
   - Single joint involvement is called **'monoarthritis'**.
   - Involvement of >1 joint is called **'polyarthritis'**.
     - **'Oligo-/pauci-arthritis':** Within the 'polyarthritis' group, there are certain diseases that are characterised by the involvement of 2, 3 or 4 joints only, e.g. peripheral arthritis in patients with a group of diseases called 'spondyloarthritis' where 'below waist asymmetrical oligoarthritis of knee and ankle' is a common feature.
2. **Duration of the joint symptoms**
   - <6 weeks—called *acute arthritis*.
   - 6 weeks or more—called *chronic arthritis*.

3. Is the joint disease **inflammatory** or **noninflammatory** in nature?
4. In those with more than one joint—What is the **pattern of joint involvement**?

Based upon the information obtained above, the *joint diseases* can be classified into *8 categories*; 4 of them in the '*inflammatory*' group and the other 4 of them in the '*noninflammatory*' group as shown in **Table 2.1**.

Table 2.1: The 8 common forms of arthritides classified based on duration, number of affected joints and whether the disease is of inflammatory or noninflammatory aetiology

Inflammatory arthritis	***Chronic***	*Poly- (or oligo-) arthritis*	*Monoarthritis*
		• Rheumatoid arthritis, spondyloarthritis, CTDs, vasculitis, etc.	• Tuberculous monoarthritis
	Acute	• Viral parainfectious, reactive arthritides	• Crystal arthritis (acute gout, pseudogout), septic arthritis
Noninflammatory arthritis	***Chronic***	• Primary generalised nodular osteoarthritis	• Osteoarthritis in a knee
	Acute	• Fibromyalgia, 'functional'	• Haemophilia joint bleed, joint trauma

Note: Prototype diseases are mentioned in this table. Each of these categories may have several additional RMDs in the group.

Based upon the information gathered on clinical history and physical examination discussed above, and establishing which of the above 8 categories the patient belongs to, making a diagnosis of a patient with RMD becomes easy (discussed in Part I, Chapter 3).

The details of investigations to be carried out in RMDs are discussed in Part I, Chapter 8. However, it is to be noted here that an elevated levels of *C-reactive protein* (CRP) *level* and *erythrocyte sedimentation rate* (ESR) would further confirmation of the inflammatory nature of the RMD. Such a classification of RMDs is essential for appropriate triage of the patients with different types RMDs to appropriate caregivers for timely, efficient and effective treatment. **Figure 2.4** shows a patient with rheumatoid arthritis (RA) who did not go through the evaluation path described above. She was

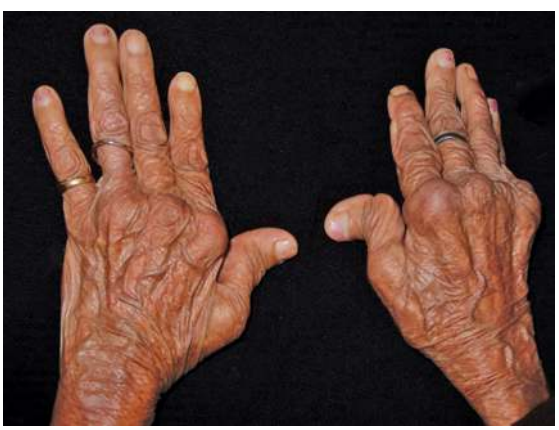


Fig. 2.4: Hands of patient with rheumatoid arthritis. Note the advanced deformities in the hands and fingers as a result of delayed diagnosis and inappropriate/inadequate treatment

treated for years by non-rheumatologists who delayed the appropriate treatment and then treated her suboptimally. The tragic consequence of delayed treatment is evident in advanced joint damage and deformities, often resulting in severe disability. In this day and age, such outcomes should be considered unacceptable. The issue of appropriate triage of RMD patients is discussed in detail in Part I, Chapter 4.

CONCLUSION

As in other fields of clinical medicine, rheumatological diagnosis relies heavily on clinical history, which provides approximately 80% of the information towards making a diagnosis. Physical examination of the MSK system contributes an additional 15%, while laboratory investigations account for only about 5% in confirming the diagnosis. A thorough clinical evaluation enables effective triage, ensuring that patients are referred to the appropriate specialist with expertise in managing their specific RMD. Proper triage is essential for optimizing patient care, minimizing delays, reducing unnecessary specialist consultations, and avoiding the financial burden of unnecessary investigations. Using the knowledge gained in this chapter, the next chapter (Part I, Chapter 3) explores the details making a diagnosis of RMDs.

CHAPTER 3

Clinical Approach to Diagnosing Joint Diseases

A layperson typically refers to any joint-related symptom as "**arthritis**", a broad term encompassing various joint ailments. In Hindi, it is commonly called "*Gathiya-Byie*", often associated with the belief that "*bad gases in the joints*" cause pain. The previous chapter (Part I, Chapter 2) outlined the clinical evaluation of RMDs through a detailed assessment of medical history and physical examination. It highlighted the critical role of key diagnostic factors, including the *duration* of joint symptoms, the number of affected joints, the distinction between *inflammatory and non-inflammatory* involvement, and, in cases of multiple joint involvement, the specific *pattern of joint distribution*. Steps that a rheumatologist takes towards making a diagnosis of any joint disease, consists of obtaining answers to the following 4 clinical questions that have also been discussed in the previous chapter (Part I, Chapter 2) in depth and, may be recalled as follows:

1. *How many* joints are affected?
2. What is the total *duration* of the joint symptom?
3. Is it *inflammatory* or *noninflammatory* in nature?
4. In those with >1 joint involvement, what is the *pattern of joint involvement*?

Based upon these clinical features and a few preliminary tests, namely erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, the rheumatologist classifies RMDs into 8 basic categories given in **Table 3.1**:

Table 3.1: The *8 common forms* of arthritides classified based on *duration*, *number* of affected joints and whether the disease is of *inflammatory* or *noninflammatory* aetiology

Inflammatory arthritis	***Chronic***	*Poly- (or oligo-) arthritis*	*Monoarthritis*
		• Rheumatoid arthritis, spondyloarthritis, CTDs, vasculitis, etc.	• Tuberculous monoarthritis
	Acute	• Viral parainfectious, reactive arthritides	• Crystal arthritis (acute gout, pseudogout), septic arthritis
Noninflammatory arthritis	***Chronic***	• Primary generalised nodular osteoarthritis	• Osteoarthritis in a knee
	Acute	• Fibromyalgia, 'functional'	• Haemophilia joint bleed, joint trauma

DISTINGUISHING 'CHRONIC' VS 'ACUTE' INFLAMMATION: KEY DIAGNOSTIC POINT IN RMDs

'Chronic' Versus 'Acute' Inflammation

Out of the above 4 features, the 3rd feature, namely '***inflammation***' requires certain clarifications. The features of chronic inflammation are in stark contrast to the classical clinical features of *acute inflammation*, described as '*rubor (redness), calor (warmth), tumor (swelling), dolor (pain), and functio laesa (loss of function)*. In contrast, there are a different set of clinical features for recognising chronic inflammatory joint diseases, as shown in **Table 3.2**.

Table 3.2: Clinical distinguishing features between *chronic* and *acute* inflammatory *joint disease*

Clinical features	*Chronic inflammation*	*Acute inflammation*
Early morning stiffness—a prominent feature	With gentle movements, e.g. doing daily chores, stiffness improves in ~30–60 minutes	Movements increase pains; stiffness is not a major clinical feature
Pain in joint(s)	Mild to moderate pain	Severe pain
Resting the joints	Worsens stiffness	Resting joints reduce the pains; stiffness not an issue
Constitutional features	Loss of weight and appetite, fatigue, fever/feverish feeling	Not notable due to a short duration of illness except fever or feverish feeling that may be present
Colour of the overlying skin	Mostly normal, in chronic cases, may be dusky red	Reddish colour of the overlying skin
Skin temperature	Raised	Raised much more than in chronic cases
Swelling of the joint	May be present, occasionally prominent	Prominent swelling
Loss of function	Slowly increasing over time	Loss of function—acutely

Following the above clinical principles, it will be easily possible for any physician to distinguish between acute inflammatory arthritis from chronic inflammatory arthritis. Thus, there should not be any confusion between these 2 entirely different types of inflammation, former for the rheumatologists and latter for all the other specialities.

As already mentioned in Part I, Chapter 2, based upon the ***number*** of affected joints, ***duration*** of arthritis and the ***presence or absence of features of inflammation***, joint diseases can be easily classified in the following 8 categories **(Table 3.3)**.

Table 3.3: The 8 categories of rheumatic and musculoskeletal diseases based upon whether they are inflammatory or non-inflammatory in nature, disease duration and the number of affected joints

		Poly- (or oligo-) arthritis	*Monoarthritis*
Inflammatory arthritis	***Chronic***	• Rheumatoid arthritis, • Spondyloarthritis, CTDs, vasculitis, etc.	• Tuberculous, other chronic infections
	Acute	• Viral parainfectious reactive arthritides, autoinflammatory syndromes	• Crystal arthritis (gout, pseudogout), septic arthritis
Noninflammatory arthritis	***Chronic***	• Primary generalised nodular osteoarthritis	• Osteoarthritis in a knee, several rare diseases
	Acute	• Fibromyalgia, other nociplastic states	• Haemophilia joint bleed, joint trauma

Note: Commonest acute and chronic arthritides in clinical practise

Recognising the *Pattern of Joint Involvement* Towards Making the Diagnosis of the Joint Disease

In patients presenting with *polyarthritis*, the pattern of distribution of the affected joints provides strong clue towards the likely diagnosis. The common patterns are as follows:

1. *Symmetrical peripheral chronic inflammatory polyarthritis affecting both the upper and the lower extremities*. Classical examples include *rheumatoid arthritis* and arthritis in connective tissue diseases and systemic vasculitis, several additional uncommon/rare diseases.
2. *Asymmetrical peripheral chronic inflammatory polyarthritis affecting both the upper and the lower extremities*. Classical example is that of arthritis seen in patients with psoriasis. *Psoriatic arthritis* also has a characteristic feature of the presence of dactylitis (swelling, and pain with features of acute inflammation where the whole of the toe(s) or finger(s) gets swollen and painful) (*see* Fig. 3.2 on page 29).
3. *Below-waist asymmetrical inflammatory oligoarthritis/polyarthritis often associated with involvement of spine* (causing back pain, mainly lower back pain) and *sacroiliac joints* (causing pain the upper-outer area of the buttocks often called 'back-pocket pain') as seen in the group of diseases called *spondyloarthritis*. This group of diseases often have additional clinical features called *enthesitis* (inflammation at the site of the attachment of tendons and ligaments to bones; classical example is the attachment of Achilles tendon on the posterior surface of calcaneus).

Figure 3.1 shows the different patterns of joint involvement in diseases causing polyarthritis or oligoarthritis.

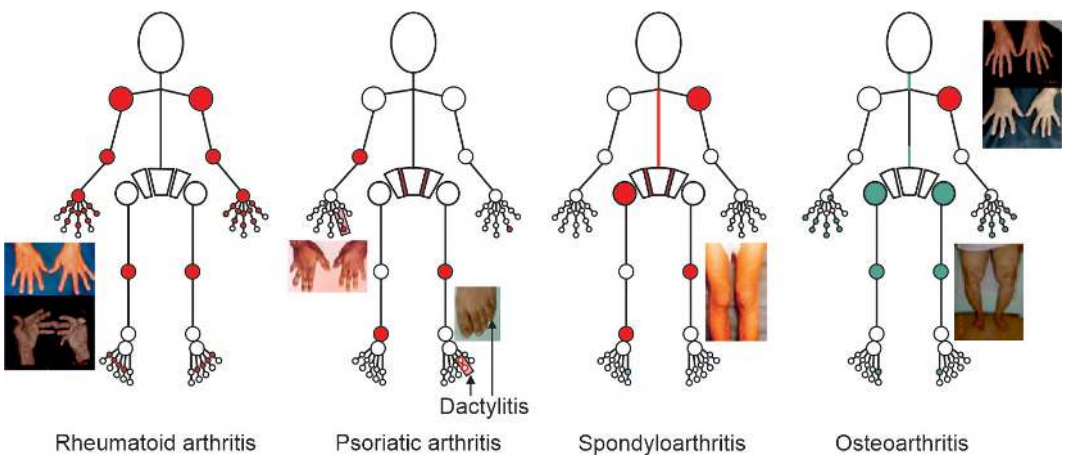


Fig. 3.1: Patients with *polyarthritis (or oligoarthritis)* can be further classified based upon the pattern of joint involvement as shown in this figure. (*Courtesy:* Dr Niti Kedia, Fellow in Rheumatology, ISIC Superspeciality Hospital, Vasant Kunj, New Delhi)

In this diagram the *inflammatory nature* of the involvement of the joints are depicted in different shades of *red-pink colour* in the following patterns of joint involvements: '*symmetrical peripheral*' pattern of joint involvement in *rheumatoid arthritis*; '*asymmetrical peripheral pattern with dactylitis*' in *psoriatic arthritis*; '*below-waist asymmetrical large*

joint involvement with sacroiliac joint and spine involvement' typically seen in spondyloarthritis; and joints depicted in *green colour* in patients with generalised primary osteoarthritis having symmetrical pattern of joint involvement (somewhat like rheumatoid arthritis) but with the involvement of distal interphalangeal joints, often with hard bony nodules called *Heberden's nodules*.

Figure 3.2 is of a patient with psoriatic arthritis who shows dactylitis ('sausage-like swelling') in one of his toes in the left foot.

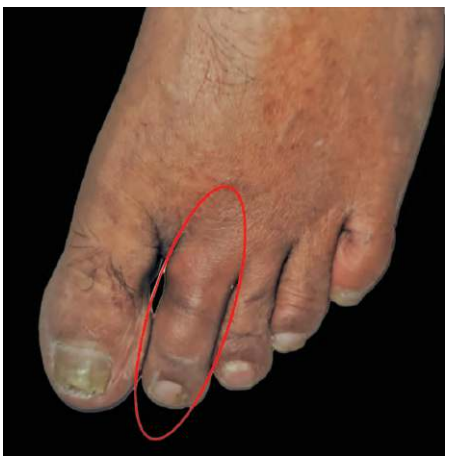


Fig. 3.2: 'Sausage-like' swelling of the left 2nd to clinically called '*dactylitis*', rather typical for *psoriatic arthritis*

Further details of diseases within the above-mentioned 8 categories, are described *vide infra*.

1. **Acute inflammatory monoarthritis:** This class of arthritis can be further categorised based upon common causes as follows:
   i. **Acute crystal arthropathies** that include acute attack of *gout* and, less commonly *pseudogout*. Diagnosing acute flare of gout is easy because of clinical history of past recurrent episodes and a family history of gout, in addition to the patients' physiognomy (majority having metabolic syndrome). Accompanying **Fig. 3.3** shows severely painful acute gouty inflammatory swelling at the base of the left big toe.

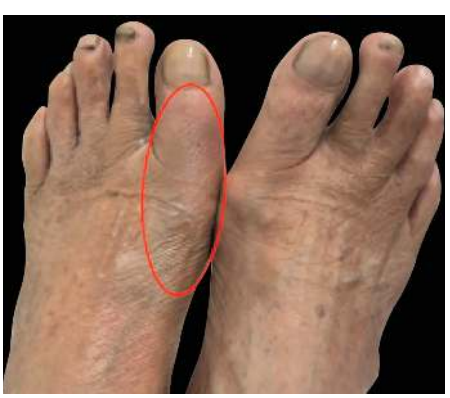


Fig. 3.3: An elderly man with *acute gouty attack in the left 1st metatarsophalangeal joint*

   ii. Pseudogout (*calcium* pyrophosphate dihydrate deposition disease or CPPD disease) can be suspected due to its clinical characteristics, i.e. elderly person, with knee (the commonest joint to be affected) swelling and pain of a short duration associated with constitutional symptoms that may give the impression of an infection. Examination of the synovial fluid aspirated from the affected joint gives the diagnosis, with a caveat. CPPD crystals are difficult to demonstrate because of their very small size as compared to monosodium urate (MSU) crystals of gout that are large and easily identified even in low-power view of the polarised light microscopy. Therefore, only a well-trained experienced person would be able to identify CPPD crystals. This problem seems to have been resolved with a recent report that MSK-ultrasound technique can recognise CPPD disease without any invasive procedure (*see* Part I, Chapter 9).
   iii. **Acute septic arthritis:** An uncommon condition because of the unique anatomy of joints. The diagnosis of septic arthritis follows a simple rule: '*Do not diagnose*

septic arthritis unless there is an underlying cause'! These include background conditions that cause *'immunocompromised states'*. Examples include piercing injuries to the joints, extremes of age (very young, very old), *malnutrition*, certain *drugs/treatments* (chemotherapy, radiation, immunosuppressive drugs, malnutrition), chronic underlying *debilitating diseases* of organ systems of the body (e.g. diabetes mellitus, chronic diseases of the lung, liver, gastrointestinal tract, kidney, haematological conditions, others). An example of acute arthritis is shown in **Fig. 3.4**.

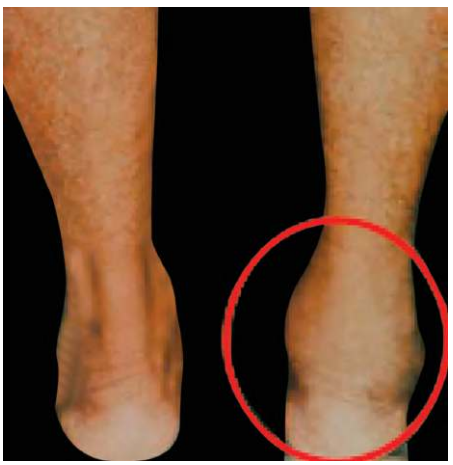


Fig. 3.4: A young boy with septic arthritis of the ankle following a thorn-piercing injury sustained one week ago

iv. **Acute arthritis over a preexisting joint disease:** Chronic joint diseases of any category could cause damage in the joint that may provide nidus for bacterial growth causing acute monoarthritis on the background of a chronic arthritis (e.g. uncontrolled rheumatoid arthritis, chronic tophaceous gout, even osteoarthritis, although uncommon).

v. **Acute inflammatory monoarthritis in a chronically injured joint:** Repeated unphysiological use of the joint, mostly 'occupation related', cause joint damage (secondary osteoarthritis) that often provides nidus for bacterial growth.

Exception: *Acute gonococcal septic arthritis* is an exception to the rule: '*Do not diagnose septic arthritis unless there is an underlying cause*'. However, a careful detailed personal history and certain specific clinical features help suspect the diagnosis. Confirmation is done with aspiration and microbiological examination.

2. **Acute noninflammatory monoarthritis:** Joint injury and bleeding in the joint due to coagulation disorders (hemarthrosis, e.g. haemophilia) are the 2 common causes. Most such patients present in 'emergency room' of the hospitals. Therefore, all medical caregivers must be aware of this presentation of a joint disease and its basic management.
3. **Acute inflammatory polyarthritis:** This used to be a relatively uncommon presentation of patients with arthritis. However, in recent years, viral arthritides have become common in the community frequently presenting with acute inflammatory polyarthritis. Traditionally, arthritis seen in rheumatic fever (a condition that is becoming almost extinct), Lyme disease (not seen in tropical countries like Bharat), and occasionally in patients with inflammatory bowel disease. The following are the important categories of acute inflammatory polyarthritis:
   i. **Viral arthritis:** Several viral diseases may cause acute inflammatory polyarthritis, chikungunya arthritis being one of the commonest. Hepatitis viruses, parvovirus, dengue virus and several other viruses may cause acute inflammatory polyarthritis. Fortunately, most of them are self-limiting.

ii. **Gonococcal arthritis:** Among septic arthritis, gonococcal arthritis can present as an acute oligo- or polyarthritis. Typical acute septic arthritis of the knees is shown in **Fig. 3.5**.

There are certain characteristic features including migratory tenosynovitis on the dorsum of the hand, shifting from one hand to the other, and the typical skin lesions that help making a diagnosis. Of course, history of unprotected sexual contact may be forthcoming. In females, contact history may not be forthcoming.

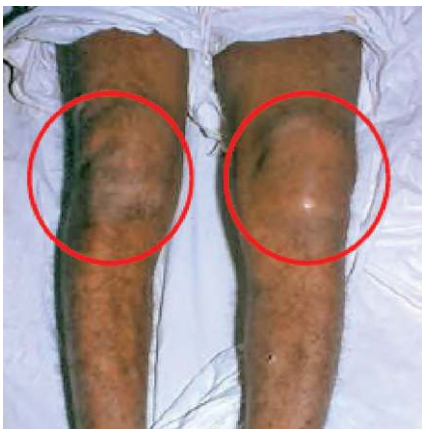


Fig. 3.5: Acute gonococcal arthritis in a young man affecting both the knees with skin lesions

iii. **Autoinflammatory syndromes:** This group of diseases is a relatively recent addition to the list of 'inflammatory rheumatic diseases' first reported in 1999. These are a family of clinical disorders characterized by episodes of seemingly unprovoked inflammation (including that of joints) without any evidence of autoimmunity (absence of any detectable autoantibodies in the circulation). Their numbers are increasing rapidly with discovery of newer genetic mutations that explain over reactivity of the innate immune system in these conditions. Diagnosing these diseases requires detailed genetic testing that is available only at a limited number of centres in the world.

iv. **Others:** Occasionally, acute arthritis may present as an uncommon feature of common diseases, e.g. rheumatoid arthritis, systemic lupus erythematosus, others.

4. **Acute noninflammatory polyarthritis:** Interestingly, there is no definite disease that belongs to this category. However, generalised nonspecific body pains are seen in fibromyalgia and other ill-defined nociplastic pain states, e.g. *temporomandibular pain disorders, low back pain*. These could be acute but quite often, become chronic (*vide infra*).
5. **Chronic inflammatory monoarthritis**, e.g. chronic infection (*tuberculosis*, others). Tuberculous infection is an important cause of chronic monoarthritis in our country, mainly due to malnutrition. **Figure 3.6A and B** shows examples of tuberculous arthritis.
6. **Chronic noninflammatory monoarthritis**, e.g. osteoarthritis, developmental defects (seen children, juveniles), and a benign (but rare) condition, e.g. synovial chondromatosis, can be an oligoarthritis with the involvement of both the knees.
7. **Chronic inflammatory polyarthritis:** It is one of the most common presentations of patients to a rheumatology clinic. *Rheumatoid arthritis is the prototype* of this group of diseases. Other diseases in this group, therefore, are often identified' as '*rheumatoid mimics*', and include arthritis seen in a group of diseases called 'spondyloarthritis' (including psoriatic arthritis, arthritis associated with inflammatory bowel disease, a condition called 'reactive arthritis'), arthritis associated with connective

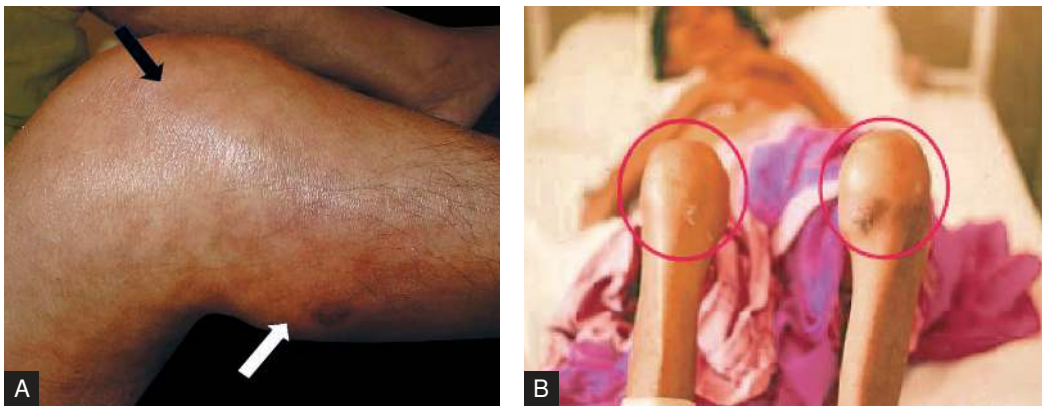


Fig. 3.6A and B: (A) A patient with chronic tuberculous monoarthritis in a knee (black arrow) with cold abscess (white arrow). (B) It shows an uncommon case of an elderly, socially neglected, severely malnourished woman acid-fast bacilli positive tuberculosis was seen in both the knee joints. Rarely malignant involvement of the synovium, e.g. synovial sarcoma can cause chronic inflammatory monoarthritis

tissue diseases ({new name 'anti-nuclear antibody-associated diseases} including systemic lupus erythematosus. Sjögren's syndrome, systemic sclerosis, dermato-polymyositis, 'undifferentiated' and 'overlap' and 'mixed' connective tissue diseases), and arthritis seen in systemic vasculitides. Then, there is a huge list of other uncommon diseases that can present with arthritis mimicking RA. These include relapsing polychondritis, multicentric reticulohistiocytosis, primary amyloidosis, thyroid-related joint disease and histiocytoses of different types. Also, there are several infection-related arthritides that have a generic name 'reactive arthritis' and include Parvovirus B19, Hepatitis B, Hepatitis C, Chikungunya and other alphaviruses, human immunodeficiency virus (HIV) and various other viruses. 'Reactive arthritides' are also associated with mycobacterial infections (Poncet's disease, some forms of arthritis seen in leprosy), certain bacterial infections, e.g. streptococcal, meningococcal, brucellosis and borrelia infection (causing Lyme disease) are among them. In most of these patients, the clinical history gives away the diagnosis while in others, more detailed investigations including microbiological and serological tests, imaging and/or histopathological examination may be required.

8. **Chronic noninflammatory polyarthritis:** Prototype disease in this category is *osteoarthritis*. At the community and the population level, it is the commonest disease. It is this disease that a lay person calls 'arthritis' with the corollary that 'arthritis is a disease of old age'! This is also the disease that places a heavy burden on rheumatologists because such patients insist on 'drug treatment' for osteoarthritis not accepting any advice on lifestyle change and help from physical medicine. The problem gets compounded in patients who have chronic inflammatory arthritis (e.g. RA) that is under treatment of a rheumatologist and doing well. Such patients over time, may develop age-related osteoarthritis or osteoarthritis secondary to joint damage accrued in patients with RA before the appropriate treatment was initiated. They usually insist on drug treatment for this and adamant against lifestyle

change, physiotherapy and/or joint replacement surgery. There are a large number of developmental defects that may cause premature osteoarthritis. Also, there are diseases like acromegaly that cause premature OA.

Making a Diagnosis of Joint Disease

The major clinical characteristics of joint diseases described above, lead to a *provisional diagnosis* in the majority of the cases. Then, based upon the provisional diagnosis, focused and relevant investigations chosen wisely, are carried out along with equally focused and wisely chosen imaging investigations. Usually these are sufficient for *confirming* the diagnosis. Occasionally, it becomes imperative to carry out biopsy of relevant tissue for making or confirming a diagnosis. Interestingly, contrary to commonly held belief, synovial biopsy to diagnose arthritis is one of the uncommon investigations! However, there is one exception, namely '*chronic monoarthritis*', which requires synovial biopsy for reaching the correct diagnosis. Other common biopsies in patients with joint complaints include minor salivary gland biopsy (Sjogren's disease), biopsy of affected organs (e.g. renal biopsy in SLE, systemic vasculitides, biopsy of other affected organs), biopsy of skin-subcutaneous lesions of different types associated with arthritis (psoriasis is a common example, may be required in connective tissue diseases, systemic vasculitides and other uncommon/rare conditions, e.g. different types of panniculitides {inflammatory diseases of the subcutaneous tissue}, histiocytosis, multicentric reticulohistiocytosis, amyloidosis), sural-nerve biopsy in some of the systemic vasculitides is another common biopsies for establishing the correct diagnosis. A point that needs emphasis is widespread misuse of investigations (including routine as well as advanced, complicated, and expensive imaging tests). It not only creates more diagnostic confusion (due to false positivity as well as false negativity) but wastes a lot of time and money. Therefore, this practise must be firmly discouraged (discussed in detail in Part I, Chapter 8).

CHAPTER 4

Triage of Patients with RMDs: Differentiating Inflammatory from Non-Inflammatory Conditions

Rheumatology is a relatively new medical discipline and remains poorly understood, even in advanced countries. The situation is even more challenging in developing nations like India, where most patients with musculoskeletal (MSK) diseases seek care from orthopaedic surgeons or neurologists, often perceiving these conditions as nerve-related ailments ("*naso ki bimari*").

To bridge this gap, it is essential to integrate a fundamental understanding of rheumatic and musculoskeletal diseases (RMDs) into the undergraduate medical curriculum. To this end, the preceding chapters of this book have provided a clear and accessible framework for understanding the three main categories of RMDs: (i) **Inflammatory RMDs**, (ii) **Mechanical–structural damage-related RMDs**, and (iii) **Nociplastic pain syndromes or pain amplification disorders affecting the musculoskeletal (MSK) system**. **Table 4.1** summarises the key differences in clinical and laboratory features between inflammatory rheumatic and musculoskeletal diseases (i-RMDs), which are further classified into chronic inflammatory (ci-), acute inflammatory (ai-), and non-inflammatory (ni-) RMDs.

Equipping primary care physicians and general practitioners with this knowledge will enable them to accurately recognise and classify RMDs into these three distinct categories. This classification is crucial for ensuring appropriate triage to specialists with expertise in managing each of these groups. Given the global shortage of rheumatologists, such an approach is vital to optimizing specialist care. It allows rheumatologists to focus their expertise where it is most impactful—managing systemic and multisystem inflammatory RMDs—while ensuring that other RMDs are appropriately directed to relevant specialists.

At the same time, rheumatologists must maintain a broad and comprehensive knowledge base to accurately diagnose all patients presenting with MSK symptoms. This ability enables them to distinguish between systemic inflammatory RMDs and other conditions that fall outside their primary domain, ensuring patients receive the most appropriate specialized care. The following sections will further elaborate on this approach.

Table 4.1: Key clinical and laboratory distinctions among rheumatic and musculoskeletal diseases (RMDs), classified into chronic inflammatory (ci-RMDs), acute inflammatory (ai-RMDs), and non-inflammatory (ni-RMDs) categories

Key clinical features and essential laboratory investigations	*i-RMDs*		*ni- RMDs*
	ci-RMDs	*ai-RMDs*	
Early morning stiffness: Presence or absence: A key clinical criterion in the diagnosis of RMDs	Stiffness in and around the joints lasting for **at least 1 hour** after waking up Usually **accompanied by pain and limited joint mobility**	Pain and limited mobility overshadow any stiffness, even if it may be present, therefore not relevant	None or minimal stiffness
Gentle movements: Examples—taking a shower bath, starting routine morning chores	**Help** improve stiffness	Brings about severe pain	Movements of any kind, especially carrying out routine daily chores usually **increase pains**
Constitutional symptoms: Fatigue on carrying out routine daily chores requiring frequent rest, feverish feeling (may have some) weight loss	Present	Except for fever, other components of constitutional symptoms would be minimal	None, but a feeling of 'tiredness' (not true fatigue) may be present
Fluctuating course	Symptoms may show fluctuation in their severity over days	Constant pain with little fluctuation	Complains remain constant over days and months
Physical examination of the join(s)	Local temperature over joint—raised (warm joint, may show some redness) Painful range of movement Joint effusion (inflammatory in nature, confirmed on raised synovial fluid cell count of >2000 up to <50,000/cu mm)	Local temperature over joint—raised (warm joint, may show some redness) Painful range of movement Effusion (if present) would be highly inflammatory with cell count usually >50,000/cu mm	Local temperature over the joint normal Pain may be felt in range of movement testing but only at certain positions In acute cases synovial fluid cell count may be >50,000/cu mm
Laboratory features indicative of systemic inflammation	Raised erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), other acute-phase reactants, e.g. alkaline phosphatase, reversal of serum albumin/globulin ratio	Only raised ESR and CRP	Acute phase reactants in the normal range

Patients who do not present with joint pain or enthesitis as their primary symptom may be more challenging to categorise within the spectrum of rheumatic and musculoskeletal diseases (RMDs). In such cases, other clinical features can aid in recognition. These include **Raynaud's phenomenon, skin and/or mucosal lesions, sicca symptoms** (dryness of the eyes and mouth), **proximal muscle weakness, and soft tissue involvement**.

In some instances, patients may present with serious multisystem involvement that is not immediately identifiable as an inflammatory RMD. This includes **connective tissue diseases, systemic vasculitides, IgG4-related diseases (IgG4-RDs)**, and other rare conditions such as certain forms of generalized lymphadenopathy.

Uncommon rheumatological disorders can also manifest with involvement of various organ systems, including the **nervous system, eyes, ears, lungs, kidneys, gastrointestinal tract, and haematological system**. However, a detailed discussion of these conditions is beyond the scope of this book.

Inflammation from a Rheumatological Perspective: A Brief Overview

In the broader field of clinical medicine and surgery, infection is the most common cause of inflammation. However, in rheumatology, inflammation is typically driven by *immunoinflammation* (also known as *immune-mediated inflammation*), followed by *crystal-induced inflammation*. In contrast, infectious causes of musculoskeletal inflammation are relatively rare.

A key distinction in rheumatology is that most rheumatic and musculoskeletal diseases (RMDs) are chronic conditions requiring long-term management. However, infectious arthritis and other musculoskeletal infections stand out as some of the few inflammatory conditions that can be completely cured with appropriate treatment. This presents a rare but critical opportunity in rheumatology—one that should never be overlooked. Prompt recognition and proper management of infectious arthritis are essential, as achieving a full cure remains an uncommon outcome in most RMDs.

RMDs where Rheumatologists must be the Primary Caregiver

The field of rheumatic and musculoskeletal diseases (RMDs) is vast. However, due to their foundational training in general internal medicine or paediatrics, rheumatologists are uniquely qualified to excel in the evaluation, investigation, assessment, and treatment of systemic or multisystem inflammatory RMDs. The preceding chapters in this book have provided easy understanding for recognising inflammatory rheumatic disease. That knowledge will help the primary care physician to triage such patients directly to a rheumatologist and help rheumatologists dedicating much of their time and expertise in managing systemic and multisystem inflammatory RMDs, where their skills are most needed and highly impactful. Such an approach is essential because there is a world-wide shortage of rheumatologists. Therefore, it is important that the rheumatologists dedicate much of their time and expertise to managing systemic and multisystem inflammatory RMDs, where their skills are most needed and highly impactful. At the same time, rheumatologists must possess a broad knowledge base to accurately recognise and diagnose the ailments of all patients who present to them. This enables them to

identify those whose conditions fall outside the domain of systemic or multisystem RMDs and appropriately direct them to other specialized services best suited for their care, as discussed below.

RMDs where Orthopaedic Surgeons must be the Primary Caregivers

In developing countries, rheumatology is still not widely recognised as a separate speciality especially among laypersons. Most such patients traditionally consult orthopaedic surgeons. By-and-large, the orthopaedic surgeons look at the MSK complaints from the standpoint of **structural-mechanical** cause, their main field of expertise. Thus, quite often, inflammatory rheumatic and musculoskeletal diseases (i-RMDs) go undiagnosed leading to delayed **diagnosis and its consequences**. Therefore, efforts must be made to improve the **basic understanding about inflammatory versus noninflammatory MSKs** among orthopaedic surgeons. As stated above, the i-RMDs require expertise in areas like immunology and molecular biology aiming at 'precision medicine' that may not be a strong point of an otherwise highly competent orthopaedic surgeon. Therefore, it would be a major step towards improving the outcome of MSK diseases if orthopaedic surgeons recognise and immediately refer patients with inflammatory MSK diseases to a rheumatologist. On the other hand, the younger generation of freshly trained rheumatologists, especially when starting clinical practise, have a tendency for not saying 'no' to patients with noninflammatory, mainly mechanical–structural, developmental and sports injury-related complaints in the musculoskeletal system. Over a period of time, such an approach would dilute their basic strength of evaluation, diagnosis and treatment of systemic inflammatory rheumatic diseases. They must learn to say that such patients need advice and help from colleagues with expertise in mechanical–structural musculoskeletal issues, e.g. orthopaedic surgeons and/or experts in physical medicine and rehabilitation (as stated below).

RMDs where Experts in 'Physical Medicine and Rehabilitation' ('Physiatrists') must be the Primary Caregivers

Experts in this field of medicine are invaluable both for patients with inflammatory as well as noninflammatory RMDs. For the patients with inflammatory RMDs, their help, and advice is invaluable for several aspects of this group of diseases. Once the inflammation is controlled with appropriate medicines prescribed by the rheumatologists, the experts in physiatry help the patient regain their MSK functions through appropriate exercises training and appropriate minor or major physical aids. They are invaluable in advising the type of physical aids and other measures in patients who may have already developed damage and deformities hindering in carrying daily chores. Similarly, in patients whose MSK needed orthopaedic surgical intervention, they always require the help of specialist physiatrists to regain functions with the major or minor change in the anatomical structures post-surgery. There is a third category of patients where physiatrists should ideally be the primary caregivers. Classic example is that of 'nonspecific low back pain'. Regular exercise and posture-related advice play a central role in the management of such patients. Similarly, several 'regional pain syndromes' [frozen shoulder, nonspecific cervical pains, lateral and medial epicondylitis

('Tennis' elbow, 'Golfer's elbow')], are ailments where physiatrists must be the primary caregivers.

Summary

The clinical background of rheumatologists is rooted in internal medicine or paediatrics, positioning them as the natural leaders of the team responsible for managing patients with I-RMDs or immune-mediated inflammatory rheumatic diseases (IM-iRMDs). All patients suspected of having these conditions should be triaged to a rheumatologist or rheumatology service. However, several categories of RMDs, discussed in subsequent chapters, are often mistakenly referred to rheumatology. Rheumatologists must be trained to recognize these cases and appropriately triage patients to ancillary services with greater expertise in managing such conditions. Establishing a structured management system for patients with RMDs is essential to optimize the efficiency of rheumatologists, who are in limited supply globally. **Figure 4.1** outlines the ideal triage process for patients with rheumatic and musculoskeletal diseases.

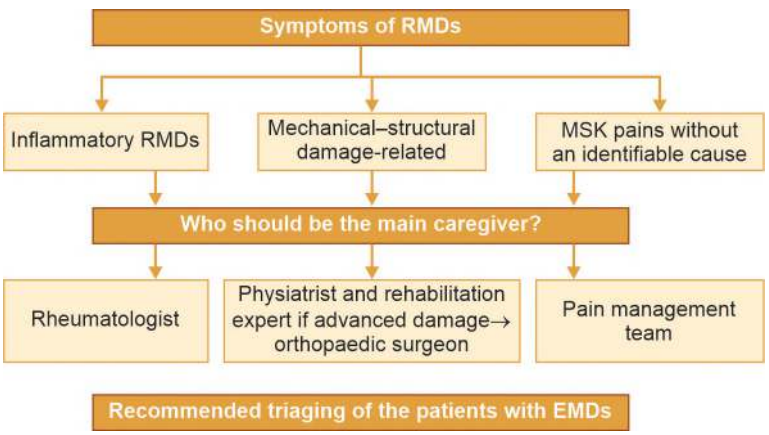


Fig. 4.1: Ideal triage process of rheumatic and musculoskeletal diseases based upon their symptomatology

A common scenario is depicted in **Fig. 4.2** regarding patients with RMDs in the community. The figure shows the dilemma of the neighbourhood general physician practitioner when such a patient consults him/her for help.

The primary care physician evaluates the patient clinically and attempts to classify the condition into one of three common categories of RMDs:

1. **Inflammatory RMDs:** Conditions with an underlying inflammatory etiopathology.
2. **Mechanical–structural RMDs:** Musculoskeletal symptoms caused by mechanical stress, strain, sprains, or structural damage.
3. **Nociplastic pain RMDs:** Pain arising from a biopsychosocial basis, without any identifiable anatomical or tissue damage.

Depending on the expertise and confidence of the primary-care physician, they may choose to manage the patient themselves or refer them to an appropriate specialist. For instance:

- Patients with inflammatory RMDs should ideally be referred to a rheumatologist.

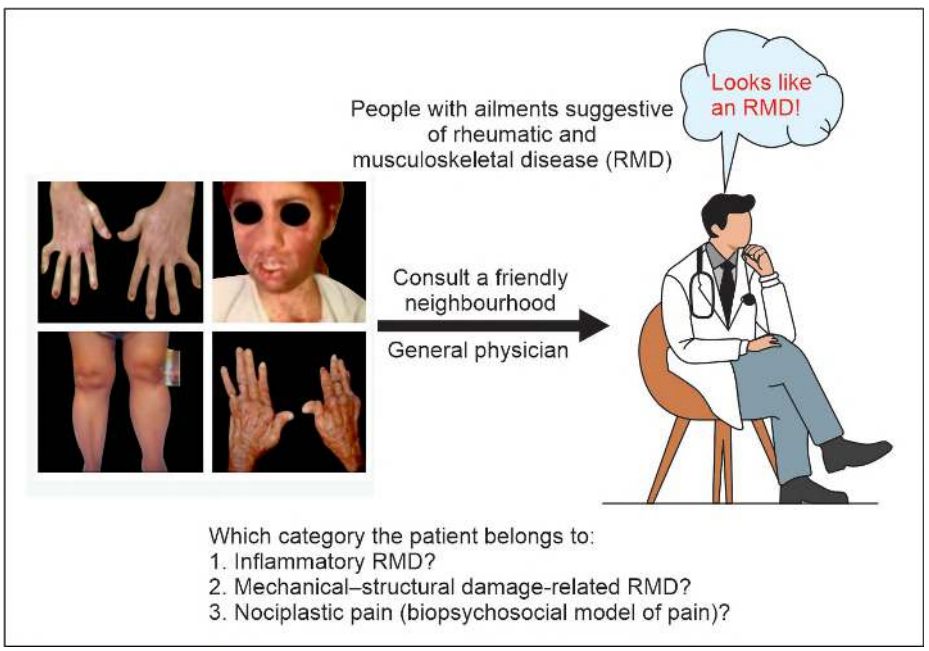


Fig. 4.2: Depiction of patients with different RMD presentations consulting a general physician—illustrating the diagnostic challenge in primary care

- Those with mechanical–structural damage-related RMDs may benefit from evaluation and treatment by a physical medicine and rehabilitation specialist (physiatrist). If the structural damage is advanced, the physiatrist may refer the patient to an orthopaedic surgeon for consideration of surgical intervention.
- Patients with nociplastic pain are best referred to a multidisciplinary 'Pain Management' team with expertise in treating such conditions.

This structured approach ensures that patients receive specialised care tailored to their specific condition.

This chapter offers a clear understanding of the various categories of RMDs and the specialised caregivers best suited to address each category.

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should be referred for appropriate management. As a reminder, the 3 main categories of RMDs are reiterated below:

1. **Inflammatory RMDs:** Conditions with an underlying inflammatory etiopathology.
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This structured approach ensures that patients receive specialised care tailored to their specific condition. This chapter offers a clear understanding of the various categories of rheumatic and musculoskeletal diseases and the specialised caregivers best suited to address each category.

CHAPTER 5

Back Pain

INTRODUCTION

Epidemiological studies conducted worldwide have shown that back pain is the most common musculoskeletal (MSK) symptom. It is estimated to affect at least 40% of the global adult population during their lifetime, equating to approximately half a billion people experiencing back pain at any given time (as of 2020).

However, in this book, back pain is not addressed in the first chapter. This is because some of its major common causes, discussed below, do not fall directly within the field of rheumatology. Nevertheless, rheumatologists must have a working knowledge of the different types of back pain to ensure appropriate triage to other relevant specialties.

Like joint diseases and other MSK disorders, back pain can be broadly classified into two main categories:

1. **Noninflammatory back pain**
2. **Inflammatory back pain**

1. Noninflammatory Back Pain

At the community level, non-inflammatory back pain is significantly more common than inflammatory back pain, with an approximate ratio of 9 to 1. The former is often attributed to stress, strain, or sprain-related mechanical and structural issues.

As discussed in Part I, Chapter 1, the lumbosacral region of the spine has one of the most complex anatomical structures. It is designed to provide both flexibility and the strength required to support substantial weight-bearing loads. Anatomically, it includes intervertebral disks, muscles, fascia, bone, facet joints including the capsule, sacroiliac joints, symphysis pubis, and ligaments. Consequently, each of these tissues is naturally susceptible to mechanical and structural stress, which can lead to back pain. However, identifying the exact tissue responsible for the pain is neither possible nor necessary.

A key characteristic of this type of back pain is that even advanced imaging techniques—such as magnetic resonance imaging (MRI), computed tomography (CT), and other newer modalities—fail to detect anatomical damage in most cases that would account for the symptoms. Therefore, unless there are clear physical signs of progressive neurological deterioration over several days, or the patient exhibits

features of 'red flag' back pain, there is a strong recommendation against performing any form of imaging in such cases.

The majority of these patients recover within days or weeks with appropriate rest and exercise under the direct supervision of physiotherapists and specialists in physical medicine.

It is important to emphasise that leading authorities strongly **advise against prolonged bed rest** for such patients. Instead, there is a clear recommendation for minimal use of painkillers and a **strong emphasis on early mobilisation**, encouraging a return to normal movement and daily activities as soon as possible.

This category of nonspecific back pain is often labelled '**green flag**' back pain indicating that such back pain has a good prognosis requiring minimum investigations and minimum use of pain-relieving drugs or surgical interventions. This broad category of back pain is commonly referred to as nonspecific back pain, meaning that no specific pathoanatomical cause can be identified to explain the pain or associated disability.

As previously mentioned, there is a strong recommendation against conducting any form of imaging in such cases, as it would be a waste of resources without contributing meaningfully to diagnosis or management. It needs to be mentioned here that in this category of patients with back pain, the majority would recover within 3 months. However, there are some who would have a tendency for chronicity of back pain (persisting beyond 3 months) due to '**somatisation of symptoms**'. They have certain underlying neuropsychiatric personality traits that make them prone to develop chronicity of their back pain. They are highly prone to become dependent on painkillers of different types. Such patients are often labelled as having '**yellow flag**' back pain. Such patients are strongly encouraged to resume normal activities as soon as possible explaining that this will help to relieve symptoms and reduce the risk of chronic disability. However, some of them may require help from a '**pain management team**' including psychiatric help. New research in recent times has advanced the theory of a biopsychosocial basis for such pains that have been given the name '**nociplastic pain**'. Several similar categories of pains are often identified as '**pain amplification syndromes**'. Besides chronic nonspecific low-back pain, this category includes **fibromyalgia, chronic temporomandibular pain** disorders, **irritable bowel syndrome, chronic primary pelvic pain/bladder pain syndrome,** and other similar conditions.

It is of note that in the 'noninflammatory back pain' category (discussed above) there is a subcategory of a small number of patients that can have 'sinister back pain' back pain. It is important to note that within the category of 'non-inflammatory back pain' (as discussed above), there exists a small subcategory of patients who may actually have 'sinister back pain'—a term used for cases with clinical features suggestive of serious spinal pathology that warrant urgent evaluation by a specialist spinal surgeon. The following two patient examples illustrate this concept: First is a short story of a 25-year-old male who presented at our rheumatology clinic with a short history of ~2 weeks of severe continuous round-the-clock back pain, low-grade fever, night sweats, and loss of appetite. On palpating the areas of pain, there were localized tender spots over sacroiliac joints and on the 2nd lumbar vertebra. The CT-scan images revealed what appeared like 'lytic' lesions (arrows) in the iliac bones and the 2nd lumbar vertebra (**Fig. 5.1A to C**). The short duration of severe continuous pain with alarming constitutional symptoms

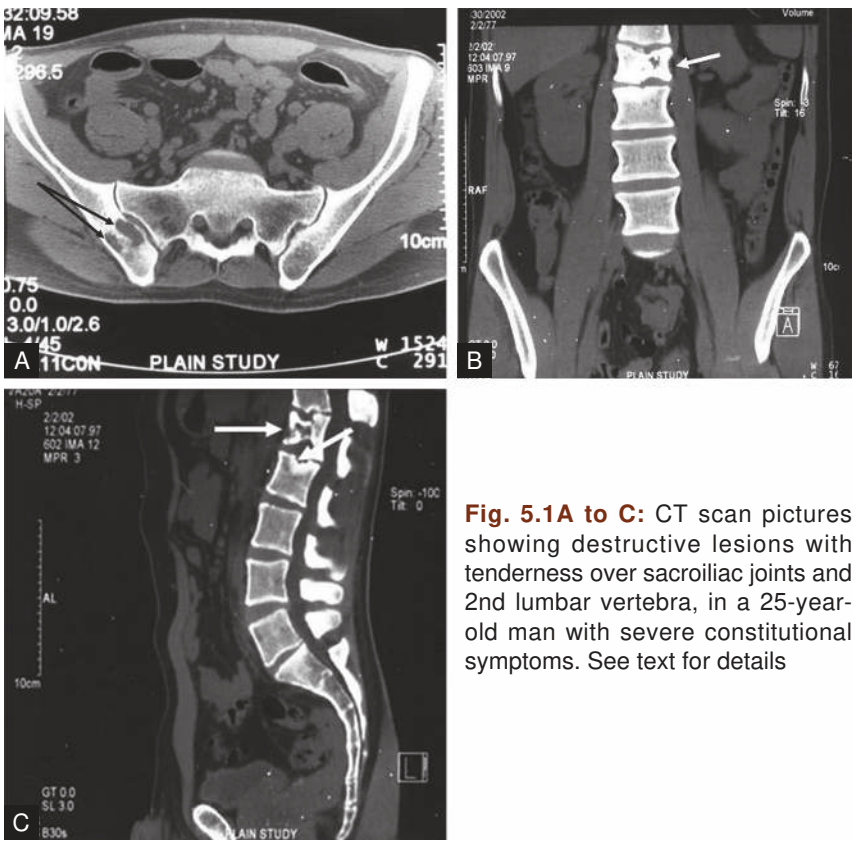


Fig. 5.1A to C: CT scan pictures showing destructive lesions with tenderness over sacroiliac joints and 2nd lumbar vertebra, in a 25-year-old man with severe constitutional symptoms. See text for details

indicated a serious underlying pathology requiring an urgent biopsy of the affected bone. Histopathology showed caseous granulomatous lesions confirming the diagnosis of 'bone tuberculosis'. With a full course of anti-tuberculosis treatment, the patient recovered quickly and gained normal health within a few months. The second patient was a 51-year-old male suffering from prostate cancer developed severe back pain with point tenderness over one of the lumbar vertebrae. The CT-scan image of this man showed metastatic destruction of the vertebral body as shown in **Fig. 5.2**. The distinction between 'yellow flag' and 'red flag' back pain in most patients can be easily made based on the symptoms of the patient, as given in **Table 5.1**.

