Rheumatology for Primary Care Providers

A Clinical Casebook

Yousaf Ali
Editor

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Preface

This textbook is designed to be a useful, up-to-date primer for physicians and providers who take care of patients with musculoskeletal problems. I would like to thank all the authors for all their tireless work and dedicate this book to my wife and parents who have made many sacrifices for my career.

New York, NY, USA — Yousaf Ali, MD

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1 An Approach to a Patient with Joint Pain

Tom Walton

Introduction

Musculoskeletal conditions represent a considerable disease burden, and the majority of patients who present to medical services are managed in the primary care setting [1]. It is important therefore that general practitioners (GPs) are able to correctly diagnose and treat patients with joint pain.

It is well established that patients with inflammatory arthritis benefit from early treatment [2], so timely, effective triage and referral are essential. There is also good evidence that prompt treatment of acute soft tissue pain produces sustained benefit [3].

The aim of the initial assessment in primary care should be to differentiate musculoskeletal from non-musculoskeletal pain and to determine whether the joint pain arises from inflammatory joint disease or from a non-inflammatory cause.

Globally, healthcare systems are struggling to meet demand due to a combination of an ageing population and increasing disease burden [4]. At the same time, there are significant workforce shortages, making it difficult to maintain a high quality service. Therefore, any assessment should aim to provide an accurate, timely diagnosis and an effective management plan.

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Epidemiology

Musculoskeletal pain is common and accounts for 14% of GP consultations in the UK [5] and over 38 million primary care visits annually in the USA [6].

Doctor-diagnosed arthritis is associated with severe joint pain in 15 million patients in the USA [7] and results in a limitation of activity in 24 million patients [8].

In addition to the direct impact on the patient, the annual economic cost of arthritis is also considerable and has been estimated to be at least $303 billion annually in the USA [9].

The role of the family physician is important as they are the most common point of first contact, accounting for 37% of initial consultations for joint pain in the USA [6].

Not only is musculoskeletal pain widespread, but the prevalence of symptomatic arthritis is also increasing [10] due to an increase in risk factors such as obesity and an ageing population [11]. This is reflected in epidemiological studies of specific rheumatological diseases, including gout [12], osteoarthritis (OA) [13] and inflammatory arthritis. If current trends continue, projections suggest that 78.4 million adults in the USA will have some form of arthritis by 2040 [14].

Recent evidence in the medical literature [15] has suggested that epidemiological studies based on doctor-diagnosed arthritis have significantly underestimated the disease burden with a sensitivity of only 52.5% in patients aged 45–64 years. It is likely therefore that the true burden of arthritis is significantly greater than that reported.

The Assessment of a Patient with Joint Pain

The average duration of consultation in primary care in the UK is only 9 min [16] and 21 min in the USA [17]. It is important therefore to have a structured approach to the assessment that narrows the differential diagnosis, aids appropriate investigation and provides effective treatment.

General History

The aim of taking a history of joint pain is to localise the source of the pain, identify if it is musculoskeletal in origin and ascertain the likely underlying rheumatological condition.

The most important points to be considered in the approach to the history are illustrated in Fig. 1.1:

Rather than adopt a 'scattergun' approach, the history should be adapted to the patient and the most likely diagnosis. For

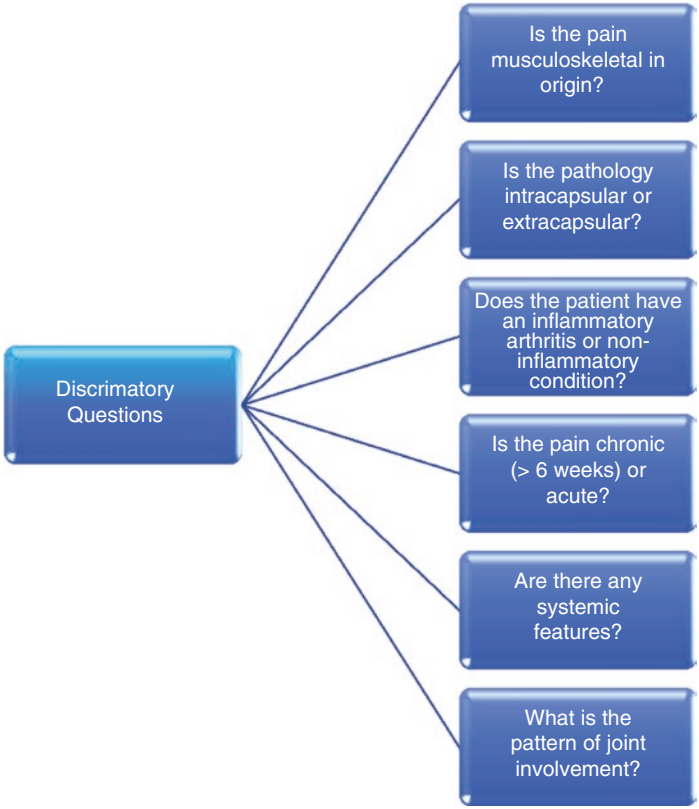

Fig. 1.1 Key discriminatory questions

example, an elderly male presenting with intermittent inflammatory oligoarthritis is unlikely to have connective tissue disease, so the focus of the history should be altered accordingly.

Firstly, the duration and temporal pattern of the pain must be established as this is a key differentiating feature of specific diseases. The pain of degenerative joint disease will present gradually over several months and be slowly progressive. Inflammatory arthritis usually has a subacute onset over several days or weeks. In contrast, gout has a very distinctive time course, with the pain reaching maximum intensity within 12 hours of onset, often overnight, and is followed by prolonged pain-free periods between attacks that last several weeks or even months.

The location of the pain and any radiation are important, although it must be appreciated that patients struggle to localise pain precisely and it may be useful to use targeted closed questions to determine the origin of the discomfort.

The distribution of joints involved is also pivotal and helps to narrow the differential diagnosis, as shown in Fig. 1.2. For example, rheumatoid arthritis (RA) is usually a symmetrical condition that affects the proximal small joints of the hands, wrists and feet whereas both OA and tendinopathy tend to be asymmetric and, in the case of OA, involves the distal interphalangeal joints of the hands, the carpometacarpal joint of the thumb and weight-bearing joints.

The character of the pain is important. Nociceptive pain is the most common type of pain and is caused by physical damage to the bone, skin or connective tissue, which activates peripheral nociceptors. It is usually well localised and described as throbbing or aching.

Neuropathic pain arises from neuronal damage and is poorly localised. It is chronic, sometimes worse at night and often characterised by descriptions such as ‘burning’ or ‘pins and needles’ together with an altered temperature sensation. Patients can have multiple aetiologies of their pain, which can result in a delay in diagnosis.

Aggravating and alleviating factors are important to identify. Patients with osteoarthritis find that their pain is worse with weight-bearing and activity and alleviated by rest, whereas the

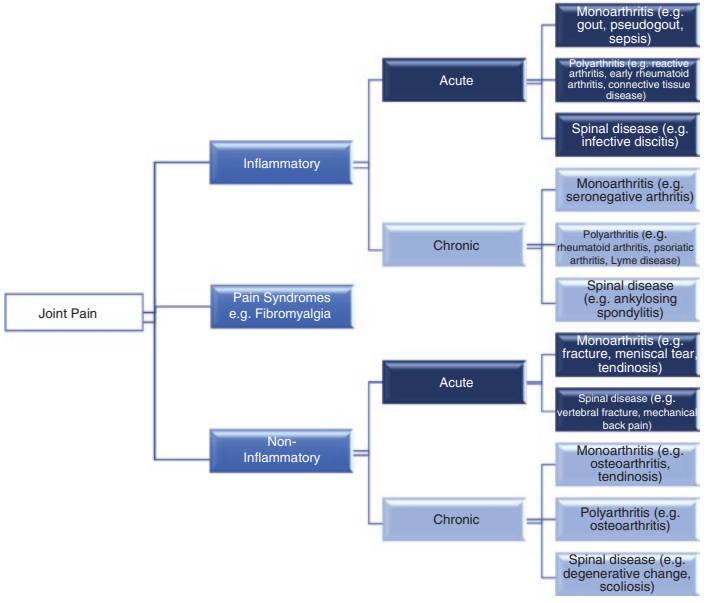

Fig. 1.2 Categorisation of joint pain by distribution and chronicity

converse is true with inflammatory arthritis. Specific activities will worsen tendinopathies and peripheral nerve entrapment; for example, carpal tunnel syndrome can be exacerbated by driving or holding a mobile phone.

A history of trauma may be overlooked by the patient but should result in a low threshold for arranging imaging to exclude a fracture, particularly in older patients or those at risk of recurrent falls.

Early morning stiffness of the joints is a feature of both degenerative disease and inflammatory disease but is more severe and prolonged with the latter, often lasting for several hours. An underlying inflammatory process is also suggested by a history of post-inactivity 'gelling' with symptoms worsening after a period of immobility.

A systemic enquiry asking about weight loss, fatigue and 'flu-like' symptoms or any history of fever should be taken as these

symptoms imply a systemic cytokine-mediated inflammatory response.

Relevant past medical history and in particular any associated conditions such as recurrent pregnancy loss, thromboembolic events, inflammatory bowel or eye disease are potential red flags for systemic autoimmune disease. Psoriasis may be occult, and direct enquiry about the involvement of the natal cleft, scalp and umbilicus is important.

If a diagnosis of connective tissue disease is suspected, extra-articular symptoms such as malar rash, nasal or mouth ulcers, sicca symptoms and Raynaud's syndrome should be elicited.

As infectious diseases such as Lyme disease, sexually transmitted disease and bacterial gastrointestinal infection can be a precipitant for arthritis, a detailed sexual, travel and tick exposure history is vital. Transient arthritis can also arise after viral infections such as parvovirus and more persistent symptoms after streptococcal infection.

In patients with chronic diffuse pain, a history of childhood sexual trauma or post-traumatic stress disorder should be elicited since this has been shown to be present in up to 45% of patients with fibromyalgia syndrome [18].

In those who present with podagra or intermittent monoarthritis, it is important to ask about potential risk factors for gout such as a high purine or fructose diet, family history, alcohol consumption, diuretic use or even chronic lead exposure.

Occupational risk factors such as repetitive load-bearing tasks increase the risk of tendinopathies and degenerative change over the longer term.

Secondary depression is a common feature in patients with chronic musculoskeletal pain with a prevalence up to 48% higher than controls [19], and this can contribute significantly to an adverse outcome. One study has found that 20% of the disability score was attributable to psychological status in patients with rheumatoid arthritis [20]. The biological basis for this association is suggested by the fact that inflammatory cytokines can reduce neurotransmitter release and affect neuroplasticity [21].

In order to assess the impact of the disease, the patient should also be asked directly about their functional capacity. If this is not

A Five Minute History of Joint Pain in Primary Care	How long have symptoms been present?
	Does the pain come and go?
	Is early morning stiffness present?
	Is pain better or worse with activity?
	Does the patient have swelling of the joints?
	Which joints are involved?
	Is there a background history of psoriasis, inflammatory bowel disease, uveitis, prolonged back stiffness or gout?
	Is there a history of trauma?
	If relevant, are there extra-articular symptoms?

Fig. 1.3 A 5-min musculoskeletal history

immediately possible due to time constraints, the involvement of a physiotherapist can help assess the patient to ascertain the impact of arthritis [22].

A '5-min history' providing a focussed approach to the history is illustrated in Fig. 1.3.

Rheumatological Emergencies

Although rheumatology is predominantly an outpatient-based speciality, there are a small number of rheumatological presentations that require urgent treatment. These include joint sepsis, systemic necrotizing vasculitis, giant cell arteritis (GCA), multiorgan failure from systemic lupus erythematosus (SLE) and cauda equina syndrome.

These will be covered in more detail in subsequent chapters, but a detailed initial history and examination are vital in order to identify these conditions at an early stage and organising prompt investigation and treatment.

Patterns of Rheumatological Conditions

There are over 200 rheumatological conditions, which means that it is important to categorise them in order to arrive at a meaningful differential diagnosis.

Figure 1.4 categorises the seven most common types of rheumatological conditions in adults. They will be discussed in turn, with the exception of osteoporosis, which is covered in a further chapter.

Referred Visceral Pain

Although it is beyond the scope of this chapter, it is important to be aware of the possibility of referred visceral pain as a cause of musculoskeletal pain. For example, cholecystitis or diaphragmatic pain can be referred to the right shoulder and ischemic cardiac pain to the left shoulder tip.

The main sources of visceral pain are detailed in Fig. 1.5.

Visceral pain may be exacerbated by specific provoking factors; for example, exertion can worsen myocardial ischemia.

Fig. 1.4 Patterns of rheumatological disease

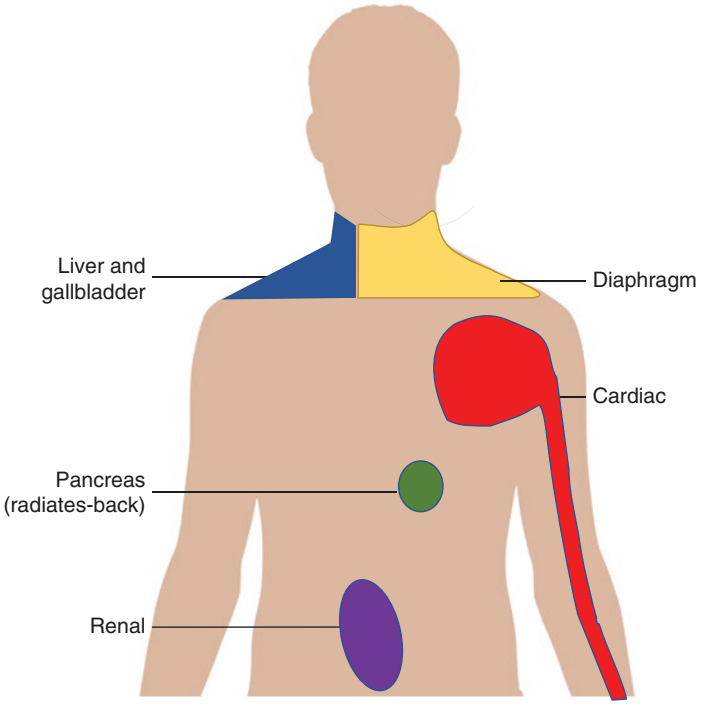

Fig. 1.5 Visceral pain

Pain referred from internal organs has a different quality from musculoskeletal pain and is not worsened by the movement of the joint itself.

Spinal Disease

Spinal pain is common, affecting up to 79% [23] of the population at some stage of their lives. As there are a number of structures within the spine that can be a source of pain, including nerves, ligaments, muscles and soft tissues, it is not possible to identify the precise anatomic cause of spinal pain in the majority of cases.

The main aim of the history therefore is to differentiate inflammatory from non-inflammatory pain and to exclude causes that need more urgent investigation and treatment.

Inflammatory spinal disease typically affects males in the 20–40 age group and is less common in females by a factor of 2:1 [24].

Ankylosing spondylitis (AS) will cause significant axial stiffness in the morning, often lasting several hours, and is also associated with nocturnal pain, which is less common in mechanical back pain. The symptoms are commonly alleviated by exercise and NSAIDs and exacerbated by immobility.

Extra-articular features such as a history of iritis, psoriasis and inflammatory bowel disease should raise the index of suspicion for a seronegative spondyloarthropathy (SpA). A family history of AS is frequently seen in patients with the condition.

However, the vast majority of back pain presenting to a GP is mechanical in origin. It is important to clarify if there is any history of paraesthesia or numbness and if the pain is referred to the lower limb as pain radiating the calf is suggestive of lower lumbar radiculopathy.

There are however a number of 'red flags' in the history that increase the probability of a more serious underlying cause. These are listed in Fig. 1.6.

A sudden history of back pain in an older patient means that an osteoporotic fracture needs to be excluded, and a previous history of malignancy means that urgent imaging is needed to exclude metastatic disease.

The one condition that must not be missed is cauda equina syndrome, as although it is rare with an incidence of 1/100,000 in the general population [25], this is a neurosurgical emergency where delayed treatment may lead to lifelong incontinence and disability.

All patients with back pain therefore must be asked specifically about a history of altered perineal sensation, incontinence and motor weakness. The examination should include a peripheral neurological examination, which must also exclude perineal sensory loss.

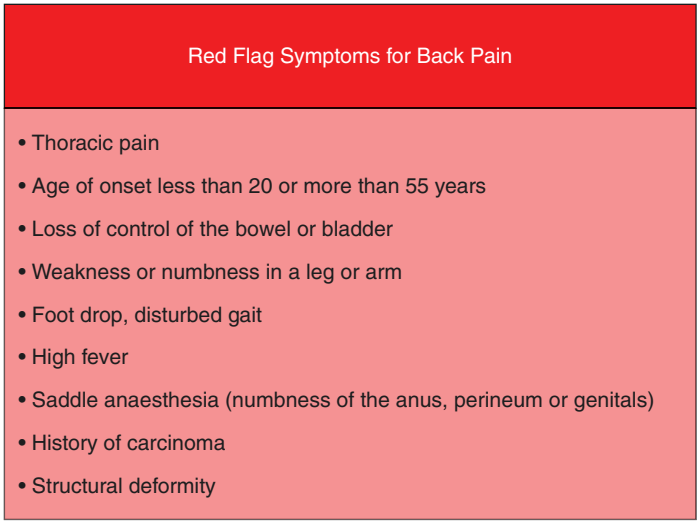

Fig. 1.6 Red flags for spinal pain

Periarticular Pain

Periarticular pain arises from structures that surround the joint and are involved in joint motion but are outside the joint capsule. Such pain is often caused by repetitive trauma or overuse but can also develop as a result of inflammatory arthritis and, in particular, seronegative arthritis.

A characteristic of periarticular pain is that in contrast to the globally restricted range of movement arising from synovitis, pain is reproduced by specific movements, for example, ulnar deviation of the wrist in De Quervain's tenosynovitis. The symptoms are worsened by loading the joint and alleviated by rest.

Active movement is more painful than passive movement by the examining clinician as the underlying joint is structurally normal. This is in contrast to patients with inflammatory joint disease where both active and passive movements reproduce the symptoms.

Examples of periarticular pain would include trochanteric bursitis, lateral epicondylitis of the elbow and rotator cuff tendinopathy of the shoulder – these will be outlined in detail in further chapters.

Inflammatory Arthritis

The pattern of joint involvement is helpful in arriving at a specific diagnosis in patients with inflammatory joint disease.

Patients can be divided into those presenting with monoarthritis (one joint), oligoarthritis (2–4 joints) or polyarthritis (5 or more joints) and may be acute, chronic or relapsing and remitting.

Rheumatoid arthritis (RA) is usually a chronic symmetrical disease typically involving the metacarpophalangeal joints and proximal interphalangeal joints of the hands together with the metatarsophalangeal joints of the feet. In contrast, seronegative arthritis such as psoriatic arthritis will often present with an asymmetrical pattern, sacroiliitis, enthesopathy or oligoarthritis [26].

Inflammatory joint pain is usually of subacute onset over several days or weeks with the exception of crystal arthropathies such as gout or pseudogout that will reach maximum intensity within 12 hours of onset. There is however a subtype of rheumatoid arthritis that is characterised by an explosive onset. This is more common in elderly onset RA (EORA) [27].

An acute monoarthritis is most commonly due to gout, pseudogout or trauma, but in the absence of a suggestive previous history for either of these two conditions, septic arthritis must be excluded. It is important to enquire after systemic symptoms such as sweats and fever, although the clinician must be mindful of the fact that up to 40% of patients with joint infection are apyrexial [28].

The duration of symptoms is also relevant, as synovitis that has been present for less than 6 weeks may be the result of transient viral-associated arthritis, but a longer duration is more likely to be indicative of systemic disease such as rheumatoid arthritis.

Osteoarthritis

Degenerative joint disease affects middle age and elderly patients. It is usually a widespread condition predominantly involving the load-bearing joints, including the knees, hips and metatarsophalangeal joints of the feet. In the hand, the distal and proximal interphalangeal joints are affected together with the carpometacarpal joint of the thumb. Spinal disease is also common.

The speed of onset is usually gradual, over many months and even years. Pain is worsened by load-bearing and alleviated by rest. Although early morning stiffness is a common complaint, it tends to last for less than 30 min and is less severe than that associated with inflammatory arthritis.

While nocturnal pain is a common feature of inflammatory disease and malignancy, it can also be due to severe degenerative disease and is felt to relate to venous hypertension.

It is important to enquire about a history of injury to a joint as this increases the risk of subsequent degenerative disease [29].

A family history of osteoarthritis is common, particularly in female patients who have premature osteoarthritis of the hand.

Muscle Syndromes

Muscular as opposed to articular disease has a number of different underlying aetiologies. Myalgic pain and weakness may be seen as a secondary phenomenon in association with severe vitamin D deficiency, hypothyroidism and sarcoidosis.

Polymyalgia rheumatica (PMR), while not a primary muscular disease, will present with symmetrical shoulder and pelvic girdle myalgia.

Primary myopathic conditions are rare but important differentials. This group would include dermatomyositis, polymyositis and inclusion body myositis.

Patients who have muscular disease will present with bilateral symptoms often involving both the upper and lower limbs with associated weakness. In addition to the physical examination, an

elevated creatinine phosphokinase (CPK) or aldolase can also help distinguish these patients from those who have localised degenerative or periarticular syndromes.

The onset of pain is usually subacute over a few days or weeks, and in the case of PMR, there may be a history of antecedent infection [30].

Early morning and post-inactivity stiffness is severe and long-lasting in patients with PMR, although it improves to some extent as the patient starts to mobilise.

It is important to specifically enquire after the symptoms of giant cell arteritis (GCA) in patients with PMR as patients can suffer sudden irreversible visual loss [31] if they do not receive immediate corticosteroid treatment. These symptoms consist of localised temporal headache and tenderness, jaw claudication and visual disturbance.

Jaw claudication is a sensation of pain within the masseter muscles of the jaw that comes on within seconds of starting to chew food and resolves within minutes afterwards. It can be difficult to distinguish from temporomandibular pain, which typically is associated with clicking and clunking within the joint.

Peripheral joint swelling can be a feature of PMR, but this is usually mild and transient involving the wrists and, less commonly, the knees.

A full medication history must be taken as statins in particular can cause muscular pain, typically within 4 weeks of starting treatment. Other medications that may be implicated include hydroxychloroquine, antiretrovirals, quinolones and colchicine with long-term use (Fig. 1.7).

A history of symptoms associated with connective tissue disease may be apparent, and it is also important to ask about the presence of a rash that may be periorbital or involve the metacarpophalangeal joints (MCPJs) in the case of dermatomyositis. A subgroup of myositis called anti-synthetase syndrome may present with ‘mechanics hands’ (fissuring), interstitial lung disease or oesophageal involvement and will need a multiorgan evaluation.

Common Medications Causing Musculoskeletal Pain
• Anastrazole • ACE inhibitors • Bisphosphonates • Colchicine • DPP-4 inhibitors • Estrogens • Fluoroquinolone antibiotics • Hydroxychloroquine • Protein Pump inhibitors • Roaccutane • Statins

Fig. 1.7 Common medications that may cause muscular pain

Connective Tissue Disease (CTD)

The label of CTD is an umbrella term that includes conditions such as systemic lupus erythematosus (SLE), Sjogren's syndrome (SS), scleroderma, vasculitis and mixed connective tissue disease.

Joint pain is a frequent symptom but can be absent in patients with connective tissue disease. The most common articular presentation is with non-erosive inflammatory arthritis [32].

If CTD is suspected, then the presence or absence of extra-articular features must be established.

Mouth ulcers are a common complaint, and if recurrent genital ulcers are also present, this raises the possibility of Behcet's syndrome. A photosensitive rash, particularly over the cheeks in a young female patient, is strongly suggestive of SLE. This rash is distinguished from acne rosacea by the fact that it spares the nasolabial folds.

The classic triphasic colour changes of Raynaud's syndrome are prevalent in the general population but are more common in patients with connective tissue disease [33, 34]. Patients should be asked about the dryness of the mouth or eyes, which is found in up to 27% of older patients [35], but this is a significant finding, particularly if present in patients below the age of 50 as it may suggest primary or secondary SS.

A history of thromboembolic disease or recurrent miscarriage raises the possibility of antiphospholipid syndrome, which may be primary or associated with other conditions, in particular SLE.

Pain Syndromes

Pain syndromes are common in rheumatological practice and include fibromyalgia (FMS), complex regional pain syndrome (CRPS) and chronic widespread musculoskeletal pain.

There is an association with depression and other functional syndromes such as chronic fatigue syndrome and irritable bowel syndrome. Some patients may present with a large number of unrelated symptoms that cause anxiety, and this is often termed 'catastrophisation' [36]. In such circumstances, it is useful to initially let the patient talk openly about their symptoms to ensure they feel listened to and then to focus specifically on areas that are relevant to the clinician.

A sleep history is vital and often overlooked, but sleep deprivation is very common [37] and contributes towards secondary depression and obesity, both of which can worsen the underlying pain. Patients will often complain of unrefreshing sleep resulting in daytime somnolence, which can also be caused by obstructive sleep apnoea (OSA), exacerbated by obesity.

Fatigue is almost universal and often ignored by physicians, but patients find this one of their most debilitating symptoms. Since thyroid disease, anaemia, OSA and depression are common, these should be excluded as potential causes of fatigue before attributing it to the underlying rheumatological disease.