2. Inflammatory Back Pain

Certain distinctive features in the clinical assessment of back pain help readily identify inflammatory back pain. The well-established clinical characteristics of inflammatory back pain include:

1. >3 months duration.
2. Onset before the age of 45 years.
3. Associated with stiffness after a period of immobility that takes >30' of gentle movements to start improving.
4. Good response to nonsteroidal anti-inflammatory drugs (NSAIDs), including nonselective (COX-1 and -2)/selective COX-2 inhibitors)).

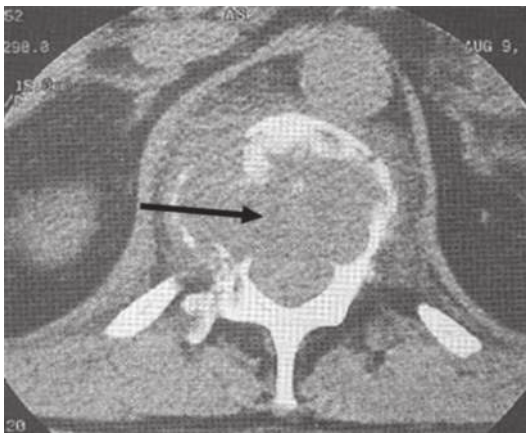


Fig. 5.2: The CT scan image of a person showing metastatic destruction of the vertebral body (black arrow).

Table 5.1: The clinical features that help distinguish 'yellow flag' from 'red flag' spinal conditions

*Symptoms of 'yellow flag' back pain**	*Symptoms of 'red flag' back pain***
The belief that back pain is a potentially severely disabling, dangerous condition (indicative of a negative attitude towards the symptoms of back pain)	Common **age of onset** <20 years or >55 years
Reduced activity levels indicative of pain on movement (often called 'fear avoidance behaviour')	Presence of **constitutional symptoms**, e.g. fever and unexplained weight loss indicative of infection or malignancy (or history of malignancy), other serious medical illnesses
Belief that 'rest' (passive treatment) will be beneficial, leads to shunning normal physical activities of daily living and causes more harm and chronicity	Progressive **neurological deficit** as indicated by gait abnormality, saddle anaesthesia, bladder or bowel dysfunction
Clinical features of depression, low morale, and social withdrawal	Pain in the region of **thoracic spine**
Social or financial implications (including possible disability benefit)	

*__Biopsychosocial factors__ indicative of long-term chronicity and disability. **Indicators of serious spinal pathology

However, these clinical features are not infallible. Yet, they serve as a 'screening' method for a quick categorisation in 'inflammatory' back pain distinguishing it from 'non-inflammatory' categories of back pain that further requires erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels to confirm the inflammatory nature. This broad category of inflammatory back pain has been given a generic name **spondyloarthritis (SpA)**. There is a subcategory of SpA that has an inherent tendency to rapid progression involving the ligaments that hold individual vertebrae together; they become rigid with calcification (visible on plain radiograph of the spine identified as **syndesmophytes**) making the spine immobile and rigid. Such spinal changes are called '**bamboo spine**' are shown in **Fig. 5.3**.

This stage of SpA is a well-defined specific subcategory of SpA given the name **'ankylosing spondylitis' (AS)**. It should be clearly understood that only a minority

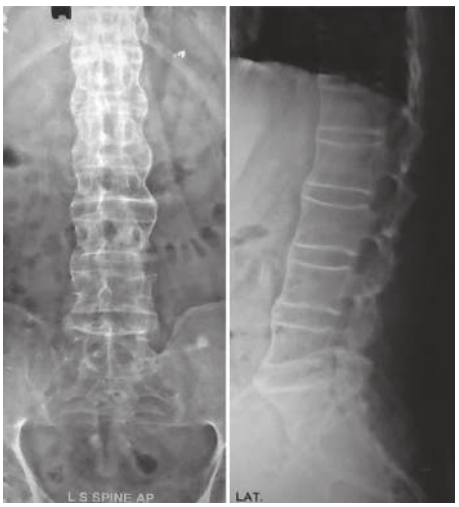


Fig. 5.3: Radiograph of a patient with late axial spondyloarthritis with classical 'bamboo spine' (the clinical stage of axial spondyloarthritis often called 'ankylosing spondylitis'). Note the calcified anterior and lateral spinal ligaments called 'syndesmophytes'

of patients with SpA progress to the stage of AS. In rheumatology practise, patients with SpA make up a major chunk of daily clinical work. Therefore, it is discussed in detail in a separate chapter in the book (Part II, Chapter 2).

Conclusion

Back pain is one of the most common musculoskeletal symptoms encountered in clinical practice. Therefore, a **clinical classification** into two main categories is essential for effective triage:

1. **Non-inflammatory back pain**
2. **Inflammatory back pain**

This classification aids in guiding appropriate diagnosis and management.

Thus, most patients with noninflammatory back pain with 'green flag' features should be triaged to the Department of 'Physical Medicine and Rehabilitation'. The majority of them recover within days, weeks or at the most within 3 months of the onset with physical medicine help and minimal rest and painkillers. If the 'green flag' back pain gets prolonged beyond 3 months becoming a 'yellow flag', then the patient must be referred to the 'Pain Management team'.

Caution

Severe, persistent round-the-clock pain of short duration, accompanied by localised tenderness at specific points in the pelvic bones or vertebrae, along with constitutional symptoms, may indicate 'sinister back pain'. This could be due to an infection (e.g. spinal tuberculosis, Pott's spine) or malignant tumour deposits in the spine.

In such cases, a spinal surgeon must be involved immediately. These patients often require a **biopsy of the bony lesion** to establish the correct diagnosis and initiate appropriate treatment.

CHAPTER 6

Soft Tissues and their Ailments

INTRODUCTION

As outlined in Chapter 1, there are two major anatomical components of the musculoskeletal system, namely the '**joints**' and the '**spine**'. It may, however, not be appreciated that there is a third and an equally important anatomical component of the musculoskeletal system, namely the '**soft tissue**'. This category includes tissues that provide shape to the tissues of the musculoskeletal system and support them to carry out their normal function of body movements and locomotion. The musculoskeletal soft tissues include the following:

1. **Striated** muscles that help move the joints and spine.
2. **Tendons** (and tendon sheath lined by synovial membrane) transmit the force generated by the contraction of muscle to the bony skeleton, to carry out joint movement.
3. **Ligaments** that hold the different bones together while permitting movement.
4. **Fascia** provides cover and support for the muscles, tendons, and other surrounding tissues. It is like a 'rapper' of these tissues. The smooth surface of fascia helps reduce friction during movement. Fascia also plays a supportive role for the muscles and tendons by transmitting mechanical tension generated by muscular activity.
5. **Bursae** that provide 'cushions' for smooth movement of the joints, tendons, and muscles.

Skeletal/Striated Muscles

Skeletal muscles also identified as 'striated' muscles (because of the presence of striations in their structure) are an integral part of the musculoskeletal system. They are the movers of the joints that provide locomotion to the body. Skeletal muscles are structurally different from the other 2 types of muscles in the body, namely the smooth muscles and the muscles of the heart, the latter 2 not being part of the musculoskeletal system. Muscles are at the crossroad of several specialities including neurology, metabolic-endocrine diseases, sports medicine, and rheumatology. Uncommonly, muscles may get affected with certain infections attracting the interest of a specialist in infectious diseases. Muscle diseases that belong to the field of rheumatology (described below) are often associated with certain characteristic skin lesions, which becomes a subject

of interest to dermatologists as well. Similarly, some of these muscle diseases show prominent association with cancers that may require the expertise of an oncologist. Description and recognition of all the diseases of the muscles is beyond the scope of this write-up. Therefore, only a single group of muscle diseases—referred to as **'idiopathic inflammatory myopathies' (IIM)** or **'immunoinflammatory myopathies' (IIM)**, also known as **'immune-mediated muscle diseases' (IMMDs)**—falls within the field of rheumatology and is discussed here.

IIM/IIMDs are relatively uncommon diseases in the community and in rheumatology clinics. Subacute onset of weakness of proximal muscles of the limbs, neck flexors and truncal muscles to a varying degree, is the most characteristic feature of this group of diseases. Involvement of neck flexors, clinically presenting as 'head drop', is an early involvement that is also said to be the last group of muscles to improve on treatment. There are certain skin lesions the presence of which are pathognomonic of the disease. These include '**heliotrope rash**' that is shown in **Fig. 6.1A**. The other pathognomonic skin lesion of dermatomyositis is called Gottron's papules as shown in **Fig. 6.1B**.

There are important clinical features to distinguish IIM from some of the other types of muscle diseases. Thus, **presence of any sensory abnormality (meticulous sensory testing necessary) rules out IIM group of conditions. Similarly, fasciculations in the muscles exclude IIM. Purely distal muscle involvement in the limbs is not compatible with IIM. Similarly, a positive family history of muscle disease excludes IIM**. The diagnosis can be confirmed with:

1. Electromyography (EMG, typically showing proximal muscle membrane irritability as shown by the presence of fibrillations, positive sharp waves, and myotonic discharges).
2. Elevated muscle enzymes (most commonly creatine phosphokinase enzyme (CK) in the blood), and
3. Specific immunohistocytochemistry of the muscle tissue obtained with appropriate biopsy. In most patients, all these 3 tests may not be needed.

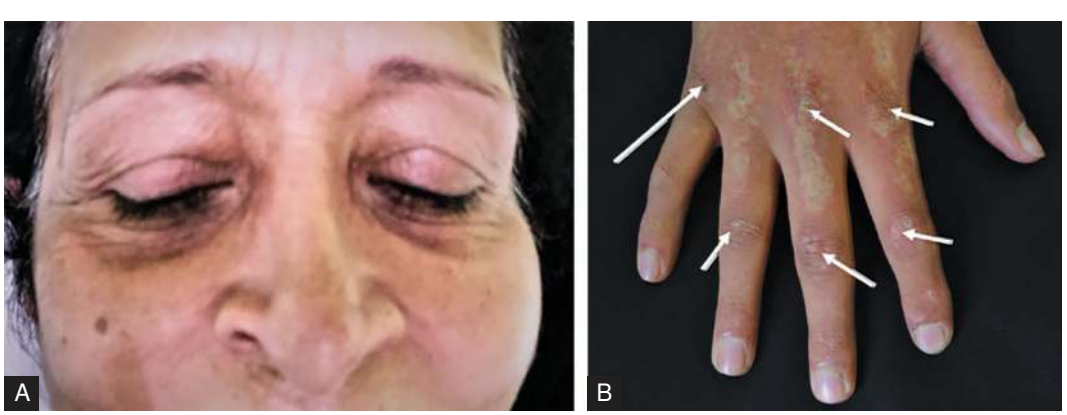


Fig. 6.1A and B: (A) Photograph of the face of a patient with dermatomyositis, which is a purple-reddish colour rash involving the eyelids and a similar but photosensitive rash on the cheeks that often crosses the nasolabial fold as in this patient; (B) **Gottron's papules** that are lesions on the dorsal surface of the small joints in the hands (white arrows)

Clinical features combined with EMG and elevated muscle enzymes in blood give away the diagnosis. A particular point related to muscle biopsy needs to be mentioned. Magnetic resonance imaging (MRI) can help to demonstrate the areas of inflammation in the muscles. This can help in obtaining accurate biopsy that will not miss a disease affected area. Once the diagnosis is made, rheumatologists would be able to plan the appropriate line of management for different subtypes of IIM.

Presence of sensory features or mononeuritis multiplex, may require careful evaluation for systemic vasculitis of small vessels (e.g. granulomatosis with polyangiitis, eosinophilia with granulomatosis polyangiitis, microscopic polyangiitis). Constitutional features with fever and weight loss and local muscle tenderness may indicate tropical pyomyositis. There are several endocrine and metabolic diseases that can simulate IIM, their discussion is beyond the scope of this book.

Tendonitis and Tenosynovitis

As already mentioned, tendons connect muscles with bones. They transmit force generated by muscle contraction to the bones that make the joints move for carrying out normal locomotion of the body. Tendons are composed of connective tissue, mainly strong collagen fibres that provide great strength and yet are pliable enough to carry out their physiological functions. As can be perceived by nature of their function, tendons are prone to strain/sprain in daily life due to their repetitive and/or overuse that could be occupation-related, or in persons participating in competitive sports, or due to unaccustomed excessive physical work. This can cause injury/overuse-related inflammation in tendons leading to their painful swelling called '**tendonitis**'. A closely related condition called '**tenosynovitis**' can be confused with tendonitis. However, these are 2 different clinical conditions with different diagnostic connotations. As already mentioned earlier, tendons are encased in a 'wrapper-like' synovial membrane that provides lubricant fluid for smooth, friction-free movement. Repetitive/overuse can also injure the synovial sheath of the tendons causing **injury-related tenosynovitis**. On the other hand, the synovial tissue is also the main 'target' tissue for I-RMDs (also called 'immune-mediated systemic rheumatic diseases'). Thus, tenosynovitis can also be a component of an I-RMD (e.g. rheumatoid arthritis (RA)). This distinction is clinically important because recent studies have shown that in one of the commonest I-RMDs, namely RA, tenosynovitis of the flexor and extensor tendons at the wrist are the earliest manifestation of the onset of the disease. Due to the proximity of tendons and the joints, and occasionally their simultaneous involvement in a disease, clinically it may not always be possible to differentiate tendonitis, tenosynovitis, or the actual joint involvement. Presence of more generalised involvement at different anatomical sites along with the clinical features of an inflammatory rheumatic disease, may make the caregiver suspicious of a possible I-RMD. In such a situation, appropriate imaging modality can be very helpful in reaching an accurate diagnosis. Thus, MRI, CT or ultrasonic examination of the affected MSK region may be able to clearly distinguish a local 'noninflammatory' injury/overuse-related problem against an inflammatory condition which could be the first 'warning-sign' of a serious systemic disease. Thus, it can be summarised that **tendonitis is primarily a noninflammatory localised problem related to injury/overuse** and therefore, mainly belonging to the field of physiatry and

sports medicine. On the other hand, **tenosynovitis may, in addition to injury/overuse, may have a more serious connotation by way of being part of an I-RMD like RA**. However, it must be mentioned that clinically it is difficult to distinguish tendonitis and tenosynovitis and both the conditions are treated similarly. The common clinical conditions in this category are: 'Tennis elbow' or lateral epicondylitis, 'Golfer's elbow' or medial epicondylitis.

There is a painful condition on the thumb side of the wrist due to irritation/inflammation affecting abductor pollicis longus (APL) and extensor pollicis brevis (EPB) tendons as they pass through the first dorsal compartment of the wrist. This inflammation leads to pain, swelling, and difficulty moving the thumb and wrist. It has been given the name **DeQuervain's tenosynovitis**, as shown in **Fig. 6.2**.

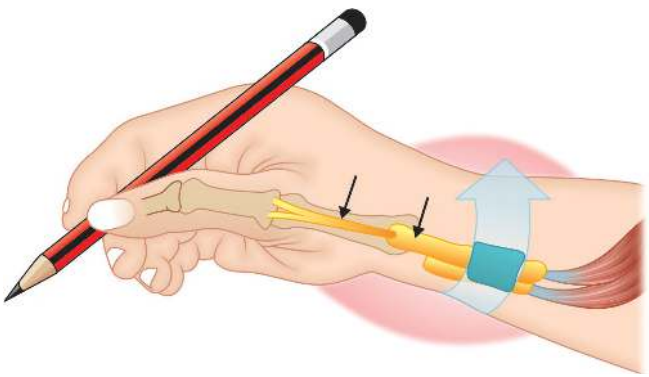


Fig. 6.2: The affected extensor-abductor tendons of the thumb that is called DeQuervain's tenosynovitis

Ligaments

Ligaments are part of 'soft tissue' that bind bones and permit movement between them. They consist of collagen fibres that give immense strength to ligaments and yet provide pliability for movement required in locomotion of the body. Therefore, by nature, ligaments are prone to injury (overstretching) and damage (actual tear) due to overuse or unaccustomed use while performing functions of daily life. The term used for ailment of ligaments is called 'sprain'. Strictly speaking, the assessment of sprains, their diagnosis and management, belong to the field of sports medicine and physiatry. Common conditions include: Anterior cruciate ligament tear (ACL tear in the knee); ankle sprain; rotator cuff tear', others. Rheumatologists would hardly ever be consulted for the diagnosis and treatment of sprain.

Fascia

Fascia is a lace-like band of connective tissue that wraps around body tissues providing form and function to every part of the body including the musculoskeletal system. It is a continuous layer of tissue that, in the context of musculoskeletal tissues, allows movement, flexibility of the bones, muscles, tendons, with the ability to resist tension. A viscous liquid called 'hyaluronan' impregnates fascia facilitating lubrication. Fascia can be affected by direct trauma or trauma related to repetitive movement/overuse. It can also be affected by inflammation as in I-RMDs or infection. These conditions lead to diminished production of hyaluronan leading to stiffness of fascia causing pain that

interferes with smooth pain-free movements. Just like the above-mentioned soft tissues, in the majority of cases the cause is same/similar to tendons and ligaments. Thus, fasciitis that is noninflammatory is managed by the sports medicine/physiatry specialists while that seen in inflammatory conditions is managed by the rheumatologists. The commonest form of fasciitis is called '**plantar fasciitis**' causing heel pain triggered by unaccustomed weight-bearing or overuse. Experts in physical medicine and rehabilitation, podiatrists and experts in sports medicine are the main providers for this ailment. *Rheumatologists may find plantar fasciitis in their patients with spondyloarthritis with severe heel pain* that may need specific treatment.

Bursae and Bursitis

A bursa (plural bursae) is a small lubricating fluid-filled pouch that provides a smooth gliding cushion between 2 moving parts in the musculoskeletal system with markedly reduced friction (also *see* Part I, Chapter 1 for a figure and description). Inflammation of a bursa is called **bursitis**. The major bursae are positioned around tendons of the large joints, e.g. the shoulders, elbows, hips, and knees. Small bursae are also present at several other areas in the musculoskeletal system including the intermetatarsal regions. Most patients with bursitis are treated by colleagues in the speciality of physical medicine and rehabilitation, and experts in sports medicine. Reducing mechanical stress by various physical means and strengthening of the muscles and soft tissue involved in these activities usually heals the problem, rarely requiring surgical intervention. In the context of 'bursitis', it may be of interest to rheumatologists that recent research studies have found the small intermetatarsal bursae in feet are the earliest to get inflamed at the onset of clinical manifestation of RA.

CHAPTER 7

The Third Pain:
"Pain other than the Nociceptive and Neuropathic Pain"

"एक दो ज़ख्म नहीं जिस्म है सारा छलनी
दर्द बेचारा परेशाँ है उट्ठे तो कहाँ से उट्ठे"

—Dr Shagufta: A patient with 'The third pain'

INTRODUCTION

Pain is an acute, unpleasant, and dynamic biopsychosocial process typically experienced in response to various forms of 'trauma' to body tissues, a phenomenon observed across species. It serves as an adaptive trait, functioning as a fundamental protective or defensive mechanism with survival value in response to actual or potential tissue injury. For this reason, pain is often the first topic covered in medical textbooks and clinical history-taking courses in medical schools.

The International Association for the Study of Pain (IASP) defines pain as: "**An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage, or described in terms of such damage.**" The term 'trauma,' in the context of body tissues, is used broadly. Trauma that triggers pain may stem from physical injury, exposure to harmful chemicals, thermal injury (extreme heat or cold), extreme pressure, radiation, or tissue damage resulting from various types of inflammation (such as infections, autoinflammatory or autoimmune disorders, or crystal-induced conditions), as well as ischaemic damage.

In rheumatology, pain is the primary symptom in most patients, whether caused by structural or mechanical damage (due to aging, occupational factors, trauma, or developmental issues) or by inflammatory pathology (including autoinflammatory, autoimmune, immune-mediated conditions, crystal-induced damage, or infections affecting the musculoskeletal system). Therefore, *a thorough understanding of the physiology of pain is essential in rheumatology to aid in the effective management of patients' pain.*

Physiology of Pain: 'Transduction and Perception'

Pain Transduction

Recalling our undergraduate days studying physiology, we learned about specialised receptor cells in the body that convert the energy from a stimulus into an electrical signal—a process known as '**transduction**'. The specialised cells responsible for this function are called '**nociceptors**.' These belong to the transient receptor potential (TRP) vanilloid receptor family of **ligand-gated ion channels** (TRPV). Several

subtypes of TRPVs are found in varying proportions across different body tissues. When tissue injury or damage occurs, nociceptors are immediately activated through transduction, triggered by various chemicals released at the site of injury or damage **(Box 7.1)**.

Box 7.1: Physiology of pain transduction and perception

Tissue injury/damage → tissue resident white blood cells (neutrophils, monocytes, macrophages) + substances released by injured tissue → oxidative stress products → engagemement of TRPVs* → development of 'action potentials' (electrical energy) → hyperexcitability → passage of the electrical signal upwards towards pain-perceiving structures in the brain (primarily thalamus) via (i) first-order somatosensory neurons (its neuronal cell is situated in the dorsal root ganglion), its efferent fibre synapsing with (and ending at) the (ii) second-order somatosensory neuron (its cell is situated in the dorsal horn of the spinal cord) → decussating and crossing over to the other side in the spinal cord → efferent going up (via unmyelinated C fibres—slow transmission, via myelinated A fibres—fast transmission) to the thalamus → synapsing with the afferent fibres of the (iii) third-order somatosensory neuron (neuronal cell situated in the thalamus) → efferent fibres going further up and ending in a certain area of the cerebral cortex.

*Transient receptor potential vanilloid channels

These chemicals bind to specific receptors at the somatosensory nerve endings, which are widely distributed throughout body tissues, functioning as detectors and transducers of pain-causing stimuli. These chemical signals are also referred to as 'peripheral sensitisers'.

Major neural pathways for pain transmission and modulation are given in **Fig. 7.1**.

Classification of Pain

Over the years, standard teaching has described only two categories of pain, namely:

1. Nociceptive pain, and
2. Neuropathic pain

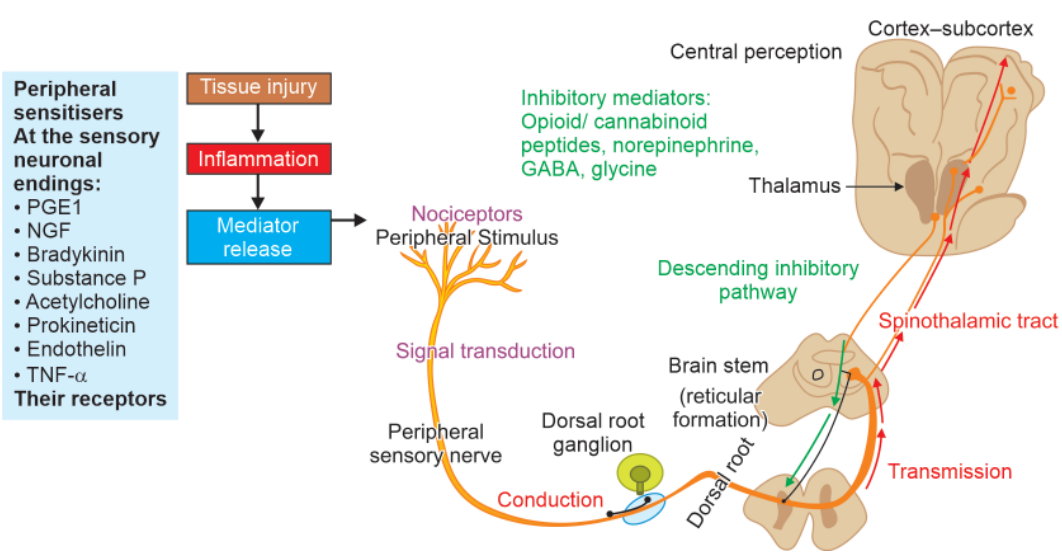


Fig. 7.1: Diagrammatic presentation of pain pathway

1. **Nociceptive pain:** Nociceptive pain is the most common form of pain we experience in daily life after any type of injury. It encompasses various sensations, including those caused by piercing, cutting, pinching, thermal, chemical, and mechanical stimuli, as well as inflammation-related pain and pain originating from the internal organs (viscera) (see below). This type of pain is often described as aching, throbbing, pressure-like, or colicky, with varying levels of intensity.

   Nociceptive pain can arise from two distinct anatomical regions of the body:

   a. **Somatic nociceptive pain:** That arises from the skin or the musculoskeletal structures.
   b. **Visceral nociceptive pain:** Nociceptive pain arising from the viscera includes various conditions, such as mucosal injury of the visceral lumen (e.g. in the gastrointestinal or genitourinary tracts), obstruction or distension of tubular visceral structures (such as the intestines, urinary tract, or biliary–pancreatic system), and obstruction or capsular distension of organs (as seen in cases of gallstones or kidney stones). It can also result from ischaemia due to arterial obstruction (e.g. angina or mesenteric ischaemia) or tissue injury associated with cancerous growths.

   In rheumatology, the majority of patients present with somatic nociceptive pain as their primary complaint.
2. **Neuropathic pain:** This type of pain is also caused by tissue injury (as noted below), but with the key condition that the **injury involves neuronal damage**. It is characterised by well-known features often described as lancinating, shooting, stabbing, or electric shock-like, and is frequently accompanied by sensations of numbness, tingling, or pricking. Neuronal damage can result from trauma, vascular occlusion, neurodegenerative conditions, infections, immunoinflammatory disorders, toxic exposures, or metabolic causes. Common examples include diabetic neuropathy, other forms of peripheral neuropathy (such as ischaemic neuropathy), nerve compression (e.g. carpal tunnel syndrome and radiculopathy), postherpetic neuralgia, phantom limb pain, complex regional pain syndrome type 2 following injury, and peripheral nerve damage caused by drug toxicity such as chemotherapy. Before introducing the concept of the recently recognised 'third pain,' it is important to first understand the distinction between 'acute' and 'chronic' pain. This foundation will help clarify how pain is classified and managed, and how the new concept fits into the broader framework of pain physiology.

'Acute' vs 'Chronic' Pain

Acute pain is an unpleasant, dynamic psychophysiological process, typically arising as a physiological response to tissue trauma or related to inflammatory processes. As previously mentioned, acute pain functions as a protective defense mechanism with survival value. It also plays a role in promoting the healing of damaged tissue. However, **when pain persists beyond the period of acute danger, it no longer serves a positive physiological purpose and instead becomes a burden, evolving into a condition of its own**.

Recent studies (according to International Association for the Study of Pain (IASP)), classify **pain that lasts beyond three months** (the typical healing period) following an acute injury as '**chronic pain**.' This type of pain is considered pathological and is regarded as a **disease in itself**. Chronic pain, also known as '**nociplastic pain**,'

is often considered difficult to treat. However, studies have shown that it can be effectively managed—and even reversed—through emotional support systems, the promotion of healthy lifestyle practices, and the cultivation of resilience, all of which play a crucial role in controlling chronic pain.

Research has shown that both *nociceptive* and *neuropathic* pain can evolve into chronic pain under certain conditions. Approximately 75% of patients with chronic pain initially experience nociceptive pain, which gradually transitions into a chronic state. On the other hand, about 25% of chronic pain cases arise from neuropathic pain, which tends to persist due to maladaptation.

Epidemiology of Chronic Pain

Chronic knee pain, primarily due to osteoarthritis, and chronic back pain, often labelled as **'nonspecific' back pain**, are two of the most common reasons patients seek help from rheumatologists. When **chronic headaches, such as migraines**, are added to the list, these three conditions become the leading causes of years lost to productive life. One study reported an overall **prevalence rate of 19.3% for chronic pain in the Indian population**. Factors such as race, sociocultural background, socioeconomic status, education, and rural or urban lifestyle have all been shown to influence the prevalence of chronic pain in any society. The economic burden of chronic pain on society, both globally and in India, is significant and far-reaching.

Chronic Pain as a Disease unto itself: A 'Biopsychosocial Model'

The concept of chronic pain as a disease unto itself emphasises the complex and multifaceted nature of pain that extends beyond mere physical injury. This approach recognises that chronic pain is not just a prolonged sensory experience but is **influenced by biological, psychological, and social factors—hence, the 'biopsychosocial model**.'

Factors that Predict Pain Chronicity

1. **Biological factors**
   - **Persistent inflammation** or ongoing tissue damage (e.g. osteoarthritis).
   - **Nervous system sensitisation**, where pain pathways remain activated even after the original injury has healed.
   - **Genetic predisposition** to chronic pain or pain sensitivity.
   - **Hormonal influences**, including changes in stress hormones (e.g. cortisol).
2. **Psychological factors**
   - **Emotional distress** such as anxiety, depression, or fear of pain, which can amplify pain perception.
   - **Catastrophising**, where patients focus on and magnify their pain, expecting the worst outcomes.
   - **Low pain tolerance** or high pain sensitivity.
   - **Lack of coping mechanisms** or poor resilience in dealing with pain.
3. **Social factors**
   - **Chronic stress** or negative social environments.
   - **Social isolation**, lack of family support, or strained relationships.

- **Economic hardships**, including the inability to afford healthcare or treatments.
- **Workplace factors**, such as job dissatisfaction or physical demands, exacerbate pain.

Together, these biological, psychological, and social factors contribute to the persistence of pain, creating a self-perpetuating cycle that can make treatment challenging. The biopsychosocial model underscores the need for a comprehensive, multidimensional approach to pain management, addressing not only the physical but also the emotional and social aspects of the patient's experience.

'Nociplastic Pain': 'The Third Pain'

Over the years, significant progress has been made in understanding the neurobiology of pain. **By 2016, it had become clear that the two traditional categories of pain—nociceptive and neuropathic—were insufficient to explain all the characteristics observed in different types of pain, particularly chronic pain**. In response, the International Association for the Study of Pain's (IASP) Terminology Task Force proposed a third category, termed **nociplastic pain**. This category describes **a chronic pain state experienced by patients without evidence of tissue damage or pathology in the somatosensory system** that would typically activate nociceptors or cause neuropathic pain.

IASP defines this third category of pain as mechanistically distinct from nociceptive pain, which arises from ongoing inflammation and tissue damage, and neuropathic pain, which is caused by nerve damage. Nociplastic pain, however, is thought to result from dysfunction in nociceptive processing and occurs without nociceptor activation or nerve injury. It is currently understood as an **altered nociceptive function**, where pain arises from changes in the function of sensory pathways in the peripheral and central nervous systems, leading to increased sensitivity.

Nociplastic pain is seen as an **umbrella term** that applies to various clinical conditions across different organ systems, all sharing common neurophysiological mechanisms. In many cases, patients with nociplastic pain have a history of nociceptive or neuropathic pain. While there are no specific biomarkers to easily identify nociplastic pain, its clinical features—often accompanied by emotional distress or disability—are distinctive enough to establish a diagnosis.

Examples of subcategories within this type of pain include **fibromyalgia (a chronic widespread pain condition), chronic primary musculoskeletal pain, complex regional pain syndrome, chronic primary headache, and orofacial pain**. Nociplastic mechanisms are frequently associated with rheumatic and musculoskeletal disorders, as well as certain neurological pain conditions, such as small fibre neuropathy. For instance, comorbid fibromyalgia is observed in approximately 20% of patients with inflammatory arthritis and 25% of those with osteoarthritis, a condition often referred to as **secondary fibromyalgia**. Many experts advocate for the use of the term **nociplastic pain syndrome** to describe this clinical state.

Nociplastic Pain: Mechanistic Considerations

At the core of nociplastic pain is a combination of **peripheral and central sensitisation**, which leads to an exaggerated response to both painful and non-painful sensory stimuli.

This hyperresponsiveness occurs due to increased connectivity and heightened reactivity within brain regions involved in pain perception. At the same time, **there is reduced activity in brain areas responsible for pain inhibition and modulation, particularly the descending inhibitory pathways**.

These abnormalities in pain processing, both in the central nervous system (CNS) and peripheral nervous system, result in amplified pain. The increased facilitative activity, combined with diminished descending inhibition, plays a key role in this process. A hallmark of this dysfunction is **allodynia**, where normally non-painful stimuli are perceived as painful, clearly indicating a supraspinal (brain level) dysfunction.

Associated Features in Patients with Nociplastic Pain

In addition to widespread pain and tenderness, patients often experience other symptoms indicative of central nervous system (CNS) involvement. These include anxiety, depression, fatigue, sleep disturbances, cognitive impairments, memory difficulties, and heightened sensitivity to non-painful environmental stimuli such as light (**photosensitivity**) and sound (**hyperacusis**). There are likely multiple initiating pathways that converge on a final common pathway, resulting in the amplification of nociceptive perception, transduction, and transmission.

Characteristic Symptoms of Nociplastic Pain

Nociplastic pain is characterised by certain easily identifiable clinical symptoms. Patients typically describe it as widespread, multifocal pain occurring simultaneously at multiple sites in the body, often perceived as severe or intense. However, despite the patient's report, clinicians usually find no objective evidence of tissue or nerve damage, even with advanced imaging techniques such as CT, MRI, or PET scans.

A key feature of nociplastic pain is its frequent association with other CNS-derived symptoms such as unexplained fatigue, poor sleep, memory issues, and mood disturbances. As mentioned earlier, nociplastic pain often coexists with chronic nociceptive and neuropathic pain, resulting in what is known as a mixed pain state, which can be particularly challenging for physicians to manage. Chronic low back pain is a typical example. Patients may attribute their pain to a "slipped" or "bulging" disc, as seen in imaging studies (CT or MRI), but convincing them that their pain has no clear pathoanatomical cause can be extremely difficult. Scientific evidence presented by the clinician often fails to change the patient's perception of the source of their pain.

Such cases frequently lead to a vicious cycle: More pain leads to more painkillers, more consultations with different caregivers, escalating anxiety and depression, and an overwhelming sense of hopelessness. It is important to note, however, that nociplastic pain can also occur without any prior history of nociceptive or neuropathic pain. Conditions like fibromyalgia and tension-type headaches are classic examples of nociplastic pain states that develop independently of these other pain mechanisms.

Clinical Conditions Included under Nociplastic Pain

Several clinical entities associated with chronic pain that are now included under the category of nociplastic pain, are given in **Box 7.2**.

Box 7.2: Entities included under the category of nociplastic pain

1. Fibromyalgia
2. Chronic low back pain (nonspecific back pain)
3. Irritable bowel syndrome related sensations
4. Chronic temporomandibular pain disorders
5. Chronic primary bladder pain syndrome
6. Chronic primary pelvic pain syndrome (in men and in women)

Making a Diagnosis of 'Nociplastic Pain'

The concept of nociplastic pain can indeed seem confusing, especially in the absence of specific biomarkers. However, in practice, identifying this so-called "third type of pain" is not particularly difficult. A thorough clinical history, coupled with the recognition of common nociplastic pain symptoms, is often sufficient for diagnosis. As previously mentioned, widespread pain at multiple anatomical sites, which fluctuates in severity and is often described as "severe" or "unbearable" (patients may even report crying from the intensity), is characteristic. This pain is typically accompanied by neuropsychiatric symptoms such as depression, mood swings, non-restorative sleep ("I wake up more tired and fatigued than when I went to bed"), poor sleep quality, memory issues, and mood disturbances.

Another important diagnostic clue is the presence of symptoms in organs unrelated to the primary pain complaint. A comprehensive physical examination is essential to rule out any obvious causes of pain that may have triggered the nociplastic state such as osteoarthritis of the knee or diabetic peripheral neuropathy. It is also important to consider conditions like hypothyroidism, which can mimic nociplastic pain. If clinical suspicion arises, appropriate laboratory tests should be conducted, both to ensure a thorough evaluation and to reassure the patient that their condition has been carefully assessed before a diagnosis is made.

It is critical to minimise unnecessary investigations and focus only on conditions suggested by the patient's history or physical examination. Excessive and poorly targeted testing such as those offered in routine "health check-up packages," can do more harm than good, as they often lead patients to believe that they have a serious organic illness that physicians are overlooking.

For example, the widespread misuse of the antinuclear antibody (ANA) test can cause confusion. False-positive ANA results are common, occurring in 3–15% of healthy individuals and 8–11% of fibromyalgia patients. A positive result can lead to further unnecessary testing, delay diagnosis and treatment, and increase patient anxiety. Similarly, the over-testing of vitamin D and B_{12} levels falls into the same category. These tests can reinforce the patient's belief that they are suffering from a specific illness, complicating their perception of health.

Once the correct diagnosis of nociplastic pain is made, a well-coordinated treatment plan involving a team of specialists, led by a pain management specialist , can effectively manage the patient's condition. **Table 7.1 outlines a simple, cost-effective approach to early diagnosis of nociplastic pain**.

Management of Nociplastic Pain

Recognising and correctly diagnosing nociplastic pain is crucial because its management and pharmacological treatment differ significantly from that of nociceptive and

Table 7.1: Suggested management approach for patients with nociplastic pain	
Basic principle of nociplastic pain management	"You have nociplastic pain; It will be adequately managed by a team of expert caregivers" • Conveying that the symptoms are "real" (not imaginary), by itself would by highly amelioratory • Gains confidence of the patient
Give it a name firmly and decisively!	"This condition does not require expensive imaging and blood tests" • Such statements will go a long way in easing anxiety and calming people suffering from chronic pain
By itself very reassuring!! "This Doctor Knows"!	Clear enunciation of "managing the condition" • As against "cure" will avoid disappointment

neuropathic pain. It is important to emphasize that nociplastic pain is not a diagnosis of exclusion. The time, money, and effort spent on ruling out other diseases (often through excessive and irrelevant laboratory testing) can delay the diagnosis and erode the patient's trust in medical professionals. Conversely, overdiagnosis or misdiagnosis of nociplastic pain may prevent the patient from receiving appropriate treatment for an underlying condition causing nociceptive or neuropathic pain.

The details of specific treatment modalities for nociplastic pain are beyond the scope of this book, but a brief overview is provided:

1. After a thorough clinical evaluation, it is helpful to be direct and reassuring by stating: "Your pain is real, not imaginary (as others might have suggested)." Next, give the pain a name: "This is called nociplastic pain, or third pain." These two steps reassure the patient that their condition is understood, fostering trust and strengthening the doctor–patient relationship.
2. In the next step, clearly communicate that the patient's pain **can be managed**. This implies that the patient is an active participant in the treatment process. Outline the members of the **pain management team**, which typically includes physiatrists (physiotherapists and occupational therapists), dieticians, nutritionists, and clinical psychologists or psychiatrists. Other specialists may be required on occasion.

A key point in managing nociplastic pain is determining **who should lead the pain management team**. With rheumatologists facing increasing patient loads, many centres have established dedicated **Pain Management Departments** led by **Pain Management specialists**. This team-based approach ensures comprehensive care for patients with nociplastic pain.

Conclusion

Pain serves as a fundamental protective mechanism across the animal kingdom. The most familiar form, often experienced from common injuries in daily life, is **nociceptive pain**. This type of pain arises from the activation of nociceptors—sensory nerve endings distributed throughout the body's tissues. When injured, these nociceptors are triggered by various chemicals, sending signals through peripheral sensory nerves along the spinothalamic pathway to the thalamus, where pain is perceived.

The second type, **neuropathic pain**, is caused by nerve injury and presents with distinctive pain characteristics.

Recently, a third type of pain has been recognised which is called nociplastic pain. A crucial aspect of pain regulation is the **descending inhibitory pathway**, which modulates the intensity of perceived pain. Specific areas in the cerebral cortex and subcortex play a key role in sending inhibitory signals that control pain. Unlike nociceptive and neuropathic pain, nociplastic pain occurs without the activation of nociceptors or any nerve injury. Research suggests that in nociplastic pain, abnormalities in the descending inhibitory pathways, particularly in the cerebral cortex and subcortex, result in amplified pain signals. This leads to the sensation of chronic widespread pain. Importantly, this pain is not imaginary; it is very real and requires proper diagnosis, evaluation, and treatment.

Both the underdiagnosis and overdiagnosis of nociplastic pain can have serious psychosocial and financial consequences for patients, caregivers, and healthcare systems. A multidisciplinary team, typically led by a rheumatologist, is best equipped to manage the complex needs of patients with nociplastic pain.

CHAPTER 8

Laboratory Investigations in Rheumatic and Musculoskeletal Diseases (RMDs)

INTRODUCTION

The current landscape of laboratory investigations in clinical medicine is approaching an unacknowledged crisis. Today, numerous clinical pathology laboratories, many lacking proper accreditations, are proliferating across metropolises, major cities, and even smaller towns. These facilities aggressively promote comprehensive "full body check-ups," claiming to provide the most accurate results. They entice the public with offers of discounted test packages for individuals, families, children, or even entire households, positioning these packages as essential for maintaining good health and uncovering elusive "cryptic" diseases.

In outpatient clinics, it is now common for patients to present caregivers with a stack of laboratory reports, often featuring prominently highlighted "out-of-range" values. This raises two important ethical questions:

1. Are clinical pathology laboratories bound by any guidelines or laws regarding the performance of laboratory tests without the recommendation of a healthcare provider?
2. Are caregivers bound by any guidelines or laws requiring them to interpret, advise on, or act upon reported abnormal test results?

To our knowledge, there are no binding regulations addressing these issues. As such, we handle these situations on a case-by-case basis. Our initial question to the patient is often a gentle inquiry: "What prompted you to have these tests done, and on whose recommendation?" If the tests were ordered in the context of a possible rheumatic musculoskeletal disease, it is advisable to postpone any discussion of abnormal results until after a thorough clinical evaluation, including a detailed history and physical examination.

If the clinical assessment reveals no evidence of rheumatic and musculoskeletal diseases (RMDs), the rheumatologist must clearly communicate that the abnormal findings are "incidental" or "not attributable" to the clinical features of the patient. A brief discussion about the possibility of false-positive results and their potential causes is necessary. Tests unrelated to RMDs, such as serum selenium levels, should be explicitly dismissed as irrelevant to the case at hand, subtly suggesting that either the laboratory

or the provider who ordered the test should be questioned about its significance—not the rheumatologist.

Novices in clinical medicine are often drawn to laboratory investigations for a variety of reasons. The allure is understandable: Sleek machines with flashing lights, screens displaying an array of numbers, and the apparent ease of obtaining data with a mere drop of blood. Within minutes, a printout filled with highlighted out-of-range values appears. But if this data becomes the starting point for diagnosis, the patient is in jeopardy.

Additionally, many individuals with minor health concerns, empowered by internet searches, rush to local pathology labs to purchase packages with enticing names like "Cardiac Panel," "Liver Function Tests," "Kidney Function Tests," "Allergy Package," "Pregnancy Package," "Arthritis Panel," "Onco-Panel," and more. In this environment, medical trainees can easily be swayed into believing that such panels are the key to diagnosis. This creates a dangerous habit of attempting to diagnose without first taking a thorough clinical history—a practice that needs to be actively discouraged.

It is easy to see why ordering laboratory tests without a provisional diagnosis—one established through a careful history and physical examination—is often more misleading and confusing than the disease itself. A fundamental understanding of the statistical principles behind laboratory test results is critical for interpreting their relevance and avoiding unnecessary confusion.

Interpreting Laboratory Tests: Importance of Biostatistics

The detailed statistical principles behind interpreting tests from clinical pathology laboratories are beyond the scope of this book. However, a basic understanding of key concepts is essential. First, any test result must be compared with reference values from healthy individuals who share the same age, sex, and population characteristics as the patient. Additionally, results should be evaluated against those from other clinically similar diseases that differ from the provisional diagnosis. For instance, if rheumatoid arthritis is suspected and a rheumatoid factor test is ordered, the result must be interpreted not only against normal population values but also in the context of related conditions like primary nodular osteoarthritis, psoriatic arthritis, or systemic lupus erythematosus. Using these comparisons, along with statistical methods, a 'likelihood ratio' (LR) can be calculated. This LR aids the rheumatologist in assessing how strongly the test result supports or refutes the provisional diagnosis. Simply put, a positive test result alone, without factoring in the LR, cannot definitively confirm or exclude a diagnosis.

Basic Principles of Requisitioning Laboratory Investigations in RMDs

Once a detailed clinical history and thorough clinical examination has been conducted, the treating rheumatologist arrives at a '**provisional diagnosis**,' along with a few additional '**differential diagnoses**' that may mimic the actual diagnosis. Then, laboratory tests are requisitioned, usually falling into the following categories:

1. **Minimal baseline investigations** for all categories of patients with RMDs.
2. Investigations in patients suspected of **inflammatory polyarthritis**.

3. Investigations in patients suspected of **spondyloarthritis**.
4. Investigations in patients suspected of **connective tissue disease** (CTD), often referred to as antinuclear antibody (ANA) positive diseases.
5. Screening for **antiphospholipid syndrome** (APS).
6. Laboratory investigations specific for patients suspected of **systemic vasculitides**.
7. Investigations in patients suspected of **crystal arthropathies**.
8. Investigations in suspected **septic arthritis**.
9. Investigations in **noninflammatory** (mechanical/structural damage-related) RMDs.

In addition to these well-defined categories of investigations for different classes of RMDs, there will always be uncommon or unusual diseases for which specific or special investigations are required. Describing this category is beyond the scope of this book.

1. **Minimal baseline investigations** to get an idea of the functioning of the different body systems. These are often called '**routine investigations**' and include:
   a. **Complete blood count (CBC):** Haemoglobin level, total and differential leucocyte count, platelet count.
   b. **Baseline renal and liver parameters:** Serum creatinine, serum bilirubin, aspartate aminotransferase (AST), alanine transaminase (ALT), serum total protein and albumin and globulin levels.
   c. **Markers of systemic inflammation:** Erythrocyte sedimentation rate (ESR, Westergren, fasting); C-reactive protein (CRP) (preferably high sensitivity CRP).
   d. **Blood lipid profile:** Total cholesterol (TC), triglyceride (Tgl), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C).
   e. **Urinalysis:** Routine and microscopic urine examination must be performed in every patient attending a rheumatology clinic.
2. **Investigations in patients suspected of inflammatory polyarthritis:** This group of diseases is primarily represented by rheumatoid arthritis (RA) and its close mimics, including psoriatic arthritis (PsA), reactive arthritis (ReA), inflammatory bowel disease (IBD)-associated arthritis, peripheral spondyloarthritis (SpA), systemic vasculitides, and several uncommon or rare forms of arthritis. Commonly requested blood tests for patients with these conditions include rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPAs).
   a. **Rheumatoid factor (RF) titre:** Historically, rheumatoid factor (RF) was first detected in the blood of patients with rheumatoid arthritis (RA), which continues to represent the largest group seen in routine rheumatology outpatient clinics. Although the diagnosis of RA is primarily clinical, the presence of elevated RF levels can help confirm the diagnosis, particularly in the subset known as 'seropositive RA'. However, approximately 20–30% of patients with RA do not have detectable RF in their blood; these cases are referred to as 'seronegative RA'. On the other hand, low levels of RF can occasionally be found in up to 10% of healthy adults and in other types of inflammatory polyarthritis, such as psoriatic arthritis or connective tissue diseases, as well as in systemic vasculitides, among others.

      Thus, interpreting a 'positive' RF result cannot be as straightforward as confirming or excluding RA. In fact, the RF test has only moderate sensitivity

(40–60%) and specificity (~70%) for the diagnosis of RA. Like most laboratory tests, RF results must always be interpreted within a broader clinical context to avoid misdiagnosis.

b. **Anti-citrullinated peptide antibodies** (ACPA), commonly measured as anti-cyclic citrullinated peptide (anti-CCP) antibodies, are similar to rheumatoid factor (RF) but have significantly higher specificity—around 95%, with a false-positive rate of approximately 10%. Therefore, compared to RF, ACPA is more reliable for confirming the diagnosis of RA. However, a positive ACPA result, in the absence of clinical symptoms, should not be considered equivalent to a diagnosis of RA. Currently, ongoing research is investigating whether individuals who test positive for ACPA but are otherwise healthy might be at an increased risk of developing RA in the future.

3. **Investigations in patients suspected of spondyloarthritis (SpA):** In addition to routine investigations, screening for the presence of human leucocyte antigen (HLA)-B27 is recommended in patients suspected of having spondyloarthritis (SpA). It is important to understand that two distinct methodologies are used to identify this specific HLA: Flow cytometry and genetic sequence-based methods. The flow cytometry assay can often result in false-negative reports and does not provide information on the various allelic variants of the HLA-B27 gene. Therefore, the preferred method for screening HLA-B27 is polymerase chain reaction (PCR), a molecular technique that identifies HLA-B27-specific DNA sequences using sequence-specific primers (PCR-SSP).

   It is essential to recognise that the HLA-B27 gene is present in varying proportions within the general population. For example, in India, 6–8% of the population carries the HLA-B27 gene. At the same time, back pain—a major symptom in SpA—affects a large portion of the general population. Studies estimate that up to one-third of people worldwide experience back pain at any given time, most of which resolves within three months and is unrelated to the disease spondyloarthritis (SpA).

   Given this, indiscriminate HLA-B27 screening in individuals with back pain is likely to yield many false-positive results. Misdiagnosing and treating these patients for SpA would be a serious clinical error. Therefore, HLA-B27 testing should be reserved for individuals who exhibit symptoms and signs of inflammatory back pain alongside additional spondyloarthritis features, as detailed in Part II, Chapter 2.

4. **Investigations in patients suspected of 'connective tissue disease' (CTD; often called 'antinuclear antibody (ANA) positive diseases'):**

   a. **Antinuclear antibodies (ANAs):** The term 'antinuclear antibody' (ANA) test is somewhat misleading because some of these antibodies also react with cytoplasmic antigens. Furthermore, the number and concentration of antigens in the nucleus and cytoplasm fluctuate depending on the stage of the cell cycle. Therefore, in theory, autoantibodies that react with nuclear or cytoplasmic antigens should more accurately be called 'anti-cellular antigen antibodies' (ACAs). However, due to long-standing international conventions—where the term 'ANA' has been used for decades in medical libraries and databases worldwide—it is impractical to replace 'ANA' with 'ACA.' As a result, the term

'ANA' remains in use, with the understanding that some of the reactive antigens are located in the cytoplasm.

The antigens that ANAs target consist of a mixture of well-defined and purified antigens, partially characterized antigens, and some that remain poorly defined or unidentified. Given this complexity, antibody testing is performed using whole cells, which theoretically contain all possible cellular antigens. The most suitable and widely accepted method for screening antibodies against these antigens is the indirect immunofluorescence test (IFT). While the details of IFT are beyond the scope of this book, it is important to note that, at present, IFT remains the recommended technique for ANA screening. An example of a positive indirect immunofluorescence test for ANA performed using Hep-2 cells, a commercially available, widely used laboratory-maintained cell line that serves as a substrate for detecting autoantibodies in laboratories worldwide, is shown in **Fig. 8.1**.

Population studies have shown that up to 30% of healthy individuals may have a positive ANA test at varying titres. Therefore, interpreting a positive ANA test requires knowing the likelihood ratio of the screening test used. Without this information, the interpretation becomes unreliable, and the test cannot be confidently used to confirm or exclude diseases like systemic lupus erythematosus (SLE), as discussed in Part II, Chapter 3.

b. **Antibodies against extract of whole cells (commonly called 'extractable nuclear antigens' or ENAs):** Despite difficulties, several antigens present in cell extracts have been identified and purified to the extent that antibodies against them can be screened using solid-phase platforms (e.g. ELISA test, plastic-bead assays, and several other advanced techniques). Most of the ENAs are directed against various nucleoproteins, including ribonucleoproteins, and some of them are directed against single- and double-stranded DNA, etc.

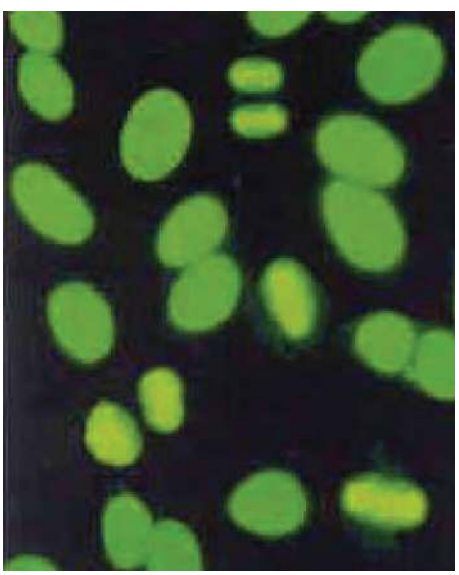


Fig. 8.1: A positive ANA test with green colour of the nuclei of the Hep-2 cells visible as a 'homogeneous' pattern, often seen in high titres in patients with systemic lupus erythematosus (*Courtesy:* Prof Ramnath Misra)

Clinical application of ANA and anti-ENA tests: The ANA test was originally developed to aid in diagnosing systemic lupus erythematosus (SLE). However, its specificity for SLE is low, as it can be positive in about 30% of the normal population and in varying percentages (from 20 to 95%) of patients with other connective tissue diseases (CTDs) such as Sjögren's disease, systemic sclerosis, inflammatory myositis, mixed and undifferentiated connective tissue diseases, approximately 20% of rheumatoid arthritis (RA) cases, about 10% of psoriatic arthritis (PsA) cases, and a range of chronic infections. Therefore, **a negative ANA test carries greater clinical significance in ruling out SLE, as almost all patients with active SLE exhibit significantly elevated ANA levels. On the other hand, a positive ANA result, without proper clinical evaluation, is less helpful in confirming SLE and can often lead to diagnostic confusion**. This underscores the importance of not ordering ANA tests without a thorough clinical assessment for SLE or other CTDs. The anxiety caused by a positive ANA result in the absence of clinical signs of SLE should be strongly discouraged. Similarly, anti-ENA (extractable nuclear antigen) testing should never be done without a detailed clinical evaluation by a rheumatologist. If a CTD is suspected, the rheumatologist will first order an ANA test. If the ANA result is positive at significant titres, anti-ENA testing can be conducted as the next step. Based on the specific CTD under consideration, a defined set of anti-ENA tests is then ordered, as these vary according to the disease being evaluated. **This highlights why only a rheumatologist should requisition such tests**.

Unlike ANA, many antigens within the ENA category are now available in purified forms, allowing for more specific testing. Anti-ENA testing is typically performed using solid-phase techniques such as line immunoassays, enzyme-linked immunosorbent assays (ELISA), bead assays, and newer methods. **Figure 8.2A and B** provides the examples of how these tests are carried out in the laboratory.

In summary, **both ANA and anti-ENA tests should only be ordered by rheumatologists experienced in diagnosing CTDs**. The standard approach involves first

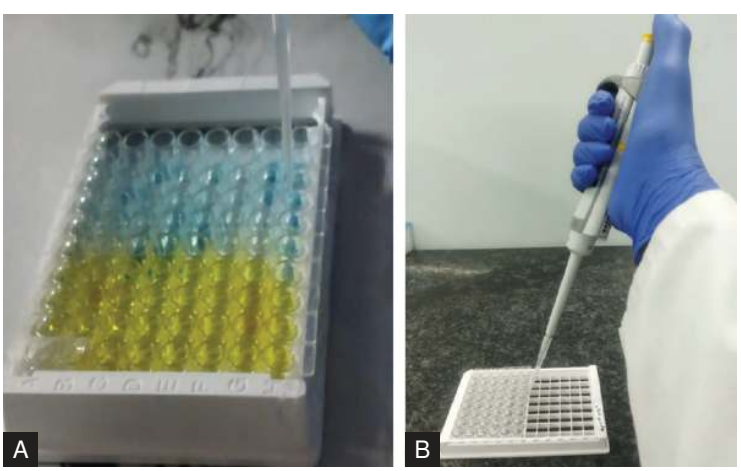


Fig. 8.2A and B: The enzyme-linked immunosorbent assay (ELISA) being performed using polystyrene plates and a horseradish peroxidase (HRP)-linked secondary antibody. (*Courtesy:* Prof Ramnath Misra.) When bound, this enzyme produces a yellow colour, indicating a positive reaction

conducting an ANA test, followed by specific anti-ENA testing based on clinical findings and the suspected CTD.

In patients with CTD, specially SLE, a few additional investigations are commonly performed as follows:

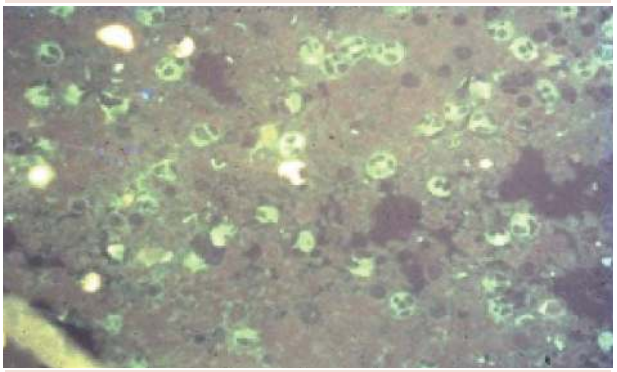
a. **Estimation of complement C3 and C4 levels:** The results help in determining the degree of disease activity in patients with SLE.
b. **Direct Coombs' test (DCT):** Besides indicating the disease severity, this test also helps in defining the type of anaemia that an SLE patient may have.

5. **Screening for antiphospholipid syndrome (APS):** Fetomaternal health and obstetric issues are common in patients with SLE. Many of these clinical features are associated with a condition called antiphospholipid syndrome (APS). Therefore, in SLE patients of reproductive age, screening for APS at the patient's first clinic visit is essential. This is carried out by testing for three antibodies associated with APS, namely:
   a. Anticardiolipin antibodies (ACA)
   b. Anti-β_2 glycoprotein 1 antibodies (anti-β_2 GP-1 antibodies)
   c. Lupus anticoagulant (LAC)

   The first two are commonly performed in clinical pathology laboratories using the ELISA technique. LAC is typically performed by clinical haematology laboratories with experience and knowledge of blood clotting tests.
6. **Laboratory investigations specific for patients suspected of systemic vasculitides:** This group consists of:
   a. **Large vessel vasculitis (LVV)**, namely giant cell arteritis and Takayasu arteritis.
   b. **Medium vessel vasculitis (MVV)** including polyarteritis nodosa (PAN), cutaneous PAN and Kawasaki disease.
   c. **Small vessel vasculitis (SVV)** group that includes granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (E-GPA) and microscopic polyangiitis (MPA).
      - *Laboratory investigations in LVV:* There are no specific laboratory investigations for diagnosing/confirming the diagnosis of LVVs. Therefore, only the category 1 of 'routine laboratory tests' (*see* above) are recommended for this group of diseases.
      - *Laboratory investigations in MVV:* Like LVVs, there are no specific laboratories for diagnosing/confirming the diagnosis of MVVs. Therefore, only the category 1 of 'routine laboratory tests' (as mentioned above) are recommended for this group of diseases.
      - *Laboratory investigations in SVV:* This group of RMD shows a highly specific laboratory test called '*anti-neutrophil cytoplasmic antibody*' (ANCA). This test has been found to be extremely helpful in confirming the diagnosis of this group of diseases as well as their subtypes. Historically, in the early 1980s when tests for ANA were being performed with indirect immunofluorescence technique, using whole cells as antigen substrates, the blood samples from some patients with a specific type of glomerulonephritis showed immunofluorescence in neutrophils. Furthermore, 2 distinct patterns of neutrophil staining were observed in such patients. Some of them showed perinuclear staining while the others showed

cytoplasmic staining. Thus, while using the indirect immunofluorescence test, ANCA were classified as C-ANCA (ANCA with cytoplasmic pattern) and P-ANCA (ANCA with perinuclear pattern). **Figure 8.3** shows a typical positive cytoplasmic ANCA test using neutrophils from a healthy human volunteer in an indirect immunofluorescence assay. Note the apple-green fluorescence in the cytoplasm (indicative of a positive result) and the black, non-fluorescent nuclei (negative for immunofluorescence). An example of a positive ANCA test with cytoplasmic pattern is provided in **Fig. 8.3**.

Indirect immunofluorescence test for anti-neutrophil cytoplasmic antibodies (ANCA)



Note the green immunofluorescence of the cytoplasm of the neutrophils

Fig. 8.3: A typical positive cytoplasmic ANCA test using neutrophils from a healthy human volunteer in an indirect immunofluorescence assay. Note the apple-green fluorescence in the cytoplasm (indicative of a positive result) and the black, non-fluorescent nuclei (negative for immunofluorescence)

Soon, the antigens with which these 2 subtypes of ANCA reacted with, were purified. Those that showed cytoplasmic immunofluorescence staining showed specific reactivity only with proteinase 3 (PR3) enzyme. On the other hand, those with perinuclear staining on immunofluorescence showed specific reactivity with myeloperoxidase (MPO). On studying their clinical correlation, it was found that anti-PR3 antibodies are seen exclusively in patients with GPA while anti-MPO antibodies only in MPA patients. Presently, the test for ANCA is conducted using purified PR3 and MPO antigens on any of the solid-phase techniques, the most popular being the ELISA test. Thus, screening for ANCA in clinically suspected patients with SVV helps provide the subtype of SVV, which also helps in their precision treatment.

7. **Investigations in patients suspected of crystal arthropathies:** There are only two main diseases in this category, namely:
   a. Gout
   b. Calcium pyrophosphate deposition disease (CPPD).

   In gout, monosodium urate (MSU) crystals are deposited in the joints, bursae, and occasionally in soft tissues. In calcium pyrophosphate deposition disease (CPPD), calcium pyrophosphate (CPP) crystals accumulate in the synovial fluid and cartilage. The definitive diagnosis of gout is made by identifying MSU crystals in the synovial

Note the needle-like, shiny structures typical of monosodium urate crystals, observed in the synovial fluid of a patient with gout under polarized light microscopy

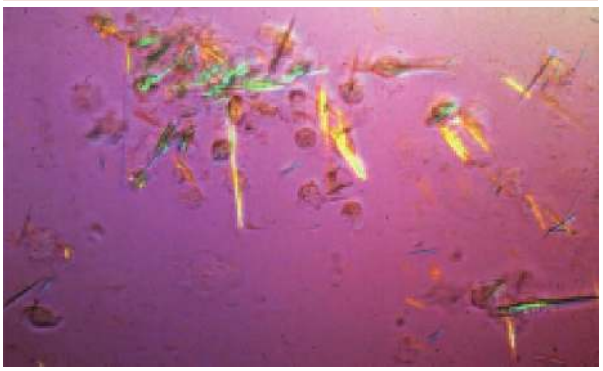


Fig. 8.4: When examined under polarized light microscopy, *negatively birefringent crystals of monosodium urate* (typically seen in gout) appear as *needle-shaped* crystals that exhibit *bright yellow* colour when aligned *parallel* to the axis of the compensator and *blue* when aligned *perpendicular* to it

fluid or fluid aspirated from bursae. Similarly, the diagnosis of CPPD is confirmed by the presence of CPP crystals in the synovial fluid.

The most accurate method for visualising these crystals is through polarised light microscopy. A sample of that is shown in **Fig. 8.4**.

8. **Investigations in suspected septic arthritis:** In suspected septic arthritis, joint aspiration and microbiological examination are usually diagnostic. However, if the patient had received prior treatment with antibiotics, the results could be false negative. The standard methods to confirm septic arthritis include:
   a. Microbiological examination of the aspirated joint fluid.
   b. Microbiological and histopathological examination of the synovial tissue obtained on biopsy.

In patients with suspected septic arthritis and synovial effusion, joint aspiration is the recommended diagnostic test. The aspirated fluid would appear like pus as shown in **Fig. 8.5**.

On Gram staining it may reveal the causative microbe. Special stains may also be used for specific infections, such as gonococcal infection or acid-fast bacilli staining for tuberculosis. If joint effusion is absent, a synovial biopsy becomes necessary. This can be done either arthroscopically or through an open surgical biopsy. Histopathological examination of the obtained synovial tissue serves as an alternative method for establishing the diagnosis.

Pus-like synovial fluid aspirated from a patient with septic arthritis

Fig. 8.5: Synovial aspirate from a patient with septic arthritis of a knee joint. Note the yellowish opaque, 'pus-like' synovial fluid typically seen in septic arthritis

9. **Investigations in noninflammatory (mechanical/structural damage related) RMDs:** Part I, Chapter 4 has already addressed the question of which types of patients fall under the primary care of rheumatologists versus other specialists, such as experts in physical medicine and rehabilitation (including physiotherapists, occupational therapists, sports medicine experts, and pain management teams).

'Choosing Wisely' Campaign of the American College of Rheumatology: Aiming at Limiting/Removing Low-value Investigations/Procedures in Medical Care

It is unfortunate that non-rheumatologist caregivers—including general physicians, internists, physiatrists (experts in physical medicine and rehabilitation), sports medicine experts, orthopaedic surgeons, pain management specialists, and other professionals—often engage in unnecessary investigations that neither aid in diagnosing nor ruling out a particular condition. Such practices must be strongly discouraged.

In 2012, the American Board of Internal Medicine Foundation (ABIMF) launched the Choosing Wisely campaign. Following this initiative, the American College of Rheumatology released a list in 2013 titled **Top 5 Things Physicians and Patients Should Question**. The first test identified as '*unnecessary*' was the antinuclear antibody (ANA) test and its related sub-serologies.

Over time, the issue of excessive and controversial investigations in rheumatology has only worsened. This not only undermines the credibility of the medical profession but also leads to the significant wastage of limited financial and human resources in the healthcare system. Below is a brief list of investigations that should not be conducted without first making a provisional diagnosis based on a carefully obtained clinical history and a thorough physical examination.

- **Antinuclear antibody (ANA) test and subserology tests [i.e. antibodies against extractable nuclear antigens (ENA)]:** As discussed earlier, ANA positivity is relatively common in the general population. Therefore, ordering an ANA test indiscriminately, without clear clinical signs of connective tissue diseases (CTDs), can result in significant diagnostic confusion and unnecessary patient anxiety, along with the waste of valuable financial resources.
- **Rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) tests:** Similar to ANA, both RF and ACPA (anti-CCP) can be present in varying proportions in the general population. Ordering these tests indiscriminately in individuals with nonspecific musculoskeletal aches and pains, particularly when the symptoms are clearly noninflammatory, can lead to diagnostic confusion, unnecessary patient anxiety, and financial waste. Additionally, some non-rheumatologists may, based solely on these test results, incorrectly initiate treatments with medications that are not indicated for such patients.
- **Serum uric acid:** Serum uric acid is considered one of the markers of metabolic syndrome, a known risk factor for atherosclerotic cardiovascular disease. However, serum uric acid levels do not aid in the diagnosis or suspicion of any rheumatic and musculoskeletal diseases (RMDs), making this test unnecessary in such patients. There is a widespread misconception among non-rheumatologists that a mild-to-moderate elevation in serum uric acid causes "arthritic pains." This notion is completely misguided, as there is no such condition as joint aches and pains resulting from a mild-to-moderate rise in serum uric acid levels.

Drug treatment for mild-to-moderate asymptomatic hyperuricemia is not recommended. Instead, such patients should be advised on lifestyle changes to mitigate the cardiovascular risks associated with metabolic syndrome and to prevent metabolic dysfunction-associated steatotic liver disease (MASLD). Notably, there is no recommendation for treating asymptomatic hyperuricemia, except in one case: Chronic tophaceous gout. Fortunately, the clinical presentation of this condition is so distinctive that minimal investigations are required to confirm the diagnosis. **The only appropriate use of the serum uric acid test is prior to initiating treatment for gouty arthritis and for monitoring during follow-up to ensure that serum uric acid levels remain below 6 mg/dl in non-tophaceous gout, and below 5 mg/dl in tophaceous gout.**

- **Anti-streptolysin O (ASO) titre:** This test measures antibodies against streptolysin O, a toxin produced by group A Streptococcus bacteria. Historically, this test was used for diagnosing rheumatic fever. However, with advancements in our understanding of inflammation and immunoinflammation, it has become clear that ASO levels reflect a nonspecific anamnestic humoral response to any inflammatory state in the body. As a result, the test has lost its specificity for rheumatic fever and has been entirely abandoned in modern clinical practice. Currently, **the ASO test has no role in the investigation of rheumatic and musculoskeletal diseases (RMDs)**.

The optimal approach for investigating patients suspected of having any RMD is the same as in other fields of medicine, namely to thoroughly assess patients by taking a detailed history and performing a comprehensive physical examination. This should be followed by conducting minimal baseline investigations (as previously discussed) for all categories of patients with rheumatic and musculoskeletal diseases (RMDs). Based on these findings, patients can then be appropriately triaged to the relevant specialist, as outlined in Part I, Chapter 4.

Conclusion

In the work-up of patients with rheumatic and musculoskeletal diseases (RMDs), clinical history and physical examination provide 90–95% of the information needed to make a provisional diagnosis. Based on this short list of possible diagnoses, the most relevant and focused investigations are then conducted, including confirmatory tests as well as those that can rule out certain conditions. Conducting a broad array of tests in the hopes of uncovering an uncommon rheumatic disease, without the support of a detailed clinical history and thorough physical examination, will likely result in misleading or irrelevant findings. This practice should be firmly discouraged.

CHAPTER 9

Imaging in Rheumatology

INTRODUCTION

Patients with rheumatic and musculoskeletal diseases (RMDs), especially those with multisystem involvement, often require a multidisciplinary approach to care. As rheumatologists, we frequently collaborate with specialists from various fields of internal medicine, such as dermatology, ophthalmology, nephrology, pulmonology, neurology, gastroenterology and hepatology, hematology, obstetrics and gynecology, and others, to ensure comprehensive patient evaluation and diagnosis.

A critical component of this collaborative care is radiology and imaging. Nearly every patient in rheumatology undergoes some form of imaging, making it essential for both primary care physicians and rheumatologists to have a foundational understanding of imaging techniques. This knowledge enables the appropriate selection of tests to diagnose conditions, assess disease severity, and detect related complications.

The level of expertise rheumatologists have in interpreting imaging results can vary. While some develop a deep interest in imaging and achieve proficiency comparable to expert radiologists, most rheumatologists maintain a 'working knowledge' of musculoskeletal imaging. In contrast, primary care physicians are not expected to possess advanced skills in interpreting imaging for RMDs. However, having a basic understanding of which imaging modalities to use for specific RMDs can significantly streamline the evaluation process, ensuring timely referral to a rheumatology specialist.

This chapter aims to outline the essential imaging investigations that can be performed at the primary care level, facilitating more efficient triage to the appropriate specialist for musculoskeletal conditions.

'Choosing Wisely' as Applied to Imaging for Rheumatic and Musculoskeletal Diseases (RMDs)

The American Board of Internal Medicine's (ABIM) 'Choosing Wisely' campaign aims to uphold the core values of medical professionalism by promoting excellence in healthcare. This initiative encourages thoughtful decision-making in diagnostic and management strategies, including medical imaging. In applying the principles of 'Choosing Wisely' to

imaging for RMDs, it is crucial to follow established guidelines that ensure appropriate and efficient use of imaging technologies.

Imaging Selection Based on Disease Type and Duration

As discussed in earlier chapters (notably Part I, Chapters 2 to 4), RMDs can be broadly categorised into three groups:

1. **Structural–mechanical damage and deformities** (caused by injuries, developmental abnormalities, or past diseases).
2. **Inflammatory RMDs** (immune-mediated systemic diseases).
3. **Biopsychosocial models of nonspecific pain** (e.g. fibromyalgia).

Each category requires a distinct approach to imaging, as the choice of investigation depends heavily on the type of disease and its duration.

Common Imaging Modalities in Routine Care of RMDs

The most frequently used imaging techniques in RMDs include:

1. **Plain radiography**
2. **Musculoskeletal ultrasound (MSK-US)**
3. **Advanced imaging techniques** such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans.

While many more advanced imaging technologies are rapidly emerging, their discussion falls outside the scope of this book.

Imaging for Patients with 'Structural/Mechanical' Damage, or Developmental Abnormalities in the Musculoskeletal System (that Leads to Degenerative Joint Damage Commonly known as Osteoarthritis)

For the evaluation of this group of disease, by-and-large osteoarthritis, **plain radiographs** are typically sufficient at the primary care level. The commonest joint to be affected in osteoarthritis (OA) is the knee joint. As a general rule, plain radiographic evaluation of the weight-bearing joints (knee, hip, spine), it is important to instruct the radiographer that the radiograph should be taken with the joint in a weight-bearing position, where applicable. For instance, if evaluating knee pain, likely due to osteoarthritis, the radiograph must be performed with the patient standing. The same applies when assessing the hip or spine for possible osteoarthritic degenerative changes.

Of course, if the clinical diagnosis suggests generalised primary osteoarthritis involving the finger or wrist joints, weight-bearing does not apply. **Advanced imaging modalities, such as computed tomography (CT) or magnetic resonance imaging (MRI), are generally not required at the primary care level for this group of conditions**. Typical examples of osteoarthritis of knee with marginal osteophytes, 'tibial spiking' and narrowing of the medial compartment of knee is shown in **Fig. 9.1**.

Primary nodular osteoarthritis also involves distal interphalangeal joints with loss of joint space and marginal osteophytes clinically felt as nodules around these joints as shown in **Fig. 9.2**.

One condition that closely mimics osteoarthritis is calcium pyrophosphate dihydrate deposition disease (CPPD or pseudogout), which will be discussed later. Imaging guidelines for diagnosing CPPD are also outlined in subsequent sections.

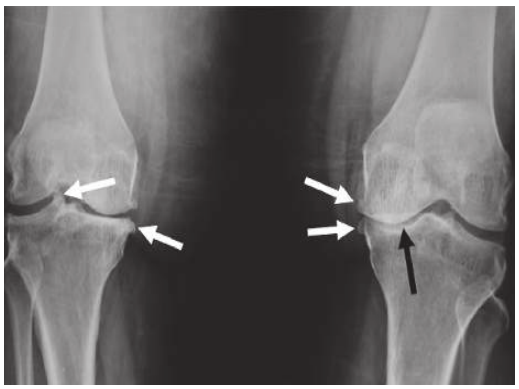


Fig. 9.1: Primary osteoarthritis of the knees. Note the marginal osteophytes and 'tibial spiking' (white arrows) and narrowed medial compartment (black arrow)

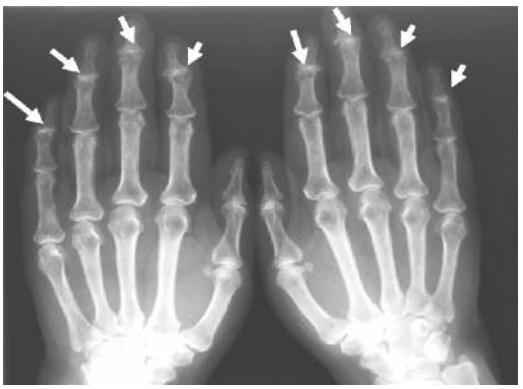


Fig. 9.2: The involvement of distal interphalangeal joints in primary osteoarthritis. Note the loss of joint space and the formation of marginal osteophytes

Inflammatory Joint Diseases

For patients presenting with clinical features of inflammatory polyarthritis, such as rheumatoid arthritis (RA), the only imaging investigation typically needed at the primary care level is point-of-care ultrasound (POCUS) examination of the affected joints. However, it is important to note that POCUS requires considerable expertise, with a steep learning curve. The quality of the results depends largely on the sensitivity of the ultrasound probe and the skill and experience of the ultrasonologist. Therefore, unless the operator is a trained musculoskeletal (MSK) ultrasonologist, the utility of this technique may be limited, and it may not be advisable to perform it in such cases.

The role of POCUS in assessing joints and surrounding soft tissues has gained significant importance in recent years. Studies on patients with RA have demonstrated that in the so-called 'pre-clinical stage,' POCUS can detect synovitis in tendon sheaths around the wrists, and bursitis in intermetatarsal bursae, as shown in **Fig. 9.3A and B**. Early detection can facilitate prompt treatment, preventing joint damage that often occurs when treatment is delayed.

Magnetic resonance imaging (MRI) can also detect early inflammatory synovitis, but the lower cost and accessibility of POCUS make it a more practical choice at this stage. While plain radiographs of the hands and feet are often ordered routinely, they provide limited diagnostic value in early RA. However, they do serve as a baseline for future follow-up radiographs, helping to monitor progression of erosion(s) and joint damage. Grossly deformed joints of the hands are shown in **Fig. 9.4**.

Inflammatory Joint Diseases other than RA

Spondyloarthritis Group of Joint Diseases

Plain radiographs of the spine and pelvis, aimed at evaluating the vertebrae, intervertebral disks, and sacroiliac joints, are commonly performed at the primary care level in such patients. However, except in advanced stages where significant damage is evident, plain radiographs offer limited information in the early stages

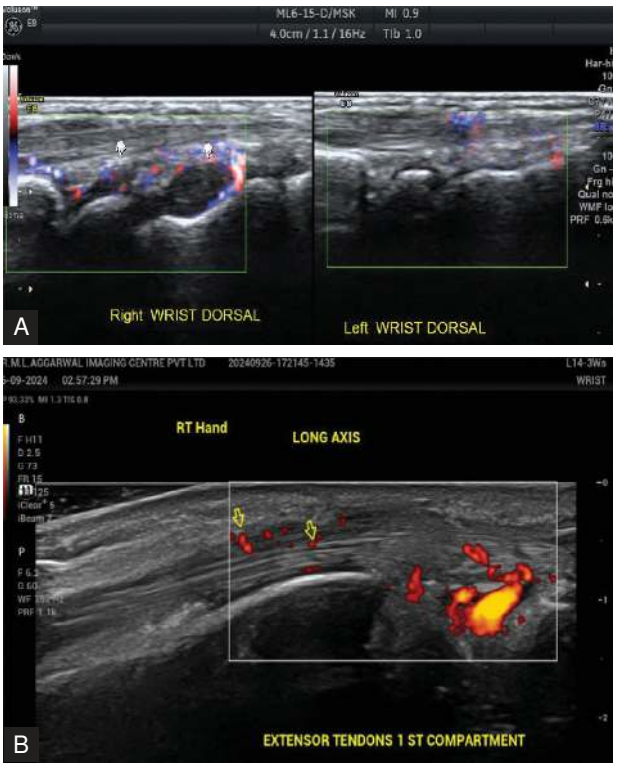


Fig. 9.3A and B: (A) POCUS of the tendons around the wrists in a patient with 'arthralgias suspicious for arthritis' (e.g. preclinical stage of rheumatoid arthritis) reveals the presence of power Doppler signals in and around the tendons, accompanied by thickened hypoechoic tissue in the tendon sheath, indicating inflammatory tenosynovitis. In cases where clinical assessment alone may not reliably confirm inflammation in the tendon sheath, POCUS serves as an early and objective tool to detect and quantify the presence of inflammatory changes. (*Courtesy:* Dr Raghav Aggarwal, Dr ML Aggrawal Imaging Center, New Delhi.) (B) POCUS of the dorsal aspect of the wrist joint reveals synovial hypertrophy, visible as hypoechoic tissue within the radiocarpal and intercarpal joints. These findings support the clinical suspicion of inflammatory synovitis in a patient with early-stage inflammatory arthritis (e.g. rheumatoid arthritis). (*Courtesy:* Dr Raghav Aggarwal, Dr ML Aggrawal Imaging Center, New Delhi.)

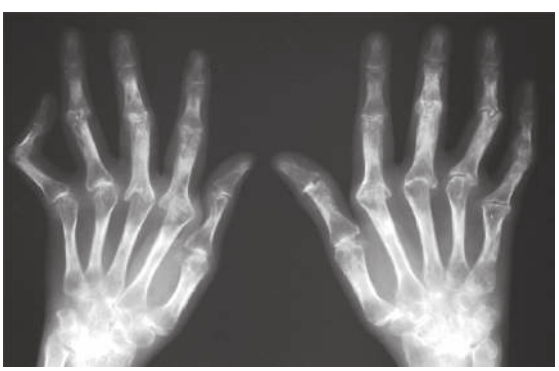


Fig. 9.4: Plain radiograph of the hands in a patient with very late RA showing deformities and extensive erosions, loss of joint space and subluxation in metacarpophalangeal. Proximal interphalangeal joints and the wrist joints

of the disease. Therefore, routine imaging at the primary care level is not necessary. Advanced imaging techniques, such as MRI (especially STIR MRI), low-dose CT, and other newer modalities, should be reserved for specialists, with the rheumatologist coordinating with an expert musculoskeletal radiologist to determine the appropriate tests. Plain radiographs showing changes of very late patients with ankylosing spondylitis is given in **Fig. 9.5**.

Figure 9.6A and B shows the MRI findings typically seen in patients with axial spondyloarthritis.

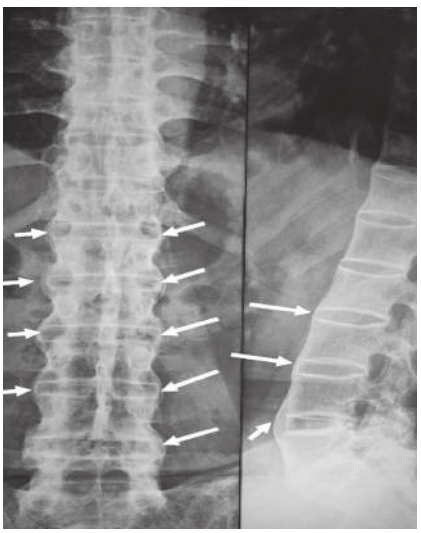


Fig. 9.5: Classical 'bamboo spine'. Plain radiograph of spine in a patient with ankylosing spondylitis (now called axial spondyloarthritis) of long duration. Note the fine calcified lateral, anterior and posterior spinal ligaments with classical syndesmophytes (white arrows)

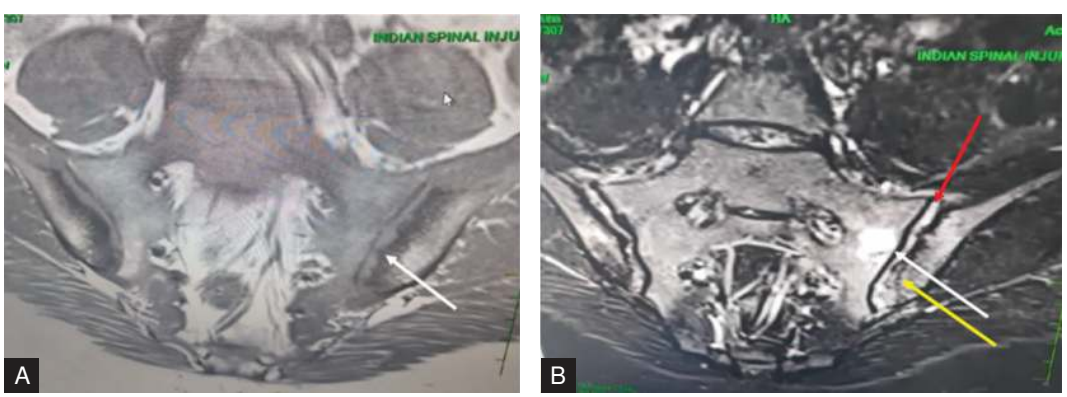


Fig. 9.6A and B: (A) MRI in a patient with axial spondyloarthritis. T1-weighted image reveals iso- to hypodense signal in the subarticular region of both the sacroiliac joints; white arrow shows subarticular erosions. (*Courtesy:* Dr Anita Agarwal, Dr Niti Bhatwal, and Dr Shriram Garg, ISIC, New Delhi.) (B) MRI in a patient with axial spondyloarthritis with active sacroiliitis. T2 fat suppressed image. Red arrow shows effusion in sacroiliac joint, white arrow shows bone marrow oedema, and yellow arrow shows erosions with minimal oedema. (*Courtesy:* Dr Anita Agarwal, Dr Niti Bhatwal, and Dr Shriram Garg, ISIC, New Delhi.)

Connective Tissue Diseases (also known as the 'ANA-positive' Group of Diseases; or 'Anti-cell Antibody' Group of Diseases)

Plain radiographs have a minimal role in the diagnostic evaluation of this group of diseases, except in cases where pleural or lung involvement is clinically suspected. In such instances, the imaging of choice is high-resolution computed tomography (HRCT). An example of the involvement of the lungs in a patient with systemic sclerosis is given in **Fig. 9.7**.

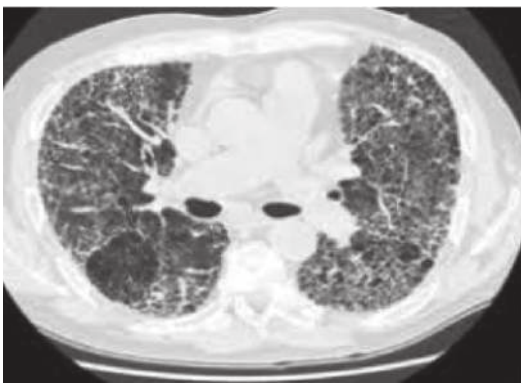


Fig. 9.7: CT findings of interstitial pneumonia in the lungs a patient with systemic sclerosis

Other Miscellaneous Inflammatory Joint Diseases

One example is sarcoidosis-related joint disease, particularly its acute form known as Lofgren syndrome, which presents with ankle arthritis of short duration. The clinical presentation of this syndrome is usually so distinctive that imaging investigations are generally not required. However, some physicians may opt for a plain chest radiograph, which can reveal the characteristic bilateral hilar lymphadenopathy of sarcoidosis as shown in **Fig. 9.8**.

Although there may be other uncommon situations where plain radiographs are helpful, a detailed discussion of such conditions is beyond the scope of this book.

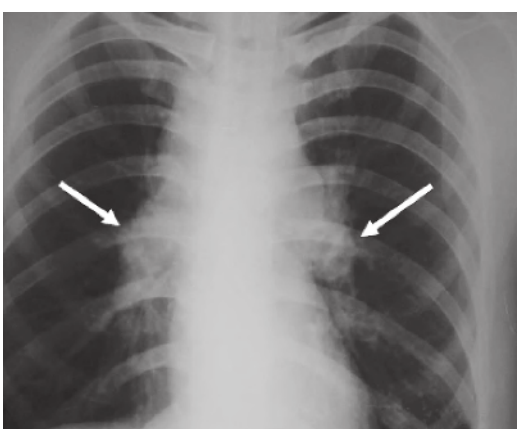


Fig. 9.8: Plain radiograph of chest showing bilateral hilar lymphadenopathy in a patient with an acute form of sarcoidosis called Lofgren syndrome

Systemic Vasculitides

Joint involvement is not a predominant feature of systemic vasculitides, although in small vessel vasculitis, joint symptoms may mimic those of RA. However, plain radiographs do not provide useful diagnostic information in these cases and should not be performed. The only exception is lung parenchymal involvement where plain chest radiograph would reveal bilateral asymmetrical lesions, as shown in **Fig. 9.9**.

The evaluation of systemic vasculitides often requires advanced imaging techniques, such as ultrasound, MRI, or ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT), which should be left to specialists experienced in diagnosing and managing these diseases.

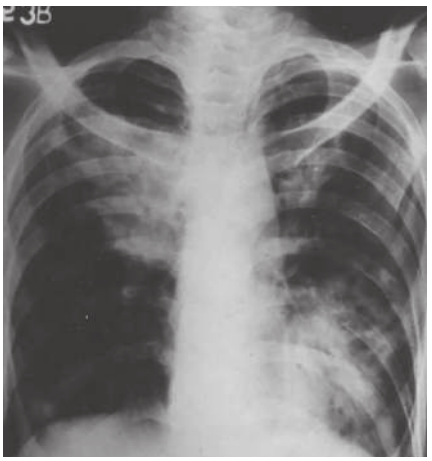


Fig. 9.9: Plain radiograph of lung involvement in a patient with granulomatosis with polyangiitis (GPA). Note the asymmetrically distributed soft fluffy parenchymal shadows, often seen in patients with this disease

Crystal Arthropathies

The traditional method for diagnosing crystal arthropathies involves examining joint or tissue fluid for the presence of crystals using polarised light microscopy (*see* Part 1, Chapter 8). However, this investigation requires both expertise and specialised equipment, namely a polarised light microscope. Visualising monosodium urate (MSU) crystals, which cause gout, is relatively straightforward, even at low magnification. Consequently, this method of MSU identification is considered the 'gold standard' for the definitive diagnosis of gout. An example of the appearance of MSU under polarised light microscopy is given in **Fig. 9.10**.

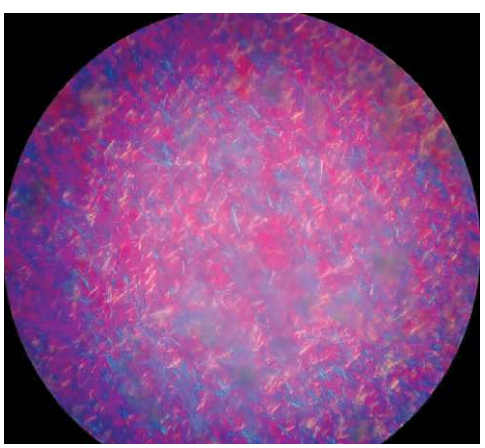


Fig. 9.10: Microphotograph of centrifugally enriched synovial fluid from the knee of a patient with gout showing small pin-like crystals of monosodium urate (MSU) visualised under a compensated polarised light microscope. MSU crystals show strong negative birefringence, i.e. appear *yellow* (or *blue*) when the MSU crystal is aligned *parallel* or *blue* when aligned *perpendicular*, with appear *yellow* when the MSU crystal is aligned parallel (or *perpendicular*) with the polarisation axis blue when at right angle to the axis

In contrast, calcium pyrophosphate (CPP) crystals are smaller and require oil-immersion microscopy under polarised light for accurate identification. Recognising these crystals demands an experienced examiner who can confirm the presence of CPP crystals with certainty. Due to these technical challenges, alternative methods for diagnosing calcium pyrophosphate deposition disease (CPPD) have been suggested. One such indicator is the presence of chondrocalcinosis, or calcification in the joint cartilage, which suggests CPPD, particularly in joints like the knee or hip.

Another advanced imaging technique, dual-energy computed tomography (DECT), can also detect crystals, offering an alternative to polarised light microscopy. However, DECT requires specialised equipment that is not routinely available in most radiology departments. Furthermore, this method is costly and may not be accessible for many patients.

Increasing Importance of Ultrasonic Examination in Rheumatology

Advancements in musculoskeletal (MSK) ultrasound have progressed rapidly, making it an indispensable extension of the rheumatologist's clinical examination, with much greater sensitivity and precision. MSK ultrasound is now the primary tool for the early detection of synovitis in inflammatory arthritis, offering precise localisation of pain and effectively distinguishing between inflammatory and noninflammatory conditions. At the primary care level, it is invaluable for triaging patients to the appropriate specialist (as described in Part I, Chapter 4). Additionally, it facilitates precise lesion-guided injections of depot glucocorticoids and other minor interventions.

A recent addition to the remarkable utility of ultrasonic examination (US) of the joints has been in suspected crystal deposition joint diseases like gout and calcium pyrophosphate disease (CPPD). The modality of US has dramatically simplified the diagnosis of crystal arthropathies making the cumbersome polarised light microscopy (PLM), almost redundant. US shows characteristic features like hyperechoic deposits (double contour sign in gout) and calcifications (CPPD) in crystal arthropathies. Further, the dynamic assessment of the double contour (DC) sign on US can also differentiate CPPD from MSU as shown in **Fig. 9.11**.

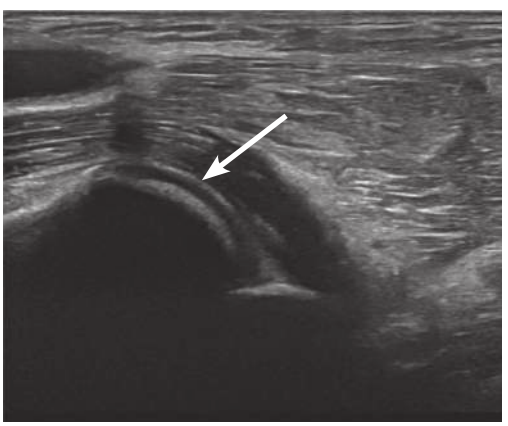


Fig. 9.11: Double contour sign (white arrow) in gout

The growing role of ultrasound in the diagnosis, prognosis, and monitoring of patients with various forms of systemic vasculitis is transforming the management of these conditions. Recent advancements include its use in diagnosing Behçet's disease by demonstrating thickening of the large vein walls, assessing characteristic changes in parotid gland enlargement in Sjögren's syndrome, evaluating the extent and severity of skin involvement in systemic sclerosis, and diagnosing and monitoring interstitial lung disease.

These are just a few examples of the expanding applications of this rapidly evolving technology. A detailed description of the use of MSK ultrasound is beyond the scope of this book.

Osteoporosis Assessment with Dual X-ray Absorptiometry (DXA) Scan

Osteoporosis is of interest to several medical specialties, including rheumatology. Its relevance in rheumatological practice is particularly notable in elderly patients, especially women within the first five years after menopause. Additionally, osteoporosis resulting from incorrect dosing or prolonged, inappropriate glucocorticoid (GC) use is commonly encountered in routine rheumatology practice. Although rare, certain clinical situations may genuinely require extended GC therapy.

In addition to a thorough clinical evaluation for potential osteoporosis, an objective assessment can be made, and follow-up done using a dual-energy X-ray absorptiometry (DXA) scan. Representative reports of DXA scan are provided in **Fig. 12A and B**.

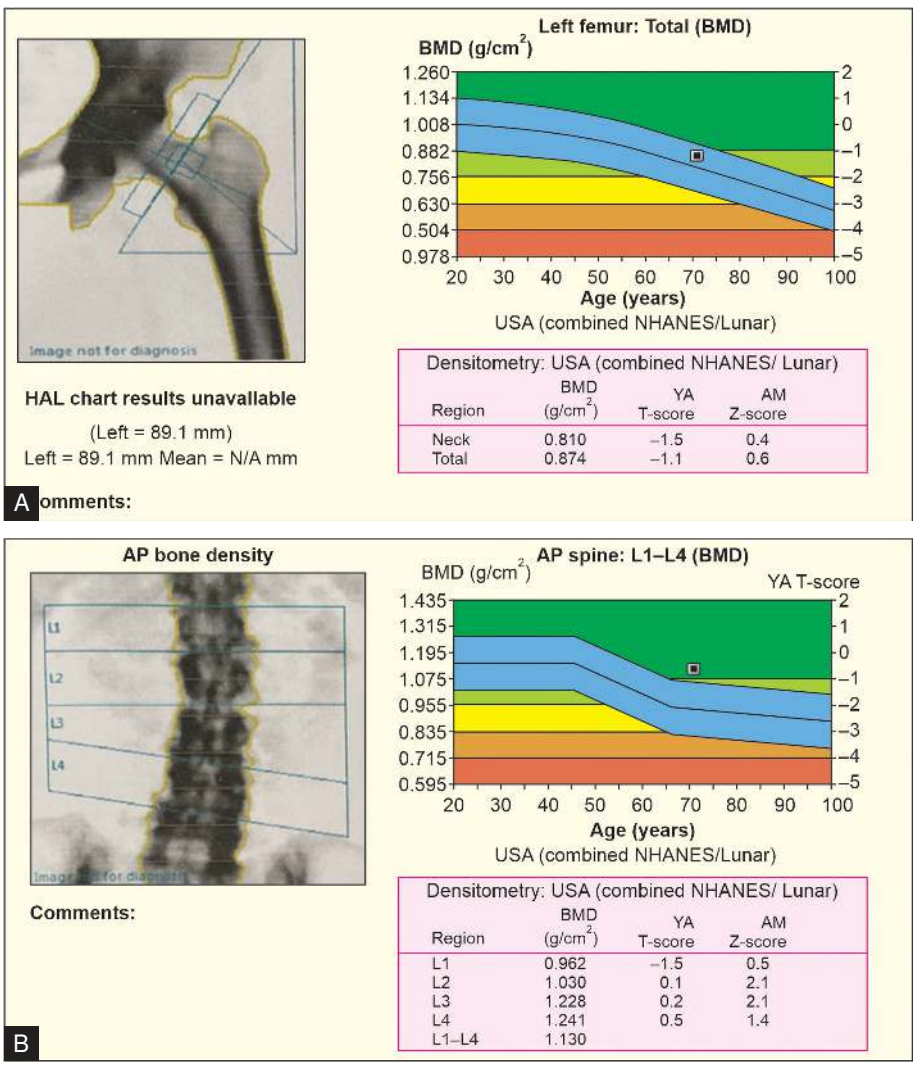


Fig. 9.12A and B: (A) Photograph showing report of DXA scan in a patient. It shows normal bone density at the femoral neck). (B) Photograph showing DXA scan report of spine. This patient has degenerative (osteoarthritis) spinal disease, a condition that produces osteosclerosis in subchondral bone. It gives a falsely 'high' bone density report, as in this patient

A well-standardized tool, the fracture risk assessment tool (FRAX), is available online (https://frax.shef.ac.uk/FRAX/tool.aspx?country=51). When DXA values are entered into the FRAX calculator, it automatically estimates an individual's fracture risk. This information is crucial for guiding treatment decisions related to osteoporosis, if necessary.

Positron Emission Tomography (PET) Scan

PET scanning uses radioactive material to detect cancers and some other unusual proliferative diseases like IgG4-related disease (IgG4-RD), an example of which is given in **Fig. 9.13**.