An abnormal sensitivity to light touch (allodynia) is a defining feature of CRPS, and subtle colour and temperature changes may

be seen in the overlying skin of the affected limb or joint. There is frequently a history of trauma or recent surgery as a precipitating factor.

Fibromyalgia will typically cause widespread muscular tenderness with only light pressure. Although patients will complain of joint swelling, synovitis is not a feature of this condition, and if present, it should lead to a reappraisal of the diagnosis.

In many patients, FMS and CTD may coexist, and it is important to differentiate which is most active in order to treat their pain [38].

Joint Examination

General Examination

As rheumatological disease has many potential systemic manifestations, it is important to perform a general examination of the patient, including measurement of the blood pressure and urinalysis. The one exception to this is when patients present with a very localised complaint involving only one joint where, as a minimum, the joint immediately distal and proximal to the affected joint should be examined.

As part of the general examination, the skin must be inspected, looking in particular for skin or nail evidence of psoriasis, livedo reticularis, sclerodactyly, rheumatoid nodules, tophi, telangiectasia or palpable purpura, which is a sign of leucocytoclastic vasculitis.

The eyes may be involved in certain autoimmune conditions, which can cause keratoconjunctivitis sicca, uveitis, scleritis and episcleritis. There are a number of different methods of measuring inadequate tear production, including Schirmer's test, which involves the use of a strip of blotting paper. These can be useful if SS is a possibility, although the reproducibility of these tests can be poor [39].

If joint sepsis is suspected, then the temperature must be measured, and immediate aspiration of the affected joint is critical. This will be discussed further in another chapter.

Auscultation of the chest and heart sounds will help to identify patients with pulmonary fibrosis, pulmonary hypertension and significant valvular disease.

Musculoskeletal Examination

As an initial screen, the GALS (gait, arms, legs and spine) examination is useful.

The gait can be assessed by asking the patient to walk and look for asymmetry and pain on walking.

Then, the upper limbs are inspected, looking for skin changes, muscle wasting and evident joint swelling.

The joints are palpated, looking for evident swelling, temperature change and tenderness. Pain on squeezing the metacarpophalangeal joints is suggestive of rheumatoid arthritis – the metacarpal 'squeeze test' as seen in Fig. 1.8.

Movement of the joints is examined by asking the patients to pronate and supinate the hands with the elbow flexed (Fig. 1.9).

The ability of the patient to perform a pinch grip is assessed and then flexion and extension of the wrist and elbow. The range of movement of the shoulder is assessed by bringing the thumb up under the scapula to assess adduction and internal rotation and by placing the hands on top of the head to assess external rotation and abduction (Fig. 1.10).

The examination of the legs is performed with the patient lying on an examination couch with an initial inspection to look for wasting, fasciculation and asymmetry. The knee joint is palpated for swelling and tenderness and is then flexed and extended with one hand on the knee joint to feel for crepitus (Fig. 1.11).

With the knee flexed, the hip is then internally and externally rotated (Fig. 1.12).

The spine is then inspected for scoliosis and viewed from the side to exclude abnormal kyphosis.

Flexion and extension of the cervical spine are assessed, and then the patients are asked to put their ear on their shoulder. Forward flexion of the lumbar spine is examined by asking the patients to bend forward with their knees held in extension and

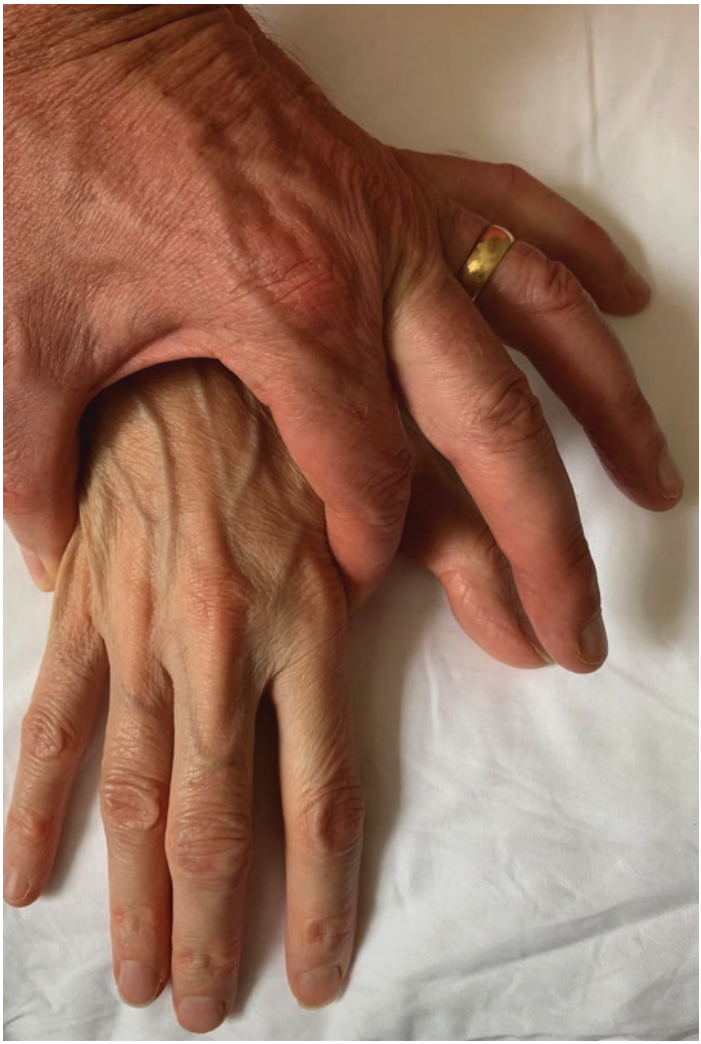

Fig. 1.8 The metacarpal squeeze test

Fig. 1.9 Pronation and supination of the forearm

Fig. 1.10 Assessment of shoulder range of movement

then movement at the thoracic spine by asking the patients to rotate the spine to one side and then the other with the pelvis held in position by the examiner.

If the patients are noticed to be hypermobile, then an assessment of this can be made using the Beighton score (Fig. 1.13), with a score of 6 or above from a potential total of 9 indicating underlying hypermobility.

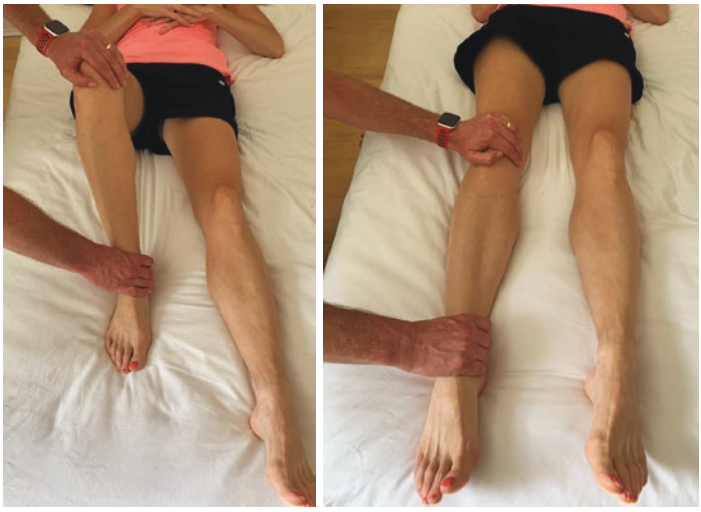

Fig. 1.11 Flexion and extension of the knee

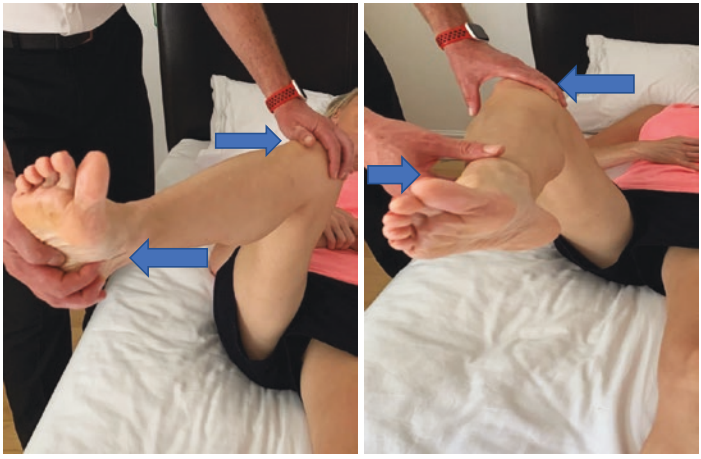

Fig. 1.12 Internal and external rotation of the hip

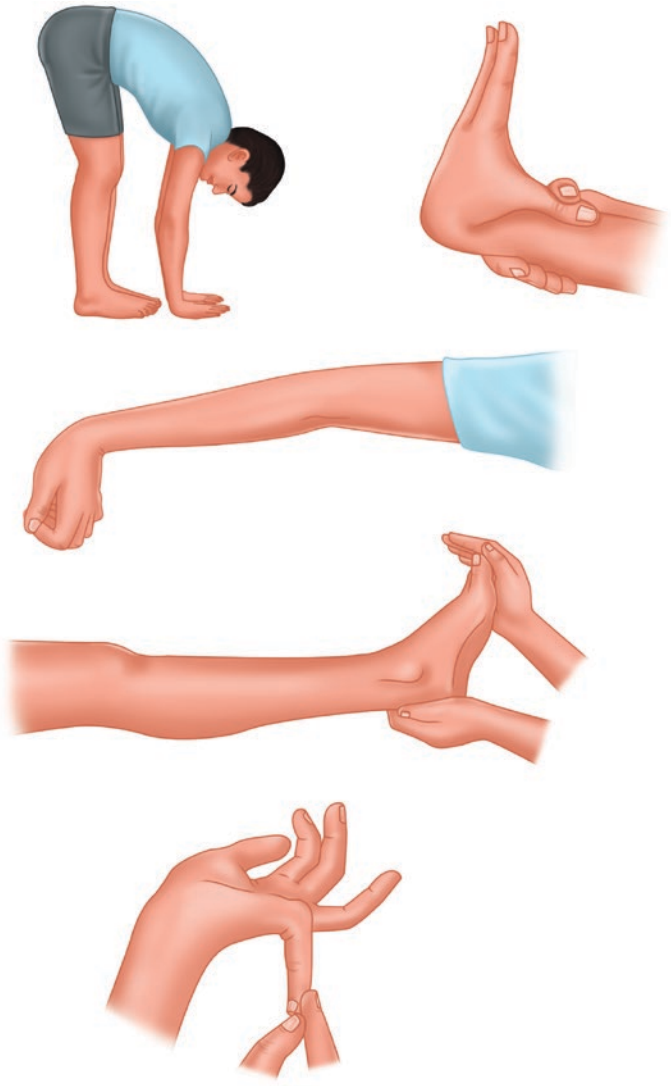

Fig. 1.13 The Beighton score to assess joint hypermobility

Individual Joint Examination

The examination of individual joints should then proceed using the principle of 'look feel move'. It is important to compare the painful joint with the opposite side and with the joint proximal to and distal to it. One of the most important objectives is to establish the presence or absence of synovitis.

The joint should be inspected for visible swelling, scars, localised wasting and alteration in colour.

Gentle palpation of the joint will elicit any tenderness or swelling. Synovitis will produce soft tissue swelling, warmth, effusion, reduced range of movement and localised tenderness.

Any fibrotic change within the tendons, as seen with Dupuytren's contracture, will also be identified by palpation of the tendon sheath.

Movements should be compared across the full range of movement of the joint, both actively and passively. This will help to differentiate extracapsular conditions such as lateral epicondylitis of the elbow or muscular injury, where the passive range of movement is normal, with intracapsular disease where it is reduced.

Patterns of joint involvement are suggestive of specific diseases, for example, periosteal new bone formation involving the distal and proximal interphalangeal joints, and the first carpometacarpal joint of the thumb is pathognomonic of nodal osteoarthritis. In contrast, asymmetrical synovitis is a feature of seronegative arthritis, whereas rheumatoid arthritis tends to produce symmetrical disease.

Widespread muscular tenderness is very suggestive of fibromyalgia, which is primary in the majority of cases but can be secondary to other rheumatic diseases.

Summary

Joint pain is a very common symptom in the general population, and with an ageing population and increasing obesity, the prevalence is likely to increase still further.

Distinguishing inflammatory from non-inflammatory disease is vital as prompt treatment of conditions such as rheumatoid arthritis significantly reduces long-term disability.

Despite significant advances in laboratory and radiological investigations, the assessment of patients with joint pain using the history and examination remains the mainstay of clinical practice. The aim is to provide an accurate differential diagnosis and therefore effective treatment.

Most patients with musculoskeletal pain will present to primary care physicians and can be investigated and treated in that setting by a clinician confident in the management of rheumatological conditions.

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Osteoarthritis

2

Jessica J. Patel

Introduction

Osteoarthritis (OA) is a slowly progressing, degenerative disease process, which affects approximately 32.5 million Americans. In 2013, OA was among the most expensive conditions to treat, especially when joint replacement surgery was involved. Due to its impact on function and mobility, OA stands as the highest cause of indirect lost earnings and medical expenditure, costing more than $100 billion to the US economy. Europe is not far behind, citing OA as one of the highest causes of healthcare cost [1, 2].

Osteoarthritis generally affects all the structures of a diarthrodial joint and commonly involves the knees, hips, hand, spine, shoulders, and feet. Although it is the leading cause of disability in the elderly, some patients remain stable, and predicting an individual's risk for progression and severity remains a challenge. It is important to understand the features of progression and risk factors given the functional impairment and global burden of dis-

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ease. Research has helped improve our understanding of pathophysiology of OA, leading to more interest in targeted therapies that are not only disease-modifying but also help pain modification.

Pathophysiology

Osteoarthritis was previously thought to be a mere "wear and tear" arthritis related to normal aging; however, there is now a better appreciation for multiple biochemical processes that contribute to the initiation and progression of the disease.

For proper functioning, a joint should allow for pain and friction-free range of motion while being able to withstand mechanical load. The joint surface is lined by articular cartilage, which is avascular and aneural, meant to absorb loading force. It is maintained by highly specialized chondrocytes that create the extracellular matrix consisting of proteoglycans and collagen.

The surrounding joint capsule includes the synovial membrane, which plays an important role in maintaining the homeostasis of the articular cartilage. Synoviocytes produce macrophage-like phagocytic cells, hyaluronan, cytokines, and growth factors that make up the synovial fluid. This viscous fluid allows for friction-free movement and normal matrix turnover in the articular cartilage. The joint capsule and articular cartilage protect the subchondral bone.

Early changes of osteoarthritis are marked by cartilage swelling: hydrophilic proteoglycans increase the water content of the articular cartilage resulting in matrix loosening. As the matrix degrades, it accelerates chondrocyte activity, increasing proteoglycan synthesis and proinflammatory cytokines, releasing destructive enzymes.

Cartilage starts to soften and thin, and in response to this, repair and remodeling are attempted but often insufficient. Bone thickening or sclerosis that represents aberrant remodeling ensues, and osteophytes form at joint margins, which contributes to the bony enlargement seen in later stages of OA [3].

Plain radiographs underestimate the joint tissue involvement in OA since they only visualize a component of the condition,

including cartilage loss that results in joint space narrowing and bony changes that result in subchondral sclerosis, cysts, and osteophyte formation. MRI studies can detect early cartilage degeneration and bone marrow edema.

Frequently, there is a disconnect between radiographic grade and symptomatic disease. The greatest predictors of pain include (1) articular grade of damage, (2) female sex, (3) BMI, (4) depression, (5) poor coping skills, and (6) lower level of educational attainment and young age [4].

Risk Factors

Osteoarthritis is mostly a mechanical process; however, several factors may come into play, which explain the variability of disease and dysfunction.

Age is the strongest risk factor in osteoarthritis. Prevalence of OA increases in women, and compared with men, women have more severe knee OA after menopause [5]. There is also a strong component of heritability in OA, nearly 50% or more, which may explain the variability in joint involvement and severity in similar age groups [6].

Obesity is a major risk factor for both development of OA and its progression, and the reason is twofold. The first is increased load on joints especially of the knees and hips, and second, there is now a growing body of evidence that adipose tissue can induce proinflammatory cytokines such as IL 6, leptin, and adiponectin, which contribute to joint damage and may explain OA in non–weight-bearing joints [7].

Women are more likely to develop OA of the hand, knees, and hip compared with men, potentially due to hormonal influences, although the exact cause is unclear. There are also known racial differences in knee OA; African American males are at higher risk of medial knee OA than African American and white women [8].

Studies have been conflicting on the roles of vitamin D and bone metabolism in OA, and vitamin D deficiency may have little effect on joint degeneration.

Table 2.1 Causes of secondary osteoarthritis

Obesity	Inflammatory arthritis
Ligamentous laxity/joint trauma	Alkaptonuria
Congenital abnormalities	Ehlers–Danlos syndrome
Diabetes	Hemochromatosis/Wilson's disease
Septic arthritis	Calcium pyrophosphate arthropathy

Secondary causes of OA should be considered, especially when atypical joints are affected or when seen at a young age. Congenital disorders due to dysplasia and malalignment of joints may lead to early OA. Metabolic syndromes and endocrinopathies can lead to early OA. For example, hemochromatosis causes iron deposition in the joints, leading to defects in cartilage through inflammation and calcium pyrophosphate deposition (Table 2.1).

Clinical Presentation

Some features of osteoarthritis are common, such as dull joint pain, which worsens with activity and improves with rest; however, because it is such a prevalent disease, symptoms are not homogeneous. Crepitus may be appreciated with passive motion due to cartilage degradation. Joint swelling may be due to bony enlargement from osteophytes and effusions. Osteophytes and degradation of the articular cartilage eventually lead to deformity, including varus and valgus malalignment.

Knees

Symptomatic OA of the knee is slow and progressive. There are two distinct compartments of the knee in which OA can occur: tibiofemoral (medial and lateral) and patellofemoral compartments. OA generally affects one compartment more than the others, whereas in inflammatory arthritis, all compartments are involved equally. Tibiofemoral OA can cause varus deformity

when the medial compartment is involved and valgus deformity with lateral involvement.

Patellofemoral OA causes pain with ascending and descending stairs, squatting, prolonged sitting, and standing from a seated position [9]. This is often exacerbated by poor quadriceps tone.

Tricompartmental involvement should prompt consideration of inflammatory arthritis such as rheumatoid arthritis, or concomitant crystalline arthritis with calcium pyrophosphate crystal deposition or gout.

Hips

Distinguishing hip pain secondary to OA is important as perceived pain in the hip can originate from the spine or greater trochanteric bursa. Hip OA generally causes pain in the groin, anterior hip, and can refer to the knee. Lateral thigh pain may be originating from greater trochanteric bursitis. Low back pain and lumbar radiculopathy may also cause pain radiating to the hip. Active and passive range of motion of the hip should elicit pain if there is an underlying mechanical problem.

Hands

In the upper extremities, hands are most commonly affected, involving the distal interphalangeal (DIP) joints, proximal interphalangeal (PIP) joints, and first carpometacarpal (CMC) joints. Osteophytes in the DIP and PIP joints are called Heberden's nodes and Bouchard's nodes, respectively. These are typically seen in white women, and there is a strong familial predisposition in this "nodal OA." Some individuals experience severe pain in the early stages of osteophyte formation, which results in rapid bony growth, erythema, and tenderness. Over a short period of time, the inflammatory response calms down, leaving behind only deformity and bony enlargement.

Osteoarthritis of the CMC joint is also common with individuals experiencing difficulty opening jars, grasping, and buttoning clothing. An examination may reveal crepitus and grinding at the base of the thumb and sometimes squaring of the wrist.

Erosive osteoarthritis is an aggressive form of OA that affects the hands, namely the DIP, PIP, and CMC joints. Pain is accompanied by local inflammation, which can be mistaken for synovitis; however, EOA is not a systemic inflammatory condition and involves the more distal joints rather than metacarpophalangeal joints [10]. Unfortunately, the functional impairment may be worse compared with typical osteoarthritis.

Diagnostic Testing

Generally, OA is a clinical diagnosis, and lab work and imaging are not always required. OA may accompany crystalline arthritis such as gout or pseudogout, and some patients may have a combination of inflammatory and mechanical joint symptoms. A large cohort study of over 2000 patients with a presumptive diagnosis of RA in primary care centers in South America was evaluated, and nearly half were misdiagnosed, the majority having OA. This study illustrates the need for education and early referral approaches in primary care settings [11]. Acute phase reactants (sedimentation rate, c-reactive protein), uric acid, rheumatoid factor, and anti-CCP antibodies may be considered to rule out other pathologies.

Plain radiography may show osteophytes, subchondral sclerosis, asymmetric joint space narrowing, and cysts or geodes representing remodeling of bone after damage.

Magnetic resonance imaging is not generally required to diagnose OA unless there is evidence of ligament tear or injury, which may be contributing to pain.

Ultrasonography can be used to visualize effusions, synovitis, early bony changes, and erosions. It may be used to guide intraarticular injections.

Management

Osteoarthritis may be an inevitable part of the aging process; however, a variety of therapeutic modalities are used to manage pain and disability and improve quality of life. Management involves patient education, nonpharmacologic therapy, pharmacologic therapy, and potentially surgery. Often, a combination of modalities is used to improve function. Patient education and regular discussion of OA risk factors, etiology, and the degenerative process can improve treatment compliance and manage realistic expectations of overall prognosis.

Nonpharmacologic Therapy

Exercise and Weight Loss

An exercise and weight loss program is the first and foremost recommended lifestyle measure in OA intervention. There is a high quality of evidence, especially for knee OA, that combination of low impact aerobics and strengthening exercise, as well as calorie-restricted diet leading to weight loss, improves pain and function and allows for faster walking speeds [12].

Exercise regimens should be tailored to the individual's preference and level of pain to improve compliance. The American College of Rheumatology Guidelines for the Management of Osteoarthritis published in 2019 recommends aerobic exercise with walking, cycling or stationary bicycling, and aquatic exercise. Strengthening exercises involve isometric exercise with elastic bands, quadriceps contraction, and flexibility [12, 13].

Many patients with debilitating OA also have other metabolic comorbid conditions and can benefit from weight loss if overweight. Weight loss of at least 5% has been shown to improve physical function in overweight patients with knee OA and overall has beneficial outcomes for other health conditions [14]. Exercise and weight loss programs are most effective when supervised or in a class setting, and individuals should be encouraged to participate at least three times a week.

Knee Braces

The use of braces depends on the location of arthritis. In tibiofemoral knee osteoarthritis involving the medial compartment, unloader knee braces can provide valgus force to the medial knee, decreasing pain and improving ambulation [15, 16]. In patellofemoral osteoarthritis, patellar malalignment is a cause for pain and dysfunction. There is some evidence of short-term improvement with the use of patellofemoral taping or bracing; however, this can be of limited long-term efficacy due to the patella moving in multiple planes [17].

Data is limited with the use of compression or neoprene sleeves over the knees, and they are not recommended.

For hand OA, especially of the CMC joint, orthoses to stabilize the thumb may reduce pain by reducing friction and improve pinching strength [18].

Pharmacologic Therapies

When nonpharmacologic interventions have proved insufficient, pharmacologic modalities should be pursued. Thus far, no medication has been shown to disease modify or reduce the progression of OA; therefore, therapy should be geared toward improving function and reducing pain with the least adverse effects.

Topical nonsteroidal anti-inflammatories may be used in both hand and knee OA with good efficacy and low systemic absorption and play an important role in analgesia in those who are at high risk for possible adverse effects with oral NSAIDs. In particular, in the elderly, those with gastropathy or renal dysfunction, topical diclofenac has shown better tolerability than oral diclofenac [19].

Topical capsaicin may be effective in knee OA; however, its use in hand OA has not been reviewed [19, 20].

Nonsteroidal anti-inflammatory drugs and acetaminophen or paracetamol are often first-line oral treatment options for OA. Often, acetaminophen is used for the long term due to potential cardiovascular and GI side effects related to long-term NSAID use. A large-scale meta-analysis from 2017 found that acetamino-

phen was not clinically effective in pain relief for knee or hip OA, though it may provide minimal short-term benefit. A maximum daily dose of 3 g is conditionally recommended by the ACR for OA [21, 22].

NSAIDs are widely used for OA, especially with polyarticular involvement, though their use is often limited by comorbidities and potential adverse effects. The lowest effective dose for the shortest period of time is suggested. Based on a meta-analysis comparing the effectiveness of NSAIDs, diclofenac (150 mg/daily) was most effective, followed by naproxen [21]. If nonselective NSAIDs are used in individuals with risk for GI comorbidities, a proton pump inhibitor (PPI) may be added for gastric protection, or COX-2 inhibitor monotherapy can be used. Celecoxib was recommended by the Osteoarthritis Research Society International (OARSI) [23].

Duloxetine is increasingly employed in individuals who are at high risk of potential adverse effects from NSAIDs or have not responded adequately to NSAIDs. Its analgesic effect comes from the modulation of central pain pathways via inhibition of serotonin and norepinephrine reuptake [24, 25]. The dose is gradually titrated from 30 mg daily to 60–120 mg/daily. Generally, it is well tolerated with observed side effects of nausea, fatigue, dry mouth, gastrointestinal upset, and somnolence. These adverse effects tend to be early on in treatment and self-limited.