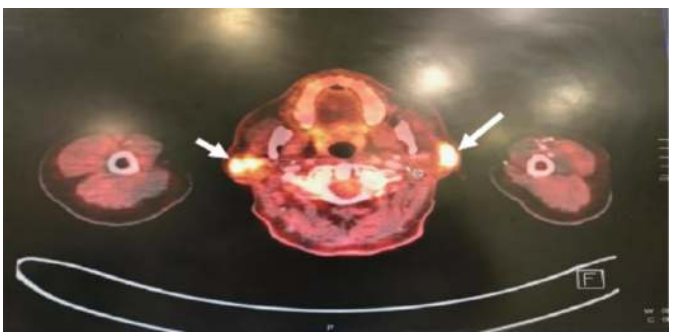


Fig. 9.13: Higher uptake of the radioactive tracer in both the parotid glands (arrows) aiding the clinical diagnosis of IgG4-related disease involving parotid glands

Summary

The introduction of new drugs for the treatment of inflammatory disorders has significantly improved patient outcomes.

- Imaging plays a critical role in enabling earlier diagnosis of these conditions.
- Early diagnosis and timely treatment can often prevent the progression to debilitating disease manifestations.
- Optimal imaging strategies are best achieved through collaboration between rheumatologists and radiologists, ensuring tailored examinations that guide effective treatment.

Part II

Inflammatory Rheumatic and Musculoskeletal Diseases

1. Rheumatoid Arthritis
2. Spondyloarthritis (Ankylosing Spondylitis)
3. Connective Tissue Diseases
4. Systemic Vasculitides
5. Crystal Arthropathies

6i. Septic Arthritis
6ii. Chronic Infections in the Joints
6iii. Parainfectious Arthritis
6iv. Reactive Arthritis

7. Uncommon and Rare Rheumatic and Musculoskeletal Diseases (RMDs)
8. Treatment of Rheumatic and Musculoskeletal Diseases (RMDs)

CHAPTER 1

Rheumatoid Arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is the most prevalent chronic inflammatory polyarthritis in humans. The prominence of rheumatology as a specialty is largely attributable to RA's profound impact on patients' health, its severe complications, and the markedly elevated risk of premature mortality, primarily driven by late-stage complications such as atherosclerotic cardiovascular disease (ASCVD).

Epidemiology of RA

The point prevalence of RA in the general population is approximately 0.5–1%, making it the most common inflammatory polyarthritis in the community. While RA can occur at almost any age and affect both sexes, it is 2–4 times more common in females, with a typical onset during middle age (30–60 years). In the paediatric population, a similar condition exists and is classified under the broader category of juvenile idiopathic arthritis (JIA).

Understanding the nature of inflammation in RA is fundamental to developing an effective treatment approach: Historically, RA was considered a relatively "benign" disease, which led to the conservative treatment philosophy of "go low and go slow," often referred to as the **pyramidal approach** to RA management. This strategy, widely accepted during the early to mid-20th century, was based on the mistaken belief that RA progressed slowly, and that aggressive treatment poses greater risks due to medication side effects.

However, this perception underwent a dramatic shift in the 1980s and 1990s with emerging evidence revealing the aggressive and destructive nature of RA inflammation from the very onset of clinical disease. In a seminal 1990 paper, the renowned American rheumatologist Dr Daniel McCarty famously remarked: **'Suppress rheumatoid inflammation early and leave the pyramid to the Egyptians'**. This statement underscored the need for early and decisive intervention, as peak inflammatory activity was shown to occur within the first few weeks to months of disease onset.

Echoing this modern approach, Dr Rohini Handa, a leading rheumatologist from Indraprastha Apollo Hospital, New Delhi, has emphasized the "3-T" philosophy for RA treatment: "**Treat early**," "**Treat-to-target**," and for those not responding adequately to standard DMARDs, use "**Targeted Therapy**." These principles highlight the importance of early diagnosis, goal-oriented treatment, and the judicious use of advanced therapies to optimise patient outcomes.

Figure 1.1 depicts the rapidity with which the severity of inflammation reaches its peak within a very short period from the onset of the clinical disease, the time when the clinical symptoms are not very severe, fluctuating and shifting in nature.

If not treated adequately during this critical early phase, the groundwork for irreversible joint damage is established, resulting in progressive erosion and the eventual development of characteristic deformities, even as the intensity of inflammation declines over time **(Fig. 1.1)**. This pivotal early period, before the onset of relentless joint destruction, is now recognised as the '**window of opportunity**'. It represents a crucial timeframe when timely and effective intervention can significantly alter the disease trajectory, preventing long-term damage and improving overall outcomes. **Figure 1.2A and B** depicts the same principle, namely delayed treatment leads to structural damage as opposed to early aggressive treatment that prevents joint damage and deformities.

Key Insights on Early Rheumatoid Arthritis Progression

- **Inflammation peaks in the earliest stage:** Inflammation is most intense in the initial phase of RA, often presenting with minimal clinical symptoms.
- **Rapid joint destruction in early disease:** Joint erosions and cartilage destruction, characterised by joint space narrowing, occur at their fastest rate in the earliest stages of RA.

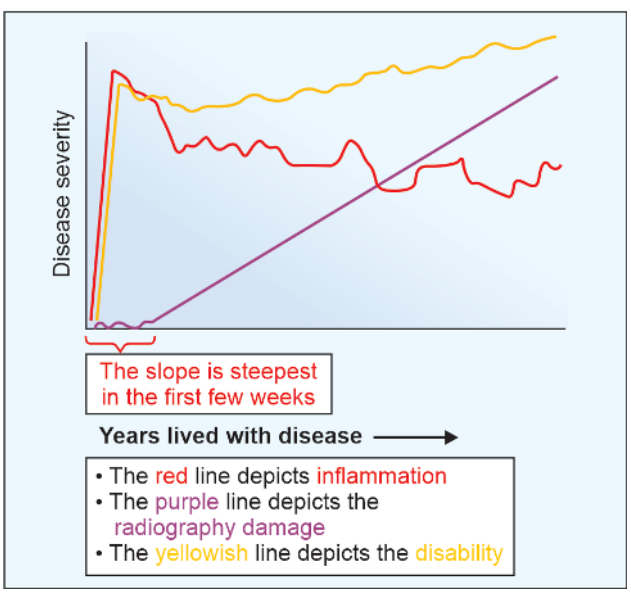


Fig. 1.1: Illustrates the nature of inflammation in rheumatoid arthritis (RA) as described above

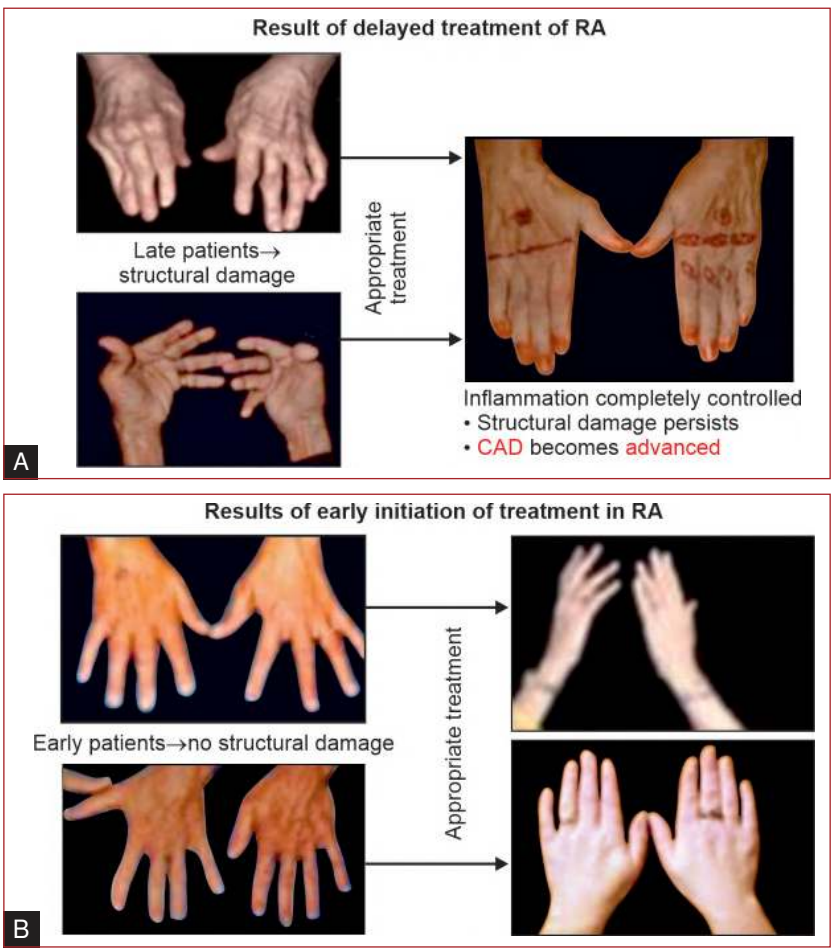


Fig. 1.2A and B: (A) Effect of delayed treatment that leads to structural damage and deformities; (B) Effect of early appropriate treatment that prevents joint damage and deformities. CAD: Coronary artery disease

- **If not treated according to international guidelines complete joint and destruction occurs in 2–3 years:** If left untreated, joint damage often reaches completion within the first 2–3 years of disease onset.
- **Functional decline accrued during this period is irreversible:** Once significant functional deterioration occurs, reversing it becomes exceedingly challenging, making early intervention critical.

Consequently, the modern approach to RA management emphasises **early diagnosis**, **rapid assessment of disease activity** and severity, and the prompt initiation of highly effective disease-modifying anti-rheumatic drugs (DMARDs) to achieve **remission or low disease activity**. This strategy, known as the '**treat-to-target**' approach, aims to halt disease progression and minimise long-term joint damage. **Figure 1.3** illustrates the fundamental philosophy underlying the current understanding and management of RA. It graphically depicts that if the treatment is delayed, there is much more joint damage as compared to treatment started early in the course of the disease.

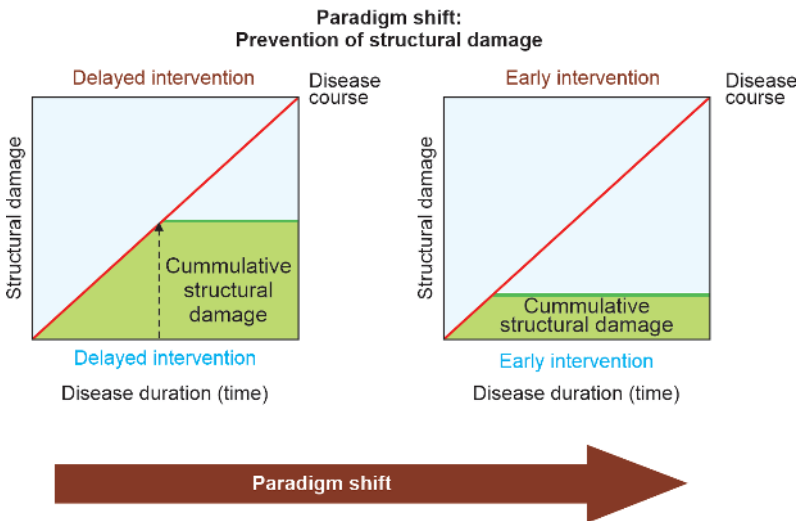


Fig. 1.3: The graph illustrates how delayed treatment in rheumatoid arthritis leads to significantly greater cumulative structural damage, akin to the 'compound interest'. In contrast, early and appropriate treatment, aligned with international RA management guidelines, effectively minimises long-term joint damage. (*Courtesy:* Retd. Lt. General Ved Chaturvedi, Senior Consultant Rheumatologist, Sir Ganga Ram Hospital, New Delhi.)

Clinical Features of RA

The following description succinctly and effectively captures the typical clinical presentation of early rheumatoid arthritis (RA).

- **Initial presentation:** RA often begins with **pain, swelling,** and **stiffness** in small and medium-sized joints (e.g. fingers, wrists, and toes), which are worse in the morning and after periods of inactivity.
- **Chronicity:** Symptoms lasting for more than 6 weeks should prompt consideration of a **chronic inflammatory rheumatic disease**.
- **Functional impact:** Patients may report difficulties in performing daily tasks that require **grip strength** (e.g. making dough, kneading, or using a rolling pin) due to hand and wrist involvement.
- **Morning stiffness:** A classic feature, with **prolonged stiffness upon waking**, often affecting mobility and contributing to **difficulty getting out of bed**.
- Being a **systemic inflammatory disease**, RA is characterized by **stiffness after periods of inactivity that typically starts to improve within about an hour of movement—a hallmark feature of inflammatory RMDs**, including RA (discussed in detail in Part I, Chapter 3). The characteristic joints involved in RA are the proximal interphalangeal (PIP) joints of the hands, metacarpophalangeal (MCP) joints, wrists, elbows, shoulders, knees, ankles, midfoot joints, and the metatarsophalangeal (MTP) joints. The symmetrical involvement of the joints in patients with RA is pictorially shown in **Fig. 1.4**.
- Hip involvement is uncommon, and the spine and sacroiliac joints are generally spared in RA. This framework should help a primary care physician recognise early RA and facilitate timely referral or management.

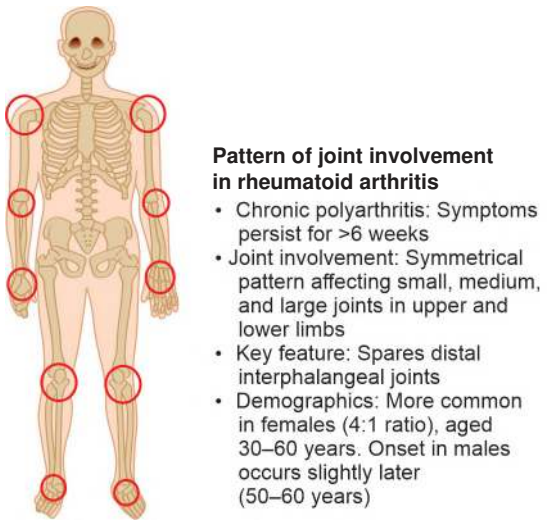


Fig. 1.4: Typical symmetrical joint involvement in the extremities, with the notable sparing of the distal interphalangeal (DIP) joints

Hip involvement is uncommon, and the spine and sacroiliac joints are generally spared in RA. This framework should help a primary care physician recognise early RA and facilitate timely referral or management.

This can be summarised for primary care physicians as follows:

- **Joint involvement in RA:** Specific groups of small joints (e.g. PIPs, MCPs, MTPs), wrist, or midfoot joints) are each considered as a **single joint unit**.
- **Diagnostic clue:** The involvement of at least **three joints** (counting these joint units) with a **symmetrical pattern** (e.g. affecting the same joint on both sides or symmetrical involvement in different small joints) persisting for more than 6 weeks is highly suggestive of RA.
- **Example:** Symptoms in the right PIP of the index finger, left PIP of the middle finger, and the right wrist are sufficient to establish a clinical suspicion of RA.
  This clarity on joint grouping and symmetrical pattern recognition aids in early diagnosis and appropriate management.
- **Joints rarely involved in RA:** The **distal interphalangeal (DIP) joints** of the fingers and the **hip joints** are typically **not affected** in rheumatoid arthritis. Their involvement should prompt consideration of other conditions, such as osteoarthritis or psoriatic arthritis.
- **Notable exception:** The **atlantoaxial joint** in the cervical spine may be involved, presenting as **neck pain** and, in severe cases, risking **spinal cord compression** and serious neurological complications.

This distinction is essential for differentiating RA from other joint disorders and for identifying potentially serious complications.

Photographs provided here illustrate the joints typically affected in RA, highlighting the deformities and complications that can develop if the disease is not correctly diagnosed and treated promptly after the onset of symptoms. Note the presence of nodules on the extensor surfaces of the forearms, which may appear in

untreated patients during the later stages of the disease. Some examples of early and late hand-finger joint deformities along with radiographic changes in patients with RA, are given in **Figs 1.5 to 1.13**.

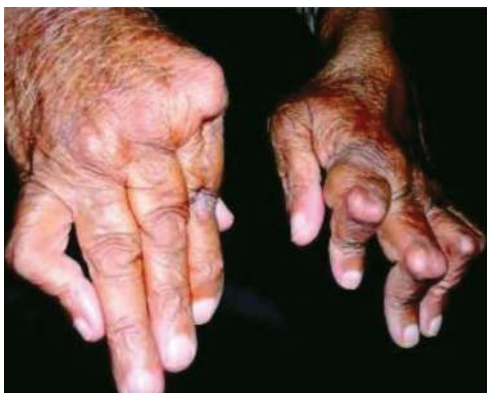


Fig. 1.5: Boutonniere deformity of several fingers in a patient with late RA

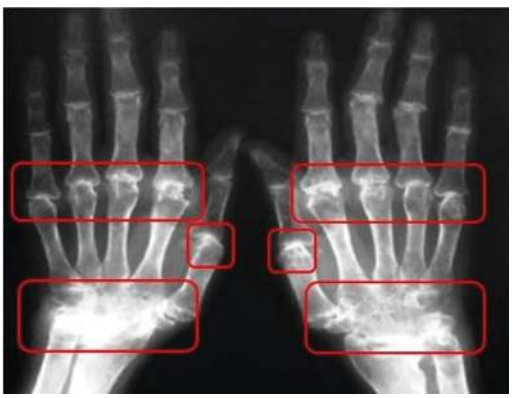


Fig. 1.6: Radiographic changes in late RA—note the joint erosions and damage of the articular surface of several metacarpophalangeal joints; advanced damage, destruction, subluxation and ankylosis of the wrist joints (shown as red boxes)

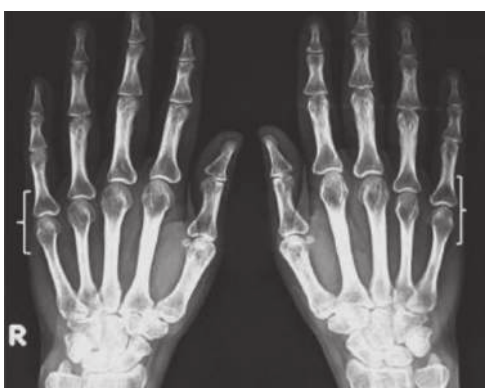


Fig. 1.7: Radiographic changes in early RA—note the periarticular osteopenia (region shown adjacent to the brackets)

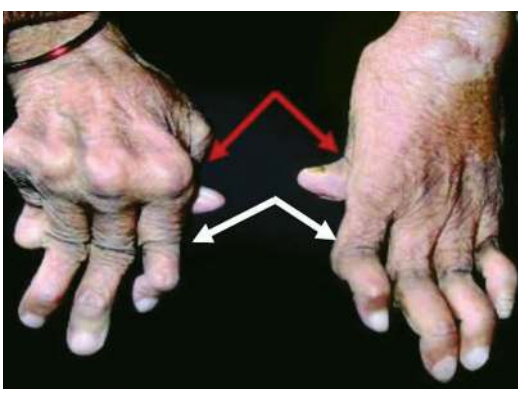


Fig. 1.8: 'Swan-neck' (white arrows) and 'Z' (red arrows) deformities in the finger-thumb joints in a patient with late RA

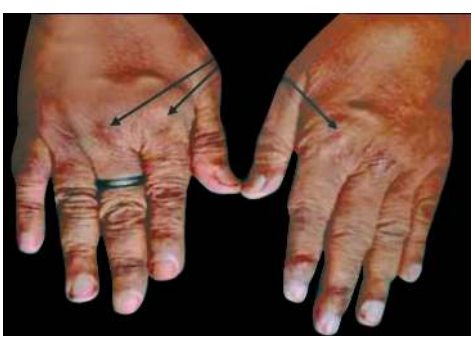


Fig. 1.9: Swellings in some of the metacarpophalangeal joints (arrows) in a patient with early rheumatoid arthritis

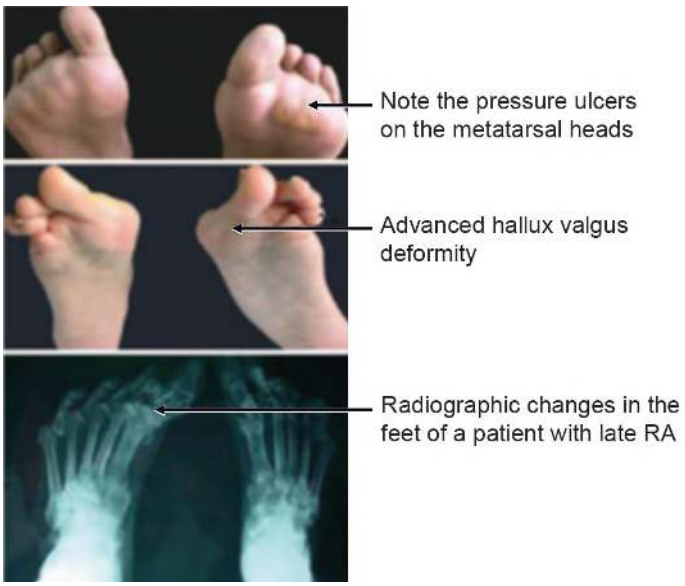


Fig. 1.10: Toe deformities and damage in patients with RA

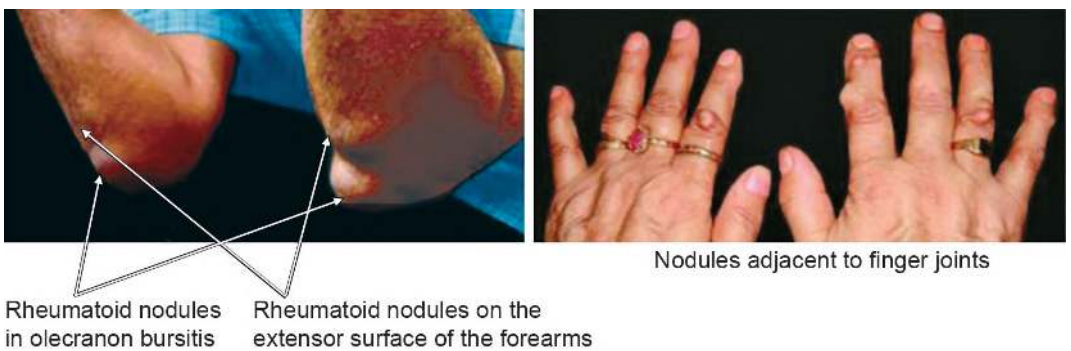


Fig. 1.11: Rheumatoid nodules

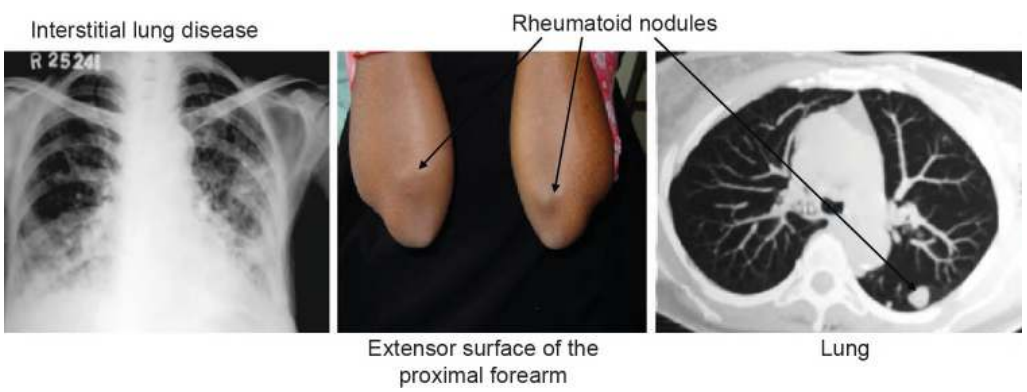
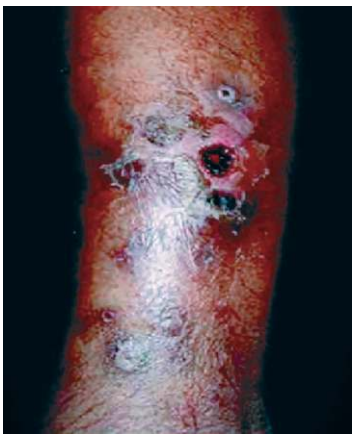


Fig. 1.12: Extra-articular manifestations of RA



Cutaneous and vascular features
Vasculitis can vary from:

- Relatively benign *nail-fold infarcts* to:
  - Widespread *cutaneous ulceration* and *skin necrosis.*
  - *Pyoderma gangrenosum*
  - Rarely, involvement of *medium-sized arteries* can lead to:
    - *Mesenteric*
    - *Renal*
    - *Coronary artery occlusion*

Fig. 1.13: Pyoderma gangrenosum

Making a Diagnosis of RA

Clinical Characteristics

This can be summarised for a primary care audience as follows:

- **Diagnostic features:** Suspect RA in adults with a history of **>6 weeks of bilaterally symmetrical involvement** of small and medium-sized joints (e.g. PIPs, MCPs, and wrists), of **inflammatory nature** (presenting with **pain, swelling,** and **stiffness**.
- **Minimum requirement:** Diagnosis requires involvement of at **least 3 joints**, with **symmetry in at least one joint** (e.g. 2nd MCP on the right hand, 3rd MCP on the left hand, and one wrist).
- **Functional impact:** Symmetrical joint involvement often leads to **difficulty using** (e.g.) **hands** for tasks requiring a firm grip.
- **Progression without treatment:** In advanced, untreated cases, patients develop characteristic **joint deformities** and may present with visible **rheumatoid nodules** (*see* figures above).

Laboratory Investigations in Patients Suspected of RA

The key points for primary care physicians regarding laboratory testing in suspected RA can be summarised as follows:

- **Judicious use of tests:** Order lab investigations **selectively** based on the most likely clinical diagnosis. Avoid broad panels to 'rule out' unlikely rheumatic conditions.
- **Essential baseline tests:** For a provisional diagnosis of RA, focus on basic tests to confirm **systemic inflammation** and assess overall health, such as:
  - Complete blood count (CBC)
  - Erythrocyte sedimentation rate (ESR)
  - C-reactive protein (CRP)
  - Liver and renal function tests
- **Rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA):** Routine testing for RF and ACPA is **not recommended at the primary care level** due to:
  - Limited sensitivity and specificity
  - Potential for **false positives** in healthy individuals, particularly in the elderly or those with a family history of RA.

- **Seronegative RA:** Up to **20–30%** of RA patients may be **negative for both RF and ACPA**. These are classified as **seronegative RA**, and typically have a better prognosis.

This approach minimises unnecessary testing, reduces confusion, and ensures that the clinical presentation remains the cornerstone of RA diagnosis.

Mimics of RA

Several systemic inflammatory diseases can present with **inflammatory arthritis** resembling RA, making initial diagnosis challenging. These include:

1. **Systemic connective tissue diseases** (e.g. lupus, systemic sclerosis, Sjögren's disease, inflammatory myopathies, overlap syndromes).
2. **Systemic vasculitides**
3. **Peripheral spondyloarthritis** (e.g. psoriatic arthritis, reactive arthritis, arthritis associated with inflammatory bowel disease)
4. **Chronic tophaceous gout**
5. **Miscellaneous conditions** (e.g. sarcoidosis, relapsing polychondritis, inflammatory osteoarthritis, and rare diseases, e.g. multicentric reticulohistiocytosis, storage diseases).
   - **Diagnosis requires expertise:** The *characteristic features* of these conditions may only appear *during follow-up* visits. A rheumatologist's detailed history and examination can reveal *extra-articular symptoms* or organ involvement, providing critical diagnostic clues.
   - **Specialised investigations:** Further workup may require *specific tests* or *tissue biopsies* of affected organs, necessitating referral.
   - **Referral is key:** Refer suspected cases to a *rheumatologist* for *definitive diagnosis* and appropriate management.

This approach helps avoid misdiagnosis and ensures accurate treatment for patients with complex inflammatory diseases.

Management of RA

The management of RA has seen dramatic advancements since the mid-1990s, when four high-quality randomized controlled trials demonstrated the high efficacy of low-dose methotrexate (LD-MTX). The ability of low-dose methotrexate (LD-MTX) to swiftly control inflammation and safeguard against long-term joint damage has firmly established it as the cornerstone of the treatment of RA. Due to its high efficacy in a substantial proportion of patients, LD-MTX has earned the nickname "anchor drug" for the treatment of rheumatoid arthritis. (For further details of LD-MTX, the reader may like to read Part II, Chapter 8 of this book.) Over period of time several additional drugs have been developed for the treatment of rheumatoid arthritis with varying effectiveness in controlling inflammation and preventing joint damage. Collectively, these medications are known as disease-modifying anti-rheumatic drugs (DMARDs).

A comprehensive discussion of the various classes of DMARDs, including their efficacy, dosage, adverse effects, and clinical applications, lies beyond the scope of this

book. However, some of these aspects are covered in Part II, Chapter 8 which readers are encouraged to consult for further details.

As emphasized earlier in this chapter, the severity of inflammation during the first few months after disease onset plays a crucial role in determining long-term outcomes in RA. Therefore, based on the clinical features outlined above, primary care physicians must be prepared to suspect RA, confirm systemic inflammation through basic investigations (such as ESR and CRP), and promptly refer patients to a rheumatologist for specialized care and management. Early intervention remains key to improving disease prognosis and preventing irreversible joint damage.

For a primary care physician, the modern approach to treating rheumatoid arthritis can be succinctly summarised as follows:

1. **Early diagnosis and prompt treatment:** Early identification and initiation of therapy, ideally within the first few months of symptom onset, is critical to prevent irreversible joint damage.
2. **Use of DMARDs:** Start treatment with **conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs)**, typically **low-dose methotrexate** as the first-line agent. csDMARDs are essential for controlling disease activity and halting disease progression.
3. **Treat-to-target strategy:** The goal is to achieve **low disease activity** or **clinical remission**. Monitor disease activity using validated 'instruments' (e.g. 'Disease Activity Score 28' (DAS28), or 'Simplified Disease Activity Index' (SDAI), or 'Clinical Disease Activity Index' (CDAI) regularly (every 1–3 months initially then 6 monthly in stable cases) and adjust treatment until the target is achieved.
4. **Combination therapy options:** If response to methotrexate is inadequate, consider combination therapy with other csDMARDs (hydroxychloroquine, sulfasalazine, leflunomide, iguratimod); or introduce **biologic DMARDs** (like TNF inhibitors, B cell targeted therapy, IL-6 inhibitors) or **targeted synthetic (ts) DMARDs** (e.g. JAK inhibitors).
5. **Individualized approach:** Tailor the treatment based on patient characteristics, comorbidities, and preferences. Use a risk-benefit approach when selecting advanced therapies.
6. **Multidisciplinary care:** Emphasise patient education, physiotherapy, and comorbidity management (e.g. cardiovascular risk, infection prevention with vaccines).
7. **Safety monitoring:** Regularly monitor for adverse effects (e.g. liver, renal function) and must carefully look for any contraindications, especially in the elderly or those with comorbidities.

This structured approach helps to optimise outcomes and improve quality of life for RA patients in a primary care setting.

Summary

Key considerations for summarising modern RA management for primary care physicians include:

- **Critical early treatment window:** The *first 6 months* following symptom onset are critical for influencing long-term outcomes in RA.

- **DMARD initiation:** Initiate *DMARDs immediately* after diagnosis to prevent irreversible joint damage.
- **Treatment paradigm:** The approach is: "*Treat early, treat aggressively, and treat-to-target*" with the aim of achieving *low disease activity* or *remission*.
- **Disease activity monitoring:** Regularly assess disease activity using validated tools such as the (CDAI, SDAI, or DAS-28). Adjust treatment based on internationally accepted definitions of remission and levels of disease activity to ensure optimal patient outcomes.
- **Rheumatologist supervision:** Optimal management should involve a rheumatologist to ensure adherence to the treat-to-target approach and to prevent severe complications.

This approach has significantly reduced the risk of joint deformities, and the incidence of several severe, long-term complications historically associated with RA. These include debilitating joint damage that impairs daily activities, premature atherosclerotic cardiovascular disease, extra-articular organ involvement (such as ocular and pulmonary complications), severe rheumatoid vasculitis, Felty's syndrome, and other health issues stemming from chronic, uncontrolled inflammation. By addressing inflammation early and effectively, the burden of these complications has been markedly alleviated, greatly improving patient outcomes and quality of life.

CHAPTER 2

Spondyloarthritis (Ankylosing Spondylitis)

INTRODUCTION

The spondyloarthritis (SpA) group of conditions is potentially as common as rheumatoid arthritis (RA). However, for reasons not yet fully understood, there is a striking lack of awareness and recognition of SpA at the primary care level. This knowledge gap leads to an average diagnostic delay of nearly nine years before an accurate diagnosis is made. Such delays have profound implications for disease outcomes, as frequently observed by rheumatologists in clinical practice. During this time, irreversible structural damage often accumulates, resulting in lifelong disability and significant physical, psychological, social and financial burdens. Additionally, complications such as premature atherosclerotic cardiovascular disease (ASCVD) further contribute to reduced life expectancy in these patients. Therefore, early identification of SpA and prompt referral to a rheumatologist—akin to the established approach for RA—are essential for achieving effective management and improving long-term outcomes.

Components of the Musculoskeletal System Involvement in SpA

The Spinal Component Called Axial Spondyloarthritis (axSpA)

Spondyloarthritis (SpA) is an umbrella term encompassing a group of related inflammatory joint disorders that primarily target **the spine and associated joints**, where the **sacroiliac joint (SIJ) involvement is central to its identity**. Inflammation of SIJ is called **sacroiliitis**.

Additionally, SpA also causes **inflammatory involvement of other spinal elements** as well as **extra-spinal elements** of the musculoskeletal (MSK) system. These include:

- **Intervertebral disks** and its components.
- **Ligamentous entheses** are the sites where tendons, ligaments, and joint capsules attach to the bone. Inflammation at entheseal sites, called '**enthesitis**', is a hallmark feature of SpA. Enthesitis commonly involves the vertebral bodies, attachment of the **Achilles** tendon to the calcaneus (main cause of heel pain in patients with SpA), other entheseal sites, e.g. plantar fascia, tibial tubercle, sites around the elbow and pelvis (e.g. lateral and medial epicondyle, anterior superior iliac spine, iliac crest, and others).

- Other '**central joints**' (besides SIJ) including the **facet joints**, **atlantoaxial joint** (can result in joint instability, potentially causing clinical manifestations of spinal cord compression), **costovertebral and costosternal** joints causing **chest pain** (that may be confused with heart disease presenting as anginal pain), **restrict chest wall expansion**, causing reduced pulmonary function.
- **Dactylitis**, which is a **diffuse swelling of an entire finger or toe**, giving it a characteristic '**sausage digit**' appearance, often due to inflammation of the joints, tendons, and surrounding soft tissues (highly characteristic of **psoriatic arthritis**).

Inflammatory involvement of the various **elements of the spine**, mentioned above, **typically progresses upwards** from the sacroiliac joints to the lumbar, thoracic, and cervical spine. In some patients (only about 1/3rd of the patients with SpA), chronic inflammation leads to **ossification** of the ligaments (e.g. longitudinal ligaments of the spine), tendons, and intervertebral disks, resulting in a loss of **spinal flexibility** eventual spinal fusion with loss of normal curvatures of spine contributing to the characteristic abnormal spinal deformity leading to the abnormal posture of the affected person. This specific pattern, seen as an bold **result** of untreated/suboptimally treated persistent chronic inflammation is called **ankylosing spondylitis (AS)** (described later).

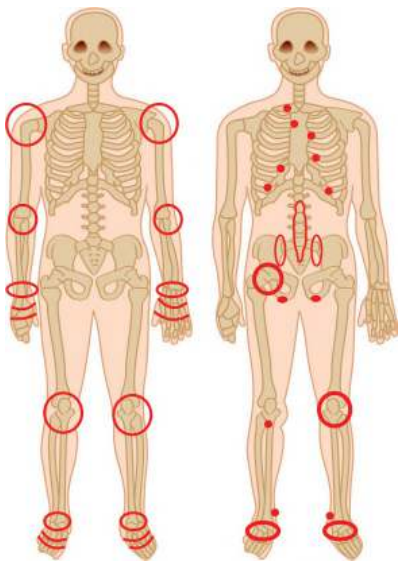
Peripheral Arthritis in SpA

In approximately 40% of patients SpA can involve peripheral joints that has a distinct pattern of involvement which is different from that of rheumatoid arthritis. It often initially presents as monoarthritis (involvement of a single joint), typically affecting the knee or ankle—especially in individuals under 18—and may be misdiagnosed as tuberculous arthritis. It is further characterised by progression into asymmetrical oligoarticular involvement (2, 3 or 4 joints) predominantly "below the waist". Another important feature of the disease is the involvement of the so-called "root joints", such as the hips—often severely affected in individuals with an earlier disease onset (typically before 18 years of age, can result in progressive joint damage functional impairment)—and, less commonly, the shoulders. As the disease advances, additional joints in the lower extremities may become involved, but the pattern generally remains an **asymmetrical oligoarthritis**. Involvement of metatarsophalangeal and interphalangeal joints in toes is also a characteristic feature of the SpA group of diseases, **especially that associated with psoriasis**. Although less common, the upper limb joints, including the shoulders, can also be affected, making their involvement uncommon but not rare. Involvement of the small and medium joints of the arms is distinctly uncommon, serving as a key distinguishing feature from RA. **Figure 2.1** highlights and contrasts the patterns of joint involvement in spondyloarthritis (SpA) and RA.

Primary Versus Secondary SpA

It is also important to distinguish between two categories within the SpA group, namely:

- **Primary SpA:** Occurring independently, without any associated underlying condition.
- **Secondary SpA:** Associated with a pre-existing condition, such as: (a) **Psoriasis** (PSO); (b) **Inflammatory bowel disease** (IBD), including Crohn's disease or ulcerative colitis; (c) **Reactive arthritis** (ReA; a subtype with a triad of acute arthritis, urethritis/



- **Left: Rheumatoid pattern**
  - Peripheral large and small joints
  - Symmetrical involvement
  - Upper and lower segment involvement
  - Spares distal interphalangeal joints
  - Young-middle-aged females; F:M ratio 4:1
- **Right: Spondyloarthritis pattern**
  - Below waist
  - Asymmetrical
  - Sacroiliac joint and spine involvement
  - Enthesitis common
  - Young persons onset ≤45 years of age
  - Male-to-female ratio: ~1:1*

*But 'atypical' presentation in females

Fig. 2.1: Inflammatory polyarthritis—patterns of joint in RA vs spondyloarthritis

cervicitis, and conjunctivitis, which is called '**Reiter's disease**'), typically triggered by a recent gastrointestinal (usually at prepubertal age) or urogenital infection (usually after the age of puberty).

There are 2 additional categories of SpA as follows:

- **'Undifferentiated spondyloarthritis'** (uSpA) is a term used to describe patients who exhibit clinical features suggestive of spondyloarthritis but do not have all the clinical features of well-defined SpA subtypes like AS, psoriatic SpA or reactive SpA. These patients may present with symptoms like inflammatory back pain, peripheral arthritis, enthesitis, or extra-articular manifestations (e.g. uveitis), but the pattern is incomplete or atypical, making it challenging to categorise them into a defined subtype of SpA. Over time, some cases of uSpA may evolve into a more specific subtype, while others may remain undifferentiated.
- **'Enthesitis-related arthritis' (ERA):** It is typically seen in paediatric age group (children and adolescents), predominantly affecting boys. It is a subtype of juvenile idiopathic arthritis (JIA) characterised by inflammation at the entheses—the sites where tendons, ligaments, or joint capsules attach to bone. The most common sites of enthesitis include the Achilles tendon, plantar fascia, and the insertions around the knee.

Key Features of ERA

These include:

- **Peripheral arthritis:** Usually involves the large joints of the lower extremities such as the knees and ankles.
- **Axial involvement:** Some patients may develop inflammatory back pain due to sacroiliitis or spondylitis.
- **HLA-B27 association:** A significant proportion of patients is HLA-B27 positive, linking it to other spondyloarthritis subtypes.

Table 2.1: A list of the various subtypes of spondyloarthritis classified as *'primary'* and the *'secondary'* form	
Primary SpA	*Secondary SpA*
1. Ankylosing spondylitis	1. Psoriatic SpA
2. Undifferentiated SpA*	2. IBD-related SpA
3. Enthesitis related arthritis (ERA; paediatric age SpA)	3. Reactive arthritis-related SpA
4. Pure peripheral SpA	

*This category includes patients who present with suggestive or incomplete features of spondyloarthritis (SpA), making a definitive diagnosis challenging. In such cases, consultation with a specialist rheumatologist is essential to establish an accurate diagnosis.

- **Extra-articular manifestations** may include acute anterior uveitis and inflammatory bowel disease.
- ERA is part of the broader spondyloarthritis spectrum and is associated with a higher risk of evolving into adult spondyloarthritis over time.

Major differences between these 2 categories are given in the **Table 2.2**.

Table 2.2: Major differences between primary and secondary SpA	
Primary SpA: Common presenting features	*Secondary SpA: Common presenting features*
Inflammatory lower back and buttock pain	Inflammatory lower back and buttock pain may or may not be present
Enthesitis (costochondral region, Achilles tendon insertion enthesitis on the posterior aspect of the heels)	Enthesitis may or may not be present
Extra-musculoskeletal features mainly unilateral acute (non-granulomatous) anterior uveitis	Extra-musculoskeletal features commonly in skin subcutaneous tissues (psoriasis, erythema nodosum, pyoderma gangrenosum), acute (non-granulomatous) anterior uveitis often bilateral
SpA pattern of peripheral arthritis is seen only in a minority	SpA pattern of peripheral arthritis almost always present
~95% carry HLA-B27 gene	Much lower and variable % of patients carry HLA-B27

Spondyloarthritis Spectrum: The Axial (ax-) and the Peripheral (p-) SpA Form

Axial spondyloarthritis (axSpA) can be viewed as a continuum of progressive spinal damage that accumulates over time. The disease may pause at any stage of its progression, but in about one-third of patients, it advances to a severe, late-stage of the disease characterised by significant spinal deformity with distinctive postural abnormalities and associated articular and extra-articular manifestations. This advanced clinical stage is referred to as **ankylosing spondylitis (AS)**.

Risk factors for the progression of axSpA to its most destructive form, namely AS, include the following:

1. The presence of the HLA-B27 gene is strongly associated with AS.
2. Male gender is also a risk for progressive disease leading to AS.
3. A positive family history is also a predictor of disease severity and progression.

4. Increased levels of inflammatory markers [C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)] are associated with higher disease activity and structural damage.
5. MRI evidence of active sacroiliitis or spinal inflammation (bone marrow edema) is a strong predictor of future radiographic progression.
   - Disease onset in adolescence or early adulthood is linked to a higher risk of structural damage. Structural damage in SIJ or the presence of syndesmophytes at the presentation is also strongly predictive of progression to the stage of AS.
   - Ongoing high disease activity and symptom persistence without effective treatment can accelerate progression.
   - Environmental and 'lifestyle factors' associated with radiographic progression of disease include **obesity** and **smoking**.

A diagrammatic continuum of SpA that may culminate in AS in some of the patients is shown in **Fig. 2.2**.

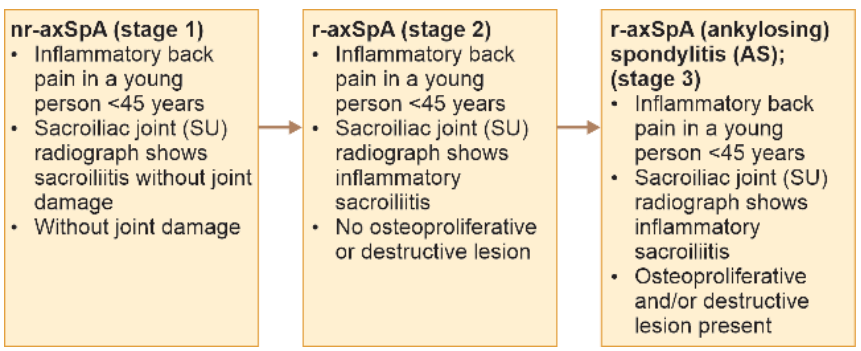


Fig. 2.2: Timeline over years decades. The figure illustrates the progression of spondyloarthritis (SpA) over time, beginning with the non-radiographic stage, progressing to radiographic spondyloarthritis, and eventually reaching a stage marked by both proliferative changes (syndesmophyte formation) and destructive lesions in the sacroiliac joints. In the United States, as well as in India, rheumatologists and other caregivers, often refer to this advanced stage as "ankylosing spondylitis"

However, not all patients follow this linear progression. Approximately one-third remain at each stage without further advancement. Early and appropriate treatment can halt disease progression, enabling some patients to achieve long-term stability. Such patients show a classical **stooped posture** marked by severe **thoracic kyphosis**, a **flattened lumbar spine** (loss of lumbar lordosis), and **hyperextension of the cervical spine**. The **pelvis is tilted anteriorly**, accompanied by **hip** and **knee flexion**, resulting in a distinctive **forward-stooping** gait. In advanced cases, this deformity severely restricts the patient's ability **to look straight ahead** ("cannot see the Sun'), disrupting their field of vision and making horizontal gaze alignment challenging. **Figure 2.3A and B** shows these deformities in 2 patients with late stage ankylosing spondylitis.

Palin radiographs of spine in such patients show features that are known as 'bamboo spine', shown in **Fig. 2.4A and B**.

However, in some patients, there may be 'skip' areas of spinal involvement, while in others—particularly women and individuals with psoriasis—the disease may begin in the cervical spine and then spread to the rest of the spine in a patchy pattern.

Fig. 2.3A and B: (A) Side-view of a patient with typical posture of ankylosing spondylitis, as described in the text. *Cervical spine hyperextension* is clearly visible (marked '1') as also severe *upper thoracic kyphosis* (Dowager's hump; marked '2'). He also had the following additional postural abnormalities (that were not visible due to clothing): Loss of lumbar lordosis, anterior pelvic tilt, and mild knee flexion. (B) Frontal view of a patient with late AS. The patient cannot look ahead while walking; 'Cannot see the Sun'! (*Courtesy:* Retd. Lt. General Ved Chaturvedi, Consultant Rheumatologist, Sir Ganga Ram Hospital, New Delhi.)

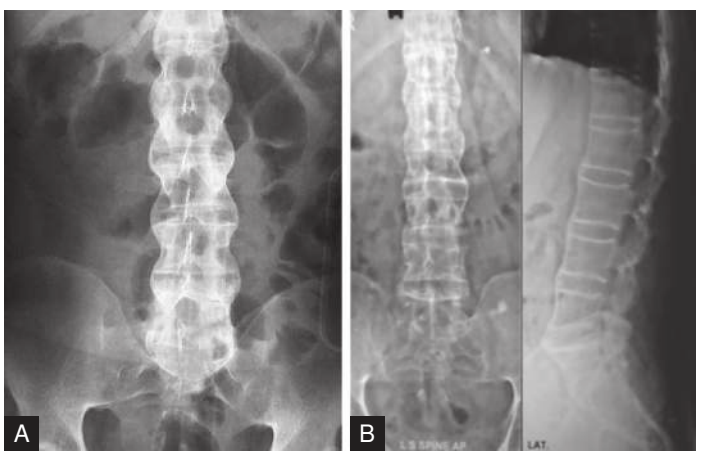


Fig. 2.4A and B: The features that on plain radiograph is recognised as "bamboo spine". Note the calcified ossification of the longitudinal spinal ligaments that start at lower lumbar vertebrae and progress upwards to involve thoracic and cervical vertebrae. Sacroiliac joints are also narrowed, irregular and appear ossified. These radiographic abnormalities are a well-recognised late terminal clinical form of axSpA that has been historically referred to as ankylosing spondylitis (AS)

Making a Diagnosis of SpA

In most cases, SpA begins in the teenage years or early 20s, but almost always before the age of 45 years. It affects both males and females with similar frequency. Yet, due to various clinical atypicalities, a significant proportion of female patients remain undiagnosed compared to their male counterparts. At its earliest stage, the disease has two distinct clinical presentations:

1. In the **paediatric age**, the disease may manifest as monoarticular or oligoarticular asymmetrical inflammatory arthritis, primarily affecting the large joints of the lower extremities as shown in **Fig. 2.5**. In regions where tuberculosis is prevalent, such patients are often misdiagnosed with 'joint tuberculosis' and treated as such for months, thereby missing the opportunity for early aggressive treatment that could have prevented major complications, such as early permanent damage to the hip joint. Such patients must be immediately assessed by paediatric rheumatologists for proper evaluation and treatment.
2. In adults, the most frequent age group for the first appearance of SpA symptoms is 18–45 years. The commonest presenting feature is with inflammatory low back and gluteal pain (often described by patients as 'trouser back-pocket' pain, anatomically corresponding to the sacroiliac joints). As elaborated in Part 1, Chapter 5, recognising the inflammatory nature of back pain is pivotal to making the diagnosis of SpA. This pain arises from inflammation of the sacroiliac joints, the hallmark of this disease. Upper extremity joints, including the finger joints and wrists, may also be affected, but the pronounced asymmetry (in contrast to the symmetrical involvement typical of RA) hints at a SpA diagnosis. Additionally, inflammatory involvement of distal interphalangeal (DIP) joints suggests SpA. It is useful to note that inflammatory DIP joint involvement is seen exclusively in SpA (mainly with psoriatic arthritis or SpA associated with inflammatory bowel disease) and uniquely in sarcoidosis. Of course, non-inflammatory DIP involvement is one of the most common forms of arthritis in the elderly, primarily seen in primary nodular osteoarthritis.