Intraarticular (IA) therapy with glucocorticoids has been recommended by several guidelines and can offer several months of relief, especially in the knee. For patients with hip OA, ultrasound guidance is useful for localizing the joint space. Onset is rapid, and effects may last from 3 to 6 months. IA corticosteroids should be used with caution in diabetic patients due to the short-term risk of transient hyperglycemia [24].

Viscosupplementation with intraarticular injections of hyaluronic acid is FDA approved for moderate knee OA. Hyaluronate is a polysaccharide produced by synovial lining cells, lubricating the surface between synovium and cartilage. It is also responsible for the viscosity of the synovial fluid. In 2015, a series of intraarticular Hyaluronic Acid injections in the USA cost approximately $500 per course [26]. Generally, the intraarticular injections are

well tolerated, although side effects include local injection site reactions, and rarely, sterile pseudoseptic reactions. The role of viscosupplementation is not clearly established and remains controversial. A meta-analysis published in 2012 in the *Annals of Internal Medicine* showed small, but clinically irrelevant, benefits in knee OA. Given the cost of viscosupplementation and lack of benefit, recent ACR guidelines for OA conditionally recommend against hyaluronic acid injection to the knee [26, 27].

Complimentary Therapies

Dietary supplements often come up during the conversation with patients looking for alternative treatment for osteoarthritis. Two common supplements are glucosamine and chondroitin sulfate, though there are conflicting results in the efficacy of these agents on knee OA, suggesting perceived improvement by the patient or placebo effect [28]. One placebo-controlled trial demonstrated that chondroitin was superior to placebo in decreasing in the duration of morning stiffness and global hand pain [29]. Given low potential toxicity, if patients wish to take these supplements, doses of glucosamine 1500 mg/daily and chondroitin 800 mg/daily may be trialed.

Curcumin, found in turmeric spice, and *Boswellia* tree resin, have been long viewed as anti-inflammatory compounds in Ayurvedic medicine. It has been suggested that they may slow down the catabolic actions of early OA and may have a role in adjunctive therapy for OA; however, long-term, high-quality studies are lacking.

Future Direction

Nerve growth factor and its role in tissue injury and pain were recognized in the early 1990s. Its expression in the nervous system, inflammatory cells, and chondrocytes quickly became a focus as a potential therapeutic target for OA [30]. Tanezumab, a humanized monoclonal antibody against nerve growth factor, is the first of its kind to show positive results in refractory moderate-to-severe osteoarthritis of the knee. It has had a disappointing

early start with phase III trials showing significant improvement in pain and physical function. Unfortunately, rapidly progressing OA in tanezumab-treated patients was observed, and some patients required joint replacement [31]. In March 2020, the FDA accepted a regulatory submission for tanezumab in those with moderate-to-severe OA who cannot tolerate or have not responded to conventional therapies.

Another potential target for treatment is the Wnt pathway. The Wnt signaling cascade is important in chondrocyte proliferation, differentiation, and function, and overexpression may lead to OA. Lorecivivint (novel small molecule, SM04690) intraarticular injection has demonstrated disease-modifying effects with improvement in pain and function in Phase II studies [32].

A recent safety phase IIa study showed promising results for a cathepsin K inhibitor (MIV-711), which reduced bone and cartilage progression in mild-to-moderate OA of the knee. Cathepsin K is expressed in osteoclasts and involved in bone resorption [33].

Summary

Osteoarthritis is a complex disease and is a source of high societal cost, reduced quality of life, and increased disability. Optimal management involves both nonpharmaceutical and pharmaceutical interventions. A multidisciplinary approach needs to be individualized based on patients' particular needs and disabilities. As we gain a better appreciation of the multifaceted degenerative process of OA, targeted therapies and hopefully disease-modifying agents can be developed to prevent both progression and deformity.

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Rheumatoid Arthritis

3

Clemens Scheinecker and Daniel Aletaha

Rheumatoid arthritis (RA) is a systemic chronic autoinflammatory disease that, if untreated, eventually results in erosive destructive arthritis.

RA affects between 0.5% and 1% of the population. Women are affected on average twice more often than men. Although RA can start at any age, the average age of disease onset is between 30 and 50 years.

Pathophysiology

The exact cause of RA is not known. Genetic susceptibility and certain environmental triggers, however, contribute to the initiation of the disease. Specific gene loci, in particular, of HLA-class II antigens that mediate antigen presentation to T cells are most closely associated with RA. Important environmental factors that are associated with an increased risk of developing RA include smoking, infection (e.g., epstein barr virus (EBV)), periodontitis, and alterations of the microbiome of the gut and other mucosal surfaces.

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The underlying cause of joint swelling is the inflammation and expansion of the synovial tissue, often termed "pannus." This synovitis is characterized by hyperplasia of the synovial lining layer, infiltration of immune cells, and hypervascularization. Proinflammatory cytokines, including tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, and IL-1, are produced by macrophage-like synoviocytes and fibroblast-like synoviocytes (FLSs). These cytokines act as a signaling network in a paracrine or autocrine fashion and develop autonomous feedback loops that cause continuous recruitment of immune cells and perpetuation of the inflammatory process. Matrix degrading enzymes such as metalloproteinases (MMPs) and small-molecule mediators such as prostaglandins and leukotrienes are mainly produced by FLSs. FLSs develop an aggressive and invasive phenotype and are responsible for cartilage destruction. On the other hand, destruction of bone tissue is mainly mediated by bone-resorbing osteoclasts upon maturation and activation from monocytic precursor cells [1].

In addition, cells of the adaptive immune system, including $CD4^+$ memory T cells and B cells, infiltrate the synovial tissue. In up to 15–20% of patients, the formation of ectopic germinal centers can be found in which B cells proliferate, differentiate, and produce antibodies, suggesting an ongoing immune response to native or altered peptides.

Clinical Presentation and Diagnosis

Although RA can affect any joint with a synovial membrane, the typical clinical presentation consists of a symmetric swelling of small joints, including the metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal joints of the hands and feet. Joint swelling in RA is usually soft in contrast to the hard, bony swelling that is observed in patients with osteoarthritis. The distal interphalangeal, the sacroiliac, and the lumbar spine joints are usually spared, but the atlantoaxial (C1–C2) joint is a locus of preference of severe RA. Patients typically complain about joint pain and morning stiffness with the inability to make a fist. This often lasts for more than 1 hour and does not improve upon movement.

In up to two-thirds of RA patients, autoantibodies can be detected in the serum. IgM and IgA rheumatoid factor (RF) is the classic autoantibody in RA and is directed against the Fc part of IgG. More recently identified autoantibodies are directed against citrullinated peptides (anti-citrullinated peptide antibodies [ACPAs]). Most, but not all, ACPA-positive patients are also RF positive. ACPAs seem to be more specific and sensitive for the diagnosis, although their superiority over a high cutoff for positivity of RF (e.g., 50 U/ml) is questionable [2]. Both are predictors of poor prognostic features and joint damage [3]. ACPAs, RF, and proinflammatory cytokines can be detected up to 10 years before clinical signs of the disease, suggesting an activation of the immune system during the preclinical phase of the disease.

Besides these rather specific autoantibodies for RA, a small percentage of patients are positive for anti-nuclear antibodies (ANAs).

For the diagnosis of RA, no validated criteria have been developed so far. However, the 2010 classification criteria can serve in the establishment of RA diagnosis and are used in clinical practice as well as for the conduction of clinical trials [4]. They require the presence of at least one swollen joint that cannot be explained by other rheumatic diseases in addition to a minimum of six points from a ten-point scoring system (see Table 3.1). Some important aspects, however, have to be considered. Patients with a score of less than 6 are not classifiable as having RA, but their status can be reassessed and they might fulfill the criteria cumulatively over time. “Large joints” refers to shoulders, elbows, hips, knees, and ankles. “Small joints” refers to the metacarpophalangeal joints, proximal interphalangeal joints, second to fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from the assessment.

In particular at disease onset, however, the exact diagnosis is not always clear, and a number of differential diagnoses have to be considered (see Table 3.2) [5].

In addition to the peripheral polyarthritis, RA can also involve other tissues and organs [6]. Among the most common extra-articular features are rheumatoid nodules that can be observed in

Table 3.1 The American College of Rheumatology/Europen League Against Rheumatism classification criteria for RA

Target population (who should be tested?): patients who	
1. Have at least one joint with definite clinical synovitis (swelling)	
2. With the synovitis not better explained by another disease	
Classification criteria for RA (score-based algorithm): add the score of categories A–D; a score of ≥6/10 is needed for the classification of a patient as having definite RA.	
A. Joint involvement	
1 large joint	0
2–10 large joints	1
1–3 small joints (with or without the involvement of large joints)	2
4–10 small joints (with or without the involvement of large joints)	3
>10 joints (at least one small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF and negative ACPA	0
Low positive RF or low positive ACPA	2
High positive RF or high positive ACPA	3
C. Acute phase reactants (at least 1 test result is needed for classification)	
Normal CRP and normal ESR	0
Abnormal CRP or normal EST	1
D. Duration of symptoms	
<6 weeks	0
≥6 weeks	1

ACPA anti-citrullinated protein antibody, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *RF* rheumatoid factor

up to 30% of the patients. Nodules are usually subcutaneous, painless, and classically located at pressure points on extensor surfaces, for example, at the elbow or the toes. Nodule involvement of pleura, lung, pericardium, and myocardium is fortunately rare but can present a diagnostic challenge. Furthermore, relatively common manifestations can be observed in 6–10% of

Table 3.2 Differential diagnosis of a patient with polyarthritis

Inflammatory arthritis
Rheumatoid arthritis
Postviral arthritis
Psoriatic arthritis
Reactive arthritis
Peripheral spondyloarthritis
Enteropathic arthritis
Polyarticular gout/pseudogout
Connective tissue diseases
Systemic lupus erythematosus
Scleroderma
Behcet's disease
Polyarteritis nodosa
Undifferentiated connective tissues disease
Noninflammatory joint conditions
Generalized osteoarthritis
Soft tissue rheumatism/fibromyalgia
Others
Septic arthritis
Polymyalgia rheumatica
Paraneoplastic syndrome
Subacute bacterial endocarditis

patients and include secondary Sjögren's syndrome, anemia of chronic disease, and pulmonary involvement (inflammatory lung disease and/or pulmonary fibrosis). Vasculitic manifestations can occur as cutaneous, ocular, and systemic vasculitis. In general, extra-articular features are frequently present in early disease and are related to worse outcome measures of the disease.

RA patients have an increased risk of total mortality. This is mainly due to higher prevalence rates of cardiovascular and pulmonary diseases. Current treatment strategies, however, have substantially decreased premature mortality [1].

Approach to Patients with Suspected RA

For patients with suspected RA in general, early referral for specialist advice is recommended and is associated with improved health status [7].

For the diagnosis of RA, a physical examination should be performed to check for swollen or tender joints or loss of motion. In addition, a careful medical history should be obtained including family history. The following laboratory examinations are recommended: whole (complete) blood count; erythrocyte sedimentation rate (ESR); liver and kidney assessment including C-reactive protein (CRP) values, blood coagulation parameters, and urinalysis; and immunological parameters including IgG, IgM, and IgA levels, rheumatoid factors, anti-CCP antibodies, and anti-nuclear antibodies (ANA).

Conventional radiography (CR) should be performed of both hands, feet, and ankle joints as the initial imaging technique to detect bone damage. Key radiographic findings in RA are marginal and central osseous erosions and cysts, fusiform soft tissue swelling, diffuse loss of joint space, and regional and periarticular osteopenia.

In patients with clinical suspicion of cervical involvement, monitoring of functional instability of the cervical spine by lateral radiography obtained in flexion and neutral should be performed.

Although CR has been considered the gold standard for imaging in RA, its sensitivity for structural damage in RA diagnosis is low, and disease activity cannot be assessed. Therefore, when there is diagnostic doubt or for the assessment of disease activity, ultrasound or MRI can be used in particular in the absence of serum antibodies [8].

Assessment of Clinical Disease Activity

Several tools have been developed over the years to monitor disease activity. Among them are the clinical disease activity index (CDAI), the disease activity score with 28 joint counts (DAS28), and the simplified disease activity index (SDAI). These scores are

composite measures of the number of tender and swollen joints, an assessment of the disease activity by the patient and by the treating physician, and sometimes also include laboratory parameters that reflect inflammation like the CRP value or the erythrocyte sedimentation rate (ESR). The CDAI is the easiest index to perform. It consists of a numerical summation of the number of tender and swollen joints and the global assessment of the patient and the evaluator on a 10-cm visual analog scale (VAS). It does not require a laboratory parameter and therefore can be performed directly in the presence of the patient. The CDAI ranges from 0 (remission) up to 76 (highest possible disease activity). It contains defined cutoff levels for remission (<2,8), low (2.8–10), medium (10–22), and high (>22) disease activity. The treatment target in RA is to achieve a state of remission or at least of low disease activity in order to prevent otherwise progressive and irreversible joint destruction. The treatment target should be achieved in a "treat-to-target" approach. This strategy is based on a 50% improvement within 3 months of therapy and should lead to remission or at least low disease activity within 6 months.

Therapy

Patients with a definite diagnosis of RA need to be treated with a disease-modifying drug (disease-modifying antirheumatic drugs [DMARDs]). These drugs have proven to be capable of preventing cartilage and bone destruction. DMARDs are subdivided into conventional synthetic (cs)DMARDs (e.g., methotrexate), targeted synthetic (ts)DMARDS (e.g., JAK-inhibitors), biological (b)DMARDs (monoclonal antibodies or receptor constructs), and biosimilar (bs)DMARDs. Their molecular target, structure, and selected side effects are summarized in Table 3.3.

Symptomatic drugs such as analgesics or nonsteroidal antiinflammatory drugs (NSAIDs) can be used in addition to relieve joint pain and swelling. In contrast to DMARDs, however, they do not interfere with pathophysiologic mechanisms of the disease and therefore are not able to prevent joint damage. Glucocorticoids

Table 3.3 Currently approved DMARDs for the treatment of RA

Subgroup and type	Molecular target	Structure	Selected side effects
csDMARDs			
Methotrexate	Unknown	Small chemical molecules (oral)	Nausea, stomatitis, liver enzyme increase, leukocytopenia, teratogenicity
Sulfasalazine	Unknown		Hypersensitivity, nausea, diarrhea, agranulocytosis
Leflunomide	Dihydroorotate dehydrogenase		Diarrhea, hypertension, hypersensitivity, liver enzyme increase, leukocytopenia, teratogenicity
Hydroxychloroquine	Unknown		Retinopathy
tsDMARDs			
Tofacitinib	JAK 1,2,3	Small chemical molecules (oral)	Infections, herpes zoster, cytopenias, hyperlipidemia
Baricitinib	JAK 1,2		
boDMARDs			
Adalimumab	TNF-alpha	Human monoclonal antibody (Ab)	Infections, reactivation of tuberculosis, psoriasiform skin disease, exacerbation of demyelinating disease, drug-induced lupus, nonmelanoma skin cancer
Certolizumab	TNF-alpha	Fab′ fragment of humanized monoclonal Ab	
Etanercept	TNF-alpha	Receptor construct	

Golimumab	TNF-alpha	Human monoclonal Ab	
Infliximab	TNF-alpha	Chimeric monoclonal Ab	
Tocilizumab	IL-6 receptor	Humanized monoclonal Ab	Infections, reactivation of tuberculosis, bowel perforation, hypersensitivity, neutropenia, hyperlipidemia
Sarilumab	IL-6	Human monoclonal Ab	
Abatacept	CD80/CD86	Receptor construct	Infections, reactivation of tuberculosis, leukocytopenia
Rituximab	CD20	Chimeric monoclonal Ab	Hypersensitivity, reactivation of hepatitis B, leukocytopenia, hypogammaglobulinemia
bsDMARDs			
Adalimumab	See above	See above	See above
Etanercept			
Infliximab			
Rituximab			

(GCs) do work as DMARDs but cannot be used in the long term because of their side effects. Because of their potent and rapid anti-inflammatory activity, patients should be treated with GC in combination with csDMARDs for a limited time. This is preferentially done at the initiation of therapy due to the delayed onset of DMARD action or during flares of disease activity.

The EULAR recommendations for the management of RA suggest in their 2019 update to start treatment with methotrexate (MTX) together with short-term (aiming at discontinuation within 3 months) GC at a low dose (<7.5 mg/d) or intermediate dose [9]. MTX is given once a week and is usually started at 15 mg. The dose should be escalated to a maximum of 25 mg weekly in the absence of potential side effects within 4–6 weeks. The most common gastrointestinal (GI) side effects are nausea, vomiting, or abdominal pain. In addition, MTX can cause elevated liver enzymes, mucositis, and leukopenia due to bone marrow suppression. Therefore, patients should receive folic or folinic acid (vitamin B9), which has been shown to improve GI side effects and reduces the chance of developing abnormal liver blood tests [10]. If MTX cannot be used, alternative csDMARDs like sulfasalazine or leflunomide can be substituted. MTX (and leflunomide) are teratogenic and therefore cannot be used before conception or during pregnancy.

MTX is still regarded as an anchor drug in the treatment of RA. On average, 25% of patients achieve a state of disease remission with the combination of MTX plus GC within 6 months. A higher proportion of patients achieve a state of low disease activity.

In case this treatment target cannot be reached, patients should be stratified according to prognostic factors. These include the autoantibody positivity at high titers, a state of high disease activity, early radiological signs of joint damage but also persistent disease activity after a trial of two csDMARDs. In patients without adverse prognostic factors, a different csDMARD can be given either as monotherapy or in combination with MTX together with short-term GC. In the presence of adverse prognostic factors, patients should receive a bDMARD or a tsDMARD (JAK-inhibitor).

bDMARDs can be divided into TNF-alpha inhibitors (adalimumab, certolizumab, etanercept, golimumab, and infliximab), IL-6 inhibitors (tocilizumab and sarilumab), CD80 and CD86 inhibitors (abatacept), and anti-CD20 drugs (rituximab). Due to their chemical structure, bDMARDs exhibit lower stability and a greater sensitivity to enzymatic degradation, making them prone to degradation in the stomach. Thus, bDMARDs are currently not administered orally but through subcutaneous injection or via intravenous infusion.

TNF-alpha inhibitors were the first group of bDMARDs that were developed and have dramatically improved the therapeutic options for RA patients over the last 25 years. TNF-alpha inhibitors are either monoclonal antibodies (mAbs) that directly block the proinflammatory cytokine TNF-alpha or receptor constructs (e.g., etanercept) that act as a soluble decoy receptor. mAbs against TNF were first produced as chimeric antibodies, partially mouse and partially human, like, for example, infliximab. They were followed by humanized antibodies that are of nonhuman origin, but their protein sequence has been modified to make them essentially identical to a human variant except for the antigen-binding region. Certolizumab is a humanized antigen-binding fragment (Fab′) against TNF-alpha that is conjugated to a polyethylene glycol moiety that replaces the Fc antibody region. The latest developments are fully human mAbs against TNF-alpha. They are produced by phage display technology and do not contain any foreign parts. Examples are adalimumab and golimumab. Reducing foreign sequences in mAbs is believed to reduce their ability to provoke an immune response against the therapeutic compound. This can lead to the production of anti-drug antibodies, inactivating the therapeutic effect of the compound and, in rare cases, the induction of adverse events. However also fully human antibodies are—to a certain extent—still immunogenic suggesting that other factors than the presence of foreign sequences contribute to the immunogenicity of mAbs [11].

Tocilizumab is a humanized mAb that competitively inhibits the binding of the proinflammatory cytokine interleukin (IL)-6 to the IL-6 receptor (IL-6R). IL-6 binds to the IL-6R and a signal

transducer, called glycoprotein 130 (gp130), which is expressed on the surface of most cells. Tocilizumab can bind to both the membrane-bound and soluble forms of the IL-6R and thereby blocks the conventional signaling and trans-signaling, respectively. Sarilumab is a fully human mAb against the IL-6R and exerts the same mechanism of action as tocilizumab.

IL-1 is another proinflammatory cytokine that is believed to be involved in the pathogenesis of RA. IL-1ra is an endogenous receptor antagonist that binds and blocks membrane-bound IL-1R, thereby preventing binding and signal transduction by IL-1. Anakinra represents a recombinant form of IL-1ra that differs from the natural IL-1 receptor antagonist by only one amino acid. Clinical trials of anakinra in RA patients, however, demonstrated only a modest efficacy with less improvement when compared with studies using other bDMARDs [12]. Therefore, although anakinra is licensed for the treatment of RA, it is not used in clinical practice.

Abatacept is a fusion protein of the Fc region of immunoglobulin IgG1 fused to the extracellular domain of CTLA-4. Abatacept binds to CD80 and CD86 molecules (also known as B7-1 and B7-2) on antigen-presenting cells, thereby inhibiting the binding of CD80 and CD86 molecules to CD28 on the surface of T cells, which is required for T cell activation.

Rituximab is chimeric mAb against the CD20 surface molecule on B cells that is expressed from a pre-B cell stage to mature B cells but not on plasma cells or memory B cells. Rituximab depletes CD20-positive B cells via antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and induction of apoptosis.

Biosimilars are biological medical compounds that are produced as versions of the original "innovator" product when the original product patent has expired. Biosimilars, however, cannot be regarded as generic drugs (like available for small molecule synthetic drugs). This is due to the natural variability and complex manufacturing of biological compounds that do not allow an exact replication at a molecular level. Nevertheless, biosimilars are licensed according to the same standards concerning quality,

safety, and efficacy that apply to all biological compounds. Therefore, bsDMARDs, if approved by the European Medicines Agency or the FDA, can be regarded as equivalent in effectiveness and safety to the originator products. In some countries, bsDMARDs are available at much lower costs than the originator, or their advent has led to a general price reduction among the originator compounds. In any case, this might facilitate access to optimal care and help to reduce healthcare budgets. These aspects have also been considered in the latest update of the EULAR recommendations for the management of RA. Currently, biosimilars are available for the originator products infliximab, etanercept, adalimumab, and rituximab.

The most recent development during the last decade among DMARDs is tsDMARDs. This group so far mainly consists of JAK-inhibitors (JAKinibs). JAK-inhibitors target JAK kinases that represent a family of four tyrosine receptor kinases (JAK 1, 2, and 3 and TYK2). They play a pivotal role in cytokine receptor signaling pathways via their interaction with signal transducers and activators of transcriptional proteins (STATs) [13]. The first generation of JAK inhibitors (tofacitinib, baricitinib) do not display high specificity with activity against three or even all four JAK family members. Selective JAK inhibitors against specific JAKs have recently been developed (e.g., upadacitinib) with the aim of reducing side effects. In contrast to bDMARDs, tsDMARDs can be given orally.

Based on the currently available data from clinical trials, all bDMARDs (including bsDMARDs) and tsDMARDs when combined with MTX are regarded as equally effective.

If the treatment target is not reached with a first bDMARD or tsDMARD, any other bDMARD or tsDMARD can be used. This also includes the use of a bDMARD or tsDMARD that targets the same pathway as the first one. Although this might sound counterintuitive, evidence from randomized clinical trials has shown that using a second TNF-alpha inhibitor after the failure of a first TNF-alpha inhibitor can still be as efficacious as using a drug with a different mode of action.

All biological DMARDs and tsDMARDS are more efficacious when combined with a csDMARD as compared to monotherapy. On the other hand, treatment with an IL-6 inhibitor alone has been shown to be more effective than monotherapy with an anti-TNF-alpha compound, and JAK inhibitors alone are more effective as compared to monotherapy with MTX.

Nonpharmacological Interventions

In addition to pharmacological therapies, a wide range of non-pharmacological interventions exist. These include exercise therapy, physical modalities, orthoses and assistive devices, self-management, and dietary instructions [14]. Interventions involve various health professionals in the form of a multidisciplinary team. This may include, apart from the rheumatologist, nurse specialists, physical therapists, occupational therapists, social workers, dieticians, podiatrists, psychologists, and additional physicians such as orthopedic surgeons or rehabilitation specialists. Supervised exercise with sufficient intensity, duration, and frequency to improve aerobic capacity and/ or muscle strength is recommended in all RA patients. This is often combined with patient education in self-management strategies in joint protection with the aim of an enhanced awareness of posture and joint position and the use of orthotic devices and assistive devices. Electrophysical modalities comprise various strategies, including thermal, electrical, light, sound, and magnetic energy, used to generate therapeutic physiological effects with the aim of reducing pain or restoring function. Psychological interventions include treatment modalities such as cognitive behavioral therapy, psychoeducational interventions, relaxation, or biofeedback. RA patients often inquire about dietary interventions to improve RA symptoms. The effects of dietary manipulation, including vegetarian, Mediterranean, elemental, and elimination diets on RA, however, are still uncertain, and additional well-designed studies of dietary patterns and nutrients are needed before RA-specific recommendations can be made [15].

Comorbidities, Vaccination, and Pregnancy

RA is associated with several comorbidities. They include cardiovascular disease, pulmonary disorders, infections, osteoporosis, and depression. In particular, cardiovascular disease, pulmonary disorders, and infections are associated with an increased risk of mortality [16]. Therefore, treating physicians have to be aware of comorbidities as part of a holistic, multisystem approach to the management of RA.