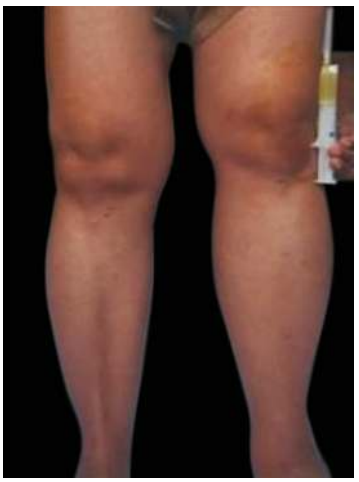


Fig. 2.5: Left knee arthritis in a young boy of 13 years of age suffering from juvenile spondyloarthritis that is called 'enthesitis-related arthritis'

In patients with late stage of axial spondyloarthritis (also called ankylosing spondylitis) certain characteristic damage-related changes occur that are shown in **Fig. 2.6**.

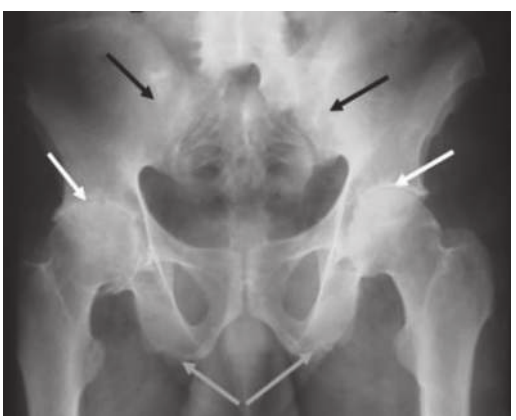


Fig. 2.6: Radiograph of pelvis in a patient with very late axSpA (AS stage) with bilateral grade IV sacroiliitis (complete fusion of the SI joints, black arrows), bilateral hip joint damage (loss of joint space with irregularity of the joint surface, white arrows) and severe enthesitis at the ischial tuberosities (grey arrows)

A mnemonic, '**IPAIN**', can help recall the key characteristics of axSpA in adult patients:

- Insidious onset (>3 months duration)

- Pain at night (with improvement upon getting up and starting daily chores)
- Age of onset <45 years
- Improvement with exercise
- No improvement with rest

Physical immobility during sleep exacerbates stiffness and pain, disrupting restorative sleep. Turning in bed may trigger sudden, severe back or buttock pain that awakens the patient, who may resort to performing back exercises in the middle of the night to alleviate stiffness and pain—one of the major reasons for severe sleep disturbance. Morning stiffness and heightened pain make routine early morning activities (e.g. getting out of bed, using the toilet, showering, grooming, and preparing for the day) extremely difficult. The gluteal pain often radiates down the back of the thighs.

There are additional so-called '**SpA features**' that may or may not be present in all patients, but their presence strengthens the diagnosis of SpA. These include **extra-articular** (e.g. dactylitis, enthesitis) as well as **extra-musculoskeletal manifestations** (e.g. skin disease, eye disease, bowel disease). A mnemonic, **'SPINEACHE'**, can aid in remembering these features:

- Sausage digit (dactylitis)
- Psoriasis/positive family history of SpA
- Inflammatory back pain
- NSAID (nonsteroidal anti-inflammatory drugs) good response
- Enthesitis (heel)
- Arthritis (below—waist, asymmetrical oligoarticular pattern)
- Crohn's/colitis (ulcerative) disease—elevated CRP
- HLA-B27 positivity
- Eye (acute non-granulomatous anterior uveitis, usually unilateral)

When a history of **inflammatory** gluteal and lower spinal pain is present, each additional SpA feature increases the diagnostic certainty. In the presence of clinical features described above, the **HLA-B27 positivity** strongly supports the diagnosis of axSpA. Inflammation and erosions with 'fatty back-fill' demonstrated on **MRI** (using specific STIR protocol) finally clinches the diagnosis of 'active' axSpA. Unfortunately, in females, symptoms can be quite nonspecific, making SpA diagnosis challenging. They may not experience lower back pain but instead present with pain starting in the middle, upper, or even cervical spine regions. Not all typical features of **inflammatory** back pain may be evident, and additional overlapping features resembling fibromyalgia can further complicate the diagnosis. Another important point is that HLA-B27 is present in ~6% of normal persons in our country's population. Therefore, unless it is attributable to the clinical symptoms of axSpA, as described above, presence of **HLA-B27 may be false positive**.

There is a specific lesion characteristic of psoriatic arthritis where whole of the toe(s) and/or finger(s) swell up like 'sausage' (therefore often identified as '**sausage digit**'). This clinical sign is called 'dactylitis', shown in **Fig. 2.7**.

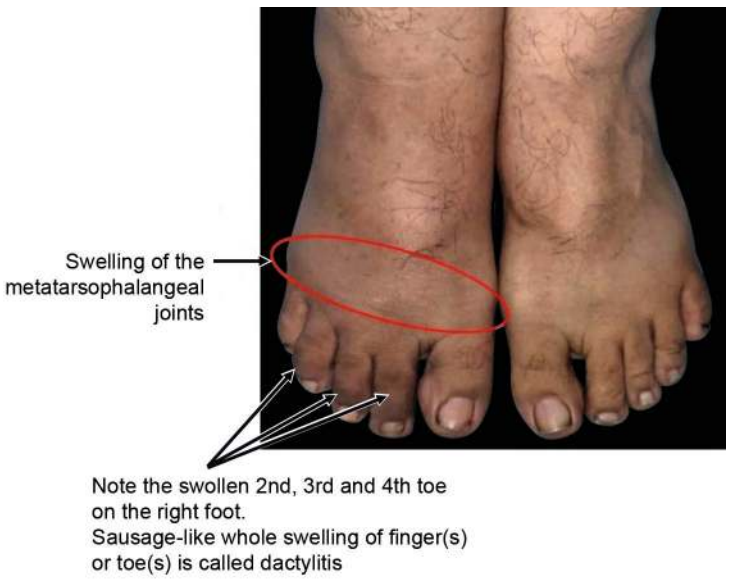


Fig. 2.7: Dactylitis of the right 2nd to 4th toe and swellings in the metatarsophalangeal joints (arrows) in a patient with *psoriatic spondyloarthritis*

Extra-articular Complications in SpA

1. **Bone involvement:** Osteoporosis and fractures are common in AS due to chronic inflammation and immobility, increasing the risk of vertebral fractures. These may occur even with minor trauma and can lead to severe spinal injuries due to reduced bone density.
2. **Extraskeletal involvement:** These are common and can significantly impact patient management and quality of life. These manifestations may affect multiple organ systems beyond the musculoskeletal system, as follows:

3.1. **Ocular involvement:** Acute anterior uveitis (iritis): It is the most frequent extra-articular manifestation that presents with eye pain, redness, photophobia, and blurred vision. It can be recurrent and usually affects only one eye, bilateral involvement is uncommon.

3.2. **Cardiac involvement:** Aortic regurgitation: Caused by inflammation of the aortic root and valve, leading to valvular dysfunction. **Conduction abnormalities:** Such as atrioventricular block, associated with fibrosis and inflammation near the atrioventricular node. **Cardiomegaly:** In advanced cases due to chronic cardiac stress.

3.3. **Pulmonary involvement:** **Restrictive lung disease** that is as resulting from decreased chest wall and spinal mobility. **Upper lobe fibrosis:** Rare, but when present, it can be mistaken for tuberculosis or other chronic lung diseases.

3.4. **Gastrointestinal involvement:** **Inflammatory bowel disease (IBD):** Crohn's disease or ulcerative colitis can coexist with AS, leading to symptoms like abdominal pain, diarrhoea, and weight loss.

3.5. **Renal involvement:** **IgA nephropathy:** Rare, presenting with microscopic haematuria or proteinuria. **Secondary amyloidosis:** Can occur in long standing disease, leading to nephrotic syndrome.

3.6. **Neurological involvement:** **Atlantoaxial subluxation:** Instability at the cervical spine's C1-C2 level can cause neurological deficits if left undetected. **Cauda equina syndrome:** Rare but may develop due to chronic inflammation and scarring at the lumbosacral level.

3.7. **Cutaneous involvement:** Some patients may develop psoriatic skin lesions or develop SpA in patients with a background of psoriasis, characterized by erythematous, scaly plaques as shown in **Fig. 2.8**.

Other skin lesions, e.g. **keratoderma blennorrhagicum**, seen in reactive arthritis (old name 'Reiter's syndrome', characterised by **hyperkeratotic skin lesions**, primarily affecting the palms and soles), may be seen in some cases. Another skin lesion seen in Reiter's syndrome is keratoderma blennorrhagicum as shown in **Fig. 2.9**.

3.8. **Systemic symptoms:** **Fatigue** is one of the most common complaints, linked to ongoing inflammation and chronic disease burden.

Recognising and managing these extra-articular manifestations is crucial for the comprehensive treatment of AS.

Understanding SpA Subtypes: Essential for Primary Care Physicians

In summary, the primary anatomical targets in SpA are the sacroiliac joints, axial skeleton (spine), entheses, and occasionally, root joints such as the hips and, less commonly, shoulders. The resulting structural changes lead to the classic features of stiffness, loss of mobility, and spinal deformities associated with the disease. Peripheral joints may also be involved in ~40% of patients with characteristic 'below the waist' asymmetrical oligoarticular pattern.

One reason for the limited understanding of spondyloarthritis (SpA) among non-rheumatologists is the confusion surrounding its diverse subtypes. SpA can present in various forms: Some patients exhibit asymmetrical inflammatory arthritis predominantly affecting the lower limbs, while others experience inflammatory lower back pain. Certain cases involve upper extremity joints with a pattern resembling rheumatoid arthritis (RA) but characterised by prominent asymmetry. Additionally, some patients

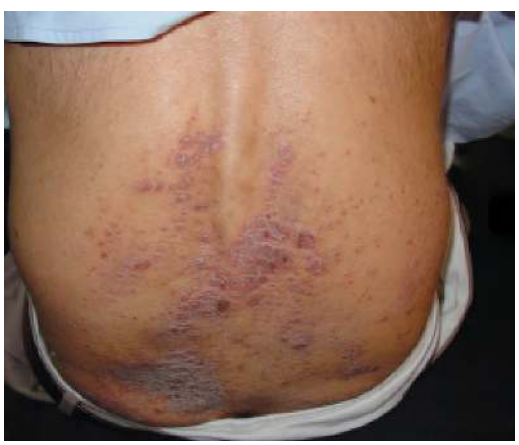


Fig. 2.8: Psoriatic lesions on the back in a person with axSpA

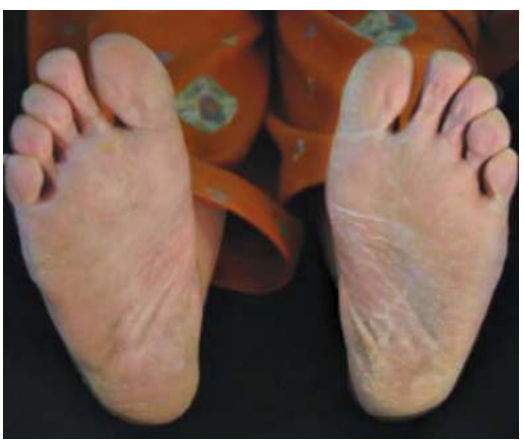


Fig. 2.9: Typical hyperkeratotic skin lesions of keratoderma blennorrhagicum

present solely with extra-articular features, such as heel enthesitis or dactylitis, while others display only extra-musculoskeletal manifestations, including psoriatic skin disease, acute anterior uveitis, or inflammatory bowel conditions like Crohn's disease or ulcerative colitis.

An in-depth discussion of spondyloarthritis (SpA), as outlined above, is essential given the widespread lack of awareness among non-rheumatologists. This knowledge gap often results in significant delays in diagnosis and treatment, leading to potentially devastating consequences, particularly for young patients. Recent advancements in understanding the pathogenesis and pathobiology of SpA have paved the way for a broad spectrum of highly effective therapies, each designed to target specific mechanisms and tailored to various SpA subtypes. Consequently, it is vital for primary care physicians to recognise the possibility of SpA at an early stage and promptly refer patients to rheumatologists. Early recognition and timely intervention not only provide access to optimal treatment options but also enable patients to achieve better health outcomes and lead more fulfilling lives.

CHAPTER 3

Connective Tissue Diseases

INTRODUCTION

Connective tissue diseases (CTD; also referred to as 'antinuclear antibody (ANA)-positive' or 'anti-cell antibody (ACA)-positive diseases').

This group of diseases includes:

- **Systemic lupus erythematosus (SLE or simply 'lupus')**
- **Sjögren's disease** (commonly termed primary Sjögren's disease or 'pSS'; distinct from secondary Sjogren's disease, which can develop in association with rheumatoid arthritis, other CTDs, or certain systemic vasculitides).
- **Systemic sclerosis (SSc)** (characterised by prominent skin involvement, often referred to as 'scleroderma' by dermatologists)
- **Idiopathic inflammatory myopathies (IIMs)**
- **Undifferentiated and mixed connective tissue diseases (UCTD, MCTD)**.

Making a Diagnosis of CTDs

Recognising and diagnosing this group of diseases can be challenging for primary care physicians. The reasons are multifaceted. These conditions are relatively uncommon, meaning that they may not be frequently encountered or thoroughly covered during undergraduate or postgraduate training. Additionally, these are complex, multisystem disorders with diverse and variable presentations. Many symptoms may not initially appear as musculoskeletal issues, which can delay consideration of a rheumatology consultation. This chapter highlights key clinical signs that should raise suspicion of CTD or systemic vasculitis.

Suspect any of the CTDs if some of the Following Clinical Features are Present in the Patient

- **Suspect SLE in persons with the following features:**
  - **Age and sex predilection:** Majority young–middle aged woman
  - **Insidiously evolving constitutional symptoms:** Feverish feeling/actual fever off and on, increasing fatigue.

- **Skin and subcutaneous lesions:** A photosensitive skin rash—lesions that are exacerbated by exposure to sunlight, primarily due to the ultraviolet spectrum—is a key clinical feature of SLE, and dermatomyositis. The rash typically appears on sun-exposed areas of the body, such as the face, hands, and distal arms. The facial rash is particularly distinctive, often involving the bridge of the nose and cheeks commonly referred to as a '*butterfly rash*'. In *SLE*, this rash spares the nasolabial folds but in dermatomyositis the photosensitive rash on the face, unlike lupus, often crosses the nasolabial folds.
- **Figure 3.1A to D** illustrates the various forms of butterfly rash seen in SLE patients.
  The main differential diagnosis of facial rash of SLE is 'rosacea', a common skin condition that causes flushing or long-term redness on the face as shown in **Fig. 3.2**.
  The other skin lesion on the face called 'chloasma' (also called 'melasma'), is a pigmentation disorder of the skin characterised by dusky brownish skin patches on the cheeks and the bridge of the nose related to pregnancy as shown in **Fig. 3.3**.

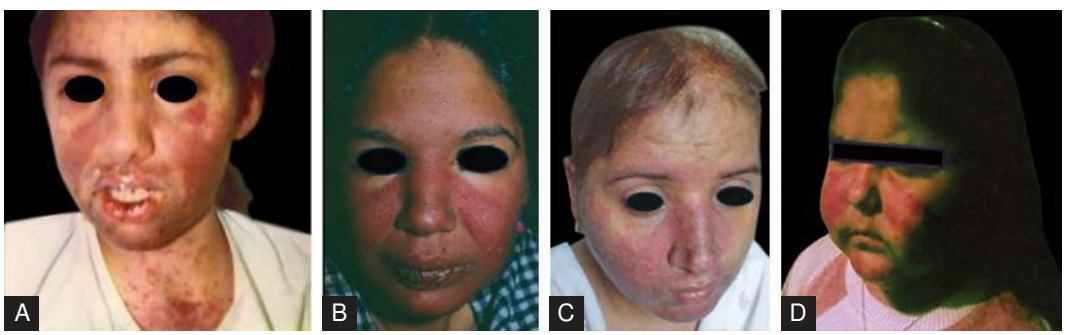


Fig. 3.1A and D: (A and B) Facial rash as well as mucosal ulcers. Such mucosal ulcers are frequently observed inside the mouth as well; (C) Alopecia (hair loss), which is another common manifestation; (D) The butterfly rash in a child, who also exhibits cushingoid facial swelling, suggestive of long-term glucocorticoid therapy

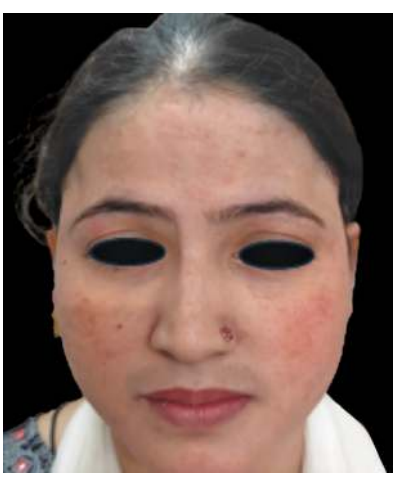


Fig. 3.2: This young woman's face exhibits a characteristic skin lesion on the cheeks, known as rosacea

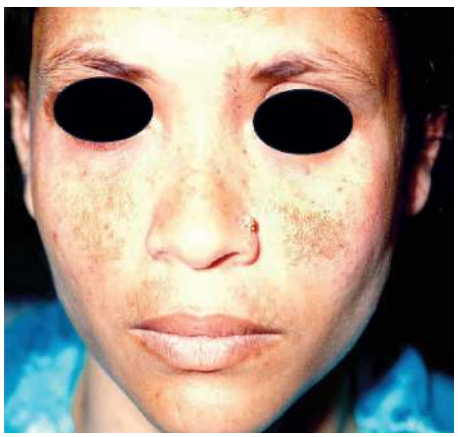


Fig. 3.3: This photograph shows the typical features of melasma on the cheeks

- **Raynaud's phenomenon:** It is a clinical condition where distal fingers and toes becoming bluish in colour on any type of cold exposure, then turning pale white then, on warming, develop reddish hue. **Figure 3.4A and B** depicts features of Raynaud's phenomenon.
- **Joint disease** seen in SLE is also **inflammatory in nature** involving the small joints in fingers, wrists, ankle-feet, in a symmetrical pattern resembling rheumatoid arthritis (RA). However, the severity of joint involvement, joint erosions and the typical deformities seen in late RA patients, are usually not seen in this group of diseases, as shown in **Fig. 3.5**.
- **Cognitive abnormalities:** These are rather subtle and may need to be evaluated by an expert psychiatrist.
- **Renal involvement:** In most cases it is only detected by routine urine examination that may show the presence of abnormal numbers of red blood cells (RBC), red cell casts and proteinuria.

• **Suspect primary Sjögren's disease in persons with the following features**

- **Age and sex predilection:** Majority middle aged-elder woman.
- **Dryness** of eyes and mouth; may also feel dryness in vagina as well as in skin.

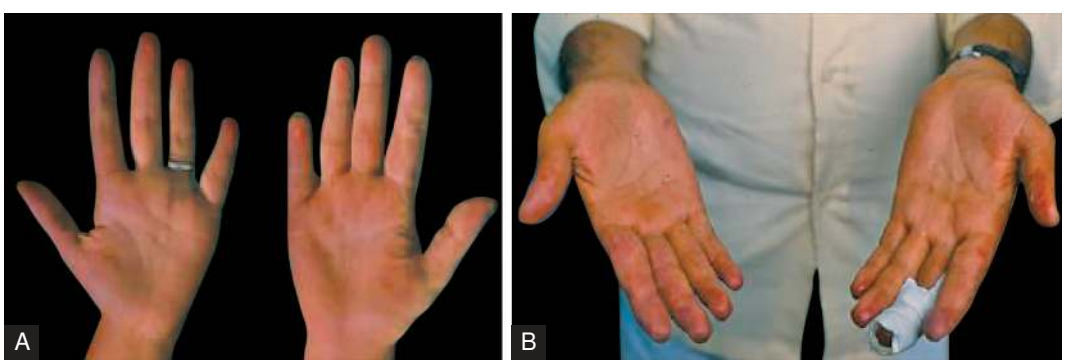


Fig. 3.4A and B: (A) Woman and (B) Man show the colour change in the distal parts of fingers on exposure to cold temperature

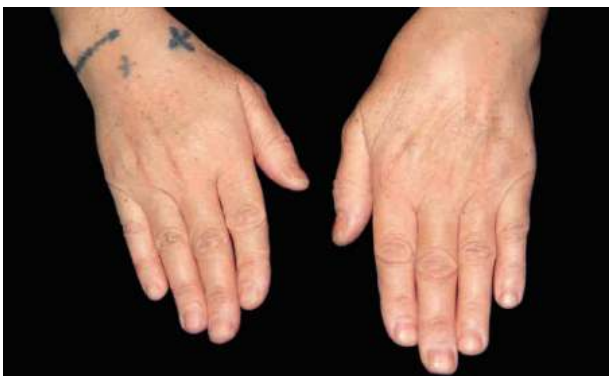


Fig. 3.5: Hands of a patient with SLE with symptoms of inflammatory arthritis without typical deformities seen in patients with late RA. There is a condition called 'Jaccoud arthropathy'. It causes reversible deformity in MCP joints during flexion with ulnar deviation and swan-neck-like appearance of the fingers. Therefore, it may be confused with deformities seen in patients with RA

- **Constitutional** symptoms that are prominent, associated with nonspecific body and muscular pains.
- **Inflammatory arthritis:** Mild to moderate nondeforming pattern resembling RA.
- **Parotid gland swelling** (behind the jaw and in front of the ears), subtle more often than prominent. **Figure 6A and B** shows certain characteristic findings in patients with Sjögren's disease.

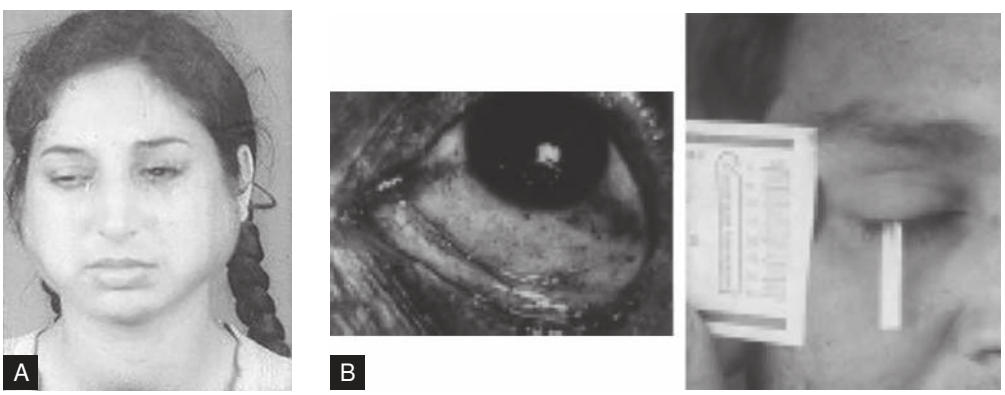


Fig. 3.6A and B: A. The bilateral parotid swellings in a patient with Sjögren's disease; (B) The 2 investigations that confirm decreased tear formation, namely 'Rose-Bengal staining test' (left) and the 'Schirmer's test (right)

- **Several additional subtle symptoms:** Weakness felt in muscles with diminished reflexes (early sign of renal tubular acidosis), subtle features of peripheral neuritis, scattered enlarged lymph nodes, and dry cough that may herald lung involvement.

- **Suspect SSc in persons with the following features:**
  - **Age and sex predilection:** Majority young—middle-aged woman
  - **Raynaud's phenomenon:** Already described (*see* above), Raynaud's phenomenon (shown in **Fig. 3.7**) is '*Sine qua non*' for SSc; it would be difficult to diagnose SSc in its absence. It is much more severe and causes many more complications in SSc

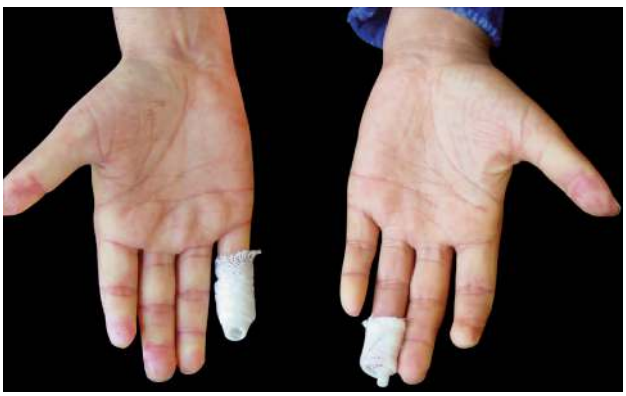


Fig. 3.7: Hands in a patient with severe Raynaud's phenomenon, the bandaged tips of the fingers cover the gangrenous changes that have occurred due to ischaemia

than in SLE and other CTDs. In severe cases it may lead to fingertip ulcerations or even gangrene as shown in **Fig. 3.7**. Note the pale-white discolouration of fingers (indicative of severe Raynaud's phenomenon), gangrenous shortening of the distal phalanx (most prominent in the left index finger), and ulcers on fingertips (covered with bandage).

- **Skin thickening:** Slowly increasing skin involvement is the main feature in this disease. Visible swelling of the skin with itching is usually the earliest symptom. Increasing difficulty in fully opening the moth because of the hardening of the skin around it. The skin changes around the mouth gives it a 'puckered appearance', as shown in **Fig. 3.8A**.
- Affected skin feels very 'tight' making it difficult to pinch it. It can change its complexion with areas that are dark contrasting with adjacent skin becoming lighter in colour (resembling the colour of vitiligo). This may sometimes be described as 'salt and pepper appearance', shown in **Fig. 3.8B**.

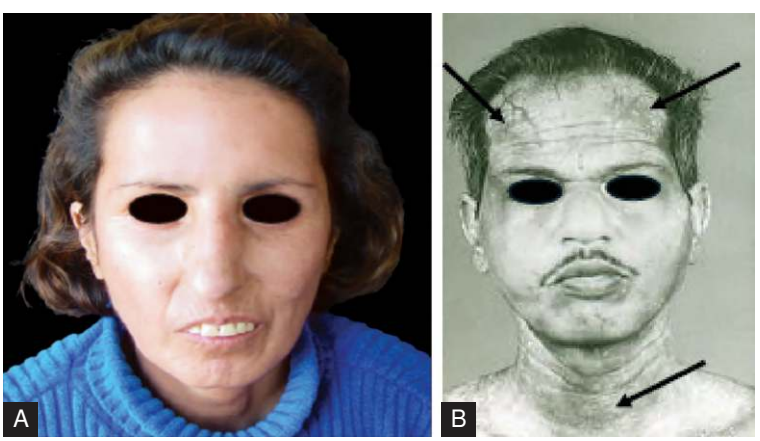


Fig. 3.8A and B: (A) Typical puckered appearance of the mouth. The pattern of skin involvement is also rather characteristic and includes thickening and tightness in the fingers, hands, feet and face, increasing slowly to involve the forearms, upper arms, chest, abdomen, lower legs and thighs. (B) 'Salt-and-pepper appearance' shown by arrows

– **Lung involvement:** Interstitial lung disease (ILD) is one of the most serious complications of this disease. Therefore, the treating physician should be extravigilant about it. Besides other investigations, a baseline high resolution computerised tomography of the lung must be a part of the basic minimum investigations so that the ILD, as seen in **Fig. 3.9**, may be detected as early as possible and appropriate treatment can be initiated before it is too late.

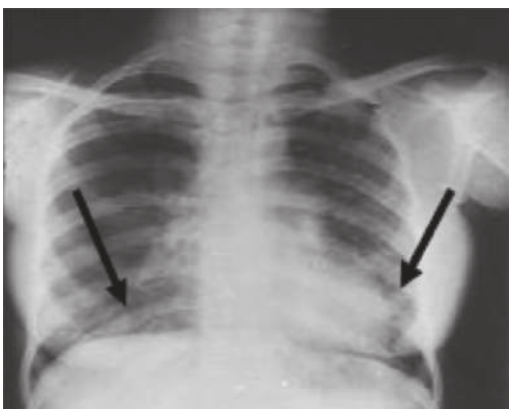


Fig. 3.9: Radiographic changes of early ILD in a patient with SSc

– **Gastrointestinal tract involvement:** Patulous oesophagus with features of gastro-oesophageal reflux disease (GERD) is one of the severe and disturbing clinical features of this disease. Also, abnormalities in intestinal motility-related clinical features are another important manifestation. These include, bloating, flatulence, constipation.
– **A few additional features:** Inflammatory joint disease may be prominent in some patients that resemble RA, as shown in **Fig. 3.10**.

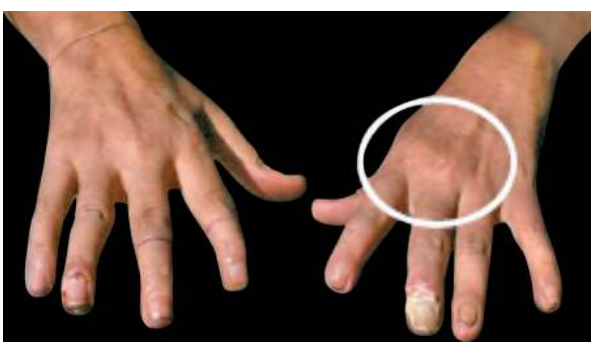


Fig. 3.10: Inflammatory arthritis in SSc. Swelling in the left 2nd and 3rd MCP joints (white circle) is clearly visible. Digital ulcers and gangrene are also visible. Another important clinical finding in patients with SSc is the presence of 'friction-rub' that may be felt or, could be better appreciated by placing a stethoscope over the wrist tendons while moving the wrists

- **Suspect dermatopolymyositis—IIM in persons with the following features**
  – **Age and sex predilection:** Majority young–middle-aged woman but sex no bar.
  – **Proximal muscle weakness:** Subacute onset of difficulty in performing daily chores that involve shoulder and thigh muscles, e.g. reaching for any item kept at

the shoulder height or above; getting up from a sitting position from a low chair, climbing stairs.

– **Skin rash of specific appearance:** Erythematous or violaceous papules typically found on the skin over the knuckles, PIP and DIP joints, called '*Gottron's papules*', are pathognomonic of IIM, shown in **Fig. 3.11A and B**.

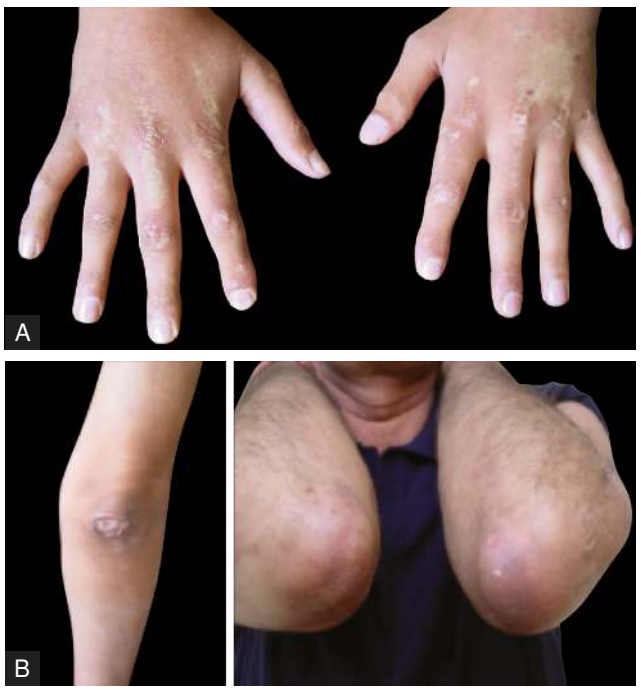


Fig. 3.11A and B: (A) Typical (healing) Gottron's papules. These papules are often accompanied by Gottron's sign, which involves similar discolouration and changes over the extensor surfaces of joints without raised papules. elbows, and knees; (B) Typical Gottron's sign on the skin overlying the elbows

Another characteristic skin lesion seen in patients with IIM is a typical lilac-coloured photosensitive facial rash on the forehead, on the skin over eyelids, and cheeks, resembling facial skin rash, SLE, shown in **Fig. 3.12**.

– **Lung disease:** In some patients the skin and muscle manifestations may be minimal or even absent. But they present with progressive breathlessness due to interstitial lung disease (ILD), shown in **Fig. 3.13**. It is a rapidly progressive serious complication of this group of diseases that must be recognised early and treated by specialists.

Fig. 3.12: Typical rash lilac-coloured rash in a patient with IIM. The difference from SLE is that the rash is of lilac colour, and it crosses nasolabial fold

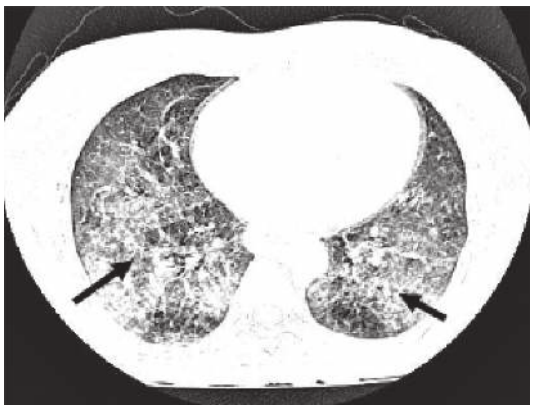


Fig. 3.13: Photograph of a high resolution computed tomographic (HR-CT) image in a patient with IIM showing a severe form of ILD (arrows)

- **Gastrointestinal manifestations:** Pharyngeal muscle involvement may cause swallowing difficulty, patulous oesophageal involvement cause symptoms of gastroesophageal reflux disease (GERD).
- **Association with cancer:** Presence after the onset of any form of cancer from 3 years before the onset of symptoms of IIM till 3 years of the IIM symptoms, are defined as cancer-associated IIM.

- **Suspect MCTD/UCTD in persons with the following features**
  - **Mixed connective tissue disease (MCTD):** This name was given by an American Rheumatologist Gordon Sharp therefore, often called 'Sharp syndrome'. The patients have clinical features overlapping between SLE, SSc and IIM. To be noted that the appearance of symptoms of these CTDs may not be present simultaneously but could be staggered. Thus, a patient with symptoms of SLE may start to develop features of IIM that later develop features of SSc. A particular autoantibody called anti-U1-ribonucleoprotein (anti-U1-RNP) antibody is said to be a marker of this form of CTD.
  - **Undifferentiated CTD (UCTD):** Raynaud's phenomenon is one of the earliest clinical manifestations in most of the CTDs. Over a period of time, they may show additional subtle involvements in skin mucosa, minor joint pains, minimal fluctuating muscle weakness, some features of dryness in the eyes and mouth and other nonspecific features. However, definite features of any of the above mentioned CTDs may not develop even over prolonged periods. Such patients are labelled 'UCTD'.

Patients with symptoms of any of the groups of disease mentioned above, must be immediately referred to a rheumatologist. It cannot be overemphasised that, except for routine blood tests (CBC, ESR, CRP, renal, liver and metabolic profile), and urine examination, **no other special blood tests for CTD need to be performed at the primary care level. Selecting specific immunological tests to be performed in patients suspected of CTD is a highly specialised field that should be left for the rheumatologist** to decide.

CHAPTER 4

Systemic Vasculitides

INTRODUCTION

Vasculitides encompasses a diverse group of rare disorders characterised by inflammation of blood vessels, resulting in vessel wall damage and subsequent tissue ischaemia. The clinical presentation varies widely, depending on the size and type of vessels involved, ranging from mild, self-limiting symptoms to severe, life-threatening organ dysfunction. Vasculitis can be primary (idiopathic or immune-mediated) or secondary to factors such as infections, malignancies, or drug exposure. A thorough understanding of its pathogenesis, classification, and distinct clinical syndromes is essential for accurate diagnosis and optimal management, as treatment approaches differ significantly based on the type and severity of the disease. Recent advances in immunopathology, imaging techniques, and targeted therapies have markedly improved outcomes in these complex conditions.

Classification of Immune-mediated Systemic Vasculitides

Currently, immune-mediated (immunoinflammatory) diseases affecting the blood vessels, known as **vasculitis**, are classified based on the size of the affected vessels and the structural variations within the three layers of the arterial wall: The **tunica intima**, **tunica media**, and **tunica adventitia**. This classification system, therefore, follows an anatomical and histological approach to categorising blood vessels described below.

1. **Large vessel (elastic arteries):** By definition, aorta and its **main branches** are classified as large vessels with muscular arteries having **diameters typically larger than 10 mm** ascending aorta.

   These include the **aortic arch** with its **major branches** (subclavian, carotid, and innominate arteries) and the **descending aorta**, and iliac arteries. They have the following features:

   - **Tunica intima:** Well-developed, with prominent internal elastic lamina.
   - **Tunica media:** Thick, dominated by elastic fibres interspersed with smooth muscle to accommodate high-pressure blood flow.
   - **Tunica adventitia:** Relatively thin, with vasa vasorum for nourishment.

2. **Medium vessels (muscular arteries)**
   - **Examples:** Radial, coronary, femoral, brachial, renal and splenic arteries.
   - **Tunica intima:** Thin, with a clear internal elastic lamina.
   - **Tunica media:** Predominantly smooth muscle, with fewer elastic fibres, enabling precise control of blood flow and pressure.
   - **Tunica adventitia:** Well-developed, providing structural support.

   By definition, the primary branches of blood vessels supplying any organ—specifically the main visceral arteries and veins, along with their branches before penetrating the organ parenchyma—are classified as medium-sized vessels. These are also muscular arteries, having diameters ranging from approximately 1 to 10 mm. Segmental arteries in the kidney fall into this category because they branch off the main renal artery and supply specific segments of the kidney.
3. **Small vessels (arterioles and small arteries)**
   - **Examples:** Interlobar, arcuate arteries.
   - **Tunica intima:** Minimal, often lacking an internal elastic lamina.
   - **Tunica media:** Few layers of smooth muscle, primarily for regulating local blood flow.
   - **Tunica adventitia:** Thin and sparse.

By definition, small vessels have diameter that typically ranges from 50 to 300 µm. Examples include intraparenchymal arteries, arterioles, capillaries, venules, and veins.

The progression from large to small vessels shows decreasing elastic content and decreasing smooth muscle dominance, with thinner walls overall.

Figure 4.1 provides a diagrammatic representation of the classification of blood vessels into large, medium, and small categories.

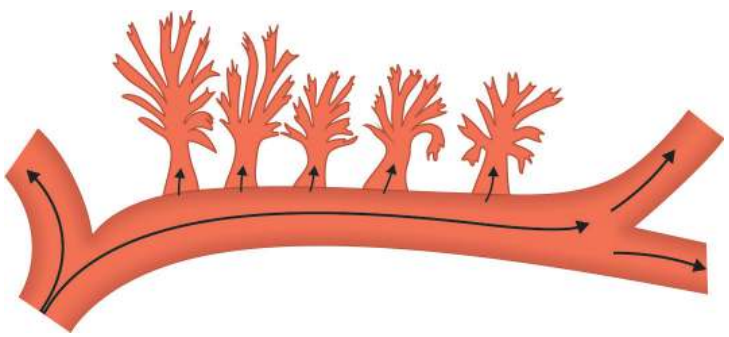


Fig. 4.1: Diagrammatic depiction of the definition of *different sizes of blood vessels*: **(1) Aorta and its main branches** shown with long **black** arrows, are classified as **'Large vessels'. (2)** The aortic branches **after entering any viscera** *but before entering the visceral parenchyma*, depicted by **short black arrows**, are classified as **'medium vessels'. (3)** The branches of the medium vessels, that have entered the visceral parenchyma, depicted as '*flower-shaped*' structures, are classified as **'small vessels'** (for details, see text).

Diseases Included under the 3 Classes of Vasculitides

Following is a categorised list of diseases based on the classification of vasculitides:

1. **Large vessel vasculitis**
   - Giant cell arteritis (temporal arteritis)
   - Takayasu arteritis

2. **Medium vessel vasculitis**
   - Polyarteritis nodosa (PAN)
   - Kawasaki disease
3. **Small vessel vasculitis**
   - **Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis**
     - Granulomatosis with polyangiitis (GPA, formerly Wegener)
     - Microscopic polyangiitis (MPA)
     - Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss)
   - **Immune complex-mediated vasculitis**
     - Henoch-Schönlein purpura (IgA vasculitis)
     - Cryoglobulinemic vasculitis
     - Hypersensitivity vasculitis (leukocytoclastic vasculitis)

This classification helps guide diagnosis and management based on the size of the blood vessels primarily involved in the disease process.

Clinical Features of Systemic Vasculitides

1. **Small vessel vasculitis:** This is an uncommon group of disorders characterised by inflammation of small blood vessels, including capillaries, arterioles, and venules. The diseases are further classified into 2 groups as follows:

   1.1 **Small vessel vasculitides** associated with the presence of a specific autoantibody in the blood called *anti-neutrophil cytoplasmic antibody (ANCA)*. Therefore, these diseases are often called '*ANCA-associated vasculitides*' *(AAV)*. The 3 diseases in this group (GPA, MPA and EGPA), have some common clinical features. These include:
   - *Constitutional symptoms:* Fever, weight loss, fatigue
   - *Skin manifestations:* Palpable purpura, ulcers, or nodules.
   - *Renal involvement:* Haematuria or proteinuria indicating glomerulonephritis.
   - *Neurological symptoms:* Peripheral neuropathy.
   - *Respiratory symptoms (both upper as well as lower respiratory tract):* Excessive nasal crusting, sinusitis (often obstinate, severe, resistant to standard treatment), cough and haemoptysis (often misdiagnosed as pulmonary tuberculosis).

   Within this group of AAV, certain specific features of each of these diseases that help in their specific diagnosis, are as follows:

   1.1.1 **Granulomatosis with polyangiitis (GPA):** A hallmark of this disease is upper respiratory tract involvement, affecting the nasal passages, paranasal sinuses, and middle and inner ear, presenting with severe nasal crusting, nasal bleeds, and sinusitis. Middle ear involvement causes serous otitis media and mastoiditis, while inner ear damage results in sensorineural hearing loss and vestibular dysfunction. Severe lower respiratory tract involvement can lead to tracheal ectasia and haemoptysis. Renal involvement causes glomerulonephritis with haematuria and proteinuria. Eye manifestations include scleritis, episcleritis, uveitis, and orbital pseudotumour, which may progress to vision loss or optic nerve

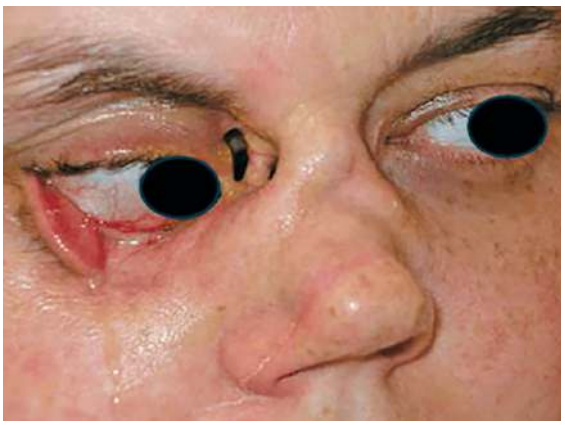


Fig. 4.2: Granulomatous lesion and conjunctivitis in the right eye and damage of the nasal cartilage causing 'depressed bridge of nose', typical lesions in a patient with GPA

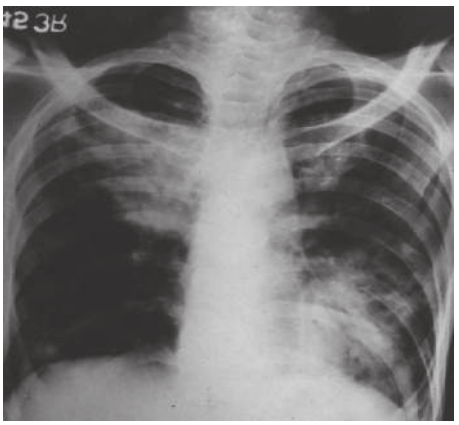


Fig. 4.3: Chest radiograph of a patient with GPA shows parenchymal lesions in the lungs in an asymmetrical pattern; these shadows may keep changing their size, shape and position in patients with GPA over days

compression. Diagnosis is supported by positive ANCA (anti-proteinase-3/PR3) and granulomatous vasculitis on histopathology. **Figures 4.2 and 4.3** show some of the typical findings seen in GPA.

A disease closely resembling GPA is Cogan's syndrome. It is a rare form of small vessel vasculitis characterised by a combination of ocular and inner ear inflammation. It typically presents with interstitial keratitis (corneal inflammation) and audio-vestibular symptoms such as vertigo, hearing loss, and tinnitus, resembling Meniere's disease.

1.1.2 **Microscopic polyangiitis (MPA):** Clinically, it is a small vessel vasculitis closely related to GPA but without granulomas, a feature that differentiates it from other ANCA-associated vasculitides. It is characterised by renal involvement (pauci-immune glomerulonephritis) and pulmonary manifestations like cough, haemoptysis and occasionally, in its severe form, causing alveolar haemorrhage. Diagnosis is confirmed by the presence of an autoantibody specific for myeloperoxidase (MPO-ANCA).

1.1.3 **Eosinophilic granulomatosis with polyangiitis (EGPA):** It is a comparatively less common small vessel vasculitis characterised by *asthma, prominent eosinophilia, and vasculitis* affecting multiple organs. In most patients, there is a background history of asthmatic attacks for several years or decades, followed by constitutional symptoms and features overlapping with GPA. The diagnosis of EGPA is confirmed by the presence of eosinophilia, a history of asthma, and biopsy evidence of eosinophilic tissue infiltration or vasculitis. ANCA test is positive in approximately 30–40% of EGPA patients, typically with specificity for MPO-ANCA. Its presence is often associated with more severe vasculitic manifestations such as renal and peripheral nerve involvement. The purpuric rash on lower legs, often *seen* in EGPA is shown in **Fig. 4.4**.

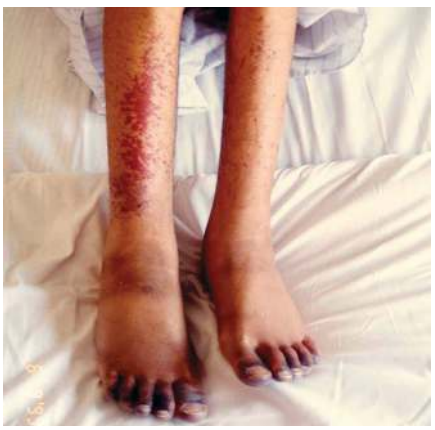


Fig. 4.4: Lesions of palpable purpura and gangrene in toes in a patient with EGPA

1.1.4 **Henoch-Schönlein purpura (HSP):** Henoch-Schönlein purpura (HSP), also known as IgA vasculitis, is a small vessel vasculitis *primarily affecting children*, characterised by the deposition of IgA immune complexes. It typically presents with a classic triad of symptoms: *Palpable purpura* (usually on the lower limbs, shown in **Fig. 4.5A to D**), *arthritis* or *arthralgia*, *abdominal pain*, and *renal involvement* (haematuria or proteinuria). HSP is often triggered by infections and usually follows a benign, self-limiting course, but severe renal involvement can occur in some cases, necessitating close monitoring and management.

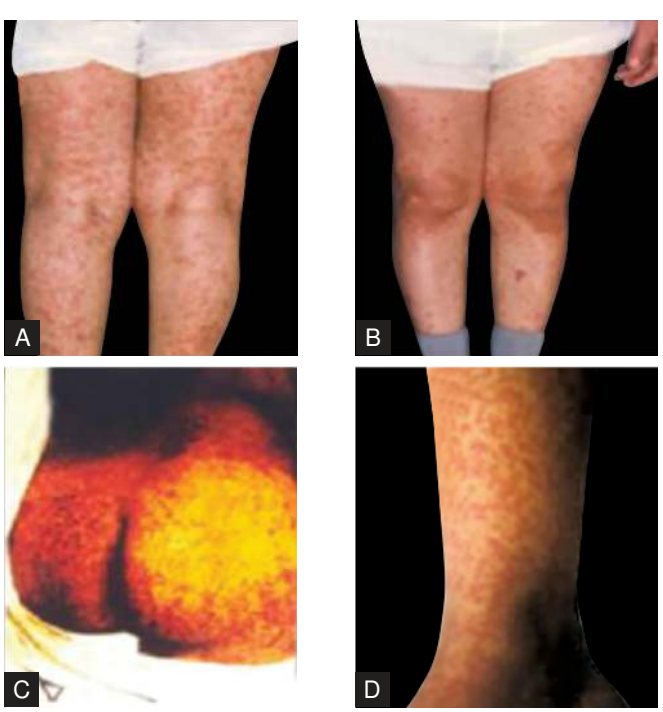


Fig. 4.5A to D: HSP skin lesions of different severity and distribution

2. **Medium vessel vasculitis:** Medium vessel vasculitides are a group of disorders involving inflammation of medium-sized arteries. Clinically, they often present with:
   - **Systemic symptoms:** Fever, weight loss, fatigue.
   - **Skin manifestations:** Livedo reticularis, nodules, ulcers.
   - **Mononeuritis multiplex:**
   - **Gastrointestinal symptoms:** Abdominal pain, sometimes due to bowel ischaemia.
   - **Cardiovascular symptoms:** Hypertension, aneurysms.

   There are **three** primary types of **medium vessel vasculitides**:

   2.1 **Polyarteritis nodosa (PAN)** is a medium vessel vasculitis characterised by necrotising inflammation of muscular arteries that leads to organ-specific manifestations such as peripheral neuropathy, skin ulcers, and renal infarctions. It commonly presents with systemic symptoms such as fever, weight loss, hypertension, and anaemia. The disease often affects the kidneys (medium-sized arteries leading to hypertension), skin (causing vasculitic ulcers), joints (resulting in arthralgias like those seen in rheumatoid arthritis), muscles (mimicking myositis with sensory involvement), peripheral nerves (manifesting as 'wrist drop' and 'foot drop'), and the gastrointestinal tract (leading to bleeding lesions in the small intestine). The lesions in the mesenteric artery have been shown in **Figs 4.6 and 4.7**.