Many infections are preventable with vaccination. Immunosuppressive therapies, however, might impair the protective immune response induced by vaccination. Therefore, the vaccination status of RA patients should be reviewed and updated at the time of diagnosis but in particular before the commencement of immunosuppressive therapy [17] and local immunization guidelines should be adhered to.

Disease activity usually improves in RA patients during pregnancy. Pregnancy outcomes are slightly less favorable as compared to the general population and related to disease activity. Therefore, the patients' disease should be well controlled and stable for the last 3–6 months prior to conception. Due to a lack of safety data, however, not every treatment option is compatible with pregnancy, which sometimes makes it difficult to follow a treat-to-target approach in pregnant RA patients [18].

Summary

The clinical picture of RA has dramatically changed during the last 25 years. RA has turned from a highly destructive disease with limited therapeutic options into a manageable disorder where a substantial proportion of patients enter a state of remission. This improvement is certainly due to the development of novel therapies, notably of biologics, as well as the implementation of stringent treat-to-target guidelines. Nevertheless, several unmet needs still exist. Although RA can be brought into remission, still no definite cure or prevention is possible. Therefore, further insights

from basic research are required to uncover the cause(s) of RA. Second, not all patients can reach remission even with current therapeutic strategies. We therefore clearly need to develop further therapeutic options. Finally, further research is required for the identification of biomarkers that allow us to reliably identify patients at risk. This will help to identify a more streamlined targeted therapeutic response that results in early, safe remission.

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4 SLE for Primary Care Providers

Trina Pal and Robert G. Lahita

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease affecting many organ systems that may manifest in patients with a multitude of signs and symptoms. It is a condition that has an immune response characterized by specific autoantibodies. The pathophysiology of SLE has been widely studied and has come a long way in terms of medical treatment and management over the years. The pathogenesis includes immune complex formation with deposition into tissues and the presence of multiple autoantibodies that cause damage to the tissues, which then perpetuate the disease.

SLE is more prevalent in women than men, but the predilection cannot be fully explained. Sex hormones have a role in the clinical presentation and clinical activity of the disease, but the role of the X chromosome is now suspect as a factor in etiology. Patients with Klinefelter's syndrome (XXY) have an increase risk when compared with patients with Turner's syndrome (XO).

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The prevalence of this disease is increased in African American women (1:250), Latinos, and Asians. The lowest prevalence is in Caucasian women (1:1000).

The disease has many diverse manifestations in multiple organ systems: the musculoskeletal system, central and peripheral nervous system, cardiovascular system, gastroenterological system, hematologic system, renal system, skin, and mucus membranes. SLE may present early in its disease course with vague generalized symptoms such as fatigue, weight loss, and low-grade fevers, so it is important to differentiate it from other illnesses. However, it may be many years until a diagnosis is officially made, therefore affecting the patient's prognosis. Autoimmune diseases often overlap, and patients who suffer from one illness have a higher likelihood of having another.

Pathogenesis

Generally, the pathogenesis can be attributed to many predisposing factors that cause an abnormal immune response and inflammation, which eventually lead to organ damage [1]. These predisposing factors may include genetics such as polymorphisms, epigenetics, and environmental factors such as UV light, Epstein–Barr virus (EBV), and smoking. Increased immunogenicity also plays a role, including enhanced immune complex formation and deposition. Genetic markers like HLA DRB1 and DR3 and enhanced innate immunity lead to the production of interferons, altered antigen presentation, neutrophil death, and altered B or T cell signaling and are part of the pathogenesis.

Classification

The classification criteria for SLE according to the 2019 European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) was updated recently [2]. Before this update, the 1982 Revised ACR classification criteria with a 1997

revision was being used. Later, the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification addressed further laboratory testing as well as neuropsychiatric signs and highlighted that autoantibodies were an important component of diagnosing lupus in patients. A score is to be calculated based on the ANA with a titer greater than or equal to 1:80 on HEp-2 cells. If negative, the patient may not be classified as having SLE. If positive, the following criteria may be used to calculate the total score: classified as SLE if the total score is greater than or equal to 10 [2]. Caution that this scale is not used for diagnostic purposes.

Domain	Criterion	Weight
Antiphospholipid antibodies	Anti-cardiolipin antibodies or anti-B_2GP1 antibodies or lupus anticoagulant	2
Constitutional	Fever >38.3 °C	2
Complement proteins	Low C3 or low C4	3
	Low C3 and low C4	4
Hematologic	Leukopenia <4000/mm^3	3
	Autoimmune hemolysis	4
	Thrombocytopenia <100,000/mm^3	4
Mucocutaneous	Oral ulcers	2
	Nonscarring alopecia	2
	Subacute cutaneous LE or discoid LE	4
	Malar rash/acute cutaneous LE	6
Musculoskeletal	Joint involvement	6
Neuropsychiatric	Delirium	2
	Psychosis with delusions or hallucinations	3
	Seizure	5
Renal	Proteinuria >0.5 g/24 h	4
	Class II or V nephritis via renal biopsy	8
	Class III or IV nephritis via renal biopsy	10
Serosal	Pleural/pericardial effusion	5
	Acute pericarditis	6
SLE-specific antibodies	Anti-dsDNA Ab or anti-Smith Ab	6

Clinical Evaluation

A patient presenting with signs and symptoms of SLE will need a thorough history and physical examination as the diagnosis is made clinically. Laboratory evaluation will be used as well to evaluate the disease activity and to monitor the levels of activity as to try to reduce the number of complications that may occur in various organ systems. Laboratory evidence may be supportive of a diagnosis but is not the sole indicator of having SLE. A patient may present with any of the manifestations described under classification.

General

Patients may manifest with constitutional symptoms including fever, fatigue, weight loss, and myalgias/arthralgias. Early in the disease, patients may not have a full range of symptoms that involve multiple organ systems. During fulminant illness, disease activity is monitored for flares, and patients are treated accordingly. It is rare that patients ever go into full remission, but the disease can be controlled with hydroxychloroquine, corticosteroids, or chemotherapeutics. There is one biological agent, a monoclonal antibody that is useful in some cases.

CNS

One of the more difficult forms of SLE to manage is that of the central nervous system (CNS). The clinical features of neuropsychiatric lupus are diffuse and focal. Diffuse forms of the disease include coma or acute confusional state, cognitive dysfunction, psychosis, depression and anxiety, and intractable headache as a result of pseudotumor cerebri. Migraines are also common in secondary antiphospholipid syndrome. The more chronic neurological complications like fatigue and mood changes are not visualized on imaging and have a treatment plan geared toward symptomatic

relief with antipsychotics or antidepressants [16]. Focal forms of the disease include strokes, seizures, movement disorders like chorea, ataxia, hemiballismus, demyelinating syndromes, and transverse myelopathy. It is often difficult to differentiate multiple sclerosis from SLE, but this, among other myelopathies, must be immediately treated with high-dose glucocorticoids. Patients that require more than 40 mg of prednisone may present with glucocorticoid-induced psychosis, which resolves after medications have been stopped or tapered down. Cerebrospinal fluid analysis for proteins: IgG index and oligoclonal bands are indicators of CNS disease as well imaging such as MRI and PET scans. Serology, namely the antiribosomal antibody titer, might be helpful but is typically nonspecific for CNS lupus. The MRI is usually normal, but the PET scan can show increased activity in rare instances.

The treatment of underlying causes is the first step to patients that present with neuropsychiatric manifestations such as migraines, infections, and hypertension. Aseptic meningitis developing after the use of NSAIDs, especially ibuprofen, is found in less than 2% of patients with SLE but may be one of the first signs of SLE [17]. The mechanism remains unknown but may be due to immune complex deposition in the brain, specifically the choroid plexus, as well as a result of low complement levels.

Cardiovascular

Coronary artery disease, valvular disease, and structural damage to the heart are a few of the many forms of cardiac involvement in patients with SLE. These patients have an increased risk of cardiovascular complications, including myocardial infarctions, acute thrombotic events, or other forms of heart disease. Lupus is inflammatory in nature and can affect the cardiovascular system. Cardiac events in young people are common and often related to inflammation or in some cases microemboli. Antiphospholipid antibody itself increases the risk of thrombotic events, including deep vein thrombosis, cerebral vascular events, and fetal loss,

although the mechanism of action is still being investigated. The presence of antiphospholipid antibodies may also increase the risk of patients that present with valvular disease and require an echocardiogram and blood cultures for diagnosis. Valvular disease in these patients may include nonbacterial thrombotic endocarditis, Libman–Sacks endocarditis, marantic endocarditis, and mitral valve prolapse. A primary care physician (PCP) can measure factors that cause procoagulation like anticardiolipin antibodies, lupus anticoagulants, and beta-2 glycoprotein antibodies prior to sending the patient to a specialist.

Pericarditis and myocarditis are other inflammatory cardiac manifestations of this disease. Although rare, myocarditis may require a muscle biopsy, and acute coronary syndrome must be ruled out as a patient presents with elevated troponins. A patient with pericarditis may have an associated pericardial effusion and can be evaluated by echocardiography. Physicians should be aware that patients with lupus have accelerated atherosclerosis and should look for dyslipidemias by obtaining a lipid profile and obtain cardiac measures like a sensitive CRP, troponins, and EKG if there is any suspicion of cardiac illness regardless of patient age and atypia of symptoms.

Gastrointestinal

The entirety of the gastrointestinal system may be involved in an SLE patient. There is a plethora of manifestations in the GI tract that must be evaluated when a patient presents including oral/nasal ulcers, esophageal dysmotility causing dysphagia, gastroesophageal reflux disease or esophagitis, pancreatitis, serositis, vasculitis (intestinal), hepatitis, and pseudo-obstruction. Many of these manifestations may be secondary to adverse effects of immunosuppressive medications prescribed to the patient or the disease activity. Other causes of GI-related symptoms need to be ruled out such as *H. pylori* infection, excessive NSAID use, and prolonged glucocorticoid use. Hepatitis in SLE is broad and can include autoimmune hepatitis and thrombotic complications from antiphospholipid antibodies like Budd–Chiari syndrome. Protein-

losing enteropathy is another rare GI involvement that can also be seen in patients with SLE.

Hematologic

The most common hematologic abnormalities include anemia, leukopenia, and thrombocytopenia. The most common form of anemia found in patients is anemia of chronic disease or inflammation, but iron deficiency, medications, hemolysis, and kidney disease are among many causes of anemia in lupus patients. Anemia, most frequently normochromic and normocytic, is diagnosed in more than 50% of patients and may be related to decreased erythropoietin (EPO) activity or response in the body as well as inadequate iron homeostasis [11]. Later in the course of the disease, iron deficiency anemia is prevalent in about 30% due to the medications a patient may be taking (NSAIDs or glucocorticoids) affecting the gastrointestinal system or chronic inflammation [12]. Bone marrow suppression and immune hemolysis are adverse effects of commonly used medications. Leukopenias, usually lymphopenia, and thrombocytopenia are seen but usually do not require treatment unless the patient is actively bleeding and platelet counts remain over 40,000. A hematologic evaluation is appropriate in all lupus patients, and severe anemia without obvious blood loss can also be caused by autoimmune hemolytic anemia. This can be identified through the Coombs assay and careful analysis of the blood smear.

Musculoskeletal

Patients with musculoskeletal involvement present with joint or soft tissue swelling and/or tenderness more commonly in the knees, wrists, and hands. Arthritis most commonly presents in patients with SLE with an incidence of up to 95% [13]. Inflammation of the joints may lead to tendonitis, tenosynovitis, tendon rupture, and, although rare, avascular necrosis of the larger joints. Usually, musculoskeletal involvement is nondeforming unless it is Jaccoud's

arthropathy occurring in 10–35% of SLE patients, which can cause ulnar deviation, thumb subluxation, and swan neck deformities without erosive changes on X-ray [14]. The differential diagnosis should include rheumatoid arthritis, although erosive changes are not found, ankylosing spondyloarthropathy, mixed connective tissue disease, and scleroderma. Most of these diseases can be readily eliminated from the differential with careful clinical examination and specific laboratory testing. Polyarthritis can be managed with NSAIDs or corticosteroids for acute flares and usually resolve within 24 h. Imaging modalities such as X-rays and MRI can be used to diagnose joint deformities found in 10% of lupus patients, and in rare cases, a condition called "rhupus" can be associated with joint erosions. Myositis is also common in lupus patients, but an elevated creatine phosphokinase (CPK) on laboratory evaluation would be modest. Imaging can also help to rule out avascular necrosis, which can occur in one-third of SLE patients, caused by secondary antiphospholipid syndrome or long-term corticosteroid therapy [15].

Pulmonary

The most common involvement of the lungs manifests as serositis associated with elevated acute phase reactants like ESR and CRP, and clinically chest pain, pleurisy, and a possible pleural effusion. Infections have to be ruled out in this setting, especially with elevated inflammatory markers, as well as other diseases that can cause typical symptoms such as heart failure, malignancy, and acute respiratory distress syndrome. Generally, pulmonary disease is treated with systemic glucocorticoids and immunosuppressive drugs like azathioprine.

For patients who have an overlap disease with mixed connective tissue disease, there may be a chronic interstitial lung disease causing fibrosis, especially when associated with antisynthetase antibody syndrome. Less commonly, pneumonitis will cause more generalized symptoms with fever, cough, and shortness of

breath. In all cases of lung involvement, imaging may be obtained showing ground glass changes or "tree in bud" pattern (CT scan), DLCO (paradoxically increased, may suggest alveolar hemorrhage), bronchoscopy with bronchoalveolar lavage, and lung biopsy via video-assisted thoracoscopic surgery (VATS). Rarely, patients present with pulmonary hemorrhage with hemoptysis and hypoxemia, and it is thought to be related to antiphospholipid antibodies.

Renal

SLE may involve the kidneys in up to 50% of patients causing lupus nephritis [3]. Lupus nephritis is one of the major complications of SLE, and patients may progress to chronic kidney disease or end-stage renal disease in about 10% of patients, thus increasing morbidity and mortality [3]. The development of lupus nephritis and its pathogenesis is the subject of much research.

Lupus nephritis is due to the deposition of immune complexes in the glomeruli or proliferation of the mesangium or endothelium/subendothelium, causing acute or chronic glomerular injury. Immunofluorescence of these deposits shows immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), C3, and C1q. Patients should be evaluated for renal involvement during the initial encounter and during follow-up visits every year with urinalysis and serum creatinine/eGFR. In addition, renal monitoring is important as many treatment medications for SLE are nephrotoxic. Kidney involvement is diagnosed via biopsy with immunofluorescence and light microscopy and may be treated with corticosteroids, cyclophosphamide, and mycophenolate mofetil along with antiproteinuric medications. Close control of CKD to slow the progression of the disease is the main goal to treat kidney involvement. A biopsy should be considered if there is a spike in serum creatinine without other causes, proteinuria $\geq$1 g/24 h, and proteinuria $\geq$0.5 g/day with hematuria or casts.

Grades of lupus nephritis		
Grade	Manifestation	Findings
I	Minimal/ mesangial	No clinical manifestations
II	Mesangial proliferative	Hematuria, proteinuria, rare hypertension
III	Focal proliferative	Hematuria, proteinuria, +/− HTN, decreased GFR or nephrotic syndrome
IV	Diffuse	Segmental or global, hematuria, proteinuria (frequently nephrotic), casts, decreased GFR, HTN, elevated anti-DNA, low complements
V	Membranous	Proteinuria, no hematuria or renal function abnormalities
VI	Advanced sclerosing	Chronic renal disease

Skin

Major categories of cutaneous lupus erythematosus include acute cutaneous LE (ACLE), subacute cutaneous LE (SCLE), or chronic cutaneous LE (CCLE) and can be differentiated by histopathology. Hyperkeratosis, epidermal atrophy, dermatitis, inflammatory cell infiltrate, and thick basement membrane can be seen in these subtypes of cutaneous lupus [4]. Most commonly, discoid lupus erythematosus can be diagnosed clinically through observations of typical lesions. Subacute cutaneous lupus erythematosus also has typical patterns and can be suspected clinically and confirmed by biopsy [5]. Discoid lupus rarely progresses to SLE unless antinuclear antibodies are found.

A localized malar rash or "butterfly rash" that spares the nasolabial folds is the most common manifestation of ACLE, presenting as warm skin with erythema and sometimes hypopigmentation in patients with darker skin. Sun exposure usually will exacerbate the acute eruption, and generally it will last from hours to days.

Most patients with SCLE will have positive RO/SS-A antibodies and present with red scaly patches similar to psoriasis. The lesions are nonindurated and resolve without leaving a scar,

although depigmentation is common. SCLE often spares the face and is more commonly located in the upper torso, arms, and neck as they are more exposed to sunlight. CCLE includes discoid lupus (DLE), lupus erythematosus tumidus (LE tumidus), lupus profundus (lupus panniculitis), and lichenoid cutaneous lupus erythematosus–lichen planus overlap syndrome (LE-LP overlap syndrome).

DLE is the most common type of CCLE occurring in 73–85% of patients [6]. DLE also has increased photosensitivity, less serositis and joint involvement, and less progression to SLE compared with SCLE. Lesions expand from smaller plaques, extend into hair follicles, and heal with atrophy and scarring [7]. Where generalized DLE is seen on sun-exposed areas, localized DLE is usually limited to the head and neck. Due to chronic inflammation and skin changes, about 2–3% of high-risk patients who have DLE develop squamous cell carcinoma [8]. Primary care physicians should be acutely aware of this association.

The mucus membranes are involved in 12–45% of patients with SLE [9]. Usually, this appears early in the disease and is the cause of nasal ulcers that are so common to SLE patients. Patients will present with plaques, or "punched out" lesions or ulcers in the mouth, especially lips and buccal mucosa and the palate that can be quite painful. These respond to topical corticosteroids or antimalarials but take anywhere from days to months. Nasal ulcers are usually found bilaterally in the lower nasal septum. Deep inflammatory infiltrates, hyperkeratosis, and deposits of immunoglobulin and complement can be seen on histopathology [10].

Laboratory Evaluation

Laboratory evaluations assess the disease activity, and imaging may be obtained to evaluate the activity of the disease. Age-appropriate cancer screening and immunizations are also encouraged with avoidance of live attenuated vaccines if on immunosuppressive medications. The disease activity can be

measured with the SLEDAI (Systemic Lupus Erythematosus Disease Activity Index), and the long-standing disease burden can be calculated with SLICC (Systemic Lupus International Collaborating Clinics) or BILD (Brief index of Lupus Damage as measured by the patient). It is not necessary to obtain certain serological tests with frequency.

Certain testing should be performed regularly, especially in patients being treated with immunosuppressive medications. A CBC with differential should be done to rule out anemia, thrombocytopenia, and leukopenia (lymphopenia and neutropenia). Rarely, TTP (thrombotic thrombocytopenic purpura) and MAS (macrophage activating syndrome: causing fever, cytopenia, high ferritin, and multiorgan system dysfunction) can be diagnosed with a simple series of hematological tests. Leukopenia is commonly found during lupus flares.

Acute phase reactants like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are normally elevated in patients with SLE or other acute inflammatory processes. As they are not specific to SLE, they are not used markers to diagnose SLE, although they can be used to monitor disease activity. An increased CRP may suggest an infection or increased disease activity. An elevated blood urea nitrogen (BUN) and creatinine indicates renal involvement and could indicate a progression of the disease into lupus nephritis, so baselines values should be established. Complement (C3, C4) is usually decreased in the serum during a lupus flare but should not be used as a marker of therapeutic success because some patients have low complement for other genetic reasons.

A urinalysis (UA) may show proteinuria, hematuria, or casts. A kidney biopsy should be performed if proteinuria $\geq$500 mg/d and the urinary sediment is replete with white blood cells (WBCs), red blood cells (RBCs), or granular casts. Anti-dsDNA antibodies have $\geq$90% specificity and help diagnose the disease. This may also be measured during a flare to monitor the disease activity along with complement values. Tests like anti-Smith and anti-RNP (extractable nuclear antigens) are highly specific for SLE

and should only be examined once since they are not associated with disease activity [19]. Antinuclear antibody test (ANA) as a marker has high sensitivity (98%) but low specificity and is found in normal individuals. A titer of less than 1:160 is of little significance and should be watched [20]. A positive ANA does not mean a patient has lupus. Unusual antibodies like anti-beta 2-glycoprotein I antibodies (IgG, IgM, or IgA) are prevalent in 30–50% of patients with SLE and are usually measured to diagnose secondary antiphospholipid syndrome.

Ferritin is another acute-phase reactant elevated in an active inflammation but usually is underestimated and <100 in iron-deficient patients. The soluble transferrin receptor level may be a more accurate test, especially in patients with iron deficiency in the setting of SLE [12].

Antiphospholipid antibodies are associated with cerebrovascular disease in SLE as well as other neuropsychiatric disorders, including headache, mood disorders, cognitive disorders, and seizures [21]. These antibodies are more helpful in determining a focal cause, possibly from vascular abnormalities or vasculitis [22]. They should also be measured when the PT or PTT is elevated, suggesting an autoimmune procoagulant state.

Antiribosomal P antibodies are found in some SLE patients and more associated with psychosis and severe depression [23, 24]. Further evaluation by a specialist might include inflammatory cytokines and include type 1 interferons, interleukin-18 (IL-18), and tumor necrosis factor (TNF) that may increase or decrease according to disease activity [25]. These are not the purview of the primary care physician.

Clinical Management

Managing lupus flares is an important component for primary care physicians as lupus can have protean manifestations. The ability to identify patients and monitor the disease activity can be critical to the disease course, which will prevent organ damage

and reduce the amount of flares. All patients should avoid direct sunlight or use protection from ultraviolet A and B light with high SPF sunscreen. To the extent possible, patients should maintain a healthy lifestyle with diet and exercise, avoiding tobacco use, and tight control of other medical conditions and comorbidities such as hypertension and diabetes mellitus.

Mild SLE flares can be treated symptomatically with steroids, NSAIDs, and antimalarials. One rare adverse effect of taking an NSAID in SLE is aseptic meningitis, the first patient was documented in 1978 [18]. Nevertheless, NSAIDs should be used judiciously in the patient with lupus because renal disease might also be made worse. Elevated liver enzymes and increased risk of cardiovascular events are among many other adverse effects that are associated with NSAIDs. Antimalarials such as hydroxychloroquine, chloroquine, and quinacrine are useful for fatigue, skin manifestations such as malar rashes, and arthralgias. The patient may also benefit from a short course of low-dose oral prednisone until the effects of other agents like antimalarials and NSAIDs become active.

Moderate lupus flares associated with chest pains and pleural effusions may be treated with a course of prednisone. Laboratory evaluation will sometimes show elevated acute phase reactants, inflammatory markers, and increased disease activity.

Severe lupus flares may result in end-organ damage such as acute kidney injury, proteinuria, and lab abnormalities, including low complements, positive or elevated antibodies from baseline, and acutely elevated inflammatory markers may be observed. A longer or higher course of pulse steroids or immunosuppressants such as mycophenolate, cyclophosphamide, rituximab, and azathioprine may be required to treat these more severe symptoms. PCP's should work closely with the consultant specialists to comanage any complications.

Summary and Suggestions

Lupus erythematosus is a complicated prototypic autoimmune disease with protean manifestations. There are many autoimmune diseases that share some features with SLE, these include multi-

ple sclerosis, scleroderma, Sjogrens syndrome and even rheumatoid arthritis. The burden of SLE can be lessened with proper care from the PCP who may ultimately see the patient more frequently than the specialists.

Cardiovascular disease is a common cause of death in SLE, especially in those with secondary phospholipid syndrome. Patients may shower emboli to various organs and may have accelerated atherosclerosis, a common aspect of SLE by itself. Management of cardiovascular risk factors is frequently deferred by the specialist to the PCP. Tight monitoring of Blood pressure, glycemic control and lipid management is paramount to improve mortality.

Another concern for the PCP is the overall effects of treatment with steroids. The chronic use of corticosteroids in this disease can result in many morbidities like osteoporosis, ecchymoses, opportunistic infections, and avascular necrosis. The PCP must be aware of these iatrogenic comorbidities and co-monitor treatment with the rheumatologist.

The patient with SLE must not be over-immunosuppressed; this can occur in patients in clinical remission who have gaps in continuity of care. The lowest acceptable dose of immunosuppressive therapy should be chosen to minimize complications but maintain low disease activity.

Patients on certain medications like nonsteroidal drugs should have their blood pressure, metabolic profile, complete blood count and urine routinely checked. Patients on hydroxychloroquine should have their eyes examined as per local ophthalmology guidelines.

Finally, since the majority of patients with SLE are of reproductive age, close collaboration with the obstetrician is key and the PCP should be involved in routine gynecologic care. Estrogen containing contraceptives should be avoided and most patients are able to have uncomplicated pregnancies when taken care of by a multidisciplinary team.

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Fibromyalgia for the Primary Care Physician

5

Priya Chokshi

Patient Case

Jane is a 45-year-old female who states, "Everything has been hurting and I don't feel well," for the last 6 months. She notes diffuse joint and muscle pain with stiffness, difficulty concentrating, and abdominal discomfort with intermittent diarrhea. She has poor sleep, lack of energy, and sadness at times. She has a history of a motor vehicle accident 12 months ago. Extensive lab work by her PCP has been noncontributory. She has seen an orthopedics for knee arthroscopy, a gastroenterologist for a colonoscopy, and a pain management specialist for steroid injections, but without relief. She has also tried acetaminophen with mild improvement. She is frustrated and worried about what could be causing her symptoms.

Overview

What Is Fibromyalgia?

"Fibro" means connective tissues, "my" means muscle, and "algia" means pain. Fibromyalgia (FM) therefore is a disorder

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defined by chronic, widespread musculoskeletal pain for more than 3 months.

FM is caused by augmented pain or sensory processing of pain in the central nervous system (CNS), and this is referred to as *centralized pain amplification*. CNS factors magnify pain and lead to comorbid somatic symptoms. Individuals feel pain at a lower threshold and with an increased intensity out of proportion to the triggering stimulus. Therefore, although FM is a discrete disorder, it can be associated with symptoms of fatigue, sleep disturbance, mood disturbance (i.e. depression, anxiety), cognitive dysfunction (forgetfulness, decreased concentration, "fibro-fog"), irritable bowel syndrome (IBS), and headaches. FM is also associated with comorbidities including cardiac disorders, genitourinary disorders, hypertension, and obesity [1, 2].

Epidemiology

The estimated prevalence of FM in the general population is 2.7% globally and 2–5% in the US adult population. The prevalence of FM in patients with other rheumatic diseases is higher at about 11–30%. The female-to-male ratio is approximately 2:1, similar to other chronic pain conditions [3–5]. In primary care, at least one in 20 patients may have FM symptoms, and the numbers may be higher where there is increased recognition and diagnosis among providers. FM can occur at any age, but peak onset occurs in mid-life [6–8].

The term "fibromyalgia" was first coined by physicians as far back as the 1800s but described even earlier in the texts of ancient cultures. The theory was that "fibrosis" of tissue led to inflammation and the formation of tender points.

Further large-scale studies were reported during World War I and II as specialized rheumatism centers were established. Two "fibrositis" subtypes were identified, including musculoskeletal regional syndromes (i.e., bursitis, tendonitis) termed "primary fibrositis" vs. "psychogenic rheumatism." The characteristic presentation described in soldiers was an attitude that was tense, anxious, defensive, and antagonistic. Described symptoms included

burning, tightness, weakness, numbness, tingling, or tired sensation throughout the day, fatigue causing debility, and aversion to touch. Symptoms could be elicited by external factors such as heat, cold, humidity, rest, and exercise. The main treatment approach used at the time was psychotherapy or physical rehabilitation [9–11].

Misconceptions Associated with FM

There is some skepticism in the medical and general community regarding the legitimacy of FM as a medical diagnosis. This is due to several factors. For one, many of these patients are incorrectly diagnosed with peripheral or localized pain syndromes. They are inappropriately treated without adequate response, such as with injections, surgery (i.e., hysterectomy, back surgery), and opioids. Symptoms do not improve, thereby harboring frustration and doubt among both patients and providers, exacerbating the cycle of pain.

Furthermore, it is challenging to diagnose FM as it relies on patient-reported symptoms, and there is variability among patient interpretation of pain. Nevertheless, this does not discount the scientific human and animal model studies that have highlighted differences in pain transmission and perception on brain imaging studies (i.e., functional brain MRI), sleep studies, as well as neurotransmitter transmission profiles in patients with FM [12, 13].

Another challenge with FM is the associated stigma of "labeling" with the thought that it leads to medicalization and disempowerment of patients, but this has been shown to be inaccurate. There are misconceptions that it is a diagnosis given by doctors when they cannot figure out what else is wrong or that it always stems from psychiatric disease. There are also cultural and societal biases that FM is a disorder of "middle-aged women." In the general community, there is some controversy surrounding the abuse of the diagnosis to justify claims to disability or prescription medications [14]. These issues can affect appropriate diagnosis, treatment, and outcomes of patients with FM. In fact, fibromyalgia's impact on quality of life is greater than that of rheumatoid arthritis or chronic

obstructive pulmonary disease [15]. This takes a toll on the healthcare system and its resources [16].

All of these reasons explain why it is essential for frontline primary care providers to be comfortable in accurately diagnosing and treating FM, just as well as they manage other chronic diseases such as diabetes and hypertension.

What Causes Fibromyalgia?

There is no known exact cause of fibromyalgia, but it is likely secondary to an interplay of genetic and environmental factors. First-degree relatives of patients with FM are eight times more likely to develop FM [17]. Twin studies suggest a 30% concordance rate among identical female twins and 15% for nonidentical twins [18]. Environmental factors include mental or physical trauma, prior medical illness, infections, or stress.

Pathophysiology

FM is caused by a change in how the central nervous system (CNS) processes peripheral sensory signals for pain. There is amplified pain perception due to imbalances in pain transmission, neurotransmitter signaling, and stress–response pathways. This is further influenced by cognitive and emotional factors.

The brain and spinal cord process pain signals through neurotransmitters such that patients experience increased pain at a lower threshold—also known as CNS sensitization or amplification. This results in allodynia (heightened sensitivity to tactile, temperature, auditory, and electrical stimuli that are not normally painful) and hyperalgesia (increased response to painful stimuli). These CNS changes in neurotransmission also influence sleep, mood, and energy, thereby contributing to the associated symptoms seen in FM [19–21].

Most of the neurotransmitter pathways are inappropriately functioning in patients with FM, and the medications used are targeted to "correct" the pathway (Fig. 5.1).

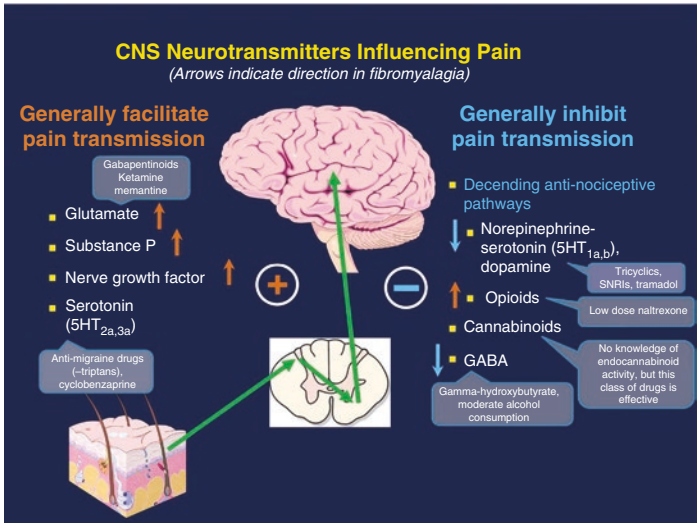

Fig. 5.1 CNS neurotransmitters and their role in pain transmission. In individuals with Fibromyalgia, neurotransmitter levels are inappropriately functioning. The neurotransmitters on the left classically facilitate pain transmission and are at abnormally high levels in patients with FM. Conversely, the neurotransmitters on the right inhibit pain transmission but are at abnormally low levels. Arrows indicate levels of these neurotransmitters in the CSF of patients with FM. These changes contribute to hyperalgesia in chronic pain states and affect mood, sleep, and energy as seen in FM patients. They are consequently the target of pharmacologic drugs. CNS central nervous system, GABA ɣ-aminobutyric acid, SNRI serotonin-norepinephrine reuptake inhibitor. (Adapted with permission from: Clauw [72])

Overall, there is an

1. Increase in neurotransmitters that facilitate pain transmission and lead to augmented pain or sensory perception (i.e., glutamate, nerve growth factor, *substance P*)
2. Decrease in neurotransmitters that inhibit pain or sensory processing [serotonin, norepinephrine, dopamine, ɣ-aminobutyric acid (GABA])

The two main neurotransmitter pathways identified in triggering musculoskeletal pain are the adrenergic and serotonergic pathways.

In the adrenergic pathway, *COMT*, the gene encoding the enzyme catechol-*O*-methyltransferase, which is responsible for the catabolism of catechol neurotransmitters (i.e., epinephrine, norepinephrine, and dopamine), is improperly modified. The same dysregulation can occur via the serotonin pathway in the genes associated with 5-hydroxytryptamin receptor 2A (HTR2A) and 5HT transporter (SLC6A4). Dysregulation in these pathways leads to chronic pain, autonomic dysfunction, sleep disturbances, and mood disorders [22].

At the anatomic level, brain structures involved in pain processing include the amygdala, anterior circulate gyrus, and hippocampus. Defects at the structural and neurochemistry level in these areas have been demonstrated [23]. Neuroimaging studies have also demonstrated differences in cerebral blood flow and neurotransmitter activity in brain areas interpreting painful stimuli in patients with FM compared to controls [24, 25].

Additionally, cerebrospinal fluid levels of inflammatory chemokines and cytokines, such as glutamate, nerve growth factor, and *substance P*, have shown to be elevated in animal models and patients with FM [20, 26].

The medications used to treat FM and associated conditions therefore often target these multiple pathways producing variable responses in differing patients.

Of note, Mu opioid receptor availability and endogenous opioid function are increased appropriately in FM patients as a compensatory mechanism for pain. Ironically, evolving data suggests that administering opioids may not be as efficacious as actually blocking the opioid pathway, such as with naltrexone [27].

In addition to the CNS, dysregulation of pain through peripheral nociceptive pathways at the level of the muscles, joints, and nerves can contribute to FM symptoms as well. For example, abnormalities in muscle tissue metabolism and small-fiber neuropathies can cause improper pain response perception [28].

There has also been data to suggest that abnormalities in the fight-or-flight stress response system mediated by the hypothalamic–pituitary–adrenal (HPA) axis of the autonomic nervous system contribute to improper response to pain signals in FM patients. This can also contribute to the symptoms of orthostatic symptoms present in some patients with FM [29, 30].

Why Is Fibromyalgia Challenging to Diagnose and Treat … and Does It Have to Be This Way?

There are several barriers to adequately diagnosing and treating fibromyalgia. For example, symptom presentation and pain interpretation vary globally and culturally. Furthermore, guidelines for diagnosis are not practiced in a standardized format, and management practices are not structured due to provider experience or preference. Availability of treatment options is limited by cost and accessibility and also affects outcomes. These factors result in inadequate control of symptoms and can lead to patient disability and debility.

Data shows that it can take two years to make a diagnosis of FM. Patients may see between three to six healthcare providers before finally getting diagnosed, leading to frustration and stress. The legitimacy of the diagnosis is questioned in society as well as by trained healthcare professionals.

As frontline providers in the community, PCPs play a key role in diagnosing patients early and are generally accurate in their impression [31, 32]. With the appropriate techniques, the majority of FM cases can be managed in a primary care setting. A patient-centered multidisciplinary approach to FM can result in earlier diagnosis, effective management, improved outcomes, and optimal use of healthcare resources [33–35].

Approach to Diagnosis and Management

Diagnosis of Fibromyalgia

Primary care providers should be able to (Fig. 5.2)

1. *Identify the symptoms of fibromyalgia and establish a diagnosis*
2. *Assess for and address associated conditions*
3. *Consider a differential diagnosis and rule out other disorders*
4. *Design a management plan with patients to address symptoms*
5. *Monitor response and provide patients with the tools to track progress*

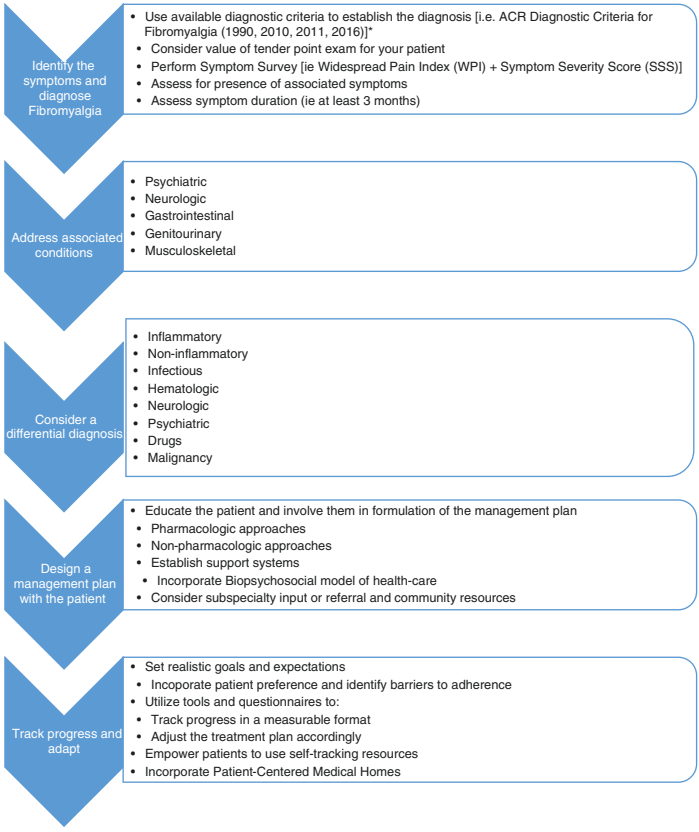

Fig. 5.2 Approach to Fibromyalgia. (*American College of Rheumatology Diagnostic Criteria for Fibromyalgia available at: https://www.rheumatology.org/Portals/0/Files/2010_Preliminary_Diagnostic_Criteria.pdf)

1. *Identify the symptoms of fibromyalgia and establish a diagnosis*

Fibromyalgia should be strongly suspected based on clinical findings. A combination of (1) tender point exam, (2) symptom survey, and (3) overall assessment by an experienced clinician can be used to identify patients with fibromyalgia. Formal symptom

surveys or tender point examination can be performed to support the diagnosis but not to exclude it [3, 36].

Fibromyalgia is diagnosed when there is widespread diffuse pain present on bilateral areas of the body above and below the waist for at least 3 months. Symptoms typically persist or progress over multiple clinic visits (Fig. 5.3).

Qualitative terms the patient may use to describe pain include throbbing, stabbing, or burning. Pain may occur intermittently, but usually daily, at varying levels of intensity. It is typically exacerbated by physical activity or weather changes. Patients may also describe muscular weakness, stiffness, or tightness without findings of focal motor deficits on examination.

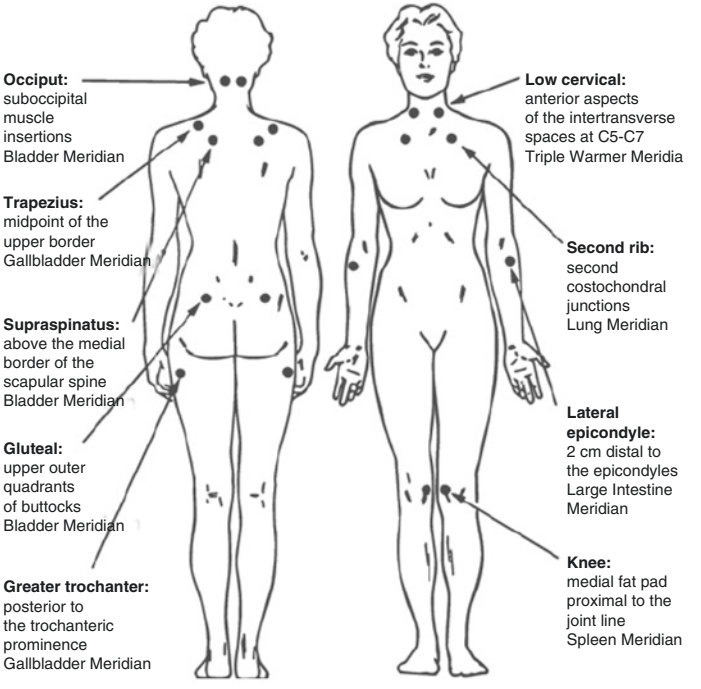

Fig. 5.3 Fibromyalgia tender point map. (Reprinted with permission from: American College of Rheumatology (ACR) 1990 criteria for the anatomic loci of tender points on examination for diagnosis of fibromyalgia)

Associated symptoms typically include (1) fatigue or tiredness, (2) sleep disturbance, (3) cognitive symptoms, such as memory problems, disorganized thinking, or issues with attention or concentration, and (4) mood disorders. Additional symptoms should also be taken into account (Fig. 5.4).

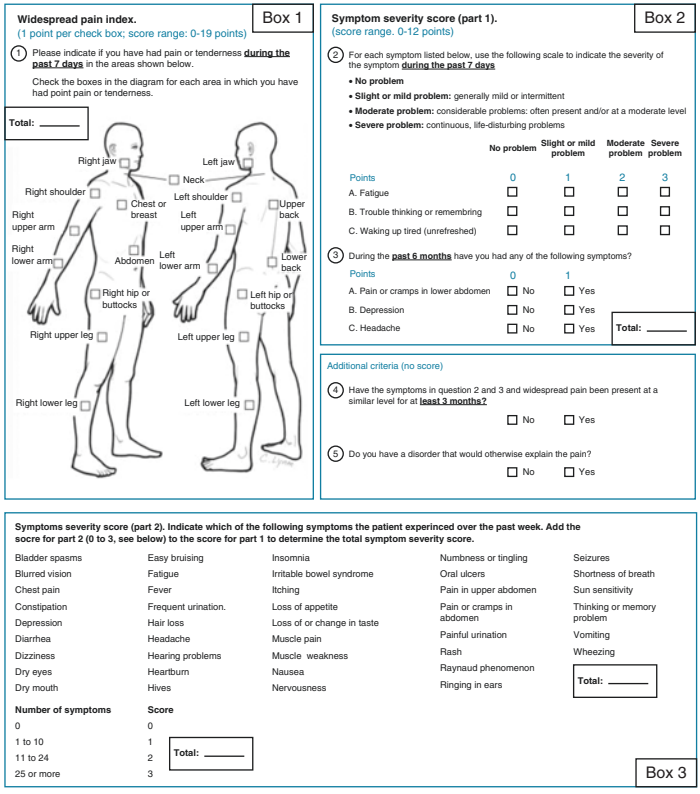

Fig. 5.4 Diagnosis of fibromyalgia. (Adapted with permission from: Wolfe et al. [3])

Criteria

The first American College of Rheumatology (ACR) Criteria for Fibromyalgia were published in 1990 and updated in 2010, 2011, and 2016 as preliminary criteria (Table 5.1 and Fig. 5.4) [3, 37, 38].

The initial 1990 criteria diagnosed FM based on the presence of widespread pain for greater than 3 months, presence of at least

Table 5.1 American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia

1. *History of widespread pain*
(a) Chronic multifocal or diffuse pain with all of the following being present: pain on left side of body, pain on right side of body, pain above the waist, and pain below the waist
(b) Axial skeleton pain must be present: cervical spine or anterior chest or thoracic spine or low back. In this definition, shoulder and buttock pain is considered as pain for each involved side. 'Low back" pain is considered lower segment pain
(c) Present for 3 months
2. *Pain in 11 of 18 tender point sites upon digital palpation*
Locations:
Occiput: bilateral, at the suboccipital muscle insertions
Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5–C7
Trapezius: bilateral, at the midpoint of the upper border
Supraspinatus: bilateral, at origins, above the scapula spine near the medial border
Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces
Lateral epicondyle: bilateral, 2 cm distal to the epicondyles
Gluteal: bilateral, in upper outer quadrants of buttocks in anterior fold of muscle
Greater trochanter: bilateral, posterior to the trochanteric prominence
Knee: bilateral, at the medial fat pad proximal to the joint line
Of note, digital palpation is performed with an approximate force of 4 kg eliciting pain. For a "tender point" to be considered "positive," the subject must state that the palpation was actually painful, not just tender.

Adapted with permission from: Wolfe et al. [37]
*Classification for fibromyalgia is met if both criteria 1 and 2 are satisfied. Widespread pain must be present for at least 3 months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia

11 of 18 established "tender points," and exclusion of another condition that could explain the pain.

The revised 2010 criteria focus more on symptoms, quantify widespread pain, do not require prior exclusion of other potentially coexisting diagnoses that can cause pain, and do not require a tender point or physical examination for diagnosis of FM.

Tender points have been controversial due to the variable nature in which they are elicited, and the migratory and diffuse nature of the pain. The tender "trigger points" included in the criteria are specific muscle, tendon, or fat pad sites that are classically more painful than surrounding tissues in patients with Fibromyalgia. According to the 1990 criteria, approximately 4-kg pressure should be applied to elicit pain, described as enough to cause the examiner's thumbnail to blanche. However, the use of tender points is limited. Men are reported to have a decreased prevalence of tender points compared to women, leading to an underdiagnosis of FM in men. Removing the requirement for tender point in the updated criteria changes the female-to-male ratio of FM prevalence from 9:1 to 2:1 [39].

Of note, the 1990 ACR criteria were intended for use in research classification and not clinical practice. Despite their limitations, they did help legitimize FM as a syndrome. The 2010 criteria were designed for practical use for FM diagnosis in the primary care setting and the 2011 survey criteria were designed to be used by patients as a self-report of FM. The 2016 criteria are currently under revision. Other criteria sets have been formulated including differing sets of signs and symptoms, but overall the basic clinical manifestations of FM are noted to be the same [40, 41].

Here we will focus on the ACR 2010 criteria as can be used in the office setting for a diagnosis of FM (Fig. 5.4).

There are two component scores: (1) Widespread Pain Index (WPI) and (2) Symptom Severity Score (SSS). The combination of scores is used to meet criteria, and the total score assesses the severity of fibromyalgia.

1. The Widespread Pain Index (WPI) assesses 19 body points for pain or tenderness present over the past 7 days and gives a score of 0–19 (*Box* 1).

2. The Symptom Severity Score (SSS) is divided into two parts:

   (a) The first part assesses for (a) fatigue, (b) cognitive issues, and (c) sleep issues and assigns 0–3 points based on severity. It additionally grants 1 point each for abdominal pain, depression, and headache (*Box* 2).
   (b) The second part assesses for 41 additional different symptoms that are reported with FM, from the presence of bladder symptoms to wheezing. Each item is given 1 point. The total number of symptoms are tabulated and assigned a score. The presence of 0 symptoms is 0 points; 1–10 symptoms is 1 point; 11–24 symptoms is 2 points; and 25 or more symptoms is 3 points (*Box* 3).

The sum of scores of the WPI index and Symptom Severity Score (Part 1 and 2) are then used to give a final score. The presence of a (1) significant score, (2) symptom duration for at least 3 months, and (3) low suspicion for another disorder more likely to explain the symptoms can help confirm the diagnosis of FM.

2. *Assess for and Address Associated Conditions*

It is important to evaluate for conditions that commonly coexist with fibromyalgia (Table 5.2). Data suggests that patients with FM are two to seven times more likely to have associated comorbid conditions [1, 42, 43].

Mood disorders that typically occur in patients with FM include anxiety, depression, bipolar disorder, panic disorder, social phobia, obsessive-compulsive disorder (OCD), eating disorder, substance abuse disorder, physical/sexual abuse history, and post-traumatic stress disorder (PTSD). Neurologic complaints include headache or migraine disorder and restless legs syndrome. Gastrointestinal associations include irritable bowel syndrome (IBS). Genitourinary associations include pelvic pain or dysmenorrhea, vulvodynia, genitourinary pain, interstitial cystitis, or irritable bladder syndrome. Musculoskeletal associations include temporomandibular joint (TMJ) pain, chronic fatigue syndrome

Table 5.2 Conditions commonly associated with fibromyalgia

Psychiatric	Anxiety, depression, bipolar disorder, panic disorder, social phobia, obsessive-compulsive disorder, eating disorder, substance abuse disorder, physical or sexual abuse history, and post-traumatic stress disorder
Neurologic	Tension headache or migraine disorder
Gastrointestinal	Irritable bowel syndrome, functional dyspepsia, functional gastrointestinal disorder
Genitourinary	Pelvic pain or dysmenorrhea, vulvodynia, genitourinary pain, interstitial cystitis, or irritable bladder syndrome
Musculoskeletal	Temporomandibular joint pain, chronic fatigue syndrome, and chronic back pain

(CFS), and chronic back pain [44]. As drugs used to treat FM and these associated conditions often overlap, an appropriate diagnosis is important, as it will guide the selection of the most effective medication while reducing the risk of polypharmacy.

3. *Consider a Differential Diagnosis and Rule Out Other Disorders*

Patients with fibromyalgia should be evaluated for comorbid diseases that present with similar symptoms but require their own individualized treatment plan and should not be missed (Table 5.3). These include osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, seronegative spondyloarthropathies, polymyalgia rheumatica, vasculitides, joint hypermobility disorders, and regional musculoskeletal disorders, such as tendonitis or bursitis.