Fig. 4.6: Mesenteric artery angiogram with aneurysm (arrow)

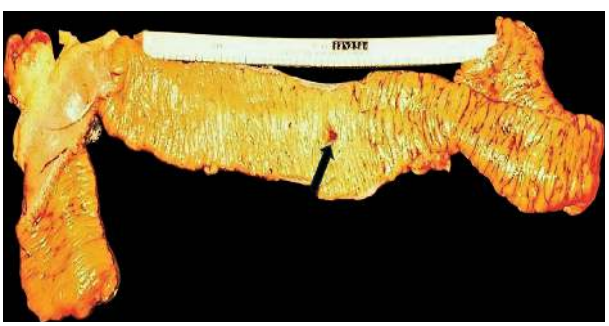


Fig. 4.7: Resected small intestine with clearly visible aneurysm that had bled causing severe anaemia. PAN spares small blood vessels and capillaries, distinguishing it from small vessel vasculitides, which typically present with glomerulonephritis or ANCA associations. Additionally, PAN may be associated with hepatitis B in some cases

2.2. **Kawasaki disease:** This disease predominantly affects children and is characterised by fever, conjunctivitis, rash, cervical lymphadenopathy, and mucocutaneous changes. A severe complication of the disease is the development of coronary artery aneurysms, which can lead to significant cardiovascular risks if not promptly treated.

2.3. **Cutaneous polyarteritis nodosa (C-PAN):** It is possibly the commonest in this category of vasculitis that affects the small to medium-sized arteries of the skin, sparing internal organs. Clinically, it often presents with: *Painful skin nodules, livedo reticularis* (mottled purplish skin), *ulcers* or *purpura, or superficial thrombophlebitis*. *The patients* may also experience *systemic symptoms* like fever, malaise, or arthralgia, but these are usually less severe than in systemic PAN. Characteristic skin lesions of C-PAN are shown in **Fig. 4.8A to C**.

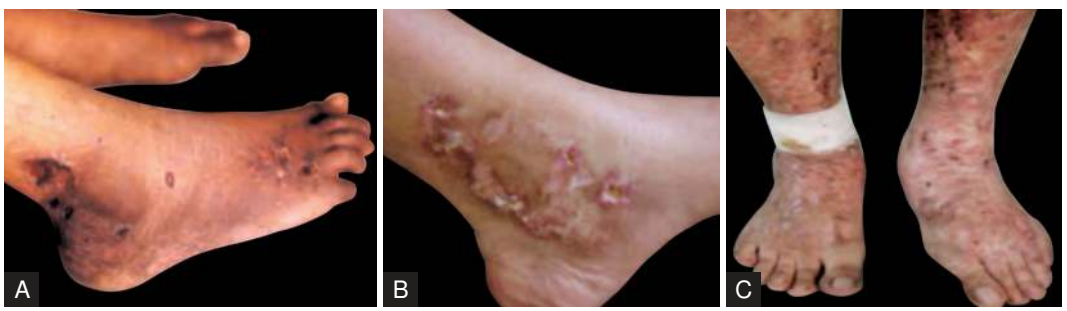


Fig. 4.8A to C: Photographs of typical skin lesions in a patient with cutaneous PAN of different severity

3. **Large vessel vasculitis:** Large vessel vasculitis involves inflammation of the large arteries, including the aorta and its major branches. Giant cell arteritis (GCA) and Takayasu arteritis (TAK)

3.1. **Giant cell arteritis (GCA):** Polymyalgia rheumatica (PMR) complex GCA is a large vessel vasculitis primarily affecting older adults (almost always >60 years of age), characterised by inflammation of the temporal and other cranial arteries. Common symptoms are as follows:

3.1.1. **Headache:** The patient usually describes it as 'pain in certain regions on the head' associated with scalp tenderness (usually over the course of the temporal arteries) as against the common headache. The histopathology of such a lesion in temporal artery is shown in **Fig. 4.9**.

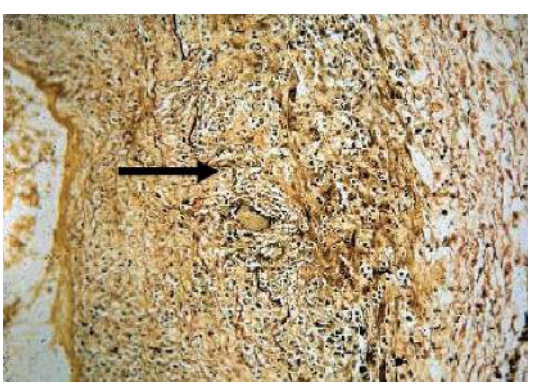


Fig. 4.9: Histopathology of temporal artery biopsy; On special staining (for elastic tissue) broken internal elastic lamina surrounded by inflammatory cells (arrow) is clearly visible, a characteristic feature of GCA

3.1.2. **Jaw claudication:** Chewing food becomes difficult with increasing pain and stiffness in masseter muscles.

3.1.3. **Visual disturbance:** It is the most serious complication of GCA causing primarily ischaemic optic neuropathy that can lead to urgent eye complications and irreversible vision loss, prompt recognition and immediate treatment with corticosteroids are crucial to prevent severe ocular complications and preserve vision. The urgency of managing eye involvement in GCA cannot be overstated, given the potential for rapid deterioration.

3.1.4. Polymyalgia rheumatica (PMR), a condition marked by muscle pain and stiffness in the proximal muscles (commonly involves shoulder girdle muscles), often occurring concurrently in patients with GCA. Visual disturbances, and scalp tenderness GCA is closely associated with PMR, which may precede or accompany GCA. The two conditions share common inflammatory pathways and may respond similarly to corticosteroid treatment. The relationship between GCA and PMR highlights the importance of monitoring for GCA in patients presenting with PMR, as early intervention is critical to prevent serious complications, particularly visual disturbances, including sudden vision changes or blindness. There is a general impression among Indian rheumatologists that this disease is rather rare in India. Whether the diagnosis is being missed at the level of primary care physicians and therefore, not reaching the rheumatologists or, it actually rare in Indias, may require an in depth epidemiological population survey.

3.1.5. Markedly elevated ESR and CRP are indicative of severe systemic inflammation in both of these diseases.

3.2. **Takayasu arteritis:** It typically affects younger women, presenting with limb claudication, blood pressure discrepancies between arms, diminished pulses (the so-called 'pulseless disease'), bruits over large arteries, and systemic symptoms like fever, fatigue, and weight loss. The diagnosis is based on clinical features, elevated inflammatory markers, and imaging studies (e.g. ultrasound, MRI, CT angiography).

Making a Diagnosis of Systemic Vasculitides

Making a diagnosis of systemic vasculitides is not as difficult as it is often wrongly perceived by the caregivers. The basic feature of this class of diseases is that they have systemic inflammation that is often severe. Clinically, this translates into constitutional symptoms, e.g. malaise, fatigue, loss of appetite and weight, fever or feverish feeling. Physical findings are more specific to each of the above 3 classes of systemic vasculitides (as already summarised above in this chapter). But one specific feature of small and medium vessel vasculitides is the presence of a skin lesion called '*palpable purpura*' (*see* Figures 4.4 and 4.5 above). It refers to a skin condition characterised by visible, raised purple spots that can be felt by fingertips. These lesions could be a symptom of a more serious systemic disease affecting blood vessels throughout the body, potentially involving organs beyond the skin.

Such lesions, however, may occur without any underlying systemic disease, often resolving on its own, including insect/mosquito bites, of no clinical relevance. However, it is not uncommon that caregivers may consider such skin lesions as 'alarming' with the connotation of it being a harbinger of some type of severe, serious, systemic life-threatening vasculitis! Without respect to the fact that such a person has absolutely no clinical features of systemic inflammation (mentioned above), is often put through irrelevant, expensive blood tests (e.g. ANCA, ANA and anti-ENA tests) as well as some of the most expensive imaging studies. It is not uncommon to get false-positive results of some of these tests which then leads to another cycle of consultations and investigations till the patient is physically and financially exhausted!

To avoid such a situation, a simple time-honoured clinical approach is as follows: Any person with palpable purpura should be asked a simple clinical question: Is skin lesion associated with systemic inflammation or not? This question can be answered simply by asking about any constitutional symptoms (clinical history as mentioned above). In addition, a look at the 'routine complete blood count' (CBC) and a 'routine urinalysis' would be more than sufficient to rule 'in' or 'out' the presence or absence of systemic inflammation. High white blood cell (WBC) count, high platelet count, along with high erythrocyte sedimentation rate (ESR) and (one additional test namely), C-reactive protein (CRP), which will also be high, will strongly point towards a systemic disease. Presence of red blood cells, casts or proteinuria, besides other causes, may suggest the possibility of a possible renal involvement due to systemic vasculitis. Thus, classifying palpable purpura into (i) 'benign palpable purpura' as against, (ii) 'palpable purpura with constitutional symptoms/organ involvement', is pivotal to correct diagnosis of small and medium vessel vasculitides. Once the systemic nature of the disease in the presence of palpable purpuric lesions is confirmed, the type of systemic vasculitis can then be further characterised based upon features discussed above in this chapter.

Treatment of Systemic Vasculitides

Early recognition and treatment are crucial to manage symptoms and prevent complications across all types of vasculitides. Diagnosis often involves a combination of clinical assessment, laboratory tests (e.g. ANCA for GPA, MPA and EGPA), and sometimes biopsy. However, which of these investigations are to be done must be left to the specialists to decide. Indiscriminate testing, especially by those not with expertise in this field, may not only be wasting precious resources but also could often be misleading. Treatment of this group of conditions is a highly specialised field, starting with accurate diagnosis that may require a number of specialised investigations including certain advanced imaging methods. Moreover, besides systemic glucocorticoids, several traditional as well as biological disease modifying anti-rheumatic drugs (DMRDs) and, more recently, certain oral targeted DMARDs (mainly JAK-inhibitor group) are being investigated for use in these diseases. Therefore, it is highly advisable to refer such patients to specialists as soon as possible.

CHAPTER 5

Crystal Arthropathies

INTRODUCTION

Crystal arthropathies are a group of joint disorders caused by the deposition of crystals in the joints and in soft tissues around the joints. These conditions usually cause acute **inflammatory arthritis**, causing pain, and swelling in the joint often with rapid joint damage. Over passage of time these conditions develop chronicity with associated complications. The most common crystal arthropathy is **gout** triggered by the deposition of monosodium urate (MSU) crystals in and around joints (in the soft tissue). Calcium pyrophosphate deposition disease (CPPD) is possibly common but often remains unrecognised. The third crystal arthritis is deposition of basic calcium phosphate crystals (**BCPC arthritis**). Like CPPD, BCPC arthritis is possibly also under recognised and could remain undiagnosed.

Gout

Traditionally, gout is said to be the commonest inflammatory arthritis of men above the age of 40 years. Unfortunately, appropriate epidemiological studies have not been carried out in India (as also possibly in other developing countries). Experience of the older generation of rheumatologists in these countries has been that it is not as common as reported from developed affluent countries. However, with rapidly changing lifestyle and socioeconomic condition in the population and rapidly rising incidence of **metabolic syndrome** (increasing central obesity (waist circumference), high blood sugar levels, low levels of high-density lipoprotein cholesterol (HDL-C, the "good" cholesterol), high levels of triglycerides in the blood, associated with hypertension) in the population it is likely that the incidence of gout would rise in the population. Another important factor in the causation of gout is the genetic background. It is well known that there are families as well as population groups around the world with high incidence of gout (e.g. Maoris of New Zealand).

Clinical Features

Gout is the commonest acute **inflammatory monoarthritis** in a **middle-aged overweight/obese man** with features of metabolic syndrome including **persistent prolonged hyperuricaemia** (normal serum uric acid (SUA) levels are: In **males 3.5–7.2 mg/dl; in females 2.6–6.0 mg/dl**).

Acute Gout Attacks

The most common scenario of acute gout attack is an overweight or obese middle-aged man (almost always >40 years of age), who wakes up in the latter part of the night (usually around 2 am), with **acute pain, swelling and redness in either of the 1st metatarsophalangeal (MTP) joint, a clinical condition identified as 'podagra'**. The symptoms of **acute inflammation** reach a peak within hours. Although the commonest joint to be affected is the 1st MTP, (base of the big toe as shown in Part I, Chapter 3, Figure 3.3, Page 29), other joints like ankles, knees, uncommonly elbows, wrists, and fingers could be the first joint to get affected in acute gout attack.

In contrast, **Fig 5.1** shown here, is rather uncommon.

Fig. 5.1: Photograph of typical acute gout attack in the right 1st MTP joint (podagra, *Courtesy:* Dr Sanjiv Kapoor, Consultant Rheumatologist and Dr Niti Bhatwal, Fellow, Department of Rheumatology, ISIC, New Delhi)

The unusual feature is that it is a young woman but with a strong family history of gout in several family members. The clinical features of acute gout attacks are so characteristic that it does not require any investigations for confirming the diagnosis. If gout attack involves a larger joint (e.g. the knee), aspirated synovial fluid can be examined under polarized light microscopy. Monosodium urate (MSU) crystals have a needle-like shape with a strong '**negative birefringence**'. **Figure 5.2** shows needle-like crystals in the synovial fluid of patients with gout. The term 'negative birefringence' means that when the crystals are aligned parallel to the slow axis of the compensator, they emit a **yellow colour** while those at 90 degrees to the slow axis of the compensator show a **light blue colour**. **Serum uric acid (SUA) is almost always markedly raised in these patients. However, SUA levels may normal during acute gout attacks.** Therefore, estimating SUA levels in the blood during acute attack may be misleading. In routine care of such patients, **immediate treatment is the priority rather than wasting time and effort in getting various investigations**; that may wait till the acute agony of the

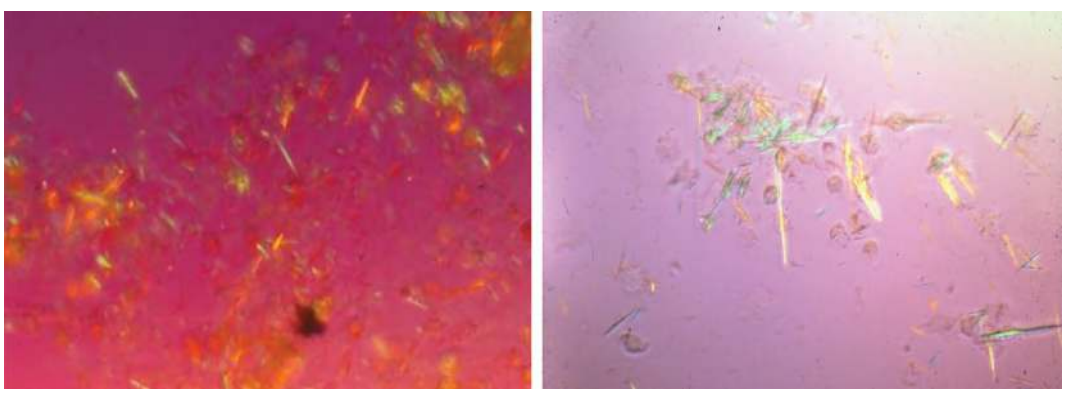


Fig. 5.2: Negatively birefringent crystals of monosodium urate as visualised under a polarised light microscope

patient is resolved. In recent times, a non-invasive investigation, namely ultrasonic examination of the joint, seems to be rapidly replacing the polarised light microscopy for the confirmation of the diagnosis of a crystal arthritis. A typical abnormality called 'Tram-track' appearance (or the double contour sign) on the ultrasonic examination of the affected joint is rather typical of gouty crystal arthritis. A typical abnormality called 'double contour' sign (often called 'tram-track' appearance) on the ultrasonic examination of the affected joint is rather typical of a crystal arthritis as shown in **Fig. 5.3**.

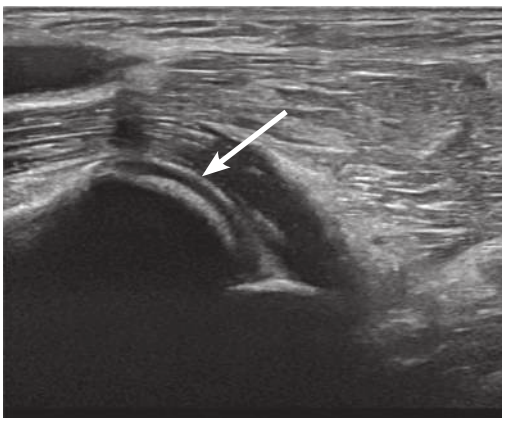


Fig. 5.3: Double contour sign (white arrow) in gout

Chronic Tophaceous Gout

Recurrent attacks of gout over years without appropriate long-term management of hyperuricaemia leads to increasing deposition of MSU crystals in and around joints called a '**gout tophus**'. It is a deposit of monosodium urate crystals in soft tissues, typically forming a firm, nodular mass that can lead to joint damage and deformity in chronic gout. These may involve several joints in the extremities that may be confused with RA. However, the presence of tophi, gives away the diagnosis. **Figure 5.4A to C** is from a patient with untreated chronic tophaceous gout.

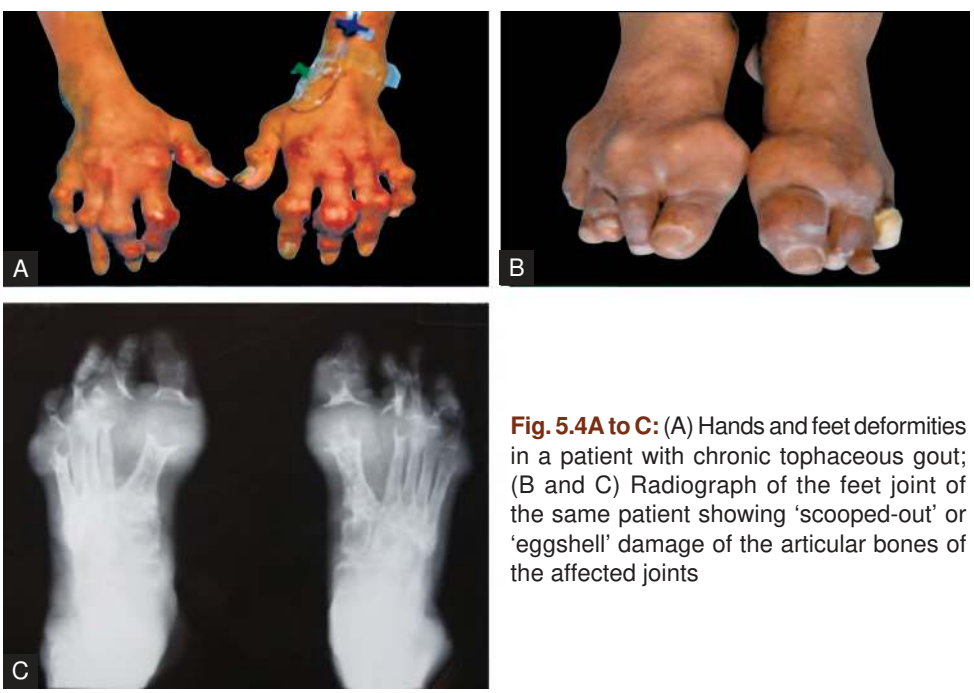


Fig. 5.4A to C: (A) Hands and feet deformities in a patient with chronic tophaceous gout; (B and C) Radiograph of the feet joint of the same patient showing 'scooped-out' or 'eggshell' damage of the articular bones of the affected joints

Misconceptions Related to Gout

There are several widespread misunderstandings about gout in non-rheumatologists, especially primary care physicians and orthopaedic surgeons that need to be addressed. The three major issues are:

1. **Age and sex predilection of gout:** Although gout is primarily a disease of middle-aged or older males, postmenopausal females are also prone to gout. Therefore, gout must be a differential diagnosis in an acute **monoarthritis in a postmenopausal woman**. Very uncommonly, young women may also suffer from acute gout attacks. Such patients have rare genetic metabolic abnormalities. Such rare patients must be immediately referred to rheumatologists for their diagnosis and management. One such case is shown in Fig. 5.1 (above). Certain treatments and clinical situations may also lead to this rare clinical condition, namely 'gout in a young female' (e.g. cyclosporine treatment in young females with compromised renal function, cancer chemotherapy with massive necrosis of cancer cells, and other similar situations that may lead to very high levels of SUA in young women).
2. **Asymptomatic hyperuricaemia:** Misunderstanding regarding SUA levels above the normal range of SUA in an otherwise normal person is called '**asymptomatic hyperuricaemia**'. As described above, asymptomatic hyperuricaemia is a feature of '**metabolic syndrome**', a clinical state that puts such a person at high-risk for atherosclerotic cardiovascular disease (ASCVD). On the other hand, **the majority of persons with metabolic syndrome and hyperuricaemia never develop gout**. Also, there is no evidence till now that reducing SUA with drug treatment reduces or prevents ASCVD. Therefore, till date, there is **no official recommendation for drug treatment for asymptomatic hyperuricaemia**. Yet, there is a widespread unproven and scientifically unsupported practices among non-rheumatologist physicians and orthopaedic surgeons for:
   a. *Wrongly attributing hyperuricaemia* as the cause of any type of chronic pains in any part of the MSK.
   b. Prescribing uric acid lowering drugs (even when the SUA levels are within the normal range), for nonspecific MSK pains or, pains related to degenerative (osteoarthritic) changes in MSK. *Avoiding such a practice* is strongly recommended. On the other hand, asymptomatic hyperuricaemia should be treated with lifestyle modification including weight loss, dietary changes with complete avoidance of red meat, no bar on any of the vegetarian food items (can regularly take: '*daals*' of any type, lentils no bar!), regular large servings of salads (spinach, tomatoes, cucumber, carrots, bell-peppers of all variety, olives and all the usual salad-items) and fruits. Cherries and dairy items of all varieties (except cheese with high fat content and calories) are specially known to reduce SUA. It may be noted that alcoholic drinks, especially beer, may increase SUA.
3. **Gout vs osteoarthritis in the 1st metatarsophalangeal (1st MTP) joint (base of the big toe):** It is important to know the following facts regarding the 1st MTP joint involvement. The *commonest joint* to be involved with acute gout attacks is the 1st MTP. Conversely, the *commonest disease* to involve 1st MCP is osteoarthritis. Therefore, a common 'catch' question in any examination is: 'What is the commonest disease

that affects the 1st MTP joint'? Usually, a prompt but wrong answer comes is 'gout'! The correct answer is 'osteoarthritis'.

Pseudogout or CPP Disease

Pseudogout, also known as calcium pyrophosphate disease (CPPD), is caused by the deposition of calcium pyrophosphate dihydrate (CPPD) crystals in the joints and soft tissues. The exact cause of these deposits is unknown.

CPPD mimics gout but, as against gout where 1st MTP is the characteristic joint involvement, in CPPD it is the knee joint. There are several other differences that are helpful in suspecting this disease. These are:

1. Elderly age as compared to patients with gout.
2. In contrast to gout that presents mostly as an acute monoarthritis, CPPD may present as an acute/subacute oligoarthritis or polyarthritis. Thus, besides the knee, other joints may be involved, e.g. the wrists, shoulders, ankles, giving some resemblance to RA. However, unlike gout and RA, the **constitutional symptoms** including fever are often present that may resemble sepsis. Diagnosis can be confirmed by demonstrating CPP crystals in the synovial fluid aspirated from any actively involved joint (usually the knee). However, CPP crystals are extremely small, requiring their examination under 'oil-immersion' microscopy using a polarised light microscope. Moreover, its recognition requires a trained and experienced observer, which is not always practical. Therefore, there are alternatives like demonstration of chondrocalcinosis (knee joint cartilage is the commonest site) that can be a surrogate for CPP crystal demonstration. More recently, ultrasonic examination of the symptomatic joint has been shown to be a sensitive and accurate method of confirming crystal arthritis. Dual-energy computed tomography (DECT), although expensive and not commonly available, is another method for demonstrating CPPD disease.

Basic Calcium Phosphate (BCP) Crystal Disease

This disease is caused by crystals that are **ultramicroscopic** crystalline substances mainly composed of **a trio of calcium phosphate crystals** consisting of carbonate substituted hydroxyapatite, octacalcium phosphate, and tricalcium phosphate hydroxyapatite (HA), mixed with small numbers of its precursor forms. Their demonstration is difficult on 'routine' laboratory investigations. This is because of their extremely small size. Moreover, **BCP crystals cannot be demonstrated in synovial fluid or tissues under polarised-light microscopy**. It has been reported that using advanced methods, the damaged cartilage pieces removed at the time of knee- or hip-replacement surgery for treating osteoarthritis, BCP crystals can be demonstrated in 100% of the damaged cartilage samples.

Pathogenesis of BCP Crystal Disease

It has also been shown that normal healthy joint cartilages do not show the presence of BCP crystals. Therefore, it is believed that BCP crystal formation occurs as a **secondary phenomenon**, after the primary step of some degree of cartilage 'wear-and-tear' incurred in daily life. However, once present in the joint cartilages (mainly knee and shoulder joints), BCP crystals are recognised as '**damage-associated molecular pattern**' (DAMP)

by the cells of the innate immune system (through toll-like receptors on macrophage-monocytes-fibroblast series of cells) **triggering low-grade inflammation** setting up a vicious cycle of increasing cartilage damage.

Clinical Features

This disease commonly affects middle-aged/elderly females although rarely it has been reported in much younger persons. There are 2 distinct clinical presentations of BCP disease:

1. **Calcific periarthritis:** Calcification in the tendons of the muscles that move hip joints, and those around shoulder joints are the commonest to be affected. Increasing pain and stiffness with difficulty in moving those joints, are the common presenting features. Plain radiograph gives away the diagnosis.
2. **Common forms of osteoarthritis in the knee, hip and shoulder joint but with rapid and severe joint destruction:** Unusually destructive and rapidly progressive OA-like disease is the characteristic of this form of BCP disease. When such destructive form affects the shoulder, it is called 'Milwaukee shoulder'.

Confirming the Diagnosis of BCP Disease

Only certain research level advanced techniques can demonstrate the presence of BCP crystals. Therefore, the diagnosis remains based entirely on clinical features described above.

Treatment of Crystal Arthritides

Discussion of the details of treatments of rheumatic and musculoskeletal diseases is beyond the scope of this book. Only certain general principles are touched upon as follows.

Acute Gout Arthritis

The acute attack of gout is aimed to control the acute inflammation as rapidly as possible. Treatment should start as soon as possible since response seems to be better. For this purpose, there are 3 drugs that can be used, namely nonsteroidal anti-inflammatory drugs (NSAIDs; nonselective as well selective cyclooxygenase-2 (COX-2) inhibitors); glucocorticoids (GC), and colchicine.

NSAIDs

All forms of NSAIDs are effective in treating acute attacks of gout. Therefore, the choice depends upon the patient's preference, presence of multimorbidities (especially in elderly, e.g. acid-peptic disease, hypertension, renal disease where NSAIDs should be avoided) and the familiarity and confidence of the treating physician. High recommended doses must be used for better efficacy. The route of administration of NSAIDs could be oral, intramuscular or rectal (suppositories) as preferred by the patients and guided by the clinical situation.

Glucocorticoids (GC)

These are effective alternatives for those in whom NSAIDs are contraindicated (as mentioned above). GC can be administered orally, intramuscularly as well as depot-GC

preparation can be administered as an intra-articular injection in the acutely inflamed joint.

Colchicine

Historically, colchicine was the main drug to control acute gout attack. But, due to its unacceptable adverse gastrointestinal effects this treatment is not used anymore.

Recurrent Acute Gout Attacks and Chronic Tophaceous Gout

Once the acute attack abates, treatment shifts towards preventing further acute attacks, preventing joint damage and reducing tissue deposits of MSU crystals (gout tophi) in the joints and surrounding soft tissue, over time. The basic principle for such a treatment is to keep serum uric acid levels <6 mg/dl using appropriate drugs (allopurinol and febuxostat are the 2 commonly used drugs).

Management of Metabolic Syndrome and Associated Atherosclerotic Cardiovascular Disease

It is important to mention that the majority of patients with gout have underlying metabolic syndrome (a cluster of biochemical and physiological abnormalities consisting of obesity, high blood pressure, high blood triglycerides, low levels of HDL cholesterol and insulin resistance associated with the development of cardiovascular disease and type 2 diabetes). Therefore, comprehensive management of chronic tophaceous gout must also include assessment and management of metabolic syndrome.

Treatment of CPPD Disease

While pseudogout can be a chronic condition, the symptoms can often be managed effectively with treatment. Unlike chronic tophaceous gout, pseudogout does not respond to medications that lower uric acid levels, as uric acid is not involved in CPPD. In the absence of any specific treatment, the aim is to focus on relieving symptoms and managing inflammation using NSAIDs, colchicine, corticosteroids, and sometimes joint aspiration. Long-term management may involve addressing underlying conditions that can contribute to CPPD, such as osteoarthritis, hyperparathyroidism, and haemochromatosis.

Treatment of BCP Crystal Disease

In the absence of any specific drug(s) for its treatment, NSAIDs and intralesional GC remain the main line therapies for BCP-related arthritis. Large calcific densities associated with chronic symptoms are often managed with a variety of interventions designed to break up the mineral deposits.

CHAPTER 6i

Septic Arthritis

INTRODUCTION

The characteristic anatomy of joints that makes them highly resistant to infection has been mentioned in Part I, Chapter 1. Therefore, **joint infections are uncommon** and typically occur only following a penetrating injury, such as an animal bite or trauma, or surgical interventions without appropriate aseptic precautions (including joint aspiration, joint injections, and joint surgery). The **knee**, being the joint most frequently injured in daily activities, is a common site for septic arthritis. Another route of joint infection is the haematogenous spread of microbes from a primary site distant from the joint. Transient bacteraemia, originating from various body reservoirs such as the teeth and mouth, skin, gut, and genitourinary tract, occurs several times a day. In a healthy individual, these microbes are quickly cleared from the bloodstream by the body's defence mechanisms. However, **preexisting joint damage** can provide a nidus for these circulating microbes, allowing them to embed at the site of joint damage and cause septic arthritis.

To diagnose septic arthritis, it is crucial to **determine the causative agent of the infection**. A general guideline is that if a penetrating injury has been definitively ruled out, then a thorough clinical history for the presence of any ongoing chronic joint disease such as rheumatoid arthritis, other inflammatory arthritides, or chronic tophaceous gout in the background, must be elicited. Such patients usually accrue some degree of joint damage during their disease course, which provides a nidus for infection. This can help explain the occurrence of septic arthritis superimposed over a background of a chronic joint disease, e.g. rheumatoid arthritis, osteoarthritis, chronic tophaceous gout, others.

It is also important to note that although osteoarthritis is the most common chronic joint disease, infection in an osteoarthritic joint is rare. This is likely because, unlike in inflammatory arthritides where the body's immune mechanisms are compromised, individuals with osteoarthritis usually have normally functioning immune systems that can effectively clear transient bacteraemia.

There is one major exception to the above-mentioned rule: **Normal joints do not get infected without a piercing injury or a preexisting chronic joint disease**. This exception is **gonococcal arthritis**, which can occur in healthy, young, sexually active

individuals, highlighting the severity of the virulence of this microbe. Additionally, the clinical features of gonococcal arthritis are notably different from other types of septic arthritis. Therefore, the broad heading of **acute septic arthritis** has been clearly classified into two distinct categories:

1. **Acute septic arthritis of the usual variety**
2. **Gonococcal arthritis**

Based on the above considerations, septic arthritis has been discussed under the following headings:

1. **Acute septic arthritis**
   a. **Usual acute septic arthritis** (most commonly due to *Staphylococcus aureus*)
   b. **Gonococcal arthritis**
2. **Chronic septic arthritis** (most commonly tuberculosis of the joint).

Acute Septic Arthritis

The majority of acute septic arthritis is caused by *S. aureus*, the common pus-forming bacterium responsible for skin boils and abscesses that many experience during childhood. Clinically, it presents as acute arthritis with all the hallmarks of inflammation in the affected joint, most commonly the knee: a painful, tender, swollen, warm joint with reddish discolouration of the overlying skin.

Key Points

1. **Clinical presentation**
   - **Acute inflammation:** The affected joint, often the knee, becomes acutely painful, red, hot, and swollen.
   - **Symptoms:** Severe pain, tenderness, warmth, and redness over the joint are typical clinical features of septic arthritis.
2. **Age and sex**
   - **Children:** More common in children, often due to piercing injuries or animal bites. The typical presentation in a child is an acutely painful, red, hot, and swollen knee.
   - **Older adults:** Older adults with poor nutritional status and multiple underlying health conditions (e.g. type 2 diabetes mellitus, cancer and chemotherapy, chronic diseases such as lung, liver, heart disease, or neurological conditions) are also susceptible, especially following fall-related joint injuries. In elderly patients, the acute clinical features may be less pronounced.
3. **Risk factors**
   - **Children:** Commonly caused by piercing injuries and animal bites.
   - **Adults and elderly:** Poor nutritional status, multimorbidity, and fall-related injuries.
4. **Importance of prompt diagnosis and treatment**
   - **Rapid joint destruction:** The disease can rapidly destroy the joint, making an early diagnosis and prompt treatment crucial to prevent irreversible damage.
   - **Quick diagnosis and effective management** of acute septic arthritis is essential due to its potentially rapidly destructive nature. This involves immediate medical attention, the appropriate use of antibiotics, and sometimes surgical intervention to drain the infected joint.

Gonococcal Arthritis

Gonococcal arthritis represents the **second category of acute septic arthritis** and is typically seen in young, sexually active individuals who do not have any underlying immunocompromised conditions. This type of arthritis spreads through **unprotected sexual contact**. Symptoms are generally more pronounced in males compared to females, leading to the seriousness of the infection often being overlooked in females. Consequently, females often become reservoirs for the infection more frequently than males. It is often remarked that males spread this infection while females bear the brunt of the disease.

After acquiring the gonococcal infection, the clinical presentation of disseminated gonococcal infection (DGI) is typically divided into a **bacteraemic form** and a **septic arthritis form**. Approximately 60% of patients with DGI present with symptoms consistent with the bacteraemic form, while the remaining 40% present with symptoms of a more localised infection (monoarthritis). However, overlapping features are not uncommon. These two forms of clinical presentation of gonococcal arthritis are discussed below:

1. **Bacteraemic form of disseminated gonococcal infection:** The conglomerate of clinical features of the bacteraemic form of DGI is often called '**arthritis-dermatitis syndrome**'. Typically, its clinical onset is 3–5 days after unprotected sexual contact. Classically, it has the following four components:
   a. **Nonspecific constitutional symptoms:** These include myalgias, fever, and malaise.
   b. **Musculoskeletal symptoms:** Develop during the early days after contracting the infection and include:
      - *Migratory asymmetrical polyarticular arthralgias:* These tend to affect the arms (wrists and elbows) more often than the legs (knees and ankles).
      - *Migratory asymmetrical tenosynovitis:* This affects the dorsum of the wrist, hand, and metacarpophalangeal joints, causing characteristic edematous swelling on the dorsum of the hands and wrists. This swelling subsides in one area and then 'migrates' to adjoining areas over a few days.
   c. **Skin rash:** The skin rash associated with the bacteraemic phase of DGI, is characteristically painless and nonpruritic, with small papular, pustular, or vesicular lesions. Occasionally, abscesses, cellulitis, petechiae, purpuric macules, or a vasculitic rash may be observed, as shown in **Fig. 6i.1**.
   d. **Evolution of gonococcal arthritis to septic arthritis:** In about a third of patients, the bacteraemic phase of gonococcal infection resolves spontaneously within a week or 10 days

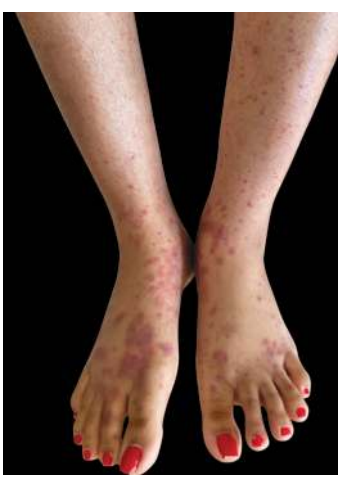


Fig. 6i.1: Typical painless non-pruritic papular purpuric rash (often called '*palpable purpura*') on the legs, characteristic of the bacteraemic phase of DGI

without treatment. In others, it transitions into septic arthritis, usually involving a single joint (most commonly the knee, as shown in **Fig. 6i.2**) or a few joints.

2. **Gonococcal septic arthritis—the localised form of gonococcal infection:** A cursory examination of gonococcal septic arthritis may not distinguish it from the usual form of septic arthritis. However, a more detailed clinical evaluation can easily reveal the diagnosis. Typically, the patient is in the sexually active age range, often women rather than men, who may even be older. There is usually a history of unprotected sexual contact in the recent past. As mentioned above, about 60% of patients would report a history of clinical features of DGI in the recent past, usually within a week or 10 days. Notably, women can become infected from their sexual partners without engaging in promiscuous behaviour and may not realise they have been infected. Therefore, a thorough clinical history, including a confidential sexual history of the sex partner(s), is crucial for making the diagnosis. An example of this clinical presentation in a patient is given in **Fig. 6i.2**.

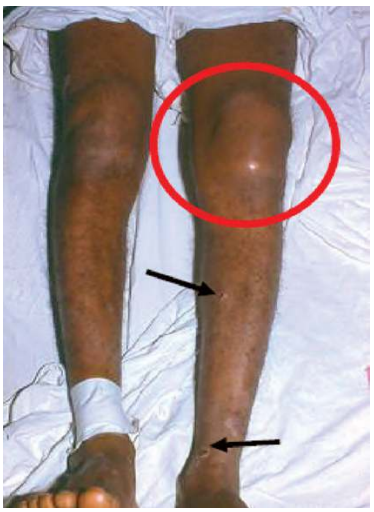


Fig. 6i.2: Patient with gonococcal arthritis that has transitioned into left knee septic arthritis (red circle). Healing gonococcal skin rashes are also visible (black arrows)

Understanding these forms and their clinical presentations helps in the accurate diagnosis and appropriate management of gonococcal arthritis. Quick and effective treatment is essential to prevent complications and ensure the best outcomes for patients.

Diagnosis of Acute Septic Arthritis

A thorough clinical history, including details of presenting complaints, past medical history, family history, and personal history, is essential for diagnosing acute septic arthritis. Special emphasis should be placed on obtaining a confidential personal history, which includes:

- Use of recreational drugs, including smoking and vaping history
- Information about sexual partners and contacts
- Sexual preference

The information gained from the clinical history, supported by the clinical features described above, is often sufficient to make a quick provisional diagnosis along with a short list of differential diagnoses. The next diagnostic steps are based on this information.

Diagnostic Steps

1. **Joint aspiration**
   - **Procedure:** Aspirate the actively swollen joint under stringent aseptic conditions.

- **Fluid analysis**
  - *Smear examination:* Examine a smear of aspirated fluid with Gram stain.
  - *Microbial culture and sensitivity testing:* Send the aspirated fluid for culture and sensitivity testing.

2. **Special considerations for gonococcal infection**
   - **Culture media:** Gonococci are fastidious microbes that require special culture media, such as chocolate agar plates, which are not routinely available in all microbiology laboratories.
   - **Laboratory preparation:** Inform the laboratory in advance if gonococcal infection is suspected so they can prepare the specific culture plates.

Additional Diagnostic Support

Dermatological consultation: Consulting a dermatologist is particularly useful in cases where arthritis of suspected infectious etiology is present. Various types of dermatological lesions associated with infectious diseases can provide important clues toward making a diagnosis.

Management of Acute Septic Arthritis

A detailed discussion of acute septic arthritis is beyond the scope of this book; only a summary is provided as follows:

1. **Initial empirical treatment**
   - **Antibiotic therapy**
     - Customarily, the most appropriate empirical antibiotic treatment is advised immediately based on the provisional clinical diagnosis (staphylococcal or gonococcal infection).
     - Further treatment is then adjusted based on culture and sensitivity reports to target the specific bacteria and its antibiotic susceptibility.
   - **Supportive therapy for gonococcal infection**
2. **Dermatological consultation**
   - Consult a dermatologist for suspected gonococcal infection to get updated advice on the prevailing antibiotic sensitivity of gonococci in the community.
3. **Orthopaedic consultation**
   - Consult an orthopaedic surgeon for the possible insertion of a small drain to prevent the collection of toxic inflammatory fluid (pus).
   - Remove the drain once the infection is controlled and suture the small surgical incision.

Additional Considerations for Elderly Patients

Crystal arthritis mimicking septic arthritis

- Recognise that acute crystal arthritis that can completely mimic septic arthritis in elderly patients.
- Be aware that acute crystal arthritis may become secondarily infected, complicating the diagnosis and management.

Diagnostic Procedures for Elderly Patients

Joint fluid analysis: Send every aspirated joint fluid for:

- Microbial culture and sensitivity testing.
- Examination under polarised light microscopy for the presence of crystals.

Summary

Effective management of acute septic arthritis begins with a thorough clinical history and immediate diagnostic procedures. A dermatology consultation can further aid in diagnosing cases with ambiguous presentations.

Joint aspiration and comprehensive fluid analysis are pivotal first steps to ensure accurate diagnosis. Prompt empirical antibiotic therapy tailored to the suspected pathogen is crucial, with modifications based on culture and sensitivity results. Preparation for specific microbial cultures, especially for fastidious organisms like gonococci, ensures precise identification of the causative agent. In cases of gonococcal infections, dermatological consultation is vital due to changing antibiotic sensitivities. In elderly patients, careful differentiation between septic and crystal arthritis is essential, necessitating detailed joint fluid analysis. Additionally, an orthopaedic consultation is advisable for surgical drainage when necessary.

CHAPTER 6ii

Chronic Infections in the Joints

INTRODUCTION

In contrast to septic arthritis, which presents as acute arthritis (discussed in the previous chapter), joints may also be involved with microbes that cause **chronic infection**. As against septic arthritis, such patients present with slowly increasing symptoms of pain, swelling and inability to use that joint. In general, chronic form of joint infection is much less common than septic arthritis.

ETIOPATHOGENESIS

The commonest chronic infection in joints is due to **tuberculosis** (TB), the causative agent being *Mycobacterium tuberculosis*. Rarely, chronic infectious arthritis can also be caused by several other species of Mycobacterium as well as other microbes, especially in immunocompromised persons (HIV infection, chemotherapy, patients with organ transplant, severe malnutrition, and other debilitating chronic illnesses). In recent times some of the infections that had become uncommon, are making a comeback. Thus syphilis, a major venereal disease caused by infection with bacterium *Treponema pallidum*, seems to be on the rise. This bacterium causes infection when it gets into broken skin or mucous membranes, usually of the genitals usually during unprotected sexual contact. It might be associated with 2 other sexually transmitted diseases, namely HIV infection and gonococcal infection. Any of the several species of **fungi** could also cause chronic joint infection in such individuals. In certain geographical regions where brucellosis is common, it could cause chronic arthritis (involving the joints in the spine as well).

As already stated above, tuberculosis is the commonest cause of chronic infection in skeletal tissue most often affecting the spine (Pott's spine). In contrast, the common term used for extraspinal skeletal tuberculosis is '**peripheral osteoarticular tuberculosis**'. This form of tuberculosis is almost always due to reactivation of tubercle bacilli that get lodged in bone-and-joint during the original primary infection, the stage at which mycobacteraemia is common. The predilection of tuberculous involvement of large joints (the knee and hip joints being the commonest) and spine is possibly due to rich vascular supply of these musculoskeletal (MSK) regions. There could be several reasons for the reactivation of primary foci of infection. Malnutrition is the commonest cause. Other

clinical states causing poor health status could also lead to the reactivation of primary foci of infection. **This chapter gives a summary of joint tuberculosis**. Description of other forms of chronic infectious joint disease is beyond the scope of this book.

Clinical Features

Peripheral Osteoarticular Tuberculosis

Commonly used term for extraspinal skeletal tuberculosis that affects joints or bones is '**peripheral osteoarticular tuberculosis**'. It presents in two different clinical forms, namely '**tuberculous arthritis**' and '**tuberculous osteomyelitis**', the latter can lead to the formation of a cold abscess. Even **tuberculous bursitis** can occur. By and large, rheumatologists would be dealing with tuberculous arthritis while other forms of peripheral osteoarticular tuberculosis, belonging to the field of orthopaedics, would be managed by orthopaedic surgeons. As already mentioned above, hip and knee are the commonest joints to be affected. Less commonly affected are sacroiliac and sternoclavicular joints. Tuberculosis of the joints is a **slowly progressive chronic disease** that most commonly presents as **monoarthritis** of the hip or the knee joint. In some cases, there may be a previous clinical history of traumatic injury, which could provide nidus for mycobacteria. Slowly increasing discomfort and pain in the joint for weeks or months is the characteristic clinical feature, much more prominent than signs of inflammation. Tuberculosis of joint(s) is almost always seen in paediatric age, and in elderly neglected, malnourished persons with multimorbidities. It is to be noted that **fever and systemic symptoms, characteristic of pulmonary tuberculosis, are usually absent.** An important clinical feature of joint tuberculosis is the striking wasting of the muscles that move the joint, much more proximal than the distal muscles. It causes a **'fusiform' appearance** of the knee, the most affected joint, as shown in **Fig. 6ii.1A**. The radiographic changes of the same joint with tuberculous infection are illustrated in **Fig. 6ii.1B**.

Other Chronic Infections in the Joint(s)

Besides peripheral osteoarticular tuberculosis, there is a large list of infectious agents that may uncommonly or rarely cause chronic joint disease. These include non-tuberculous mycobacterial diseases (*M. marinum, avium, kansasii, abscessus*), brucella infection, several fungal infections (*Candida* species, Coccidioides, Histoplasma, Cryptococcus, Blastomyces, Aspergillus, Actinomyces), spirochaetal infections including Lyme disease, syphilis, and leptospirosis. Most of these infections are uncommon, therefore not discussed in depth. For details of these infections, the reader is referred to standard textbooks.

Diagnosis and Management of Tuberculous Arthritis and Other Chronic Infectious Arthritides

A thorough clinical history is essential for diagnosing joint diseases, particularly suspected tuberculous arthritis. This includes details on presenting symptoms, past medical conditions, family history, and personal factors. Key considerations include exposure to TB patients, living conditions, and nutritional history, as these factors can be

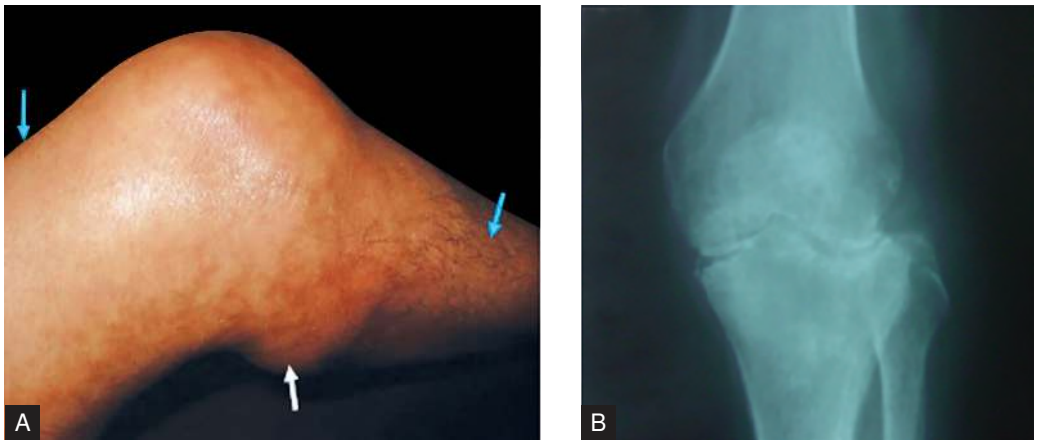


Fig. 6ii.1A and B: (A) Tuberculosis of the right knee joint (proven by synovial biopsy). Note the marked wasting of the proximal and the distal muscles of the affected knee (light blue arrows); a 'cold abscess' on the posterior aspect (white arrow) is also visible; (B) The radiograph of a tuberculous joint infection showing the right knee with the following notable abnormalities: Narrowing of joint space osteopenia (bone thinning), bone destruction (irregularities or erosion in the bony structure of the knee), periarticular osteoporosis, soft tissue swelling, formation of subluxation/dislocation: Cystic lesions/lytic areas; features typical for a chronic granulomatous inflammation caused by *Mycobacterium tuberculosis*, leading to progressive joint destruction and disability if untreated. (*Courtesy:* Dr Jitendra Maheshwari, Joint Replacement Surgeon, SRBRI, New Delhi)

crucial in diagnosis. Additionally, a confidential assessment of personal habits—such as smoking, vaping, recreational drug use, sexual history, and preferences—may provide important clues for differential diagnosis.

Diagnosis of Tuberculous Arthritis

The clinical features of joint tuberculosis are often distinctive enough to raise suspicion. However, definitive treatment should only begin after confirmation through one or more of the following methods:

- **Acid-fast bacilli (AFB) detection:** Smear examination of aspirated joint fluid.
- **Histopathology:** Biopsy of synovial tissue showing caseous granulomas.
- **Microbial culture:** Isolation of *Mycobacterium tuberculosis* from joint fluid.
- **Advanced molecular or immunological tests, such as** interferon gamma release assay (IGRA).