A systematic approach to diagnosis includes the following:

1. Careful history taking
2. Physical exam techniques to look for focal musculoskeletal, dermatologic, and neurologic findings
3. Performing necessary laboratory and imaging studies

For example, patients with inflammatory arthritis typically feel worse in the morning. They present with pain and stiffness, which improves with activity. Fibromyalgia, on the other hand, is a

Table 5.3 Differential diagnosis of musculoskeletal pain disorders

Diagnosis	Specific findings
Inflammatory	
Polymyalgia rheumatica	Elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP)
Seronegative spondyloarthropathies	Abnormal imaging, laboratory tests, exam findings
Connective tissue diseases (rheumatoid arthritis, systemic lupus erythematosus, Sjogren's, scleroderma, myositis, etc.)	Positive serologies [i.e., Rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP), antinuclear antibody (ANA), laboratory tests], exam findings
Systemic vasculitides	Multiorgan involvement findings
Noninflammatory	
Degenerative joint/spine disease; trauma	Abnormal imaging, exam findings
Fibromyalgia	Widespread allodynia/hyperalgesia; negative tests
Myofascial pain	Localized allodynia/hyperalgesia
Joint hypermobility	Exam findings, family history, genetic testing
Metabolic myopathies	Abnormal muscle enzymes, muscle biopsy
Myotonic dystrophy	Genetic testing, family history
Infectious	
Viral hepatitis	Antibodies
Human immunodeficiency virus	Antibodies
Lyme disease	Antibodies, exposure to an endemic area
Parvovirus 19	Antibodies, exposure to children
Epstein–Barr virus	Antibodies
West Nile virus	Antibodies
Hematologic	
Anemia; sickle cell disease	Symptoms, laboratory tests, family history
Neurologic diseases	
Multiple sclerosis	Abnormal neurologic examination, imaging findings

(continued)

Table 5.3 (continued)

Diagnosis	Specific findings
Myasthenia gravis	Nerve testing, antibodies
Complex regional pain syndrome (CRPS)	Exam findings, imaging
Neuropathic pain (i.e., diabetes, postherpetic neuralgia, small fiber neuropathy, post-surgical)	Exam findings, nerve testing
Psychiatric diseases	
Major depressive disorder, anxiety, etc.	History
Drugs	
Statins	Exposure, antibodies, exam findings
Aromatase inhibitors	Exposure, exam findings
Malignancy	
Cancer pain, bony metastases, lymphoma	Laboratory tests, abnormal imaging

Adapted with permission from: Crofford [73]

chronic process and can initially worsen with exercise. Inflammatory conditions also typically present with elevations in laboratory markers such as the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

Of note, the presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia. In fact, a patient may have both fibromyalgia and a comorbid condition. In one study, the prevalence of FM ranged from approximately 6% in patients with osteoarthritis to approximately 13% in patients with systemic lupus erythematosus. In this case, successful treatment of both disorders will allow for better overall control of pain symptoms [5].

4. *Design a Management Plan with Patients to Address Symptoms*

Overall Management of Fibromyalgia

Once diagnosed, treatment for FM can begin immediately, even if other tests or subspecialty input is pending for unusual signs or symptoms. Establishing a diagnosis validates the patient's experience. Educating and involving the patient in the discussion about FM and treatment options sets realistic goals and expectations, increases adherence, and improves outcomes and satisfaction [45, 46].

Minimizing symptoms, improving physical function, and reducing disability are the goals of care. Physicians can provide guidance, but it is essential for patients to practice self-management techniques as well to optimize outcomes. The focus of treatment is to improve multiple domains of the patient's life, including everyday activities of daily living (ADLs) and work productivity.

There are multiple treatment modalities for the varied symptoms. Pharmacotherapy reduces peripheral nociceptive input and augmented pain processing. Nonpharmacologic approaches address cognitive, behavioral, and psychological responses to pain. Individual patient responses will vary. The greatest treatment effectiveness results from a combination of pharmacologic and nonpharmacologic approaches.

Questionnaires and assessment tools can be used to assess pain, functionality (physical, emotional, cognitive, social), and health-related quality of life associated with fibromyalgia. The optimal care plan may take time to develop with an investment from both the patient and providers but can have positive long-term benefits for the patient's overall well-being [47].

Pharmacotherapy

There are several classes of drugs used for the treatment of fibromyalgia (Table 5.4). Evidence-based guidelines have been formulated by the American Pain Society (2005), the European League Against Rheumatism (2007), the Association of the Scientific

Table 5.4 Pharmacologic therapies for fibromyalgia

Treatment	Specifics[a]	Evidence level*	Mechanism of action (MOA)	Side effects	Suggestions	Selection preferences
Tricyclic antidepressant (TCA) compounds	Amitriptyline (Elavil) 10–70 mg qhs Cyclobenzaprine (Flexeril) 5–20 mg qhs Alternatives: nortriptyline (Pamelor), desipramine (Norpramin), trazodone (Desyrel), clonazepam (Klonopin), alprazolam (Xanax)	1, A	Inhibit reuptake of serotonin (and norepinephrine) at synaptic junctions May also have effect on CNS endorphins and peripheral pain receptors Improve Stage IV sleep	Anticholinergic properties: dry mouth, weight gain, constipation, urinary retention, blurry vision, hypotension, drowsiness, etc.	Can improve a variety of symptoms, including pain, sleep, bowel, and bladder symptoms Avoid in older patients Best to take prior to bedtime	Amitriptyline is more effective, but nortriptyline and desipramine may be better tolerated Cyclobenzaprine can be used for coexisting muscle spasm

Serotonin norepinephrine reuptake inhibitors (SNRIs)	Duloxetine (Cymbalta)[b], 20–120 mg/day Milnacipran (Savella)[b], 12.5–200 mg/day Venlafaxine (Effexor), 25–350 mg max	1, A	Increase serotonin and norepinephrine at synapses in the descending pain pathway	Nausea, palpitations, headache, fatigue, tachycardia, hypertension, increased suicidal ideation	Recommend intake with food Gradual increase in dose improves tolerability	Duloxetine preferred when coexisting depression, fatigue, OA of back/knees Milnacipran preferred when coexisting cognitive dysfunction, fatigue Duloxetine is less expensive than milnacipran

(continued)

Table 5.4 (continued)

Treatment	Specifics[a]	Evidence level*	Mechanism of action (MOA)	Side effects	Suggestions	Selection preferences
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine Sertraline Paroxetine Venlafaxine	1, A	Inhibit serotonin reuptake and increase postsynaptic serotonin availability	Nausea, sexual dysfunction, weight gain, sleep disturbance	Older class of less selective SSRIs can improve pain, especially at higher doses due to noradrenergic effects Newer class (citalopram, escitalopram, desvenlafaxine) generally less effective	SSRIs can be used if coexisting depression SSRIs that are used in FM should be generic

Gabapentinoids	Gabapentin (Neurontin) 800–2400 mg/day in divided doses Pregabalin (Lyrica)[b] max 600 mg/day in divided doses	1, A	Pregabalin works via alpha-2-delta calcium channel pathway affecting the activity of excitatory neurotransmitters (i.e., glutamate)	Sedation, weight gain, dizziness, peripheral edema, dry mouth	Dosing at bedtime can increase tolerability	Gabapentinoids preferred when coexisting sleep disturbance Gabapentin is less expensive than Pregabalin
Cannabinoids	Nabilone (Cesamet) 0.5 mg qhs–1.0 mg BID	1, A	Acts on cannabinoid receptor CB1 in CNS presynaptically to inhibit several neurotransmitters (GABA, norepinephrine, dopamine, 5-hydroxytraptamine) Various other properties under study (modulation of stress, inflammation, etc.)	Sedation, dizziness, dry mouth	No synthetic cannabinoid is approved in the United States to date for treatment of pain	Nabilone preferred when coexisting sleep disturbance

(continued)

Table 5.4 (continued)

Treatment	Specifics[a]	Evidence level*	Mechanism of action (MOA)	Side effects	Suggestions	Selection preferences
Nonsteroidal anti-inflammatory drugs (NSAIDs®)	No evidence of efficacy	5, D	Inhibit COX (i.e., COX1/2), which catalyzes synthesis of cyclic endoperoxidases from arachidonic acid to form prostaglandins—this downregulates the pain pathway and inflammation. Additional nociceptive actions possibly mediated through L-arginine-NO-cyclic GMP	Gastrointestinal, renal, and cardiac side effects	Use the lowest dose for the shortest period of time	Can be used if coexisting disorder (i.e., osteoarthritis, inflammatory arthritis, etc.) Oral and topical formulations available
Acetaminophen (Tylenol®)	No evidence of efficacy	5, consensus	Acetaminophen may activate descending serotonergic pathway in CNS and have nociceptive properties	Gastrointestinal, renal, and cardiac side effects	Use the lowest dose for the shortest period of time	Can be used if coexisting disorder (i.e., osteoarthritis, inflammatory arthritis, etc.)

Capsaicin	No evidence of efficacy	5, D	Capsaicin is a transient receptor potential vanilloid 1 receptor (TRPV1) agonist, activating channels on nociceptive nerve fibers, inhibiting pain transmission; releases *substance P*	Gastrointestinal, cardiac, respiratory, dermatologic side effects	Use as needed; repetitive use may decrease effectiveness	Can be used if coexisting disorder (i.e., osteoarthritis, inflammatory arthritis) Topical formulation
Opioids[c]	Tramadol (Ultram) with or without acetaminophen, 50–100 mg q6 hours Naltrexone (Vivitrol, Revia) 4.5 mg daily	2, D; 5, D	Tramadol most likely effective due to SNRI properties rather than mu-opioid binding Naltrexone low dose has limited data	Sedation, constipation, addiction, tolerance, opioid-induced hyperalgesia	Increasing evidence that risks outweigh benefits	Tramadol and naltrexone some data Avoid other opioids

Recommended to initiate pharmacologic therapies at low doses with gradual escalation. Choice of agent ideally based on predominant symptoms. Combination therapy may be trialed, monitoring for response and side effects

Qhs nightly, *BID* twice a day, *GABA* gamma aminobutyric acid, *COX* cyclooxygenase

Adapted with permission from:

Fitzcharles et al. [51] and Clauw [72]

[a]Food and Drug Administration (FDA) approved for the treatment of fibromyalgia in the United States

[b]Dosing minimum/maximum may vary based on the source of reference

[c]Not recommended for treatment of fibromyalgia

Medical Societies of Germany (2008), and the Canadian National Fibromyalgia Guideline Advisory Panel (2012). Several drugs classes have strong evidence (1A) for efficacy in FM, including tricyclic compounds, gabapentinoids, and serotonin-norepinephrine reuptake inhibitors.

The US Food and Drug Administration (FDA) has approved three medications for the treatment of FM: (1) pregabalin, (2) duloxetine, and (3) milnacipran. They each work on different central sensory pathways but have been shown to improve outcomes regarding pain, fatigue, sleep disturbance, depressed mood, and health-related quality of life [48].

Duloxetine and milnacipran are serotonin and norepinephrine reuptake inhibitors (SNRIs). Pregabalin works via the alpha 2-delta calcium channel pathway affecting the activity of excitatory neurotransmitters such as glutamate. Overall, changes in neurotransmission

1. Decrease the action of neurotransmitters that enhance pain signals
2. Increase the activity of neurotransmitters that downregulate pain signals

Other medication options often used in the treatment of FM include tricyclic antidepressants (TCAs) such as amitriptyline and cyclobenzaprine, gabapentinoids, selective serotonin reuptake inhibitors (SSRIs), tramadol, and ɤ-hydroxybutyrate. Although these are not FDA-approved for FM, they offer more choices for patients.

Over-the-counter options such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and capsaicin can also have benefits for coexisting peripheral pain control and inflammation but would not be targeted for FM management [49]. Steroids, benzodiazepines, and nonbenzodiazepine hypnotics, S-adenosylmethionine (SAMe), melatonin, and dehydroepiandrosterone (DHEA) have not been shown to be effective and should not be used for the treatment of FM.

Of note, opioid use is controversial and not advised. Generally speaking, for fibromyalgia, the risks outweigh the benefits for pre-

scription opioid use as they have not been proven to reduce pain and there is a potential for abuse and addiction.

The selection of drug should be based on the predominant symptoms present (i.e., sleep disorder, anxiety, depression) and anticipated side effect profile tailored to the patient's history (i.e., comorbidities) [50]. Cost or insurance coverage can also affect medication selection and accessibility [51]. It is recommended that treatment be initiated at low doses with gradual escalation and monitoring for adverse effects. The overall success of pharmacotherapy depends on prescription choice, patient tolerability of side effects, and patient adherence.

Patients need to be educated that it may take time to reach an adequate therapeutic response. Oftentimes, patients may need to be prescribed a combination of drugs that influence multiple pathways for an augmented response to treatment.

However, providers should also be cautious about polypharmacy. One of the most serious side effects associated with combining the various drugs or using them in high doses is serotonin syndrome. Symptoms of serotonin syndrome include agitation, tachycardia, hypertension, sweating/shivering, diarrhea, muscle rigidity, fever, seizures, and even death [52].

Nonpharmacologic Options

In general, appropriate medication use is only partially effective. Consequently, a multimodal treatment plan incorporating nonpharmacologic options as well is recommended [53] (Table 5.5).

The best-studied nonpharmacologic therapies are

1. Education
2. Cognitive behavioral therapy (CBT)
3. Exercise

Education, CBT, and exercise have strong evidence for use in FM management. For some patients, the benefits may exceed the gains from medication use [54].

Education of patients is a key component of fibromyalgia management, as in other chronic conditions. An open discussion between patients and providers helps describe and validate the diagnosis and highlight the associated symptoms. It involves the patient to review treatment options and participate in designing a plan that is more likely to be followed. It also emphasizes a patient-centered approach to self-management and monitoring. Education continues through the course of care.

Table 5.5 Nonpharmacologic therapies for fibromyalgia

Treatment	Specifics	Evidence level	Side effects/ risks	Considerations
Patient education[a]	Incorporate principles of self-management	1, A	Time consuming, may need additional support staff	After initial diagnosis, use educational sessions to explain the condition, offer treatment options, set expectations, and involve patients in treatment selection to adherence
Graded exercise[a]	Aerobic exercise best studied	1, A	Worsening of symptoms if initiated rapidly or done incorrectly	Counsel patients to "start low, go slow" Can start with simple activities, gradually escalating to exercise Consider land- or water-based exercise

Table 5.5 (continued)

Treatment	Specifics	Evidence level	Side effects/ risks	Considerations
Cognitive-behavioral therapy (CBT)[a]	Multiple delivery platforms (1:1, small group, self-administered, online self-help courses, books, websites, apps)	1, A	No significant side effects Patient outcome may be influenced by willingness to try	Internet-based and smartphone apps offer convenience and self-treatment approaches That is, relaxation, social skills training, coping mechanisms, mindfulness, meditation
Complementary and alternative medicine (CAM) therapies	Smaller studies, not standardized but emerging evidence	1, A	Generally safe if done correctly Not rigorously studied	May be culturally acceptable to certain patient populations Offers increased options/ modalities and adherence (i.e., Tai chi, yoga, qigong, acupuncture, biofeedback, hydrotherapy, massage)

(continued)

Table 5.5 (continued)

Treatment	Specifics	Evidence level	Side effects/ risks	Considerations
Sleep hygiene	Sleep study can rule out underlying causes (i.e., OSA, RLS)	1, A	Studies may be costly	Addresses reversible or treatable causes (i.e., caffeine, stimuli before bedtime, CPAP use, etc.)
CNS neurostimulatory therapy, transcutaneous electrical nerve stimulation (TENS)	Stimulation of peripheral sensory nerves at strong, nonpainful levels; effect mediated through gate theory of pain	5, consensus	Headache	Patient can self-administer Need to be standardized in terms of dosing, targets, etc.
Dietary changes, vitamins, supplements, homeopathy	Variation between trials	5, consensus	Side effects of some remedies Not rigorously studied	Influenced by patient preference, cultural and societal factors Open communication and discussion encouraged between patient and provider

OSA obstructive sleep apnea, *RLS* restless legs syndrome, *CPAP* continuous positive airway pressure
Adapted with permission from:
Fitzcharles et al. [51] and Clauw [72]
[a]Strong evidence for use and recommended

Cognitive behavioral therapy (CBT) involves interventions to address cognitive restructuring and behavioral training, such as mindfulness and social skills training to minimize triggers. Behavioral modifications may help to reduce pain, negative mood, and disability in patients. CBT can be administered in the office setting, through support groups, or through electronic online and smartphone apps [55].

Patients with FM may initially experience increased pain with exercise, but in the long term, exercise is shown to be the most beneficial. Therefore, exercise is implemented in a "start low, go slow" manner, and aerobic exercise is generally recommended over weight-based resistive exercises. Low-to-moderate intensity exercises such as walking, aqua therapy or swimming, and stationary cycling or biking are ideal. Patients are advised to reach a goal of 30–60 minutes of exercise about 2–3 times per week. Measurable outcomes include function, pain, stiffness, muscle strength, and fitness. It is best to choose an exercise plan the patient will practice regularly.

Poor sleep is also associated with a decreased pain threshold, increased musculoskeletal pain, and fatigue. A sleep study can help rule out organic disease, such as obstructive sleep apnea (OSA) or restless legs syndrome (RLS). Studies have shown disturbances in delta wave sleep such that stage IV of sleep is reduced in patients with FM. Improvements in sleep hygiene are correlated with favorable results. Selecting pharmacologic choices recommended for FM, which also have benefits for sleep, may also improve outcomes as they often target similar neurotransmitter pathways [56, 57].

Complementary and alternative medicine options have also shown to have benefits, including yoga, tai chi, qigong, acupuncture, biofeedback, hypnotherapy, chiropractic manipulation, myofascial release therapy, massage therapy, hydrotherapy, balneotherapy, heat therapy, trigger-point injections, relaxation training, mindfulness/meditation, transcutaneous electrical nerve stimulation (TENS), central neurostimulatory therapies, diet changes, and homeopathic remedies (e.g., vitamins, plant-based products). Alternative therapies have evidence for use in FM and, if used properly, may be even more effective than a pharmaco-

logic approach. Of note, although some of these therapies have not been proven to be effective, they often are not harmful either and should therefore be offered to patients when feasible to increase the options available to manage chronic pain [51, 58].

Support Systems

Once a patient is diagnosed with FM in the primary care setting, it may still be challenging to optimize the patient's care due to the presence of comorbidities or time constraints in the office. Therefore, it is oftentimes helpful and necessary to enlist the help of specialists and other support systems. Clinical support staff can serve to educate and enforce the treatment goals and plan. The PCP can also coordinate subspecialty referrals to rheumatology, pain management, physical and occupational therapy, psychiatry, neurology, gastroenterology, sleep specialists, dieticians, and social workers who can broaden treatment options.

The biopsychosocial model of health plays a role in FM as well. Psychological processes, including socioeconomic status, personality traits, beliefs, community and environmental situations, family factors, and cultural expectations, often influence how patients perceive and cope with pain. In these cases, it may be helpful to understand these influences and address them when designing a management plan [59].

Most importantly, it is necessary to establish realistic treatment goals with the patient, emphasizing that complete elimination of pain may not occur. The management of the most severe or problematic symptoms may be the first priority. Patient preferences may vary depending on cultural, work, or social expectations. The most successful treatment plan will be one that incorporates pharmacologic, nonpharmacologic, patient education, and support strategies. Involving and educating family members about the patient's diagnosis and treatment plan can also improve outcomes and the patient's overall sense of well-being [60].

5. *Monitor Response and Provide Patients with the Tools to Track Progress*

Tracking Symptoms and Progress

Fibromyalgia is a complex, chronic disease with a potential for "flare-ups" even when multiple strategies are employed. In general, physical activity improves outcomes, while receiving disability pension, catastrophizing (feeling that pain is severe and associated with a poor prognosis), or having experienced multiple past negative life experiences portend worse outcomes [61]. Patients may feel angry, frustrated, and helpless—especially if they have been coping with symptoms for a prolonged period without relief and it is affecting their way of life. Providers first need to acknowledge that these feelings are common and acceptable and then provide reassurance regarding the various management options [62].

PCPs can work to establish specific, realistic, and measurable goals with patients to reflect their priorities and optimize results. Available tools and questionnaires track progress in a measurable format. Tracking tools can help patients and physicians stay motivated to reach the established goals and reassess the need for modification in the treatment plan over time.

Several tools are available, including in-office questionnaires and online or smartphone applications. It is helpful to monitor symptoms, patient function (physical, emotional, cognitive, social), and overall impact on health-related quality of life associated with FM [45]. For example, self-management resources are available through the American College of Rheumatology (ACR), the EULAR Guidelines for the management of FM, the American Chronic Pain Association, and Fibromyalgia Support Groups [47, 63].

The 2010 American College of Rheumatology diagnostic criteria can be used to assess patient progress over time [3]. Various screening and diagnostic health assessment questionnaire (HAQ) tools are under development or available, such as the Fibromyalgia Impact Questionnaire (FIQR), Fibromyalgia Diagnostic Screen, FibroDetect® tool, and Fibromyalgia Rapid Screening (FiRST) tool. These instruments are useful for both patients and PCPs to assess symptoms and productivity [64–66].

Furthermore, patient-centered medical homes (PCMHs) have been shown to improve outcomes in chronic diseases and can be incorporated into the management of FM as well (see below).

Patient-Centered Medical Homes (PCMHs)

The goal of the patient-centered medical home (PCMH) is to engage multiple providers and support staff in providing hands-on management to assist patients in navigating the health care system. It integrates care between doctors, hospitals, pharmacies, and community resources to improve patient experience and outcomes while reducing waste and inefficiency. The primary care physician (PCP) can be the leader who facilitates and delegates tasks to various members within the team. The PCMH is ideally composed of

1. The primary care physician (PCP)
2. Supportive personnel such as medical assistants, nurses, physician assistants, pharmacists, and social workers
3. Subspecialists

A PCMH model may be ideal for the management of FM, especially as it is a chronic condition, which requires patient education and a multifaceted approach to management with monitoring of progress.

Although it seems that PCMHs require extensive resources and coordination, they have been used for other chronic diseases, such as diabetes, and have been shown to reduce costs and improve outcomes when adequately implemented. In fact, a diagnosis of FM is actually associated with more frequent outpatient visits, emergency room visits, hospitalizations, and prescriptions. On average, patients with FM see physicians three to four times more often than the general population (17 vs. 4 visits/year). Furthermore, patients with FM miss 16.8 days/year of work and retire prematurely [67].

PCMHs help reduce this healthcare utilization and economic burden on society by decreasing time to diagnosis of FM, unnecessary visits, and costly tests. Additionally, they provide resources to patients and empower them to take charge of their health.

Overall, this improves patient outcomes as well as provider satisfaction [68, 69].

PCMHs are becoming more popular and easier to implement with the transformation of healthcare over the last few years as institutionalized systems integrating inpatient and outpatient settings. Nevertheless, incorporating the PCMH may be more challenging in a private practice setting with fewer available staff. It can especially add to administrative costs for the development of the necessary PCMH tools. It may also be difficult to establish if the practice is located remotely from secondary resources. However, with the rise in electronic medical records (EMRs) and telehealth strategies, care is becoming more accessible and flexible. Costs to establish a PCMH may be present initially but can result in long-term benefits in efficiency and outcomes [33, 70–73].

Conclusion

Primary care providers aptly manage several complex chronic diseases by employing multiple treatment approaches through a structured framework and support system. Fibromyalgia can successfully be treated using the same strategies in the primary care setting through appropriate diagnosis, patient education, goal setting, pharmacologic and nonpharmacologic management, interdisciplinary involvement, and routine monitoring and assessment. These practices will improve patient outcomes and well-being and the overall health of society.

Patient and Provider Resources

Tools for Fibromyalgia Tracking

- *ACR Diagnostic Criteria for Fibromyalgia—available at:* https://www.rheumatology.org/Portals/0/Files/2010_Preliminary_Diagnostic_Criteria.pdf
- *American College of Rheumatology Patient/Caregiver Education materials—available at:* https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Fibromyalgia

- *European League Against Rheumatism (EULAR) Toolkit—available at:* https://ard.bmj.com/content/annrheumdis/76/2/318.full.pdf
- *Arthritis Foundation's Fibromyalgia Self-Help Course—available at:* https://www.arthritis.org/diseases/fibromyalgia
- *Fibromyalgia Impact Questionnaire (FIQ)/Revised (FIQR)—available at:* http://fiqrinfo.ipage.com/Original%20FIQ.pdf
- *FibroDetect® Tool—available at:* https://hqlo.biomedcentral.com/track/pdf/10.1186/s12955-014-0128-x
- *Fibromyalgia Rapid Screening (FiRST®) Tool—available at:* https://www.healthsadvisor.com/en/guest/qs/questionnaire-first-evaluation-fibromyalgie/
- *University of Michigan Chronic Pain and Fatigue Research Center FibroGuide—available at:* https://fibroguide.med.umich.edu
- *Chronic Fatigue Syndrome (CFIDS) and Fibromyalgia Self-Help—available at:* www.cfidsselfhelp.org; www.treatcfsfm.org
- *American Chronic Pain Association FibroLog—available at:* https://www.theacpa.org/pain-management-tools/communication-tools/tracking-tools/fibro-log/

Organizations and Support Groups

- The American College of Rheumatology
- The Arthritis Foundation
- National Institute of Arthritis and Musculoskeletal and Skin Diseases
- The American Academy of Pain Medicine
- American Chronic Pain Association
- National Fibromyalgia and Chronic Pain Association
- Fibromyalgia Coalition International
- National Fibromyalgia and Chronic Pain Association
- National Fibromyalgia Partnership Inc.
- The American Fibromyalgia Syndrome Association Inc.
- Fibromyalgia Action UK
- European Network of Fibromyalgia Associations

Books

- The Fibromyalgia Help Book: A Practical Guide to Living Better with Fibromyalgia—Fransen and Russell (1996)
- The Pain Survival Guide—Turk and Winter (2006)
- The Fibro Manual: A Complete Treatment Guide to Fibromyalgia for You and Your Doctor—Ginevra Liptan, MD (2016)
- MayoClinic Guide to Fibromyalgia—Andy Abril and Barbara Bruce (2019)

Smartphone Apps

- Manage My Pain (2011)
- My Pain Diary (2017)
- Chronic Pain Tracker (2017)
- Flaredown (2017)
- PainScale (2018)

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6 Metabolic Bone Disease and Osteoporosis

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Osteoporosis

Osteoporosis is one of the most common musculoskeletal diseases in an aging society, characterized by low bone quantity and worsening quality of the bone structure, which increases the risk of fracture. Major osteoporotic fracture, particularly hip fracture, increases mortality and morbidity and brings about a severe financial burden from a societal perspective. In the United States, 2 million Americans covered by Medicare suffered over 2.3 million osteoporotic fractures in 2015. The total annual cost of providing care for osteoporotic fractures among Medicare beneficiaries is

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Table 6.1 Clinical risk factors for fracture risk and osteoporosis

Age: ≥65 years for women and ≥70 years for men
Low body weight
Smoking Alcohol intake (3 or more units/day) Premature menopause (younger than 45 years old)
History of fracture Risk factors for falling (postrural hypotension and dehydration, polypharmacy, sedative use, visual impairment)

estimated to rise from $57 billion in 2018 to over $95 billion in 2040 [1]. Since multiple factors contribute to fracture, it is essential to evaluate both bone health and the risk of falls. All postmenopausal women and men older than 50 years need to be assessed for their risk factors of osteoporosis and risk of fracture (Table 6.1).