Xpert *Mycobacterium tuberculosis*/rifampicin (Xpert MTB/RIF) test: A PCR-based method for detecting TB and rifampicin resistance.

These advanced diagnostic techniques must be performed in validated laboratories to ensure reliable results. Once TB is confirmed, a complete course of anti-tuberculous treatment (ATT) should be initiated under the supervision of a TB specialist for optimal management, as discussed below.

Diagnosis of other chronic infectious arthritides: For chronic infectious arthritis of non-tuberculous origin, diagnosis follows a similar structured approach. A detailed history, including past illnesses, family background, and personal habits, is essential.

Identifying the causative pathogen may require:

- Serological tests for pathogen-specific antibodies.
- Microbial cultures of joint fluid or tissue samples.
- Polymerase chain reaction (PCR) and other molecular diagnostic techniques.
- Histopathological examination of joint tissue.

Once the causative organism is confirmed, treatment should be guided by an infectious disease specialist.

Role of orthopaedic consultation: In cases of suspected infectious arthritis, consultation with an orthopaedic surgeon is invaluable. They can assist in obtaining tissue samples for histopathological analysis and may recommend surgical interventions when necessary.

By integrating clinical history, laboratory diagnostics, and expert consultations, effective management of tuberculous and other chronic infectious arthritides can be ensured.

Management of chronic infectious joint disease: Effective management of chronic joint disease caused by an infection requires a multidisciplinary approach, spearheaded by a rheumatologist. The involvement of multiple specialists ensures accurate diagnosis, appropriate treatment, and optimal patient outcomes.

Diagnostic Process

1. **Rheumatologist**
   - Leads the diagnostic process.
   - Utilizes clinical history, physical examination, and preliminary laboratory tests.
   - Coordinates with a specialist joint surgeon for further diagnostic procedures.
2. **Specialist joint surgeon**
   - Assists in obtaining samples for microbiology and histopathology.
   - Performs necessary surgical interventions to manage joint damage.
3. **Microbiological and histopathological tests**
   - Samples from the affected joint are cultured to identify the infectious agent.
   - Histopathological examination helps in confirming the diagnosis.

Treatment Process

1. **Infectious disease specialist**
   - Provides expertise on the infectious agent's current sensitivity to anti-infective agents.
   - Helps determine the most effective drug regimen, including the appropriate drug, dose, and duration of treatment.
   - Monitors the patient's response to treatment and makes necessary adjustments.
2. **Multidisciplinary collaboration**
   - Continuous communication between the rheumatologist, joint surgeon, and infectious disease specialist ensures a cohesive treatment plan.
   - Regular reviews and updates of the patient's condition and treatment efficacy.

Importance of a Specialist Approach

- **Changing sensitivity of microbes:** Infectious agents often develop resistance to standard treatments over time. An infectious disease expert is crucial in navigating these changes and ensuring the use of the most effective anti-infective agents.
- **Comprehensive care:** Chronic joint infections are complex and can significantly impact a patient's quality of life. A team approach ensures all aspects of the disease are addressed, from infection control to joint function preservation.
- **Tailored treatment plans:** Each patient may require a different treatment strategy based on their specific condition, comorbidities, and response to treatment. Collaboration among specialists allows for personalised care.

By leveraging the expertise of a rheumatologist, specialist joint surgeon, and infectious disease specialist, chronic infectious joint diseases can be managed more effectively, leading to better patient outcomes and quality of life.

CHAPTER 6iii

Parainfectious Arthritis

Definition

Parainfectious arthritis is defined as acute inflammatory arthritis that occurs concurrently with an ongoing or very recent infection elsewhere in the body. Unlike reactive arthritis (discussed in the next chapter), where the arthritis develops after the primary infection has resolved and the infection is no longer present, parainfectious arthritis occurs while the primary infection is still active. In routine clinical practice, this is among the most common forms of acute arthritis and is generally self-limiting. Colloquially, this type of arthritis is often referred to as "viral arthritis".

Causative Infectious Agents

Parainfectious arthritis is most commonly associated with viral infections, including chikungunya, parvovirus B19, rubella, mumps, and hepatitis B and C. However, it can also be caused by bacterial infections such as Lyme disease, Poncet's disease (caused by *Mycobacterium tuberculosis*), and arthritis seen in leprosy during the 'reaction' phase. Additionally, several other uncommon conditions can also lead to parainfectious arthritis.

Clinical Features

Parainfectious arthritis, unlike reactive arthritis, manifests simultaneously with the infection or shortly after its onset. It is a frequent type of acute arthritis encountered in the community. Patients typically present with joint pain, swelling, and occasionally redness and warmth over the affected joints. Arthritis is typically polyarticular and acute, affecting both large and small joints, resembling the pattern seen in rheumatoid arthritis, as shown in **Fig. 6iii.1**.

Symptoms (pain and stiffness are more prominent than signs of joint involvement). Commonly associated symptoms include constitutional symptoms related to the underlying infection, such as fever, malaise, rash, and lymphadenopathy.

Diagnosis and Management

Diagnosing parainfectious arthritis involves several steps: Obtaining a detailed clinical history, conducting a thorough physical examination, and performing appropriate

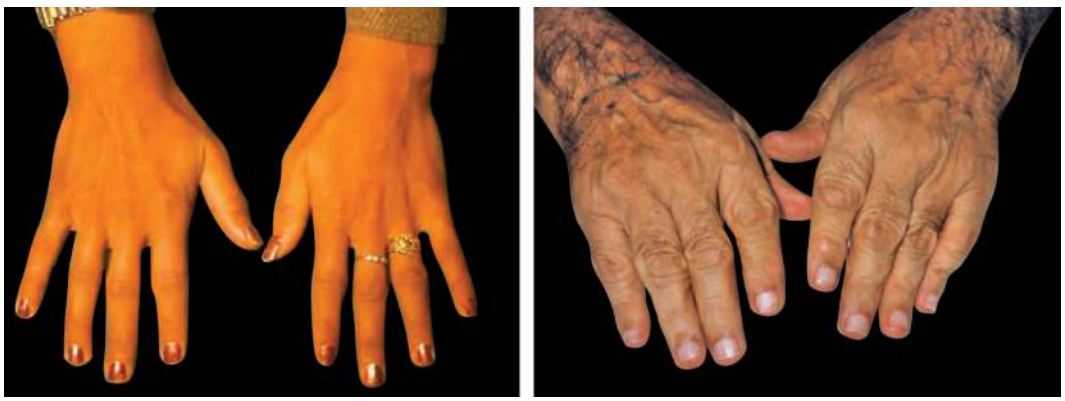


Fig. 6iii.1: Hands in a woman and a man with viral arthritis

laboratory tests or imaging studies. A positive history of similar joint symptoms in family or community members can aid in making a provisional diagnosis of parainfectious viral arthritis. Blood tests may reveal elevated inflammatory markers such as ESR (erythrocyte sedimentation rate) and CRP (C-reactive protein). Specific antibody tests, particularly of the IgM class, can sometimes confirm the diagnosis, although these are not always necessary as most viral infections causing parainfectious arthritis are self-limiting.

Parainfectious arthritis manifests concurrently with an ongoing infection or shortly after its onset. Therefore, treatment primarily targets the active infection itself, using appropriate antimicrobial therapy to eradicate the pathogen causing the arthritis. This approach helps to resolve both the infection and the associated joint symptoms. In contrast, reactive arthritis develops after the resolution of the initial infection. The inflammation in reactive arthritis is believed to be triggered by the immune system's response to the previous infection, rather than by the presence of the microbe itself. Treatment of reactive arthritis focuses on managing inflammation and relieving symptoms, typically with NSAIDs, corticosteroids, and other supportive measures.

Difference Between Parainfectious and Other Infection-related Arthritides

Understanding the differences between parainfectious arthritis and other types of arthritis, such as reactive arthritis, is crucial for accurate diagnosis and effective management. Treatment for parainfectious viral arthritis typically involves symptomatic management with nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GC), and other supportive measures to alleviate joint symptoms and manage inflammation. In patients where parainfectious arthritis is caused by bacterial infections or other pathogens, treatment focuses on addressing the underlying focus of infection with appropriate antimicrobial therapy.

By understanding these distinctions, healthcare providers can tailor their approach to diagnosis and treatment, ensuring that patients receive appropriate and timely care based on the underlying cause of their arthritis.

Prognosis

Parainfectious arthritis typically resolves once the underlying infection is adequately treated and does not usually lead to chronic joint damage.

CHAPTER 6iv

Reactive Arthritis

INTRODUCTION

Reactive arthritis is a distinct type of acute polyarthritis outlined in this chapter. However, in clinical practice, the term is frequently misinterpreted and applied to any acute inflammatory arthritis without thorough evaluation. This misuse underscores the importance of accurately understanding and diagnosing reactive arthritis based on specific criteria.

The primary objective of this chapter is to elucidate the concept of reactive arthritis in a straightforward manner. By doing so, it aims to equip primary care physicians with the knowledge needed to identify these cases accurately and initiate appropriate management strategies. This approach is crucial for ensuring effective treatment and optimal outcomes for patients presenting with reactive arthritis.

Subtypes of Reactive Arthritis

Reactive arthritis can be classified into two major types:

1. **Classical reactive arthritis**, and
2. **Non-classical reactive arthritis**

Classical reactive arthritis typically follows a bacterial infection in the **gastrointestinal** or **urogenital tract**, such as diarrhoea or urethritis. It manifests with acute onset joint symptoms shortly after the infection resolves. Non-classical reactive arthritis, on the other hand, may arise from infections at other anatomical sites (skin, upper respiratory tract), presenting with clinical features resembling any acute polyarthritis.

Differentiating between these two types is crucial for accurate diagnosis and management. It helps healthcare providers to tailor treatment strategies based on the underlying cause. For instance, in 'classical reactive arthritis', identifying and treating the preceding bacterial infection is essential, while in 'non-classical reactive arthritis', broader considerations of viral or alternative bacterial causes may be necessary. This classification system not only aids in clinical decision-making but also underscores the importance of precise diagnosis to optimize patient care and outcomes.

1. Classical Reactive Arthritis

Reactive arthritis is an acute inflammatory polyarthritis triggered by a recent bacterial infection. In its **classical form**, the infection occurs in either the **gastrointestinal tract** (**diarrhoea-dysentery**) or the **urogenital tract** (**urethrocervicitis**). Symptoms of arthritis typically begin soon after the gastrointestinal or urogenital infection subsides, with or without treatment, usually within 7–10 days but **never beyond a period of one month**. It is important to note that reactive arthritis is characterised by **sterile inflammation**, meaning that the microbial infection that initially triggered the joint disease cannot be detected in the actively inflamed joint. However, researchers using various advanced methods, such as detecting specific antibodies, advanced molecular biological techniques, and advanced imaging techniques, have provided evidence of a recent past infection in such patients.

Epidemiologic Features of Reactive Arthritis

Reactive arthritis has a distinct age and sex predilection, primarily affecting young to middle-aged men (30–50 years old). Approximately 90% of cases occur in men with a recent history of acute urethritis or urethra-cervicitis that has resolved. Most of these individuals have engaged in unprotected sexual contact, after which they develop urethritis symptoms that typically subside within 7–10 days and never persist beyond a month.

In contrast, reactive arthritis is far less common in prepubertal children and premenopausal women. When it does occur in these groups, it is more often triggered by a recent gastrointestinal infection, such as food poisoning.

Clinical Features of Reactive Arthritis

Clinically, **reactive arthritis presents as acute inflammatory arthritis, with symptoms peaking within days or weeks**. It typically affects large joints in the lower extremities in an asymmetrical pattern and may be associated with low back pain in some patients. A minority of cases show extra-articular involvement, including specific dermatologic and mucosal manifestations such as **keratoderma blennorrhagicum (Fig. 6iv.1)**, **circinate balanitis**, nail changes, **ulcerative vulvitis**, and oral lesions

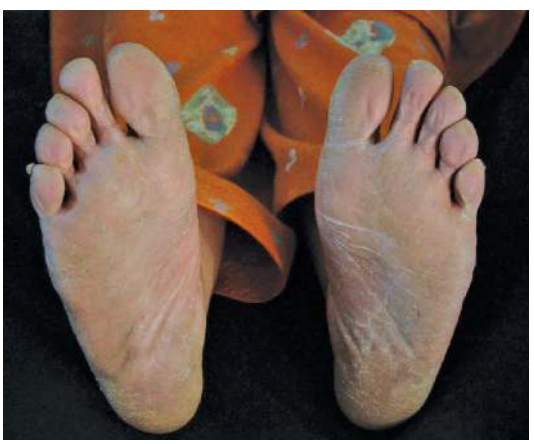


Fig. 6iv.1: Feet lesions called *keratoderma blennorrhagicum*

(**mucositis**). This combination of symptoms and signs constitutes the full form of reactive arthritis, historically known as **Reiter's syndrome**.

Initially, the symptoms of reactive arthritis can be mild but may become more severe over time. While the majority of patients experience reactive arthritis as a monocyclic (non-recurring) disease, a certain proportion develop a **remitting-relapsing** (**polycyclic**) **chronic course**. The pattern of joint involvement (asymmetrical large joint involvement below the waist), inflammatory low back pain, and extra-articular features, including heel enthesitis and mucocutaneous lesions, are reminiscent of peripheral spondyloarthritis. Approximately 60–70% of such patients carry the HLA-B27 gene, which is associated with a high likelihood of developing the chronic form of spondyloarthritis. Therefore, this form of reactive arthritis is categorized as one of the secondary forms of spondyloarthritis, along with psoriatic and enteropathic spondyloarthritis (*see* Part II, Chapter 2).

The post-dysenteric or post-urethritic reactive arthritis described above is often referred to as **classical reactive arthritis**. This contrasts with other forms of arthritis that may occur following infections at sites other than the genitourinary or gastrointestinal tract. These forms can be labelled as **nonclassical reactive arthritis**, described below.

2. Non-classical Reactive Arthritis

Arthritis in Rheumatic Fever

It is a complication of inadequately treated streptococcal sore throat or scarlet fever caused by group A Streptococcus bacterium. The clinical form of arthritis in acute rheumatic fever is characterised by a rapidly developing, migratory polyarthritis (moves from one joint to another within hours) that primarily affects larger joints, is highly inflammatory, and is associated with other systemic symptoms of acute rheumatic fever and early heart involvement (the common saying 'it licks the joints but bites the heart!).

Poststreptococcal Reactive Arthritis (PSRA)

It is an uncommon complication of group A streptococcal (GAS) infection. It must be emphasised that PSRA is clinically different from acute rheumatic fever, which is also a manifestation of GAS in the recent past. PSRA patients do not fulfil the diagnostic criteria of acute rheumatic fever. Therefore, it must not be confused with acute rheumatic fever; it is unrelated to it and has no clinical features of that disease. Symptoms include joint pain, swelling, and stiffness that come on suddenly 7–10 days after infection. Most people recover within weeks to months.

Postmeningococcal Reactive Arthritis

It is a recognised manifestation in 2–10% of **meningococcal infections**. The most frequent presentation of arthritis is during the recovery period, when large joints are affected by a sterile effusion. Certain skin lesions are often seen in these cases and consist of petechiae (non-blanching purpura-like skin lesions that do not disappear when pressure is applied to the skin; seen in ~50–75% of cases. A blanching or maculopapular rash may also occur. In some patients the rash may progress to larger red patches or purple lesions (similar to bruises) occasionally causing skin damage, as shown in **Fig. 6iv.2**.

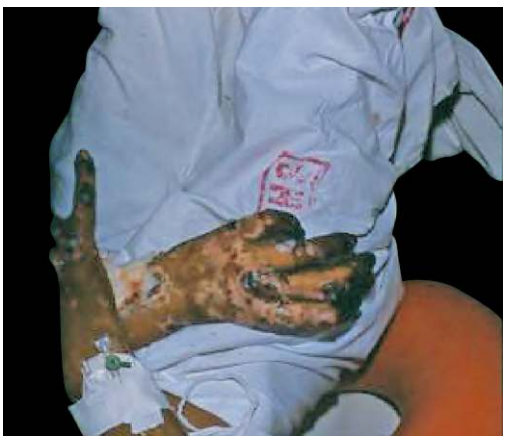


Fig. 6iv.2: Such a skin lesion in a patient with meningococcal infection

Post-viral (Reactive) Arthritides

Some of the arthritic symptoms that develop within 7–10 days after complete recovery from an acute viral infection may have similarity to reactive arthritis. In these patients, the clinical history would be that of the usual symptoms of an acute viral infection with fever, and other constitutional symptoms including arthralgias and myalgias. The symptoms of acute viral infection would abate within a few days to a week. Then, the patient remains normal for ~1–2 weeks then would start to develop slowly increasing peripheral joint disease which shows close similarity to joint involvement in rheumatoid arthritis. Over a period of about 6–8 weeks, it would become difficult to differentiate its pattern of joint involvement from that of seronegative rheumatoid arthritis. To add to further confusion, some of these patients start to show the presence of rheumatoid factor (RF) as well as anti-citrullinated peptide antibodies (ACPA) in their blood. In such cases it could be speculated that in genetically prone individuals the preceding viral infection triggered the onset of seropositive RA. The most implicated viruses in tropical-semi tropical countries (including India) are chikungunya virus, parvovirus, the alphaviruses, hepatitis B, hepatitis C, Epstein-Barr virus, and tropical viruses such as the Zika virus.

Acute Reactive Arthritis vs Arthritis in Acute Disseminated Gonococcal Infection (DGI)

Clinically, there is a close similarity between reactive arthritis and arthritis seen in disseminated gonococcal infection (DGI). Both conditions often feature a history of recent urethritis and the presence of mucocutaneous lesions. Epidemiologically, they are similar as well, both occurring in sexually active young individuals. The pattern of joint involvement in both conditions is also comparable. Therefore, a beginner might mistakenly consider the arthritis seen in DGI as a form of reactive arthritis. However, this would be scientifically incorrect. In DGI, microbial cultures from blood, fluid from prostate massage, a swab from the cervix, or synovial fluid from the involved joint will grow *Neisseria gonorrhoeae*. This contrasts with true reactive arthritis, where the microbe that triggered the disease cannot be demonstrated in the inflamed joint.

Diagnosis and Management of Reactive Arthritis

As is true for arthritides in general, a meticulous clinical history, repeatedly emphasized throughout this book, is crucial for diagnosing reactive arthritis and its subtypes. Details of the presenting complaints, past medical history, personal history (including addictions, use of recreational drugs, sexual contacts, and sexual preference), and family history usually provide vital clues for reaching the correct diagnosis.

Patients presenting with a recent history of an episode of infection (viral or bacterial) followed by a symptom-free interval of 1–2 weeks and subsequent rapid development of polyarticular symptoms should be considered for a diagnosis of reactive arthritis. Based on the clinical type and site of the recent infection, a provisional subtype of reactive arthritis can be determined: '**Classical**' (following urogenital or gastrointestinal infection) or '**non-classical**' (following infections of the skin, upper respiratory tract, or other sites).

In some cases, often as part of a research project, appropriately focused investigations (such as specific antibodies and advanced molecular biological studies) may provide proof of a specific recent infection. However, this may not be necessary for appropriate treatment, which primarily involves symptomatic management with commonly used NSAIDs and other supportive measures. Due to the potential chronicity of several forms of reactive arthritis, it is strongly advised that management be conducted under the guidance of a rheumatologist. This is especially important for patients who develop chronic inflammatory polyarthritis indistinguishable from RA and other systemic inflammatory arthritides.

CHAPTER 7

Uncommon and Rare Rheumatic and Musculoskeletal Diseases (RMDs)

INTRODUCTION

There are several rheumatological diseases that are uncommon or rare. As the saying goes, "Rheumatology is the last standing bastion of clinical medicine"! Therefore, it is often a rheumatologist who is consulted for patients with unexplained symptoms. These patients frequently have multisystem diseases that elude diagnosis by other physicians. Most of them exhibit musculoskeletal (MSK) symptoms that do not match the typical clinical features of common rheumatic and musculoskeletal diseases (RMDs).

This chapter provides a brief overview of some of these diseases to help primary care physicians (PCPs) and general practitioners (GPs) consider these conditions in their differential diagnoses. Based on these clinical features, the patient may then be referred to a rheumatologist for diagnosis confirmation and appropriate treatment.

The diseases covered in this chapter include:

- Immunoglobulin G4-related disease (IgG4-RD)
- Adult-onset Still's disease (AOSD)
- Musculoskeletal manifestations of sarcoidosis
- Behçet's disease
- Multicentric reticulohistiocytosis
- Primary amyloidosis-related musculoskeletal disease
- Histiocytoses of the various types
- Panniculitides

There are other relatively uncommon or rare RMDs that are outside the scope of this chapter. For further information, readers are encouraged to consult standard rheumatology textbooks.

Immunoglobulin G4-related Disease (IgG4-RD)

Immunoglobulin G4-related disease (IgG4-RD) is a chronic inflammatory condition characterised by tissue infiltration with IgG4-positive plasma cells and often elevated serum IgG4 levels. It can affect multiple organs, including the pancreas, salivary glands, kidneys, and lymph nodes, leading to a variety of clinical manifestations with the basic underlying pathology being laying down excessive fibrosis in different body tissues. **Retroperitoneal fibrosis** is one the most common presentations of IgG4-RD.

Other common features include tumefactive lesions, fibrosis in different organs causing dysfunction that may lead to the following common MSK symptoms:

1. **Arthritis with synovitis:** Inflammation of the synovial membrane, leading to joint swelling and pain, which can affect multiple joints.
2. **Tendonitis:** Inflammation of tendons causing pain and limited range of motion.
3. **Myositis:** Muscle inflammation leading to muscle pain, weakness, and swelling.
4. **Bone pain:** Generalised bone pain, which may be associated with bone lesions.
5. **Soft tissue masses:** Development of palpable masses or nodules in the soft tissues, which can be mistaken for tumours.

These symptoms are often part of a broader systemic involvement and can be accompanied by other signs and symptoms related to the affected organs.

Diagnosis typically involves a combination of clinical evaluation, imaging, laboratory tests, and histopathological examination. Treatment often includes glucocorticoids (GC) and immunosuppressive agents to manage inflammation and prevent organ damage. **Figure 7.1A to F** shows some of the manifestations of IgG4-RD.

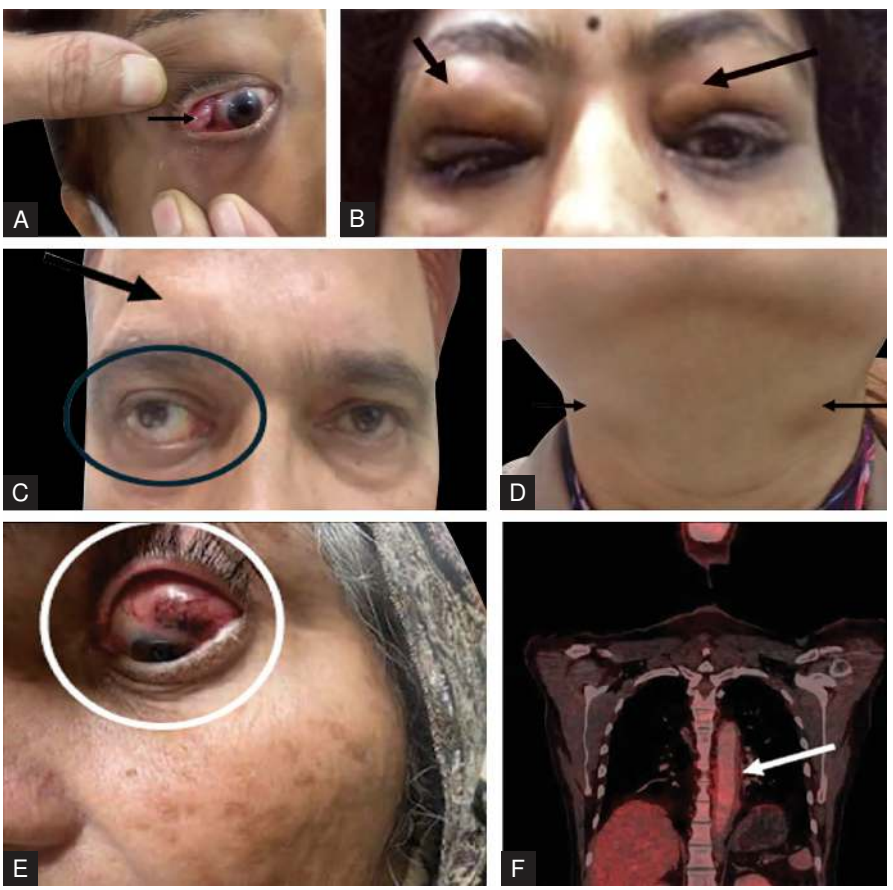


Fig. 7.1A to F: (A) Lacrimal gland involvement; (B) Dacroadenitis; (C) Orbital involvement; (D) Involvement of the lymph nodes in the neck; (E) Scleritis; (F) Peri-aortitis as increased FDG (fluorodeoxyglucose) uptake on PET (positron emission tomography) scanning. (*Courtesy:* Dr Lalit Duggal, Senior Consultant, Department of Rheumatology, Sir Ganga Ram Hospital, New Delhi)

Adult-onset Still's Disease (AOSD)

Adult-onset Still's disease (AOSD) is a rare inflammatory disorder characterised by a combination of high spiking fevers, a salmon-coloured bumpy rash, erythema nodosum, a specific type of skin rash and arthritis. It typically affects young adults and presents with systemic symptoms that can include sore throat, muscle pain, and lymphadenopathy. A skin reaction to even minor pressure injury (e.g. firmly moving a fingertip on the skin of the back, e.g. trying to write your name) would produce a salmon-coloured elevated rash). This has been named 'Koebner phenomenon' (which is not specific for AOSD but also seen in psoriasis, lichen planus, and vitiligo). Laboratory findings often show elevated white blood cell counts, **high serum ferritin levels**, and **markers of inflammation** such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Diagnosis is clinical, relying on the exclusion of other conditions with similar presentations. Plain chest radiograph may show **bilateral hilar lymphadenopathy** that can be better defined on a chest computed tomography. Treatment usually involves nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs) to control symptoms and inflammation. Several new 'targeted' treatments are under trials; early results have shown encouraging results.

Some representative photographs of the various lesions seen in AOSD are shown in **Figs 7.2 and 7.3**.

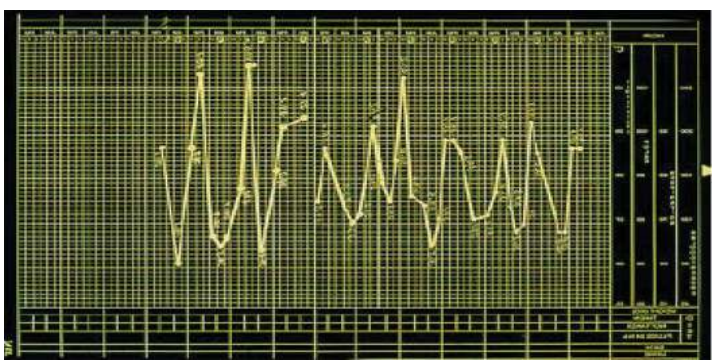


Fig. 7.2: Typical pattern of fever in AOSD

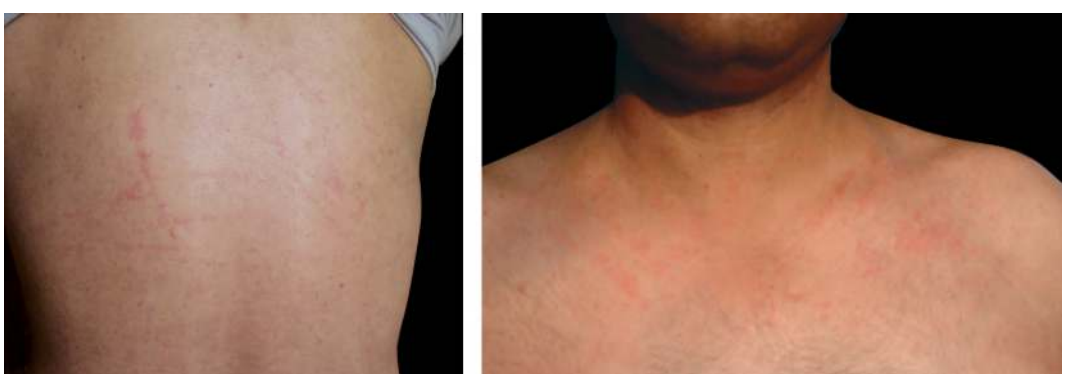


Fig. 7.3: Koebner phenomenon on the back and front of the chest of a patient with AOSD

Sarcoidosis

Sarcoidosis is a multi-organ inflammatory disease with **musculoskeletal involvement** which is part of the systemic involvement of sarcoidosis, and their severity varies among individuals.

Key features include:

1. **Fever:** Low-grade to moderate, often part of the systemic inflammatory response.
2. **Arthritis**
   - Can present as acute or chronic inflammatory arthritis, typically affecting the **ankles, knees, wrists, and hands**.
   - Sarcoidosis is known for causing almost every pattern of inflammatory arthritis, making it important to include sarcoidosis in the differential diagnosis of any form of inflammatory arthritis.
3. **Löfgren syndrome**
   - **An acute form of sarcoidosis**, characterised by:
     - *Erythema nodosum:* Painful, red nodules on the shins.
     - *Bilateral hilar lymphadenopathy:* Enlarged lymph nodes in the lungs, visible on imaging.
     - *Polyarthritis or arthralgia:* Symmetric arthritis, typically affecting the ankles.
   - **Epidemiology:** More common in women, with a seasonal pattern (spring/early summer) and favourable prognosis, usually resolving spontaneously within 1–2 years. Commonly seen in certain populations, like Scandinavians and Irish, and in *Northern India* during the spring months.
4. **Polyarthritis:** Bilateral ankle arthritis is common in young adults, particularly during spring, and can be so characteristic that it may not require extensive investigation for diagnosis.
5. **Myopathy:** Muscle involvement, causing **myalgia, weakness, and fatigue**. Chronic myopathy may result in muscle atrophy.
6. **Bone lesions:** Granulomatous involvement, especially in the **small bones of the hands and feet**, can lead to pain and deformities.
7. **Tenosynovitis:** Inflammation of tendon sheaths, causing pain and swelling along the tendons.
8. **Dactylitis:** "Sausage digit", marked by swelling of an entire finger or toe due to joint and tissue inflammation.

Some typical manifestations of sarcoidosis-related musculoskeletal manifestations are shown in the representative photographs from **Figs 7.4 to 7.7**.

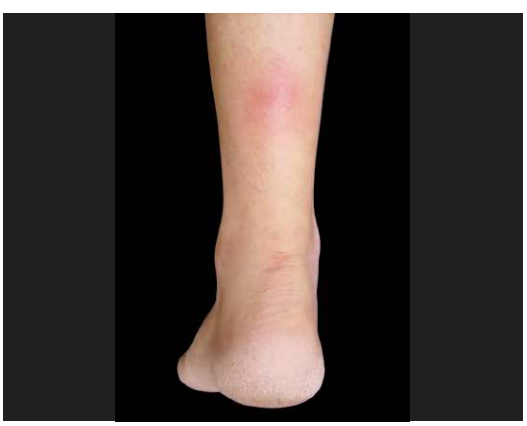


Fig. 7.4: Erythema nodosum in a patient with sarcoidosis

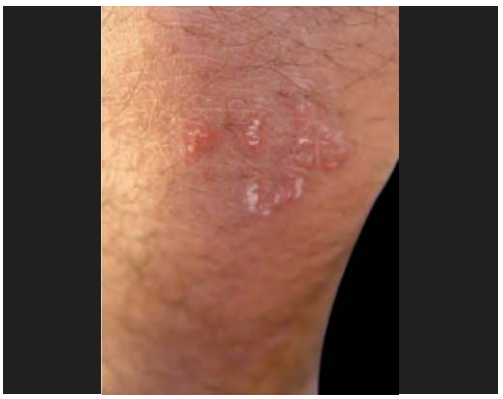


Fig. 7.5: Sarcoid skin lesions over the knee joint

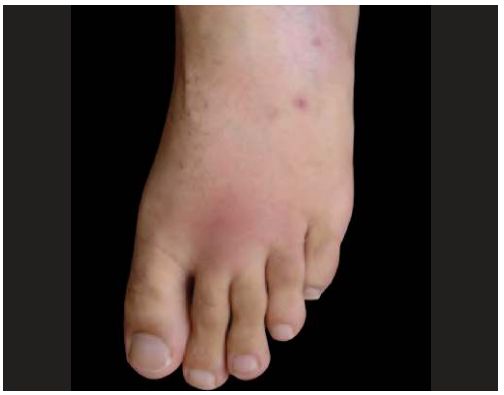


Fig. 7.6: Inflammatory arthritis in the 2nd left metatarsophalangeal joint

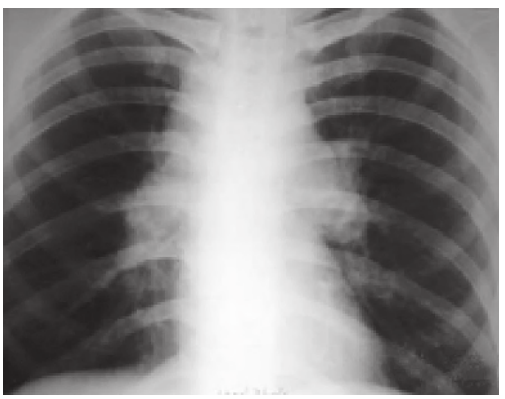


Fig. 7.7: Bilateral hilar lymphadenopathy, a characteristic feature of sarcoidosis

Behçet's Disease

It is a chronic, multi-system inflammatory disorder characterised by:

- **Oral ulcers:** Recurrent, painful mouth sores that are often the first and most common symptom.
- **Genital ulcers:** Painful sores on the genitals, which can cause scar formation over time.
- **Skin lesions:** Erythema nodosum, acne-like lesions, or pustules that appear on various parts of the body. 'Pathergy' is a unique phenomenon seen in patients with Behçet's disease. It refers to an exaggerated skin reaction to minor trauma, such as a needle prick, resulting in the formation of a red, sterile papule or pustule at the site of injury. Lower legs are the common site of these lesions. Pathergy can be elicited in a cooperative patient by lightly scratching the skin—typically on the forearm—with a sterile needle to induce minor trauma. Within a few days, the site develops a sterile papule or pustule.
- **Ocular inflammation:** Uveitis or retinal vasculitis, which can lead to vision problems and, in severe cases, blindness.
- **Arthritis:** Non-erosive arthritis affecting large joints such as the knees and ankles, leading to pain and swelling.

- **Vascular involvement:** Inflammation of blood vessels (vasculitis) which can lead to thrombosis, aneurysms, or other vascular complications.
- **Neurological involvement:** Central nervous system symptoms such as headaches, meningitis, or other neurological issues.
- **Gastrointestinal symptoms:** Ulceration in the digestive tract causing abdominal pain and bleeding.

Some characteristic lesions seen in patients with Behçet's disease are depicted in **Figs 7.8 to 7.10**.

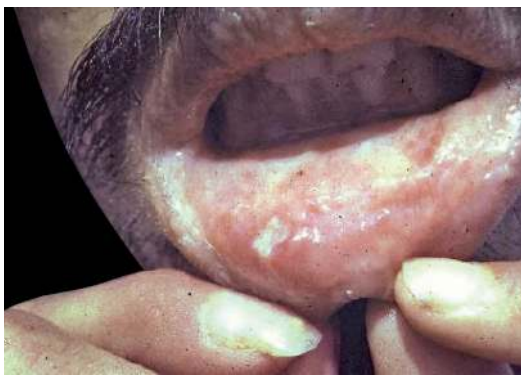


Fig. 7.8: Mucosal ulcers on the lower lips in patients with Behçet's disease

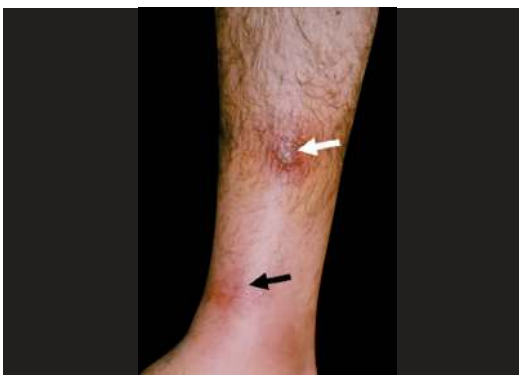


Fig. 7.9: Papulopustular lesions of 'pathergy' (white arrow) as well as lesion of erythema nodosum (black arrow) on the leg in a patient with Behçet's disease

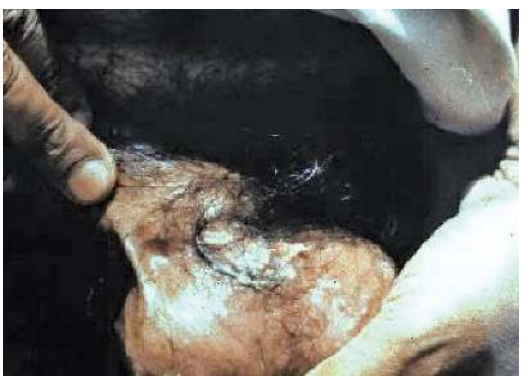


Fig. 7.10: Genital (scrotal) ulcer in a patient with Behçet's disease

Behçet's disease has a relapsing-remitting course, with periods of flare-ups and remission. It is more common along the Silk Road regions, including Turkey, the Middle East, and East Asia. In India, it is mostly seen in its Northern parts. Treatment focuses on managing symptoms and reducing inflammation, often with corticosteroids, immunosuppressive agents, and biologics.

Multicentric Reticulohistiocytosis

Multicentric reticulohistiocytosis (MRH) is a rare systemic disease characterised by:

- **Papulonodular skin lesions:** Multiple, firm, reddish-brown or yellowish papules and nodules on the skin, particularly on the hands, face, and ears.
- **Severe polyarthritis:** Symmetrical, destructive arthritis affecting multiple joints, including the fingers, wrists, and knees, often leading to joint deformities and disability. It resembles RA in its distribution.
- **Mucosal involvement:** Lesions can also appear on mucous membranes, such as the lips, tongue, and gums.
- **Systemic symptoms:** May include fatigue, fever, and weight loss.
- **Internal organ involvement:** Though less common, this disease can affect internal organs such as the lungs, heart, and gastrointestinal tract.

Figures 7.11 and 7.12 demonstrate certain specific features of this disease.

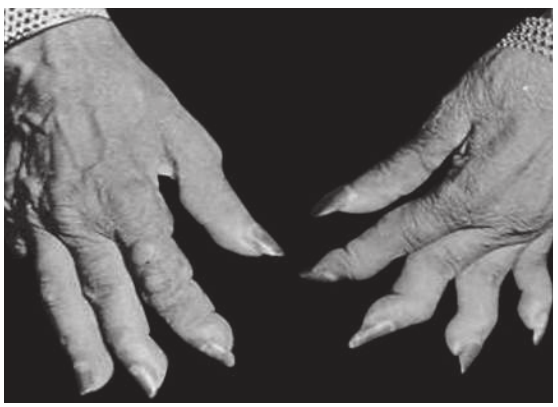


Fig. 7.11: Typical features of polyarthritis seen in multicentric reticulohistiocytosis resembling those seen in rheumatoid arthritis

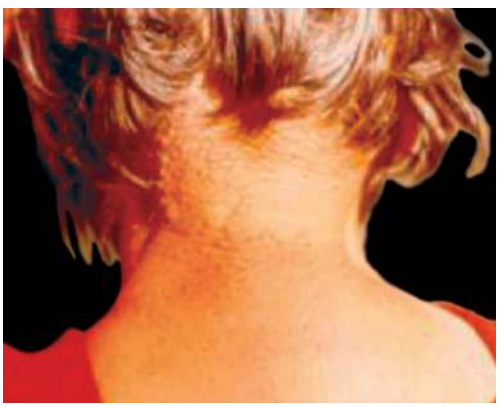


Fig. 7.12: The nodular skin lesion seen in multicentric reticulohistiocytosis

Diagnosis of multicentric reticulohistiocytosis is typically made based on clinical presentation, skin biopsy showing characteristic histiocytic infiltration (therefore it may be considered a form of histiocytosis), and imaging studies of the affected joints. Treatment aims to manage symptoms and slow disease progression, often involving corticosteroids, immunosuppressive drugs, and biologic agents.

Primary Amyloidosis-related Musculoskeletal Disease

Primary amyloidosis is a rare disorder characterised by the deposition of abnormal amyloid protein fibers in various organs and tissues throughout the body. This type of amyloid is derived from immunoglobulin light chains (therefore often identified as 'AL' amyloid) produced in excess due to an underlying malignancy, e.g. **light-chain myeloma**. Musculoskeletal symptoms of primary amyloidosis may include:

- **Arthritis:** Joint pain and swelling due to amyloid deposition in joints, often affecting large joints like the knees and medium joints, e.g. wrists.
- **Carpal tunnel syndrome:** Compression of the median nerve as it passes through the wrist, leading to hand pain, numbness, and weakness.
- **Bone pain:** Generalised bone pain, especially in areas affected by amyloid deposition.

- **Muscle weakness:** In primary amyloidosis, muscle weakness can manifest uniquely when amyloid infiltrates specific muscles like the deltoids. Despite the appearance of enlarged deltoid muscles, reminiscent of those seen in bodybuilders, patients paradoxically experience significant strength loss. This is called the **'shoulder-pad' sign**. It underscores how amyloid deposition can impair muscle function despite visible enlargement in muscle size. These symptoms can contribute to reduced mobility and overall quality of life for affected individuals.
- **Enlarged tongue:** Amyloid (macroglossia) deposition in tongue may cause its dramatic enlargement. Enlarged tongue may interfere in chewing and eating food as also in normal breathing.
- **Skin lesions:** Skin lesions in primary amyloidosis typically manifest as:
  - **Purpura:** Small, red-purple spots caused by bleeding under the skin due to fragile blood vessels affected by amyloid deposition.
  - **Petechiae:** Pinpoint-sized red or purple spots that appear on the skin due to minor haemorrhages.
  - **Ecchymoses:** Larger areas of purple discolouration caused by bleeding under the skin.
  - **Macules:** Flat, discoloured spots on the skin, ranging from brownish to reddish in color, caused by amyloid deposits affecting the skin's pigment cells.

These skin lesions are often a result of the fragility and compromised integrity of blood vessels and surrounding tissues affected by amyloidosis.

Figures 7.13 to 7.16 depict some of the above-mentioned clinical features in patients with primary (AL) amyloidosis.

Diagnosis typically involves tissue biopsy to confirm the presence of amyloid deposits and identification of the underlying protein type. Treatment aims to manage symptoms and may involve chemotherapy, targeted therapies, and supportive care to address organ-specific complications.

Fig. 7.13: Skin lesions in a patient with primary amyloidosis

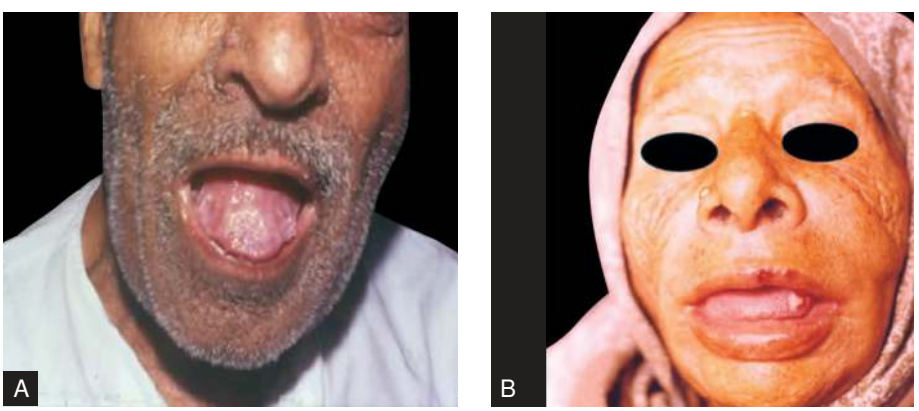


Fig. 7.14A and B: Macroglossia (enlarged tongue) in patients with primary amyloidosis

Fig. 7.15: Enlarged muscular-looking shoulders due to amyloid deposition in the muscles. This is called '**shoulder-pad sign**'

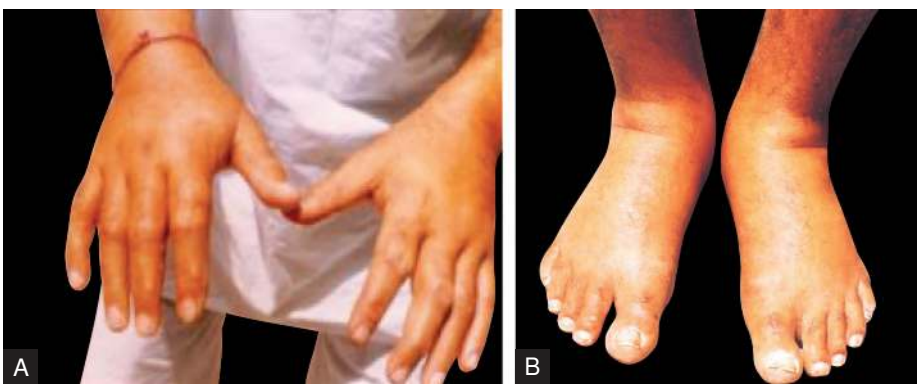


Fig. 7.16A and B: Swollen fingers and toes with some degree of joint involvement that may mimic rheumatoid arthritis

Panniculitides

Panniculitides refer to a group of disorders characterised by **inflammation of the subcutaneous fat tissue**. Anatomically, panniculus consists of lobules with septa (*see* details in Part II, Chapter 7) as shown in **Fig. 7.17**.

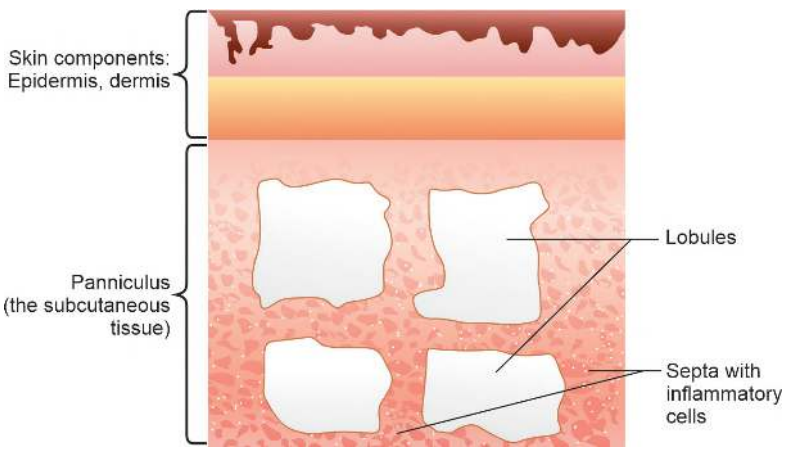


Fig. 7.17: Diagrammatic representation of the histology of panniculus

Lobules are mostly fat cells while septa are fibrous bands that support arterioles, venules and lymphatic traversing from deeper tissue regions to the dermis. Inflammation starting in the septa are called 'septal panniculitis' that are further classified into 'septal panniculitis *with vasculitis*' and 'septal panniculitis without vasculitis' depending upon whether the septal vessels are inflamed or not. In contrast, those where the inflammation is mostly limited to the lobules, are called 'lobular panniculitis'. In relation to the musculoskeletal system, panniculitides can present.

1. **Painful nodules:** Firm, tender nodules or lumps in the subcutaneous fat, often on the lower extremities.
2. **Joint symptoms:** Occasionally, joint pain and swelling may accompany certain types of panniculitides.
3. **Systemic symptoms:** Fever, malaise, and general discomfort may be present, depending on the underlying cause and severity of inflammation.

Band-like lobular panniculitis often seen secondary to systemic lupus erythematosus can be associated with profound lipoatrophy, potentially leading to severe disfigurement is often called 'lupus profundus'. Another form of panniculitis, important for rheumatologists to know is, Weber-Christian panniculitis. It is a form of lobular panniculitis that may rupture forming an ulcer that oozes fatty fluid; often associated with inflammatory arthritis of rheumatoid pattern.

Figures 7.18 to 7.20 show clinical photographs of different varieties of panniculitides.