Assessment for Fracture Risk and Osteoporosis

Fracture Risk Assessment Tool (FRAX) has been validated by a large cohort study and is most commonly used in clinical practice (www.sheffield.ac.uk/FRAX/) among risk assessment tools. FRAX uses clinical risk factors to estimate the 10-year risk of hip and major osteoporotic fractures (e.g., spine, hip, proximal humerus, and distal radius). Clinicians should evaluate BMD in patients with a high risk of osteoporosis and fracture. Older postmenopausal women (≥65 years), men (≥70 years), and younger postmenopausal women or men when 10-year major osteoporosis fracture risk is higher than 9.3% based on FRAX are recommended for further evaluation with dual-energy X-ray absorptiometry (DXA). The major strength of FRAX is to quantify the risk of fracture and help clinicians to understand and use the information for diagnosis and also treatment. For example, patients in the United States with a 10-year risk of hip fracture higher than 3% and major osteoporotic fractures higher than 20% based on FRAX are recommended to start treatment. However,

FRAX lacks the dose–response relationship for variables like significant fracture risk after initial fracture, and, although it includes several secondary osteoporosis in the calculation, it is heavily dependent on BMD change [2].

The diagnosis of osteoporosis is currently based on the T-score of BMD of the axial skeleton, which is calculated from how different a patient's BMD is from the average of BMD in the reference group (young Caucasian female). World Health Organization (WHO) defines the T-score less than −2.5 as osteoporosis, between −2.5 to −1.0 as low bone mass, and greater than −1.0 as normal. BMD is the strongest estimator with a decrease in T-score of the hip by 1 SD is associated with a 2.4-fold increase in the risk of hip fracture [3]. However, the clinicians interpret DXA results with caution as it measures areal BMD (g/cm^2), not volumetric BMD (g/cm^3). As a result, a small individual tends to have lower BMD, which may falsely underestimate one's skeletal strength. Other factors, including vertebral fracture, degenerative changes (e.g., osteophytes, osteochondrosis, etc.), scoliosis, history of laminectomy, or the malposition during the test, all can lead to an inaccurate picture [4]. What is more important is that DXA cannot evaluate the quality of bone, such as the shape, microstructure, connectedness of the bone, and bone turnover, which are also important determinants of bone strength.

The Limitation of DXA and Newer Techniques

More than 60% of fractures occur in patients with an osteopenic range of BMD [5], and patients with the same T-score have different risks of fracture [6], which suggests that measuring bone density solely does not correctly assess patients' risk of fracture. A striking example is patients with Type 2 diabetes who have a higher risk of fracture, although the bone densities are often preserved [7]. The progression of imaging and bioengineering has enabled noninvasive studies of bone quality. Trabecular Bone Scoring (TBS) is one of the noninvasive measures to evaluate bone quality. This add-on software analyzes existing 2D DXA

images, extracts gray levels in each pixel, and calculates the variance of gray levels. Dense trabecular structures with a homogeneous variance of the pixel have a high TBS score, while sparse trabecular structures render a low TBS score. TBS has been validated in postmenopausal women [8, 9] and older men [10]. TBS scores can be combined with FRAX for a better prediction of the risk of fracture. Quantitative ultrasound (QUS), which measures the attenuation of sound waves through bone tissue and outputs mechanical features of bone (e.g., stiffness and elasticity), is an inexpensive and accessible tool [11, 12]. However, the result of QUS varies depending on the site; therefore, the International Society for Clinical Densitometry (ISCD) acknowledges that calcaneus is the only skeletal structure validated for the measurement of QUS. Also, the technology incorporating computed tomography (CT) imaging can evaluate the microarchitecture of the bone. Low-resolution quantitative volumetric CT (QCT) reconstructs three-dimensional images of the areas of interest such as femur or vertebrae, which enables the geometric structure evaluation. Although the spatial resolution in the order of ~500μm is not sufficient to directly evaluate cortical and trabecular microstructure compartments separately, the texture analysis provides indirect information about the bone quality [13]. In patients with glucocorticoid-induced osteoporosis, volumetric BMD measured by QCT showed a better prediction of fracture compared with conventional areal BMD [14]. A newly developed high-resolution peripheral quantitative CT (HR-pQCT) is equipped with higher spatial resolution up to ~40μm and demonstrates a distinct structure of cortex and trabeculae [15, 16]. Also, it provides other parameters of bone quality (e.g., connectivity and cortical porosity). HR-pQCT demonstrated increased cortical bone porosity in patients with diabetes [17, 18]. Lastly, indentation testing measures bone quality—the strength of bone. An indenter with a tip sensing depth is pressed to the smooth and flat area of interest (e.g., midshaft of the tibia) with a prefixed force, and the resistance and plasticity are measured [19, 20].

Treatment of Osteoporosis

In postmenopausal osteoporosis, the approach is to slow down accelerated resorption of bone, modulate the balance between formation and resorption, and prevent further bone loss, which can be obtained through antiresorptive therapy. Previously, hormone replacement therapy (HRT) was a mainstay of the treatment, but more recently, other antiresorptive agents such as bisphosphonates and denosumab have taken over HRT. However, osteoporosis is, by definition, characterized by the impaired microstructure of bone, which cannot be repaired by blocking resorption. Thus, newer "anabolic" treatments have emerged, which include teriparatide (PTH 1–34 analog), abaloparatide (PTH-related protein [PTH-rP] analog), and romosozumab (anti-sclerostin antibody).

1. *Calcium and Vitamin D Supplements*

Calcium and vitamin D are essential for bone health. The deficiency of calcium or vitamin D should be corrected before starting treatments for osteoporosis. The US Preventive Services Task Force (USPSTF) states that there is not sufficient evidence to recommend the supplementation of calcium and vitamin D as the primary prevention of fracture in nonosteoporotic elderly. The consensus is ~1000 mg calcium and ~800 IU vitamin D per day through combined diet and other supplements for postmenopausal women and older men. National Osteoporosis Foundation (NOF) provides a website for patients to estimate their daily calcium intake (https://www.nof.org/patients/treatment/calciumvitamin-d/steps-to-estimate-your-calcium-intake/). It is also very important that patients should be cautioned of over-supplementation as over-the-counter calcium and vitamin D are widely available. Milk-alkali syndrome with hypercalcemia has surged particularly in the elderly population with decreased renal clearance [21], and although controversial, some studies suggested that over-supplementation might increase the risk of cardiovascular disease [22].

2. *Hormone Replacement Therapy and Selective Estrogen Receptor Modulators*

Hormone Replacement Therapy (HRT) used to be the mainstay of osteoporosis therapy for a long time. It was shown that both estrogen-alone and estrogen with progesterone reduce the risk of fracture by 30 to 70% [23]. However, as studies revealed the potential risks of HRT and the emergence of drugs with better efficacy, it is no longer recommended as a primary treatment for postmenopausal osteoporosis. Estrogen with progesterone is associated with an increased risk of invasive breast cancer and cardiovascular disease. For patients who underwent a hysterectomy, estrogen-alone is associated with a lower risk of breast cancer, but it still renders the risk of cardiovascular disease and venous thromboembolism. It is widely accepted that estrogen is effective in alleviating menopausal symptoms and preventing perimenopausal bone loss, which warrants short-term use of HRT, especially in symptomatic patients within 10 years after menopause or younger than age 60 years [24]. Selective estrogen receptor modulators (SERMs) are a group of synthetic compounds with tissue-specific agonistic or antagonistic activities to estrogen receptors. Raloxifene works as an agonist on bone and as an antagonist on breast tissue, which increases bone mass and decreases the risk of breast cancer. Raloxifene reduced the risk of vertebral fracture by 30–50% but did not show the efficacy in nonvertebral fractures or hip fractures reduction [25, 26]. The side effects include postmenopausal symptoms such as hot flashes and venous thromboembolism. Lasofoxifene has an exceptionally high affinity to estrogen receptor with good oral bioavailability with promising anti-fracture efficacy [27]; however, it is not yet available in the United States. As SERMs have no residual effect on the bone, clinicians should consider bridging with antiresorptive therapy without abrupt discontinuation.

3. *Antiresorptive Agents*

(a) *Bisphosphonates*

Bisphosphonates are analog of naturally occurring pyrophosphate, which bind to hydroxyapatite crystals of bone and inhibit

osteoclasts. Currently, they are the first-line treatment of osteoporosis and are also used for other disorders of bone resorption, including Paget's disease of bone and skeletal metastasis. Nitrogen-containing bisphosphonates, including alendronate, risedronate, ibandronate, and zoledronate, inhibit farnesyl diphosphonate synthase and prevent osteoclasts from forming ruffled borders where they release lysosomal enzymes and acids, which are required for bone resorption [28]. Alendronate, risedronate, and zoledronate have been shown to reduce vertebral, nonvertebral, and hip fractures significantly in multiple randomized controlled trials [29], although ibandronate has shown a benefit only on vertebral fracture reduction.

Bisphosphonates have been widely and safely used. Common side effects of bisphosphonates are gastrointestinal intolerance (oral bisphosphonates) and acute reactions (intravenous bisphosphonates). They can cause nephrotoxicity as they are mostly metabolized and excreted by the kidney. Osteonecrosis of the jaw (ONJ) and atypical subtrochanteric femoral fractures (AFFs) are two rare side effects of bisphosphonates, which have recently garnered great public attention [30–32]. ONJ is extremely rare (less than 0.1% in osteoporosis patients) and is often associated with poor oral hygiene, underlying malignancy, and dental procedures [33]. It is prudent to advise patients to complete dental evaluation before starting bisphosphonates and routinely check their dental hygiene.

AFFs are associated with longer use of bisphosphonates, particularly more than 8 years [34]. This has led to the question of optimal duration of bisphosphonate therapy and spawned the concept of "drug holidays". Currently, the American Society for Bone and Mineral Research (ASBMR) states that after 3 years of intravenous zoledronate or 5 years of oral bisphosphonates, patients should be reassessed in order to justify continuing medication [35]. Higher risk patients such as older age (≥70 years), with high FRAX score, or other strong risk factors, especially for vertebral fracture, can be considered for extended use of bisphosphonates or switching to a different agent, for example, denosumab. There is a lack of consensus in when to stop the "drug holiday".

Therefore, clinicians should assess the patient's risk of fracture and measure BMD every 2–3 years.

(b) *Denosumab*

Denosumab is a monoclonal antibody against receptor activator of nuclear factor κB ligand (RANKL). RANKL/RANK and a decoy receptor, osteoprotegerin (OPG), form a coupling mechanism between bone-forming osteoblasts and bone-resorbing osteoclasts, where RANKL from osteoblasts serves as an important signal to differentiate osteoclasts.

In phase III the Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) trial, denosumab reduced vertebral, nonvertebral, and hip fractures by 68%, 20%, and 40%, respectively [36]. The following extension trial showed continued BMD gain and further reduction of fracture up to 10 years [37]. As denosumab is not cleared by the kidney, denosumab can be used for patients who are not able to take bisphosphonates due to decreased GFR. However, clinicians should exercise extreme caution that giving denosumab to patients with CKD can further aggravate the adynamic bone disease, which is often predominant pathophysiology in an advanced stage of CKD [38].

The general safety profile of denosumab for 10 years was confirmed by the extension trial. Hypocalcemia and normocalcemic hyperparathyroidism can occur. In the FREEDOM study, denosumab was reported to be associated with a higher incidence of severe infections requiring hospitalization. Severe infections in the skin, abdomen, genitourinary tract, and ear were more commonly seen in the denosumab group [38]. Therefore, immunocompromised patients with a high risk of infection should avoid denosumab. Although extremely rare, ONJ and AFFs have been reported. Lastly, unlike bisphosphonates, the skeletal effect of denosumab is sustained only for about 6 months, and rebound vertebral fractures on discontinuation have been reported [39]. The optimal duration of denosumab is not well established, but a single infusion of zoledronate followed by 6 monthly denosumab might prevent bone loss and keep the risk of vertebral fracture low [40].

(c) *Calcitonin*

Calcitonin is a hormone secreted from thyroid C cells and acts directly on osteoclasts to inhibit resorption. Initially, injectable calcitonin was used for Paget's disease of bone, but it was later replaced by nasal spray. Its anti-fracture efficacy is minimal and not ideal for long-term treatment as patients quickly develop a tolerance. Also, there is a concern for an increased risk of malignancy with calcitonin use [41].

4. *Anabolic Agents*

(a) *Teriparatide*

Teriparatide, a parathyroid hormone (PTH) analog, is a recombinant PTH consisting of biologically active N-terminal 34 amino acids. PTH1R, a classic receptor of PTH, is expressed on osteoblasts, pre-osteoblasts, and renal tubular cells. Intermittent PTH1R activation increases bone remodeling with a net anabolic effect, whereas continuous PTH exposure (e.g., hyperparathyroidism) increases bone resorption much more than bone formation, causing a net catabolic effect. The anabolic effect of intermittent PTH is accompanied by the bone formation in the cortical and trabecular compartment and reconnection of destroyed trabeculae, which improves bone quality. In severely osteoporotic females with a history of multiple fractures, teriparatide (20 μg daily subcutaneous) reduced the risk of vertebral fracture and nonvertebral fracture by 65% and 53%, respectively. Also, BMD increased by 9% and 3% in the lumbar spine and femoral neck, respectively, but radial BMD did not show significant gain likely due to the slow bone turnover rate of cortical bone [42]. A bone formation marker, procollagen type I N-terminal propeptide (P1NP), peaked during the initial 6 to 12 months and stayed significantly above the baseline for 36 months, followed by elevation of a bone resorption marker, C-terminal telopeptide (CTX), thus creating the so-called "anabolic window" [43].

The daily subcutaneous injection can be a burden, but the clinicians ought to consider the agent for patients with severe osteoporosis who are at high risk of fracture (e.g., T-score of −3.5 or

below even in the absence of fractures; T-score of −2.5 or below plus a fragility fracture) or patients who are unable to tolerate bisphosphonates or have failed other osteoporosis therapies. There is a black box warning as the supraphysiologic dose (~60 fold higher than clinical use) caused osteosarcoma in rats. Therefore, it is not approved for patients with risk factors of osteosarcoma such as skeletal radiation exposure, open epiphyses, Paget's disease, or unexplained elevation of bone-specific alkaline phosphatase, and the recommended treatment course is 24 months at a maximum, which includes the duration of both PTH agonist and PTHrP agonist.

(b) *Abaloparatide*

Abaloparatide, a parathyroid hormone-related peptide (PTH-rP) analog, shares its amino acid sequence 76% with human PTH-rP (1–34) and 41% with human PTH (1–34). In the Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE) trial, abaloparatide (80 μg daily subcutaneous) for 18 months significantly reduced the risk of vertebral and nonvertebral fractures. Of note, in this study, abaloparatide showed a greater increase of BMD in hip compared with teriparatide [44]. The overall safety profile is similar to teriparatide; there were less hypercalcemic episodes than the teriparatide group, probably due to the less humoral effect of PTHrP than PTH [44]. Again, due to the concern of osteosarcoma, it is recommended that abaloparatide should be used for up to 2 years.

(c) *Romosozumab*

Romosozumab is a humanized monoclonal antibody against sclerostin, which is a natural antagonist to the Wnt signaling pathway and works as a negative regulator of bone formation. Romosozumab has both anabolic and antiresorptive effects on the bone. When romosozumab is administered, P1NP is rapidly increased, and CTX is continuously decreased. In phase III randomized controlled trial with cross-over with denosumab, romosozumab plus denosumab group reduced the vertebral fracture

risk by 75% at 2 years compared with placebo plus denosumab group [45]. In the Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH), which compared romosozumab against alendronate, patients who received romosozumab for 12 months followed by 12 months of alendronate had a much lower risk of vertebral (48%) and hip (38%) fractures compared with patients who received alendronate for 24 months [46]. However, romosozumab group had a higher number of cardiac events than the alendronate group in the first 12 months (2.5% vs. 1.9%, OR 1.31, 95% CI [0.85–2.00]), which raised a concern of potential risk of cardiovascular disease [46]. After careful review, the FDA approved a 1-year romosozumab treatment (210 mg monthly subcutaneous) with a black box warning of cardiovascular disease risk. In very high risk patients of fracture, clinicians can consider this agent but should weigh the benefit of reducing fractures and the risk of potential cardiovascular disease, especially in patients with a history of MI or stroke.

Combination and Sequential Treatments

As discussed above, there are many treatment options for osteoporosis. Thus, it is worthwhile discussing the first choice, combination, and the best sequence of treatment. Currently, bisphosphonates are the first choice except for patients with decreased renal clearance, for whom denosumab can be considered. Patients who sustain at least two or more fractures or show significant BMD loss while on bisphosphonates should be considered for other treatments. Patients with severely low bone density or multiple histories of fragility fracture are appropriate for anabolic agents.

The combination of two types of antiresorptive agents should be avoided. Additionally, the cumulative risk of bisphosphonates should be considered when trying to switch bisphosphonates to another antiresorptive agent.

In terms of anabolics, prior treatment with potent antiresorptive might hinder the anabolic effect of PTH or PTH-rP analog. When patients switch antiresorptive (bisphosphonates and denosumab) to anabolics, hip BMD declined during the first 1 to 2 years after

switching. However, switching teriparatide to denosumab is not associated with the decline of BMD [47]. It is also reported that adding anabolics to antiresorptive agents is associated with a greater increase of BMD compared with switching from antiresorptive agents to anabolics [48]. Therefore, if possible, anabolic agents should be followed by potent antiresorptive for severe osteoporosis or patients with a high risk of fracture, although clinicians often face a challenge starting anabolics as a first-line treatment due to its high cost, insurance coverage, and resistance from patients considering the burden of daily subcutaneous injection.

Secondary Osteoporosis

It is always important to investigate possible secondary causes of osteoporosis and treat the underlying conditions. Table 6.2 summarizes the common causes of secondary osteoporosis. One of the most common causes is vitamin D deficiency, which can be diagnosed by measuring 25-(OH) vitamin D. In patients with vitamin D deficiency, vitamin D supplementation not only increases BMD but also reduces the risk of falls, although the effect on fall risk reduction seems controversial. The optimal level of vitamin D is also controversial, but a cross-sectional study in France showed that PTH started rising with a vitamin D level below 30 ng/ml [49]. Currently, the guidelines suggest supplementing with a higher dose of vitamin D (e.g., 5000 IU daily for 2–3 months) for adults who are vitamin D deficient (25-(OH) vitamin D < 20 ng/mL), which should be followed by maintenance dose 1000–2000 IU daily [50].

Hyperparathyroidism (primary, secondary, and tertiary) should be ruled out by testing serum PTH and calcium. Hyperthyroidism or hypercortisolemia should be suspected when a patient has suggestive signs and symptoms. Hypogonadism is caused by various conditions such as eating disorders, athletic amenorrhea, hyperprolactinemia, and hypopituitarism. Cystic fibrosis, Gaucher disease, Turner syndrome, Klinefelter syndrome, osteogenesis imperfecta, X-linked hypophosphatemic rickets, and hypophosphatasia are examples of genetic disorders associated with osteoporosis. Some medications also cause bone loss and are related to the risk of frac-

Table 6.2 Causes of secondary osteoporosis

Etiology	Examples
Endocrine disease	Hyperthyroidism
	Hyperparathyroidism
	Cushing's syndrome
	Hypogonadism
	Diabetes mellitus (type 1 and type 2)
Nutritional deficiency	Vitamin D deficiency
	Anorexia nervosa
	Gastrointestinal malabsorption (e.g., Celiac disease, inflammatory bowel disease, history of gastic bypass)
Bone marrow disease	Systemic mastocytosis
	Gaucher disease
	Thalassemia major
	Amyloidosis
	Leukemia
Medication	Glucocorticoids
	Immunosuppressants (e.g., cyclosporine)
	Antiseizure medications (e.g., phenobarbital, phenytoin)
	Lithium
	Heparin
	GnRH agonist
	Chemotherapy
Others	HIV infection
	Hepatic disease
	Renal disease
	Inflammatory disease (e.g., rheumatoid arthritis)
	Organ transplant

Classified by primary etiology; some conditions are multifactorial (e.g., anorexia nervosa causes nutritional deficiency and hypogonadism)

ture (e.g., glucocorticoid, proton pump inhibitors, heparin, thiazolidinedione, sodium-glucose cotransporter (SGLT) 2 inhibitors).

1. *Premenopausal Osteoporosis*

Premenopausal bone loss is often associated with secondary causes of osteoporosis (Table 6.2). Osteoporosis is not well-defined in premenopausal women, and the WHO diagnostic classification based on T-score should not be applied. The International Society for Clinical Densitometry recommends that Z-score be used instead ("below the expected BMD for age" ≤ -2.0 and "within the expected BMD for age" ≥ -2.0) [51]. The indication for BMD testing is based on an individual's risk for osteoporosis and fracture. History of fragility fractures (especially with low trauma), premature ovarian failure, prolonged glucocorticoid use, and any secondary causes should alert clinicians and measure their BMD. The initial evaluation for young women with low BMD or fragility fractures should include complete blood counts, renal and hepatic function tests, calcium, phosphate, 25-(OH) vitamin D, thyroid stimulating hormone, and 24-hour urinary calcium excretion. In addition to treating the underlying etiology of premature bone loss, initial steps for management include lifestyle interventions such as weight-bearing exercises, smoking cessation, and limiting alcohol intake, along with calcium and vitamin D supplements. Studies on the pharmacotherapy for premenopausal bone loss are very limited, except glucocorticoid-induced osteoporosis, for which bisphosphonates have shown substantial benefit [52, 53].

Antiresorptive agents might have a therapeutic role in bone loss caused by anorexia nervosa, but clinicians must consider the risk of bisphosphonate therapy in women of child-bearing age since bisphosphonates remain in the system longer and are potentially teratogenic. HRT should be initiated and continued until the average age of menopause (~50–51 years in the United States) for those patients with premature ovarian insufficiency.

(a) *Early Menopausal Bone Loss and Role of Follicular Stimulating Hormone in Bone Remodeling*

Estrogen is undoubtedly an important hormone in skeletal remodeling, but recent studies have shown that follicular stimulat-

ing hormone (FSH), a gonadotropin stimulating follicular development and estrogen production, also has an independent effect on bone. Large epidemiologic studies such as the Study of Women's Health Across the Nation (SWAN) reported that profound BMD loss occurs around 2–3 years before menopause when there is a dramatic surge in FSH levels with relatively preserved estrogen levels [54, 55]. The direct osteoclastic effect and bone resorption of FSH were documented in the mouse studies using genetic modification and intervention [56, 57]. The studies for the potential therapeutic role of blocking the β subunit of FSH through antibodies showed not only an increased bone mass [58] but also, interestingly, decreased weight and fat mass [59]. If applicable to humans, this agent would represent a promising novel therapeutic class aimed at preventing bone loss and obesity seen during the perimenopausal period, essentially killing "two birds with one stone."

2. *Male Osteoporosis*

Male osteoporosis is an under-recognized domain, with lower rates of screening and treatment in this group. For the reason, osteoporotic fractures in men account for about 39% of all osteoporosis-related fractures [60], and, notably, hip fractures in men are associated with greater mortality than in women [61].

As men do not have a dramatic hypogonadal event like menopause in women, most bone loss in men is attributed to aging. Current guidelines recommend screening using DXA in 70-year-old or above elderly men [62]. In younger men aged 50–69 years old, screening should be individualized based on their risk factors. Patients with loss of height, history of fragiligy fracture, glucocorticoid use or androgen deprivation therapy for prostate cancer should be screened for osteoporosis. The FRAX score is useful in predicting the risk for fragility fractures; however, these scores are less validated in men than in women. The diagnosis of osteoporosis and treatment initiation is based on the T-score using the same reference group of young Caucasian female like in postmenopausal women.

There is no specific agent available for male osteoporosis. Testosterone supplementation can improve BMD in men with hypogonadism but is not recommended for eugonadal men, given

the lack of benefit and potential for adverse effects [63]. PDE5 inhibitors, commonly used male erectile dysfunction drugs, potentiate the nitric oxide pathway and have shown an osteoprotective effect in mice, but further studies are needed [64].