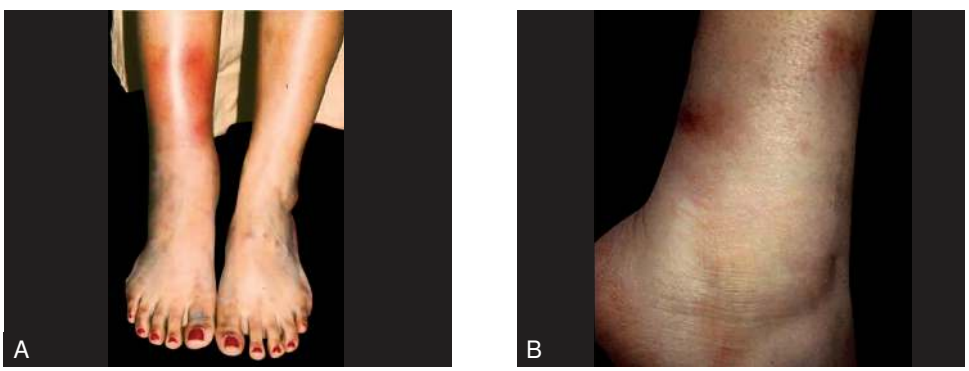


Fig. 7.18A and B: Erythema nodosum in young women; there are multiple causes of this lesion

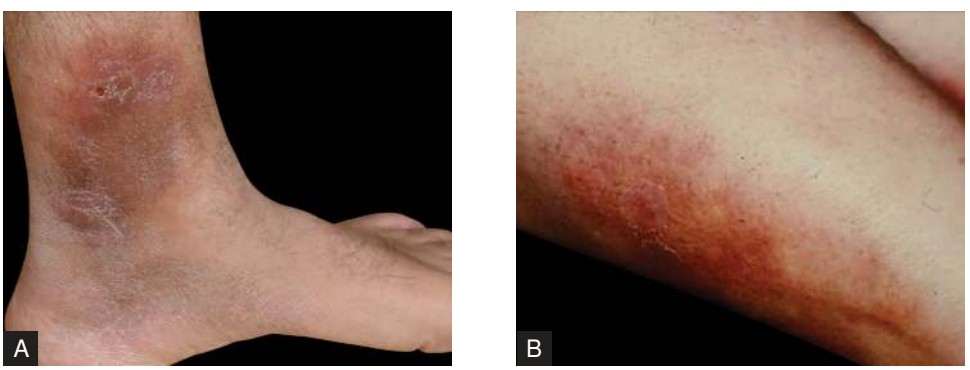


Fig. 7.19A and B: '**Erythema induratum**' a form of lobular panniculitis; also called erythema induratum (of Bazin) (EIB); supposed to be an allergic reaction to tuberculous antigens

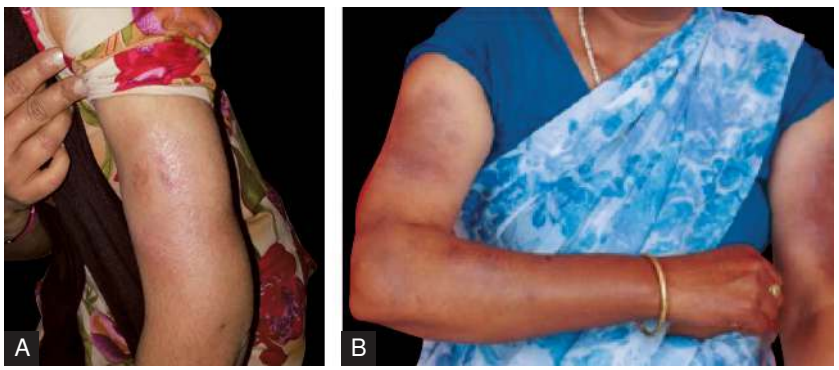


Fig. 7.20A and B: Lupus profundus

Diagnosis typically involves clinical evaluation, imaging studies such as X-rays, MRI, or CT scans, and sometimes biopsy of affected tissue to identify specific conditions like panniculitis or histiocytosis. Treatment aims to address the underlying cause, reduce inflammation, and manage symptoms. It often requires a multidisciplinary approach involving dermatologists and rheumatologists, with therapies ranging from corticosteroids, immunosuppressive drugs (sarcoidosis, SLE), treatment of infections (e.g. tuberculosis, streptococcal sore throat) and chemotherapy (in patients with underlying malignancy) to targeted treatments and supportive care, depending on the severity and type of the condition.

Histiocytosis of Various Types

Histiocytosis encompasses a group of rare disorders characterised by the excessive accumulation of histiocytes (immune cells) in various tissues. The musculoskeletal manifestations of histiocytosis include:

- **Bone lesions:** Painful lytic lesions, often in the skull, spine, pelvis, ribs, and long bones. These can lead to fractures and deformities.
- **Arthritis:** Joint pain and swelling, which can resemble other inflammatory arthritides, e.g. rheumatoid arthritis.
- **Periostitis:** Inflammation of the periosteum (the tissue surrounding bones), leading to localised pain and tenderness in relation to bones.
- **Muscle pain:** Myalgia or muscle pain due to local or systemic inflammation.
- **Soft tissue masses:** Rarely, histiocytic infiltration can present as palpable masses in soft tissues adjacent to bones or joints.

Diagnosis requires histopathological examination of the affected tissues. In most cases treatment is only symptomatic.

CHAPTER 8

Treatment of Rheumatic and Musculoskeletal Diseases (RMDs)

INTRODUCTION

A thorough understanding and accurate categorisation of patients with rheumatic and musculoskeletal diseases (RMDs) are vital for their effective and targeted management. To aid this process, readers are encouraged to revisit Part I, Chapter 3 of this book. As discussed, RMDs can be broadly classified into three main categories:

1. Mechanical or structural damage-related musculoskeletal symptoms arising from deformities or injuries.
2. **Nociplastic pain**, characterised by unexplained musculoskeletal discomfort, best understood through the biopsychosocial model.
3. **Inflammatory RMDs**, encompassing autoimmune autoinflammatory and systemic rheumatic diseases.

The management strategies for each major category of inflammatory RMDs, along with a concise overview of commonly used therapeutic approaches and medications, have been outlined in the corresponding chapters in Part II of the book.

For clarity and reinforcement, **Table 8.1** provides a visual summary of the treatment strategies for the three categories of RMDs. This framework serves as a practical guide for clinicians in tailoring their approach to the diverse presentations of these conditions.

Table 8.1: Management of the 3 major classes of rheumatic and musculoskeletal diseases (RMDs)—an overview

Category	*Aetiology*	*Management*	*Caregiver*
1. 'Wear-and-tear'-related mechanical–structural joint damage	Occupational, trauma-related, ageing, or congenital–developmental joint damage deformity	Physical Medicine and Rehabilitation; Orthopaedic surgery intervention in those with advanced damage	Specialist in **Physical Medicine and Rehabilitation**; Orthopaedic surgeon

(*Contd.*)

Table 8.1: Management of the 3 major classes of rheumatic and musculoskeletal diseases (RMDs)—an overview *(Contd.)*

Category	*Aetiology*	*Management*	*Caregiver*
2. Nociplastic pain: Pain amplification syndromes	Biopsychosocial model best explains this condition	'Pain management' team	A 'team' of specialists in pain management, Physical medicine and Rehabilitation, Psychologist and Psychiatrist, **led by a rheumatologist**
3. Inflammatory rheumatic and musculoskeletal diseases (I-RMDs)	Inflammation triggered and perpetuated by autoimmune and autoinflammatory mechanisms	Modulation/suppression of the aberrant immune response with immunomodulatory and immunosu-ppressive drugs	Rheumatologists are the primary caregivers; with help from specialists in Physical Medicine and Rehabilitation; Orthopaedic surgeons for those with advanced damage

Category 1: 'Wear-and-Tear'-related RMDs: Management

The most common causes of complaints related to rheumatic and musculoskeletal diseases (RMDs) stem from 'wear-and-tear' in various components of the musculoskeletal (MSK) system. These result from the repetitive mobility required for daily activities and are often exacerbated by minor or major traumas encountered in everyday life. Over time, the cumulative effects of these factors impair the normal functioning of the MSK system.

Adding to these mechanical causes, sociocultural factors significantly contribute to the development of 'wear-and-tear'-related RMDs. For instance, knee pain is notably prevalent in the Asian population, particularly among South Asians and Southeast Asians. This insight owes much to the landmark **Beijing Osteoarthritis Study** conducted in the mid-1990s by Chinese researchers, which highlighted the profound impact of cultural practices on the development of mechanically induced MSK damage.

Specific cultural behaviours, such as prolonged sitting in a cross-legged position, standing without adequate movement, frequent use of stairs, and lifestyle factors like weight gain and a sedentary routine devoid of physical activity or exercise, are known to cause chronic knee pain. These behaviours often lead to structural damage to knee cartilage, culminating in conditions like knee osteoarthritis.

Recognising and addressing these lifestyle and cultural factors is central in the management of 'wear-and-tear'-related RMDs, alongside interventions aimed at reducing mechanical stress and promoting joint health.

In addition to lifestyle and cultural factors, developmental issues can also contribute to 'wear-and-tear'-related RMD complaints. Certain individuals or populations may possess anatomical variations in the lower limb that result in an abnormal weight-bearing axis through the knees. This misalignment can predispose them to premature cartilage damage and early-onset knee osteoarthritis.

Another significant contributor to 'wear-and-tear'-related RMDs is occupational strain, commonly referred to as occupational RMDs. Repeated overuse or misuse of specific MSK regions due to occupational activities can lead to gradual deterioration

in their normal anatomy, causing a range of symptoms. The neck, back, shoulders, and thumbs are particularly vulnerable to such overuse or misuse, often resulting in chronic pain and discomfort. Numerous other examples of overuse injuries exist, further underscoring the importance of a comprehensive understanding of occupational and activity-related MSK issues.

Given the multifactorial nature of these conditions, primary level caregivers—typically general physicians or orthopaedic surgeons—must prioritise taking a detailed history of MSK-related complaints. This should include inquiries into overuse, misuse, or prior injuries that could explain the patient's symptoms. In most cases, such patients do not require specialized investigations or blood tests. Instead, clear communication about the cause of their symptoms is often sufficient to reassure them.

Subsequently, these patients should be referred to specialists in **Physical Medicine and Rehabilitation (PM&R)**, where a multidisciplinary team comprising physiatrists, physiotherapists, and occupational therapists can provide targeted interventions. These may include:

1. **Therapeutic exercises** to strengthen and stabilise affected joints and muscles.
2. **Ergonomic advice** to modify daily activities or occupational tasks, reducing strain on vulnerable MSK regions.
3. **Physical modalities** such as ultrasound, heat therapy, or electrical stimulation to alleviate pain and improve function.
4. **Patient education** to foster long-term self-management and prevention strategies.

This integrative approach ensures holistic management of 'wear-and-tear'-related RMDs, addressing both the root causes and symptomatic relief.

There are two additional critical considerations for managing patients with 'wear-and-tear'-related RMDs:

1. **Avoidance of unnecessary investigations:** For these patients, unnecessary imaging and the indiscriminate use of advanced blood tests should be strictly avoided. In most cases, these tests provide little value and can be misleading, often leading to misdiagnosis. The exception is the judicious use of ultrasonography for certain accessible MSK regions, as this can help pinpoint specific anatomical causes for the symptoms. However, the increasing popularity of automated diagnostic technologies has led to a surge in unwarranted investigations, which may not only escalate healthcare costs but also divert focus from the actual cause of the patient's complaints.
2. **Appropriate referrals:** Patients with mechanical–structural damage-related MSK symptoms should not be referred to rheumatologists. Such referrals unnecessarily burden rheumatology services, diverting attention from their primary focus: the diagnosis and management of systemic immunoinflammatory RMDs. Instead, late-stage 'wear-and-tear' MSK conditions, where anatomical damage has advanced significantly and functional restoration is no longer feasible through conservative measures, should be directed to orthopaedic surgeons. Orthopaedic surgeons play a vital role in these cases, often providing solutions such as corrective surgeries or joint replacements to restore mobility and alleviate pain.

By streamlining the diagnostic process and ensuring appropriate referrals, healthcare providers can optimise the care pathway for patients with 'wear-and-tear'-related RMDs

while preserving the specialised expertise of rheumatologists for cases requiring their unique skill set.

Category 2: Management of Musculoskeletal (MSK) Pains Without Obvious Causes: The Nociplastic Pains

A significant subset of patients, predominantly younger individuals and often women, present with widespread, shifting MSK pains that defy clear anatomical boundaries. These symptoms are often disproportionate to the physical findings during an MSK examination. A detailed history frequently uncovers underlying **biopsychosocial issues**, while physical examination may reveal exaggerated pain responses without objective structural abnormalities. A hallmark of nociplastic pain is its diffuse, widespread nature, often crossing anatomical boundaries in a way that mechanical or inflammatory pathologies cannot explain.

Primary care physicians and orthopaedic surgeons must recognise these '**pain amplification syndromes**', which stem from nociplastic pain and are best understood through the **biopsychosocial model of nociceptive pain**. Contributing factors often include:

- Emotional stress and poor coping mechanisms.
- Depression, anxiety, or personality traits such as somatisation or catastrophising.
- Negative cognitive attitudes, beliefs, or fears.

Typical presentations of nociplastic pain include conditions such as **chronic nonspecific (non-inflammatory) back pain, chronic temporomandibular disorders, and fibromyalgia**.

Nociplastic Pains: Early Identification and Appropriate Response

The early identification of these patients is critical, as they benefit from timely and targeted management. One of the most important messages for primary care providers is to avoid the reflexive but counterproductive approach of ordering extensive blood work.

- **Blood test pitfalls:** Even in healthy individuals, normal biological variation means that 5% of blood test results will fall outside the 'normal range'. Misinterpretation of these results can lead to erroneous diagnoses and inappropriate treatments. Furthermore, laboratory errors or false-positive results, such as low-titre antinuclear antibody (ANA) tests, can be misleading. For example, many patients with nociplastic pain are incorrectly labelled with systemic lupus erythematosus based on a positive ANA test, despite the fact that 20–30% of healthy individuals may have a low-titre positive ANA without any disease.

Instead, after a thorough history and examination, it is crucial to communicate with these patients clearly and empathetically. A suggested approach could be: **'I understand your condition. It is called nociplastic pain, and it results from a heightened pain response rather than any structural damage. It can be effectively managed by a team of specialists who focus on this type of pain'.** These patients should then be referred to a pain management team, which may include pain specialists, psychologists, physiotherapists, and occupational therapists, for multidisciplinary care.

Appropriate Referral Practices

Misreferrals—such as sending patients with nociplastic pain syndromes or mechanical–structural RMDs to rheumatologists—can significantly burden rheumatology

services, diverting their focus from serious systemic immunoinflammatory RMDs. This underscores the importance of correctly triaging patients to the appropriate specialty:

- Patients with advanced mechanical–structural RMDs should be directed to **orthopaedic surgeons**.
- Patients with nociplastic pain should be referred to a **pain management team**.
- **The services of rheumatologists should be reserved for patients with systemic immunoinflammatory RMDs**, where their expertise is most impactful.

By ensuring proper identification and referral, healthcare providers can improve patient outcomes while optimizing the use of specialised medical resources.

Category 3: Management of Systemic Immunoinflammatory Rheumatic and Musculoskeletal Diseases (I-RMDs)

Building on the foundational insights provided in Part I, Chapters 2 and 3, distinguishing between inflammatory and noninflammatory RMDs should now be a clear and straightforward process. All first-contact caregivers, including primary care physicians, specialists in physical medicine and rehabilitation, sports medicine specialists, and orthopaedic surgeons, must be adept at identifying inflammatory RMDs. These conditions, collectively termed **inflammatory rheumatic and musculoskeletal diseases (I-RMDs), necessitate urgent referral to a rheumatologist**.

I-RMDs as Medical Emergencies

Recognising I-RMDs as medical emergencies is crucial. Research has shown that inflammation is most severe during the initial phase of these diseases such as in rheumatoid arthritis (RA). This peak intensity occurs in the **first few months (3–6 months) after symptom onset**, a critical window during which structural damage and disability progressively develop, **even as clinical signs and symptoms may appear deceptively mild**.

This apparent paradox often leads to delays in diagnosis and referral:

- Patients may underestimate their symptoms due to their mild appearance.
- Caregivers (especially general physicians or orthopaedic surgeons) may not perceive the urgency of the condition.

These delays are costly. By the time patients with I-RMDs reach a rheumatologist, irreversible damage to joints or organs has often already occurred. Beyond 2 years, even the most advanced pharmacological therapies cannot reverse this damage, resulting in permanent disabilities and diminished quality of life.

Complications of Delayed Treatment

The consequences of untreated or poorly controlled inflammatory disease extend beyond the musculoskeletal system. Prolonged disease activity contributes to systemic inflammation, which:

- Accelerates blood vessel damage, increasing the risk of premature atherosclerotic cardiovascular diseases (e.g. heart attacks and strokes).
- Impairs overall health, leading to complications that extend far beyond the joints.

A Call for Timely Action

Caregivers must act swiftly and decisively to ensure early referral to rheumatologists for patients suspected of having I-RMDs. This proactive approach is essential to:

- Halt the inflammatory process during its peak phase.
- Prevent irreversible joint or organ damage.
- Mitigate long-term complications, including cardiovascular risks.

The Inflammation Damage Curve

The accompanying Fig. 8.1 highlights the inverse relationship between the degree of inflammation and the extent of joint damage over time. Early intervention during the high-inflammation phase minimises long-term structural damage, underscoring the need for timely action. By prioritising early recognition and referral of I-RMDs, healthcare providers can significantly improve outcomes, preventing permanent disabilities and enhancing patients' quality of life. Rheumatologists remain pivotal in managing these complex and time-sensitive conditions.

- On the X-axis, time progresses from symptom onset (indicated by an upward slanting dotted red arrow) through the disease course.
- On the Y-axis, the severity of inflammation, disability, and radiographic damage are depicted.

Key Features

1. **Inflammation (red dotted line)**
   - The severity of inflammation peaks early in the disease course (upward slanting dotted red arrow).
   - After this peak, inflammation begins to decline (downward solid red arrow), even in the absence of treatment.
2. **Disability (bluish-grey dotted line)**
   - Disability (bluish-grey line) starts to rise shortly after symptom onset.
   - It continues to increase progressively over time, reflecting the impact of untreated inflammation on function and mobility.
3. **Radiographic damage (black dotted line)**
   - Structural damage to joints and tissues begins insidiously.
   - Unlike inflammation, it does not decline and instead accumulates over time, becoming irreversible.

Implications

The graph, shown in **Fig. 8.1**, underscores the **short therapeutic window** between the red dotted slanting upward arrow and solid red downward arrows—when inflammation is at its peak and most amenable to treatment. Intervening during this critical period can prevent the long-term increase in disability and radiographic damage.

This concept reinforces the urgency of early diagnosis and referral to a rheumatologist, emphasising that delays lead to irreversible harm, both structurally and functionally, as shown in **Fig. 8.2**.

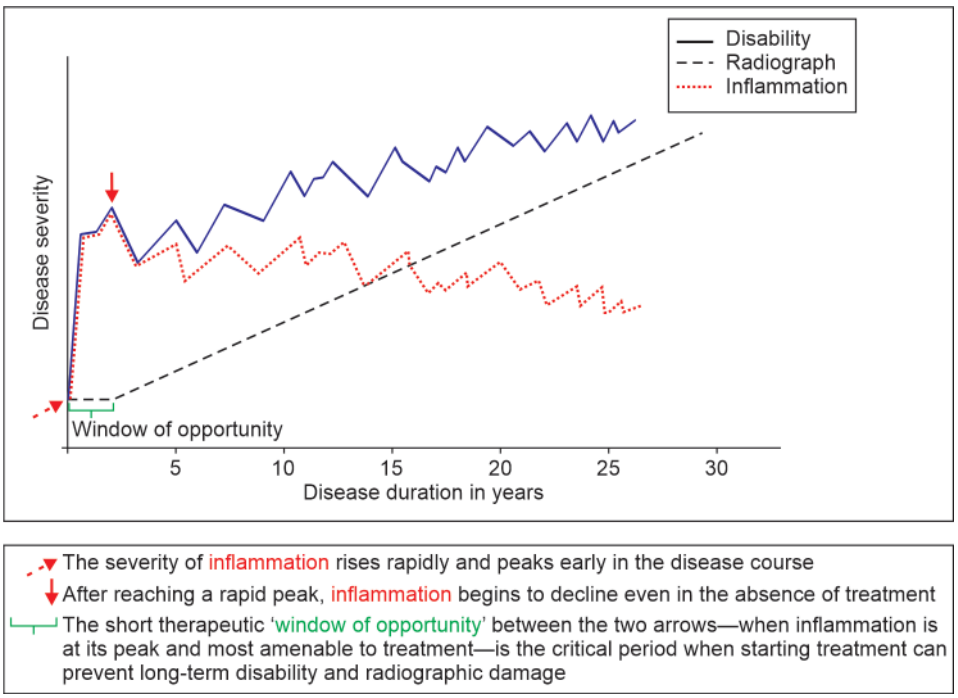


Fig. 8.1: The relationship between inflammation, disability, and radiographic damage over time (*Courtesy:* Dr Niti Kedia, Fellow in Rheumatology, ISIC Superspeciality Hospital, Vasant Kunj, New Delhi). This figure highlights the critical timeline in the progression of inflammatory rheumatic and musculoskeletal diseases (I-RMDs)

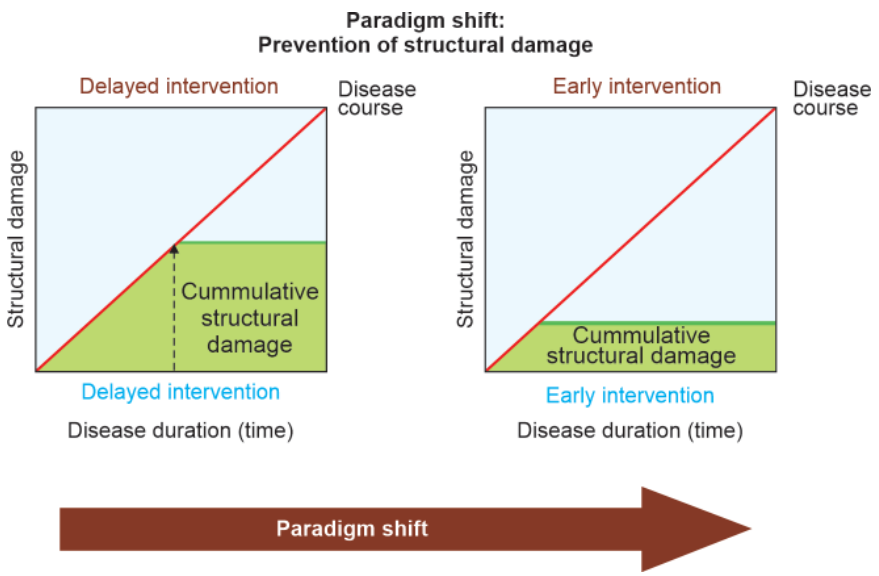


Fig. 8.2: This figure illustrates how early and appropriate treatment using a *treat-to-target strategy*, focused on achieving *low disease activity or remission*, can alter the trajectory of disease progression in inflammatory rheumatic and musculoskeletal diseases (I-RMDs). (*Courtesy:* Retd. Lt. General Ved Chaturvedi, Senior Consultant, Department of Rheumatology, Sir Ganga Ram Hospital, New Delhi)

Targeting Inflammation: The Foundation of Drug Therapy in Inflammatory Rheumatic and Musculoskeletal Diseases (I-RMDs)

In Part I, Chapters 2 and 3, the reader was introduced to the pivotal role of inflammation in causing tissue damage, disability, and, in severe cases, death in patients with I-RMDs. Understanding this is critical, as it underpins the fundamental principle of drug therapy for these conditions: Treating inflammation at its source.

The Dual Role of Inflammation

Inflammation is the body's natural defence mechanism, activated in response to injury, infection, or other harmful stimuli. While it serves to protect and repair tissues, uncontrolled or misdirected inflammation can cause significant harm, leading to the chronic tissue damage and systemic complications seen in I-RMDs. This duality presents a unique challenge:

- Suppressing harmful inflammation to prevent or limit tissue damage and disability.
- Preserving the protective role of inflammation to maintain the body's natural defences.

The Importance of Immune System Knowledge

At the heart of inflammation is the immune system, comprising innate and acquired (adaptive) components. Effective management of I-RMDs requires a nuanced understanding of how these systems function and interact:

- The innate immune system acts as the first line of defence, responding rapidly to threats.
- The acquired immune system provides a more targeted, long-term response, involving processes like antibody production and memory formation.

Precision in Modulating Inflammation

The art of managing I-RMDs lies in modulating inflammation with precision, striking a balance between:

1. Mitigating the harmful effects of chronic, uncontrolled inflammation that drive disease progression.
2. Avoiding excessive suppression, which could weaken the immune system's ability to combat infections and repair tissues.

Achieving this Balance Demands

- A deep understanding of immune pathways.
- Strategic use of therapies that target specific inflammatory mediators or immune cells.
- Regular monitoring to fine-tune treatment and minimise adverse effects.

In summary, inflammation is both a friend and a foe in I-RMDs. The ultimate goal of treatment is to harness the body's natural mechanisms in a way that alleviates disease symptoms, prevents long-term damage, and maintains overall health. This delicate interplay highlights the complexity and importance of precision medicine in managing these challenging conditions.

Anti-inflammatory Drugs: Drugs and Molecules to Modulate/Suppress Harmful Effects of Inflammation

A fundamental understanding of inflammation and the inflammatory response, as described above, highlights the intricate nature of this process. Consequently, a wide array of drugs and molecules has been developed to modulate or suppress inflammation, tailored to different types and causes of inflammation. Based on their mechanisms of action, the specific inflammatory pathways they target, and their therapeutic applications, the commonly used anti-inflammatory drugs for treating I-RMDs are categorised and described as follows.

1. Nonsteroidal Anti-inflammatory Drugs (NSAIDs) used in I-RMDs

These drugs inhibit cyclooxygenase (COX) enzymes, reducing the production of prostaglandins, which mediate pain, fever, and inflammation.

Examples

- **Non-selective COX inhibitors**
  - Aspirin
  - Ibuprofen
  - Naproxen
  - Diclofenac
  - Many others
- **Selective COX-2 inhibitors (coxibs)**
  - Celecoxib
  - Etoricoxib
  - Others

Clinical use: Symptomatic relief of pain and inflammation in conditions like osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis.

2. Glucocorticoids (Corticosteroids)

These drugs suppress inflammation by inhibiting multiple inflammatory pathways, including cytokine production and immune cell activation.

Examples

- Prednisone, prednisolone
- Methylprednisolone
- Dexamethasone
- Hydrocortisone

Clinical use

- Short-term control of severe inflammation in autoimmune and inflammatory diseases (e.g., RA, lupus, vasculitis).
- Bridging therapy while waiting for disease-modifying treatments to take effect.

3. Disease-modifying Anti-rheumatic Drugs (DMARDs)

DMARDs target underlying inflammatory mechanisms, often slowing disease progression.

a. **Conventional synthetic DMARDs (csDMARDs)**

- Low dose methotrexate* (up to 25 mg administered once a week)
- Hydroxychloroquine
- Sulfasalazine
- Leflunomide

*Not to be confused with high-dose methotrexate (~2 log orders higher dose) used as 'chemotherapy' in the treatment of cancers.

b. **Biological DMARDs (bDMARDs):** Biologics target specific inflammatory mediators or cells.
   - **Anti-TNF agents**
     – Infliximab – Adalimumab – Etanercept
     – Golimumab – Certolizumab
   - **Anti-IL-6 agents**
     – Tocilizumab – Sarilumab – Several others
   - **B cell depleters**
     – Rituximab – Several others (in the pipeline)
   - **T cell co-stimulation blockers**
     – Abatacept

c. **Targeted synthetic DMARDs (tsDMARDs):** Small molecules targeting specific **intracellular signalling pathways**.
   - **Janus kinase (JAK) inhibitors**
     – Tofacitinib – Baricitinib – Upadacitinib

Clinical use: Long-term management of I-RMDs, including conditions like rheumatoid arthritis, systemic lupus erythematosus, spondyloarthritis, psoriatic arthritis, and an ever-expanding list of other diseases, remains a critical focus.

4. Anti-cytokine and Anti-inflammatory Biologics

These drugs specifically target pro-inflammatory cytokines like IL-1, IL-6, and TNF-α.

Examples
- IL-1 inhibitors: Anakinra
- IL-17 inhibitors: Secukinumab, ixekizumab
- IL-23 inhibitors: Guselkumab
- IL-12/23 inhibitors: Ustekinumab

Clinical use: Management of psoriatic arthritis, spondyloarthritis, and other I-RMDs.

5. Immunosuppressive Drugs with Anti-inflammatory Effects

These drugs suppress the immune system, reducing inflammation.

Examples
- Azathioprine
- Mycophenolate mofetil
- Cyclosporine
- Cyclophosphamide

Clinical use: Severe I-RMDs (e.g. systemic lupus erythematosus, vasculitis).

6. Emerging Targeted Therapies

These include drugs under development or recently approved, focusing on novel inflammatory pathways.

Examples
- Anti-IFN-α agents
- Sphingosine-1-phosphate receptor modulators

Clinical use: Specialised inflammatory and autoimmune diseases.

The above categorisation offers a structured understanding of the diverse range of anti-inflammatory drugs, their targets, and therapeutic applications. A detailed exploration of the clinical pharmacology, dosing regimens, adverse effects, and long-term monitoring for efficacy and safety of all the drugs used in various I-RMDs is beyond the scope of this book. However, a summary of the available treatments for rheumatoid arthritis, the most common immunoinflammatory rheumatic disease, as well as for less common I-RMDs, is provided.

Drug Treatment of Rheumatoid Arthritis (RA) and other Inflammatory RMDs (I-RMDs)

This part of the chapter focuses on providing a foundational understanding of the medications commonly used in managing one of the most prevalent I-RMDs **rheumatoid arthritis (RA)** as well as other less commonly encountered I-RMDs. The goal is to equip the reader with a basic framework for approaching drug selection and usage in I-RMDs more broadly.

For simplicity, **Table 8.2** presents the drugs primarily used in RA. Many of these medications also find application in treating other I-RMDs. Additional drugs that are primarily utilized in managing I-RMDs other than RA are summarised in **Box 8.1**.

This structured presentation aims to provide clarity and context, ensuring a broad yet concise overview of pharmacological approaches in I-RMDs.

Table 8.2: Drugs to treat rheumatoid arthritis (approved and available in India)

cs-DMARDs; First-line drugs	*b-DMARDs (monoclonal antibodies or construct proteins); Second-line drugs*	*ts-DMARDs; Conditional second-line drugs or third-line drugs*
• *Low-dose methotrexate** • *Leflunomide* • *Sulfasalazine* • *Hydroxychloroquine*	Anti-tumour necrosis factor-α (anti-TNF-α) monoclonal drugs parenteral route: • Infliximab • Etanercept • Adalimumab • Golimumab Anti-interleukin-6 monoclonals • Tocilizumab Anti-CD20 +ve B cell targeted treatment • Rituximab	Janus kinase inhibitors: • Tofacitinib • Baricitinib

c-DMARDs: Conventional synthetic disease-modifying drugs; b-DMARDs: Biological disease-modifying drugs; ts-DMARDs: Targeted synthetic disease-modifying drugs.

*Low-dose methotrexate (LD-MTX) is the 'anchor drug' for treating rheumatoid arthritis (and several other I-RMDs). The starting dose is 15 mg/week, which is escalated stepwise at 2–3-week intervals (depending upon patient's response and tolerance), up to a maximum of 12.5 mg given 2 time at an interval of 8 to 12 hr (e.g. 12.5 mg after dinner at night and another dose of 12.5 mg next morning after breakfast), once every week, to treat RA and several other I-RMDs. At this dose, it is one of the safest drugs in persons who do not have any liver disease.

Box 8.1: Drugs often used in the treatment of severe life-threatening I-RMDs other than RA

1. Low-dose cyclophosphamide (oral as well as intravenously)
2. Azathioprine
3. Mycophenolate mofetil or mycophenolate sodium salt
4. Tacrolimus

Low-dose Methotrexate as the 'Anchor Drug' for the Treatment of Rheumatoid Arthritis and other Inflammatory RMDs (I-RMDs)

A more detailed discussion of the most widely used first-line conventional synthetic disease-modifying drug, low-dose methotrexate (LD-MTX), is warranted. This is particularly important because many medical practitioners and members of the lay public often confuse it with high-dose methotrexate, which is used in chemotherapy for cancer treatment.

Historical

Methotrexate, a cornerstone drug for leukaemia and cancer treatment, was synthesised in the late 1940s by Yellapragada Subbarow, a pioneering biochemist and pharmacologist of Indian origin at Harvard University. Subbarow's innovative work has left an enduring legacy in medicine and science.

By the mid-1940s, dihydrofolate reductase (DHFR)—an enzyme critical for DNA synthesis and cell division—was identified as essential for cellular metabolism and survival. Targeting DHFR to deprive rapidly dividing leukaemic cells of this folate-dependent enzyme was conceived as a potential therapeutic strategy. At the suggestion of Dr Sidney Farber from Boston Children's Hospital, Subbarow synthesised **aminopterin**, a precursor to methotrexate, which successfully inhibited DHFR. Farber's studies demonstrated aminopterin's efficacy in inducing remission in children with acute lymphoblastic leukaemia, published in the **New England Journal of Medicine** in 1948.

Due to aminopterin's instability, Subbarow developed **amethopterin** (later renamed **methotrexate**), which became a more practical and effective treatment. Methotrexate remains a principal drug for leukaemia and various cancers, solidifying Subbarow's pivotal role in advancing chemotherapy.

Within 3 years from the first report of the use of methotrexate in the treatment of a type of cancer (childhood lymphoblastic leukaemia), Gubner and colleagues from New York, USA published 3 remarkable papers in 1951, on the use of **2 log orders lower dose of methotrexate that did not have any effect on cellular proliferation but showed remarkable effect on immunoinflammation** in patients with **rheumatoid arthritis, psoriatic arthritis and systemic lupus erythematosus**. This groundbreaking work was overshadowed by the excitement surrounding the discovery of 'compound E' (cortisol) by Philip Showalter Hench, Edward Calvin Kendall, and Tadeus Reichstein, a breakthrough that earned them the Nobel Prize in 1950. Credit goes to Michael Weinblatt (Harvard Medical School, Boston) and Bruce N. Cronstein (New York) for reviving the legacy of Gubner and colleagues, establishing 'low-dose' methotrexate as the 'Anchor Drug'—a term coined by Ted Pincus (Rush University, Chicago, USA)—for the treatment of rheumatoid arthritis and, subsequently, several other I-RMDs.

Pharmacology and Mode of Action of 'Low-dose Methotrexate' (LD-MTX)

Extensive pharmacological studies have shown that the enzyme dihydrofolate reductase (DHFR) is highly resistant to any intervention imparting 'survival advantage' to the cell that uses this enzyme for its survival and proliferation. Even '**high-dose methotrexate**', (used in '**gram**' doses) has been demonstrated to suppress only up to 95% of the activity of DHFR. Therefore, it is obvious that LD-MTX, **used in milligram doses (not**

more than 25 mg once in a week), which is 2 log orders lower than the doses used for treating cancer, is not a cytotoxic drug. Based upon this background knowledge, 4 major appropriately controlled trials of low-dose methotrexate, conducted in the USA in mid-990s, established its high efficacy and safety in the treatment of RA. Based upon these trials, the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) recommend it as the first-line conventional synthetic disease modifying drug (cs-DMARD) for the treatment of RA. Yet, till now the exact mode of action of low-dose methotrexate in the suppression of autoinflammatory and autoimmune inflammatory response continues to be a subject of research. Adenosine release, cytokine modulation, modulating the action of the various subtypes of immune cells are some of the acclaimed modes of action of low-dose MTX. Some British workers have also shown that LD-MTX's mode of actions is somewhat like that of janus kinase inhibitors, tinkering with intracellular signalling pathways. Irrespective of the fact that the exact mechanism of its action remains not fully understood, LD-MTX remains the first-line drug for the treatment of RA and other I-RMDs.

Dose of LD-MTX in RA and other I-RMDs

International guidelines suggest a dose of **15 mg once every week** as the starting dose. Depending upon the response, it can be escalated over several weeks to the **maximum dose of 25 mg/week**. An important point to remember is that a dose above 15 mg/week given as a single dose, does not get absorbed at the intestinal level due to the presence of a rate-limiting enzyme called '**reduced folate carrier-1**' (RFC-1). It allows absorption of up to 15 mg single dose across the intestine. Any oral dose above this is not absorbed and passes out in the faeces. Therefore, it is mandatory to equally split the LD-MTX dose in half-and-half and given at an 8–12-hour interval for its full efficacy. For example, if 20 mg weekly oral dose is to be given, 10 mg can be given with breakfast and another 10 mg dose can be given at dinner time (or vice versa, after dinner and next morning after breakfast). An alternative to split dose is the subcutaneous route of administration of a dose of LD-MTX above 15 mg/week.

Adverse Effects of LD-MTX

Overall, low-dose methotrexate (LD-MTX) is among the safest drugs in the field of medicine. Studies have demonstrated that in individuals with normal kidney function, normal serum albumin levels, and healthy liver and bone marrow, adverse effects from LD-MTX at the prescribed doses are exceedingly rare. An important finding from studies on the adverse effects of low-dose methotrexate (LD-MTX) on bone marrow is that cytopenias are exceedingly rare, occurring in only about 1% of cases in routine practice. Similarly, research has shown that regular folate supplementation (ranging from 5 mg to 30 mg per week) effectively prevents transaminitis without compromising the drug's efficacy. However, maintaining normal renal function and normal serum albumin levels is essential to avoid LD-MTX toxicity. Before initiating low-dose methotrexate (LD-MTX) treatment, it is essential to perform routine baseline tests, including a complete blood count and liver and kidney function tests. These evaluations are typically repeated every three months, and after several years of stable disease and a consistent LD-MTX dose, the frequency may be reduced to once every six months.

A persistent myth surrounding LD-MTX treatment is that it causes interstitial pneumonia or interstitial lung disease (ILD). However, extensive studies conducted over the past decade have debunked this misconception, demonstrating that LD-MTX not only does not cause ILD but may actually help prevent this serious pulmonary complication in rheumatoid arthritis.

Anticipatory Adverse Effects of Low-dose Methotrexate

A major clinical issue with LD-MTX, mostly occurring at the start of the treatment, is its **anticipatory adverse effects**. These are as follows:

- **Gastrointestinal:** Nausea and vomiting (triggered by anticipation of the drug).
- **Neurological:** Headache or dizziness; Fatigue or malaise associated with treatment expectations.
- **Behavioural/Psychological:** Anxiety or aversion linked to prior experiences with methotrexate.
- **Immune system:** Flare-ups of symptoms due to psychological stress or conditioned responses that may lead to drug default.

These effects are primarily mediated by the brain's conditioning mechanisms, **possibly due to the engagement of adenosine receptors in the central nervous system**, after exposure to methotrexate. Besides reassurance, patient education, and addressing the psychosomatic components through behavioural or supportive therapies, can help. A practical and effective treatment for ameliorating these symptoms is the use of caffeine (in the form of a few extra cups of coffee, dark chocolate, or widely available so-called 'energy drinks'). Interestingly, in the majority of cases, these symptoms resolve completely on their own, often to the extent that patients may not even recall ever-experiencing such adverse effects from taking LD-MTX.

Low-dose Methotrexate for the Treatment of the other Inflammatory Diseases

Inflammatory Arthritis and Connective Tissue Diseases

1. **Psoriatic arthritis (PsA):** MTX is often used as a disease-modifying agent, particularly for joint involvement.
2. **Peripheral arthritis in spondyloarthritis**
3. **Juvenile idiopathic arthritis (JIA):** Especially useful in polyarticular and extended oligoarticular subtypes.
4. **Systemic lupus erythematosus (SLE):** Adjunctive therapy for arthritis or skin involvement.
5. **Systemic sclerosis (SSc):** Used for inflammatory arthritis or skin thickening.
6. **Mixed connective tissue disease (MCTD):** Effective for inflammatory joint and skin manifestations.
7. **Undifferentiated connective tissue disease (UCTD):** For inflammatory joint symptoms in undifferentiated presentations.
8. **Dermatomyositis (DM) and polymyositis (PM):** For skin and muscle involvement

Dermatological Diseases

1. **Psoriasis:** Commonly used for moderate-to-severe plaque psoriasis.
2. **Lichen planus:** Used off-label for severe cases.

Vasculitis

1. **Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR):** Steroid-sparing agent in GCA and PMR.
2. **Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA):** As maintenance therapy after remission induction.
3. **Takayasu arteritis (TAK):** Occasionally used for steroid-sparing effects.

Auto-inflammatory Disorders

1. **Behçet's disease:** For mucocutaneous lesions or arthritis.
2. **Adult-onset Still's disease (AOSD):** Steroid-sparing agent in chronic disease.

Other Conditions

1. **Inflammatory bowel disease (IBD):** Particularly Crohn's disease, as an adjunct to biologics or other treatments.
2. **Sarcoidosis:** For persistent arthritis or pulmonary disease.
3. **Autoimmune uveitis:** Used to control inflammation.
4. **Eosinophilic fasciitis:** For inflammatory symptoms and skin thickening.
5. **Interstitial lung disease (ILD) in autoimmune contexts:** MTX use is controversial but may be considered in some autoimmune-related ILD cases.
6. **Chronic recurrent multifocal osteomyelitis (CRMO):** Off-label for refractory cases.
7. **IgG-4-related disease**

This broad use of methotrexate is supported by its favourable cost-effectiveness and safety profile, though careful monitoring for adverse effects, particularly hepatotoxicity and cytopenias, remains essential.

CAUTION

The reader is strongly cautioned against using any of the drugs listed in this chapter without first ensuring that the patient with an I-RMD has been evaluated and diagnosed by a rheumatologist. Once a diagnosis is made, and a detailed prescription—including dosage, dosing schedule, and guidelines for monitoring efficacy and potential adverse effects—has been provided, the primary caregiver (typically a general physician) can manage the patient's day-to-day care. However, regular follow-up visits with the treating rheumatologist are crucial for adjusting, tapering, escalating, or maintaining the prescribed medications and dosages.

Epilogue

As we conclude this introductory journey into the fascinating field of rheumatology, we hope this book has served its purpose of igniting curiosity and fostering a sense of purpose among those considering their next steps in medicine.

Rheumatology, often perceived as complex and underappreciated, holds immense potential for those with a keen eye for problem-solving and a deep compassion for improving lives.

Through these pages, we have aimed to provide a foundation—not just of knowledge but also of inspiration. The challenges faced by patients with rheumatic diseases are multifaceted, requiring physicians who are not only skilled diagnosticians but also empathetic caregivers. By choosing to explore this field, you have the opportunity to make a profound difference in a domain where the need for expertise far outweighs its availability.

Medicine, at its core, is about service, and the choice of a specialty should resonate with your inner calling. Rheumatology offers a unique blend of intellectual stimulation, the opportunity to develop enduring patient relationships, and the satisfaction of witnessing transformative outcomes through precision diagnosis and treatment. In embracing this path, you will not only address a global shortage of rheumatologists but also join a vibrant, collaborative community dedicated to advancing care and knowledge in this specialty.

We encourage you to delve deeper, seek mentorship, and explore the training opportunities outlined in this book. Let your curiosity guide you toward a rewarding career that combines science, art, and compassion in equal measure.

The field of rheumatology awaits pioneers like you—individuals who are not afraid to tackle its complexities and rise to the challenge of improving the lives of those who need it most. Let this book be the spark that lights your way.

Thank you for taking this first step toward what we hope will be a lifelong journey of learning, discovery, and fulfillment in the realm of rheumatology.

With warm regards and best wishes!

Anand N Malaviya
New Delhi, India

Prashant Kaushik
Oklahoma, USA

Centres for Training in the Superspeciality of Rheumatology and Clinical Immunology

DrDNB (SuperSpecialty) in Clinical Immunology & Rheumatology*		
State	*Name of the institution*	*Seats*
Delhi	Army Hospital (R and R), Delhi Cantt, New Delhi-110010	1
-do-	Indraprastha Apollo Hospital, Delhi-Mathura Road, Sarita Vihar, New Delhi-110076	1
-do-	Max Super Specialty Hospital, 1, 2 Press Enclave Road, Saket, New Delhi-110017	1
-do-	Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi, Delhi-110060	1
Haryana	Medanta The Medicity, Sector-38, Gurgaon-122001	2
Karnataka	Manipal Hospital, No. 98, Rustum Bagh, Old Airport Road, Bangalore -560017	1
-do-	St. Johns Medical College Hospital, Sarjapur Road, Koramanagala, Bangalore-560034	2
Kerala	Kerala Institute of Medical Sciences, P B No.1, Anayara P O, Trivandrum, -695029	1
Maharashtra	P.D. Hinduja National Hospital and Medical Research Centre, Veer Savarkar Marg, Mahim, Mumbai -400016	1
-do-	Topiwala National Medical College and BYL Nair Charitable Hospital, Dr. A L Nair Road, Mumbai-400008	2
Orissa	SCB Medical College and Hospital, Mangalabag, Cuttack, Odisha Orissa-753010	2
Telangana	ESIC Medical College Hospital and Super Specialty Hospital, Sanath Nagar, Hyderabad -500038	2
Uttar Pradesh	Apollomedics Superspeciality Hospital, Sector B, Bargawan, LDA Colony, Lucknow -226012	2
West Bengal	Institute of Neurosciences, 185/1, A J C Bose Road, Kolkata-700017	2
TOTAL		**23**

DM–Clinical Immunology & Rheumatology*		
Kerala	Amrita School of Medicine, AIMS, Kochi	2
Maharashtra	Bharati Vidyapeeth (DTBU) Medical College, Pune	2
Odisha	Institute of Medical Sciences and SUM Hospital, Bhubaneswar	2
-do-	Kalinga Institute 0f Medical Sciences, Bhubaneswar	2
Tamil Nadu	Christian Medical College, Vellore	4
-do-	Madras Medical College, Chennai	2
-do-	Sri Ramachandra Medical College & Research Inst., Chennai	2
Union Territory of Chandigarh	Postgraduate Institute of Medical Sciences	3
-do-	Postgraduate Institute of Medical Sciences (*DM course in **Paediatric** Clinical Immunology & Rheumatology*)	Variable
Uttar Pradesh	King George's Medical University UP, Lucknow	5
-do-	Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow	4
West Bengal	Institute of Post Graduate Medical Education and Research, Kolkata	5
TOTAL		**30**
Training Programme in Paediatric Rheumatology*		
Delhi	Institute of Child Health, Sir Ganga Ram Hospital Offers a certification course in Paediatric Rheumatology under the Paediatric Rheumatology Society.	1
Uttar Pradesh	Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow Provides training in Pediatric Clinical Immunology and Rheumatology through a 12-month program for MD Pediatricians.	1

*__Disclaimer:__ *The authors have made every effort to ensure that the information provided in the above list is accurate and up to date. However, the list may not be exhaustive, and certain developments or relevant items may have been inadvertently omitted. Readers are therefore encouraged to conduct their own research or consult additional sources to verify and supplement the information as needed.*

(Authors would like to express thanks to Drs. Sanjiv Kapoor and Niti Kedia, Department Of Rheumatology, ISIC Superspeciality Hospital, Vasant Kunj, New Delhi-110070 for providing information for list presented in this table)

Index

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Rheumatology Essentials

A New Frontier for Aspiring Clinicians

Musculoskeletal complaints account for nearly a quarter of the general clinical visits, yet medical training worldwide often lacks essential guidance on diagnosing and triaging these conditions effectively. This introductory book empowers the physicians and the healthcare providers with a simple yet powerful approach to classifying rheumatic and musculoskeletal diseases (RMDs) into three key categories.

- Mechanical-structural wear-and-tear managed by physical medicine, rehabilitation, or orthopedic specialists.
- 'Third pain' (biopsychosocial pain without tissue damage) best addressed by pain management teams.
- Systemic immunoinflammatory rheumatic diseases requiring urgent rheumatologic care of a trained rheumatologist.

Relying on the time-honoured clinical history, physical examination, and a few targeted tests, this streamlined approach enhances diagnostic accuracy, reduces delays, and optimizes healthcare resources.

This book is a must-read for undergraduate and postgraduate students in medicine, primary-care physicians, general physicians and frontline emergency-room physicians, empowering them in appropriately handling and triaging patients with RMDs.'

Anand N Malaviya MD, FRCP (London), 'Master'-ACR & APLAR, FACP, FICP, FAMS, FNASc is widely regarded as the 'father of rheumatology and clinical immunology' in India. After training under the legendary Prof Robert Schwartz in Boston, USA, he returned to India in 1968 to pioneer rheumatology and clinical immunology. At All India Institute of Medical Sciences (AIIMS), New Delhi, he established the country's first clinical immunology laboratory and immunology clinic, revolutionizing the diagnosis and management of systemic immunoinflammatory rheumatic diseases (SIRDs).

A prolific researcher, Prof Malaviya has to his credit over 500 research papers, including a landmark 1968 Lancet study on low-dose methotrexate for inflammatory myopathies. His contributions extend to more than 50 textbook chapters, including *API Textbook of Medicine* and *Oxford Textbook of Spondyloarthritis*.

Having trained over 30 leading rheumatologists globally, he remains an ardent clinician and educator, advocating for a patient-centred, clinically driven approach to diagnosis. Through this book, he seeks to inspire young minds to explore rheumatology — the last bastion of clinical medicine. He is fondly called ANM by his students and colleagues.

Prashant Kaushik MBBS (Gold Medalist), MD, FACP, FACR is currently Clinical Professor of Medicine, Oklahoma State University's Cherokee Nation Campus, and Chief of Rheumatology, Northeastern Health System, Oklahoma, USA. He is a distinguished rheumatologist and educator who has excelled academically since his childhood. A graduate of AIIMS, New Delhi, he received numerous gold medals, the prestigious Institute Medal, and national media recognition. He trained in internal medicine and rheumatology under Prof Anand N Malaviya at AIIMS, Delhi, and later under Prof Peter E Lipsky at UT Southwestern, Dallas, USA.

A highly awarded teacher and mentor, he actively contributes to research, is board certified in lifestyle medicine, and serves as a nationwide mentor for Ultrasound School of North American Rheumatologists (USSONAR). His mission is to inspire future physicians with excellence, kindness and compassion.

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