3. *Metabolic Bone Diseases*

(a) *Primary Hyperparathyroidism*

Primary hyperparathyroidism is characterized by hypercalcemia and elevated or inappropriately normal PTH. A solitary adenoma accounts for 80% of cases, followed by four-gland hyperplasia (15–20%). Parathyroid carcinoma is very rare (<1%). Patients often develop hyperparathyroidism after menopause, mostly within 10 years, as they lose the estrogen effect, which is a potent antiresportive hormone [65].

Patients with primary hyperparathyroidism show a right-shifted set point in the PTH and calcium sigmoidal curve, so higher calcium levels are required to suppress PTH. Elevated PTH increases bone remodeling through the PTH1 receptor on osteoblasts, which activates and differentiates osteoblasts. In addition, PTH directly works on the PTH1 receptor in the distal tubule and increases calcium resorption and excretes phosphate. If the filtered loading of calcium from increased bone resorption exceeds tubular reabsorption, hypercalciuria occurs. Often, 25-(OH) vitamin D levels are low as PTH activates 1-α-hydroxylase and converts 25-(OH) vitamin D to 1,25-(OH) vitamin D. The classical biochemical profile is elevated PTH with elevated serum calcium and elevated bone alkaline phosphatase activity, with low or low normal serum phosphate. Recently, a subset of patients with normal calcium with elevated PTH without secondary causes, so-called "normocalcemic hyperparathyroidism," was noted. It might be an early stage of primary hyperparathyroidism, but the natural history of normocalcemic hyperparathyroidism is not well known yet.

Hyperparathyroidism was initially described as a bone disease with nephrolithiasis/nephrocalcinosis, peptic ulcer, or pancreatitis, the so-called "bones, stones, and groans." The pathognomonic finding of classical bone disease is demineralization of bone from

excessively high bone turnover, where bone formation lags behind bone resorption. Patients develop bone pain, skeletal deformities, and an increased risk of fracture. Salt-and-pepper degranulation of the skull, subperiosteal resorption of the distal phalanges, bone cysts, and brown tumors can be seen in the radiographic exam [66].

However, over the years, the presentation of primary hyperparathyroidism has evolved, and often patients are asymptomatic, with elevated calcium on routine blood work. Routine serum calcium assay in the 1970s and osteoporosis screening in the 1990s have significantly increased the incidence of asymptomatic or mild hyperparathyroidism [67]. Most patients with "modern" mild hyperparathyroidism have mildly elevated calcium (~10–11 mg/dl) and mildly decreased bone mass. Initial observation demonstrated that the trabecular bone–rich vertebral bone is preserved whereas cortical bone–rich radius declines, but only after almost 10 years [68]. Later, we have learned, although the bone densities of vertebral bone seemingly preserved, the bone quality is impaired, which explains the increased risk of vertebral fracture in this cohort [69, 70].

The diagnosis of primary hyperparathyroidism is based on biochemical findings. Imaging studies such as neck ultrasound, sestamibi scan with single-photon emission computerized tomography (SPECT) scan, 4D CT, or MRI can help surgical planning but are not necessary for diagnosis. For asymptomatic patients with mild hypercalcemia (<12 mg/dL) without skeletal or renal involvement, annual assessments of serum calcium and 24-hour urinary calcium with BMD testing every 1–2 years are sufficient. Symptomatic patients who meet the criteria (Table 6.3) should undergo parathyroidectomy based on the summary statement from the fourth international workshop [71].

There is a dramatic improvement in vertebral BMD after the surgery, but cortical bone–rich areas like distal 1/3 radius take longer to rebound [72]. Bisphosphonates can be used for poor surgical candidates with osteoporosis, although the long-term effect seems questionable [73, 74]. Cinacalcet is a calcium-sensing receptor agonist, indicated for parathyroid carcinoma or poor surgical candidates to manage hypercalcemia, but it does not protect patients from developing osteoporosis or fractures [75]. HRT can

Table 6.3 Criteria for surgical treatment for primary hyperparathyroidism

Category	Criteria
Symptomatic	Symptoms of hypercalcemia (neurological, nausea, constipation, polydipsia, polyuria)
	Nephrolithiasis
	Fractures
Serum calcium	>1.0 mg/dL above the upper limit of normal
Skeletal	T-score <−2.5 at the lumbar spine, total hip, femoral neck, or distal 1/3 radius
	Radiographically proven vertebral fracture
Renal	Creatinine clearance <60 mL/min 24-hour urinary calcium excretion >400 mg/day with increased stone risk[a]
Age	<50 years old

Meeting one or more of the criteria warrants surgical treatment if there is no contraindication

[a]Stone risk should be assessed by biochemical stone risk analysis

be a good option if patients are in early menopause without any contraindication [76].

(b) *Renal Osteodystrophy*

Renal osteodystrophy is defined as alterations in bone morphology associated with chronic kidney disease (CKD), ranging from secondary hyperparathyroidism or osteitis fibrosa cystica (a high-turnover bone disease), osteomalacia (defective mineralization), mixed renal osteodystrophy (hyperparathyroid bone disease with a superimposed mineralization defect), and adynamic bone disease (diminished bone formation and resorption). The term "Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)" describes the broader clinical syndrome encompassing mineral, bone, and calcific cardiovascular abnormalities that develop as a result of progressive loss of renal function. The term "renal osteodystrophy" is now used exclusively to define the bone pathology associated with CKD [77].

Physiologic changes include the failure of 1-α-hydroxylation of vitamin D in the kidneys, which results in decreased calcium absorption in the gut. Additionally, hyperphosphatemia results in decreased serum calcium. The classic biochemical picture is normo- or hypocalcemia, hyperphosphatemia, and hypocalciuria resulting in secondary hyperparathyroidism. Alkaline phosphatase may be elevated in patients with severe bone disease.

An X-ray can demonstrate abnormal bone texture and subperiosteal resorption in the fingers, particularly in the middle phalanx of the index and middle fingers (osteitis fibrosa cystica). Patchy osteosclerosis can result in the classic appearance of "rugger jersey" spine (horizontal bands of alternating intensity) and the "salt-and-pepper" skull. Large cystic lesions could suggest the possibility of amyloid deposits in the bone. However, it is prudent to note that radiographic features appear late, and even patients with marked hyperparathyroidism may not have any abnormal findings on radiographs.

BMD testing can help in assessing fracture risk and treatment decisions [78]. The gold standard for diagnosing and assessing the severity of CKD-related bone disease is bone biopsy; however, it is rarely performed given the invasiveness of the procedure. Dietary phosphate restriction, phosphate binders, calcitriol, or other active vitamin D analogs can delay secondary hyperparathyroidism but cannot prevent it entirely. Cinacalcet is also used for secondary hyperparathyroidism in adults with ESRD on dialysis. Parathyroidectomy may be considered in patients with severe hyperparathyroidism that is refractory to medical management [79].

(c) *Transplantation-Related Osteoporosis*

Because of the improved life expectancy and overall prognosis of patients with organ transplantation, more patients developed long-term complications related to transplantation, such as transplantation-related osteoporosis. Bone loss after transplantation is mostly seen in the initial 3–6 months [80]. Patients with kidney transplantation lose significant bone mass up to ~6.8% at

the vertebral skeleton in the first 6 months. Considering the overall bone loss over 18 months was about 8.8%, the transplantation-related bone loss occurs mainly in the initial phase immediately after the surgery [81]. Expectedly, metabolically active trabecular bone–rich areas such as vertebral bone undergo significant changes. This acute, rapid, and severe bone loss (ARSBL) is a multifactorial disease, which is caused by immunosuppressants, immobilization, vitamin D deficiency, preexisting osteodystrophy, and secondary hyperparathyroidism [82]. This pattern of ARSBL is observed in other organ transplantation as well. Patients after liver transplantation lose bone rapidly (~1.3% per month at lumbar spine), and more importantly, about 40% of them suffer from a fracture within 1 year after the surgery [83]. Similarly, patients with bone marrow transplantation experienced a significant decrease of BMD in the femoral neck within 3 months [84]. Therefore, clinicians should be aware of the particularly high risk of fracture in this group of patients, especially in the early phase after the transplanation.

The most important risk determinants are immunosuppressant use and pre-transplant BMD, which serves as a skeletal reserve [85]. Glucocorticoid is the oldest, but still most effective, immunosuppressant, and long-term use (e.g., more than 3 months with prednisone or its equivalent as low as 2.5 to 7.5 mg daily) is well known to cause significant harm to the skeleton. Other immunosuppressants such as cyclosporine (CsA) and tacrolimus (FK506) also damage bone. They inhibit calcium/calmodulin-sensitive phosphatase-calcineurin in osteoblasts and osteoclasts, altering bone remodeling [86]. Rapamycin, an mTOR inhibitor, causes less bone loss compared to CsA [87].

(d) *Breast Cancer– and Prostate Cancer–Related Bone Disease*

Breast cancer and prostate cancer are the most prevalent cancers in women and men, respectively. Endocrine therapy, such as aromatase inhibitor (AI) and SERMs, is often administered for patients with hormone receptor–positive breast cancer after surgery. Patients receiving AI can lose bone rapidly (1.7 to 5.8% per year), much greater than the expected 1% per year

bone loss after menopause [88]. As a result, the risk of fracture is almost doubled in postmenopausal women with breast cancer taking AI [89]. In contrast, tamoxifen, a partial estrogen agonist, has shown a different effect on BMD in pre- and postmenopausal women. In postmenopausal women with breast cancer, tamoxifen showed a preventive effect on bone loss [90]; however, it decreased BMD in premenopausal women with early breast cancer [91]. Therefore, monitoring BMD is warranted for premenopausal patients with breast cancer receiving tamoxifen. Although tamoxifen can protect from bone loss in postmenopausal women, the efficacy is much lower than antiresorptive agents and cannot be a substitute in patients with a higher risk of fracture.

Androgen deprivation therapy (ADT), such as medical (e.g., GnRH agonist or GnRH antagonist) treatment or surgical orchiectomy, is a component of the treatment for castration-sensitive prostate cancer. The patients with prostate cancer undergoing ADT lost BMD rapidly (~ 4.0% in 12 months) [92] and showed significantly increased risk of fracture in 5 years compared with the patients without ADT [93]. Therefore, the current guidelines support antiresorptives use in patients with breast or prostate cancer using endocrine therapy [94–97].

Summary

Osteoporosis or metabolic bone disease from an underlying condition can increase the risk of fracture significantly, which can be detrimental to a patient's well-being. As primary caregivers have a long-term relationship with patients and have a "holistic" understanding, they are well-positioned for addressing a patient's overall risk of osteoporosis, falls, and fracture. Measuring bone quantity alone based on DXA has its limitation in terms of assessing the risk of fracture, but can be supplemented by thorough clinical risk assessment and measuring bone quality by an advanced diagnostic tool such as trabecular bone score. Although new treatments are available, bisphosphonates remain the first-line therapy and are both cost-effective and well-tolerated. Anabolic agents such as

teriparatide and abaloparatide are excellent candidate drugs for severe osteoporosis or high risk patients. Romosozumab and denosumab, two monoclonal antibodies, have shown impressive antifracture efficacy, but long-term safety profile and the optimal duration of treatment need to be further studied.

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Crystal-Induced Arthritis

7

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Crystal-induced arthritis comprises a group of acute and/or chronic diseases related to tissue deposition of one of three crystals: monosodium urate crystals in gout, calcium pyrophosphate dihydrate crystals in pseudogout, and basic calcium phosphate crystals in calcific tendinitis and periarthritis. The crystal-induced arthritides are one of the most common causes of inflammatory arthritis and can usually be well controlled with treatment. Primary care physicians diagnose and manage most patients with gout and other crystal diseases. Less than 10% of patients diagnosed as having gout are referred to the rheumatologist [1]. In primary care, the diagnosis is based on signs and symptoms, usually without synovial fluid analysis. The chapter summarizes the clinical features, natural history, and treatment of crystal-induced

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arthritis and common clinical pitfalls encountered by the primary care physician and pearls in the diagnosis and management of these arthropathies.

Gout

Gout is characterized by the deposition of monosodium urate monohydrate (MSU) in the synovial fluid, joints, tendons, and soft tissue. MSU crystals can form when the level of serum uric acid (sUA) rises above the saturation threshold for MSU crystal formation (reflected approximately by a concentration of 329 mmol/L or 6.6 mg/dL at 37 °C) [2]. Two major factors that predispose to MSU crystal formation are (1) chronic hyperuricemia, serum uric acid >6.8 mg/dL, and (2) local tissue characteristics that facilitate MSU crystal nucleation and growth. The documentation of hyperuricemia should lead the physician to consider the presence of concomitant metabolic syndrome such as obesity, hypertriglyceridemia, hypertension, use of diuretics, heavy alcohol consumption, and other comorbid conditions. The central feature of gout is the deposition of MSU crystals, which can lead to acute inflammatory arthritis, tendonitis, periarthritis triggered by the release of these crystals from aggregates (tophi), development of granulomatous inflammation around the tophi, cartilage damage, bone remodeling, fibrosis, and organ damage. MSU-crystal deposition has been documented to occur everywhere in the body except brain tissue [3].

Gout can be classified into four different clinical stages: (a) asymptomatic hyperuricemia, (b) acute gout, (c) intercritical gout, and (d) chronic gout. However, some authors recommend taking a more comprehensive approach and only considering acute gout (episodes of acute inflammation) and chronic gout (which includes palpable tophi, joint limitation, persistent inflammation, and joint deformity) [4]. The time between asymptomatic hyperuricemia and tissue deposition of MSU and the development of the first gout flare is not known. However, it seems to directly correlate with the degree and the length of time of hyperuricemia [5]. These are useful classification for treatment decisions. Important to note

that by the time a patient has his first acute attack, microtophi are already present in the synovium, and recurrent acute attacks often ensue over a background of chronic articular gout [6].

Presentation and Progression

Cause

Gout results from increased UA production, decreased UA renal excretion, or a combination of both mechanisms (Table 7.1). Approximately two-thirds of our daily uric acid load are produced endogenously, while one-third comes from dietary sources. An increase in UA production may be caused by genetic factors, chronic hemolysis, myeloproliferative disorders, exogenous mechanisms, obesity, excess alcohol consumption, and/or high purine intake. Only a small proportion of those with urate overproduction (10%) include rare in-born error of metabolism hypoxanthine-guanine phosphoribosyl transferase deficiency (Lesh–Nyhan syndrome) or 5-phosphoribosyl-1-pyrophosphate synthetase hyperactivity. Elevated sUA occurs due to an increased production of hepatic urate through the purine synthesis de novo and salvage pathways. Renal underexcretion of uric acid is the dominant contributor with reduced fractional excretion of uric acid in hyperuricemia as seen in 90% of gout patients. Once urate has formed, about 70% is excreted via the kidneys, and the remainder 30% is eliminated by the intestines. Once in the kidneys, 95% of urate is filtered by the glomerulus and then undergoes bidirectional proximal convoluted tubule movement, which is accomplished via several transmembrane anion exchange channels known as the "*uric acid transportasome*" involved in the reabsorption and secretion of uric acid. Polymorphisms in these transporters may be associated with and explain the inadequate excretion of urate by the kidneys in some patients [7, 8]. In addition to genetic factors, several environmental risk factors contribute to the development of gout, including high intake of purine-rich beverages such as beer, purine-rich foods such as red meat and seafood, and sugar-sweetened beverages, including those with high fructose [3]. These dietary risk factors lead to an increase in

Table 7.1 Classification of hyperuricemia

Uric acid hyperproduction
Primary gout (10% of cases)
Genetic factors (HGPRT deficiency, hyperactive PRPP)
Overweight
Diet rich in purine
Excessive alcohol use
Psoriasis
Hemolysis
Lymphoma
Myeloproliferative disease
Decreased excretion
Primary gout (90%)
Renal insufficiency
Arterial hypertension
Overweight
Lead intoxication
Hyperparathyroidism
Hypothyroidism
Toxemia of pregnancy
Acidosis
Drug ingestions:
Alcohol
Diuretics
Low-dose salicylates (<2g/day)
Levapoda
Combinations
Primary gout
Overweight
Excessive alcohol (increased production; decreased excretion with lactacidosis)

purine synthesis through the hepatic salvages pathways, which in turn leads to increased urate production. Increased purine content on a background of decreased UA renal excretion resulting from decreased GFR in arterial hypertension, use of thiazide or loop diuretics, raised threshold of tubular excretion in acute alcohol consumption, chronic renal insufficiency of any etiology, in par-

ticular polycystic kidney disease, and lead intoxication contribute to hyperuricemia and risk of gouty arthritis. Although hyperuricemia is present in virtually all people with gout, this biochemical abnormality is not sufficient for the development of clinical apparent joint disease, as most people with hyperuricemia do not develop gout and may be considered asymptomatic hyperuricemia patients. The time between asymptomatic hyperuricemia and tissue deposition of MSU and development of clinical manifestation is unknown. It seems to directly correlate with the length of time of hyperuricemia [5]. Most patients with gout have a period of asymptomatic hyperuricemia prior to the development of acute and/or chronic arthritis.

Presentation

Episodes of acute inflammation are referred to as gout flares, gout attacks, gouty bouts, or gouty arthritis. They are defined by acute signs and symptoms of inflammation triggered by the release of MSU crystals in any part of the musculoskeletal system but mainly in synovial structures such as joints, tendons, and bursae; therefore, causing arthritis, tendonitis, and/or bursitis. The classic "podagra," inflammation of the first MTP, is the hallmark presentation of acute gout. It occurs in more than half the patients and is frequently involved in up to 80% of undertreated patients with gout. Other affected joints involved with decreasing frequency include the tarsal, ankle, and knee joint. In the upper extremity, the olecranon bursae are most frequently affected. The hands are usually affected in patients with long-standing or chronic tophaceous gout but are an uncommon presenting location except in elderly women with underlying osteoarthritis. Single joint involvement (monoarthritis) is most frequently seen in early disease. Oligoarticular (less than four joints) and polyarticular (more than four joints) acute gout flares usually affect individuals with long-standing, severe, untreated, or inefficiently treated disease, or during a rapid reduction in sUA caused by urate-lowering therapy, surgery, or severe dietary restrictions. Trauma and high purine diet are well recognized as triggers for acute flare. Acute inflammatory arthritis, bursitis, and periarthritis seen in gout can resemble septic arthritis, bursitis, cellulitis, or phlebitis. Low-

grade fever and malaise may be present; synovial fluid analysis, examination under compensated polarized light microscopy, Gram staining, and culture are essential in excluding an underlying infectious process. However, it is important to highlight that these two processes can coexist. Crystal demonstration of gout is considered the "*gold standard*" in early disease as a lifelong commitment to uric acid–lowering therapy is under consideration (Fig. 7.1) [9]. In 2015, the American College of Rheumatology developed classification criteria for gout to assist the primary care physicians in the diagnosis of gout (Table 7.2) [10]. The primary care physician should be aware of a substantial list of conditions that cause podagra in addition to gout, known as "pseudopodagra" (Table 7.3). Similarly, about 30% of the patients with acute gout have normal serum urate levels during an acute attack; therefore, measurement of serum urate levels is not a useful laboratory study to confirm the diagnosis of gout during an acute attack [4].

Certain clinical characteristics that are suggestive of gout include (1) podagra beginning during the night or in the early morning hours; (2) pain that is unbearable to the weight of the sheet on the affected toe; (3) pink color of the inflamed joint; and (4) absence of symptoms between attacks, a characteristic feature that lead to the accrual of MSU crystals leading to chronic destructive tophaceous arthritis. Persistent clinical manifestations are known as chronic gout arthritis or chronic gout arthropathy and entail the presence of persistent joint swelling, joint limitation, deformity, and palpable tophi. Joint deformity is a late finding of untreated gout and is usually associated with severe tophaceous deposition. Sometimes these deformities can involve the small joints of the hands and mimic rheumatoid arthritis (Fig. 7.2a) [11].

A relevant clinical question is, is it necessary to perform a joint aspiration during an acute podagra attack? Probably not, but if crystal documentation is needed, then the MTP joint or other affected joints should be aspirated to confirm the diagnosis of gout or exclude other crystal-induced arthritis or pathologies. The following is a typical case example.

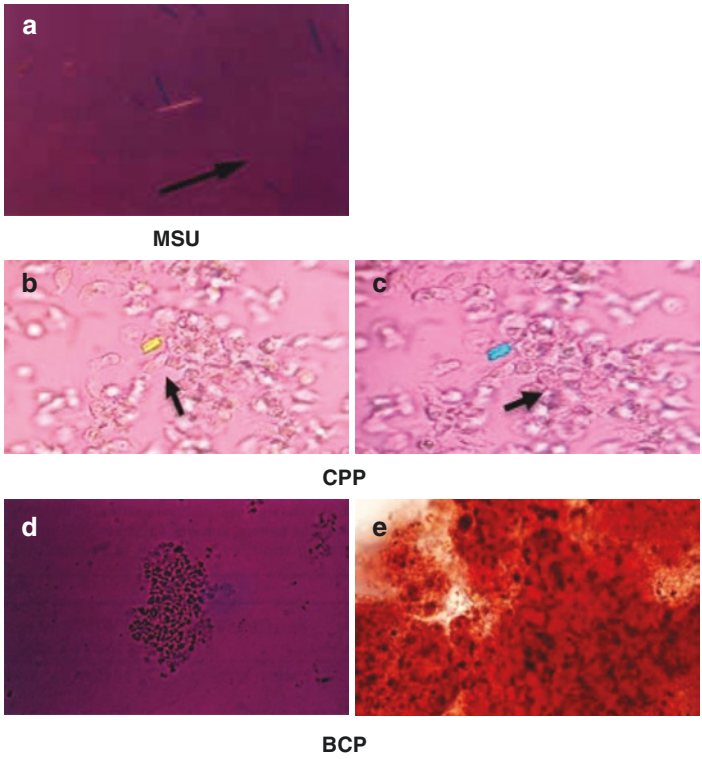

Fig. 7.1 Morphology under compensated polarized light microscopy and special stain of crystal-associated arthritis. (**a**) Needle-shaped MSU crystal with intense negative birefringent as seen under compensated polarized light microscopy (400×). (**b**) Rectangular, rhomboid shape CPP crystal with weakly positive birefringent crystal when the crystal is parallel to the axis of compensator (arrow), adopting a blue color under compensated polarized light microscopy (400×). (**c**) CPP crystal is rotated perpendicular to the axis of the compensator; it adopts a yellow color under compensated polarized light microscopy (400×). (**d**) HA and BCP crystals present with amorphic features and show no birefringence under compensated polarized microscopy (400×). (**e**) Alizarin red stain of HA staining orange-red color (400×). **Negative birefringence**—*yellow when it is parallel to the direction of the light (arrow), and blue when it is perpendicular.* **Positive birefringence**—*blue when it is parallel to the direction of the light (arrow), and yellow when it is perpendicular*

Table 7.2 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) 2015 Gout Classification Criteria

Entry criterion (only apply criteria below to those meeting these entry criteria)	At least one episode of swelling, pain, or tenderness in a peripheral joint or bursa	*Y N*
Sufficient criterion (if met, can classify as gout without applying criteria below)	Presence of MSU crystals in a symptomatic joint or bursa (i.e., in synovial fluid) or tophus	*Y N*
Criteria (to be used if sufficient criteria are not met) *Score >8 required for classification as gout*	Categories	*Score*
Pattern of joint/bursa involvement during symptomatic episode(s) ever	Joint(s) or bursa(e) other than ankle, midfoot, or 1st MTP (or their involvement only as part of polyarticular presentation) Ankle OR midfoot (as part of monoarticular or oligoarticular episode without MTP1 involvement) MTP1 (as part of monoarticular or oligoarticular episode)	0 1 2
Clinical		
Characteristics of symptomatic episode(s) ever: (i) Erythema overlying affected joint (patient-reported or physician observed) (ii) Can't bear touch or pressure on affected joint (iii) Great difficulty with walking or using affected joint	No characteristics One characteristic Two characteristics Three characteristics	0 1 2 3

Table 7.2 (continued)

Time-course of episode(s) ever: Presence (ever) of >2, irrespective of anti-inflammatory treatment: (i) Time to maximal pain <24 hours (ii) Resolution of symptoms in 14 days (iii) Complete resolution (to baseline level) between symptomatic episodes	No typical episode One typical episode Recurrent typical episodes	0 1 2
Clinical evidence of tophus: draining or chalk-like subcutaneous nodule under transparent skin, often with underlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (e.g., Achilles)	Absent Present	0 4
Laboratory		
Serum urate: measured by uricase method. Ideally should be scored at a time when the patient was not taking urate-lowering treatment and patient was beyond 4 weeks of the start of an episode (i.e., during intercritical period) if practicable, retest under those conditions. The highest value irrespective of timing should be scored	<4 mg/dL [<0.23 mM] 4–<6 mg/dL [0.24–<0.36 mM] 6–<8 mg/dL [0.36–<0.48 mM] 8–<10 mg/dL [0.48–<0.6 mM] >10 mg/dL [0.6 mM]	−4 0 2 3 4
Synovial fluid analysis of symptomatic (ever) joint or bursa: should be assessed by a trained observer	Not done MSU negative	0 −2
Imaging		
Imaging evidence of urate deposition in symptomatic (ever) joint or bursa: ultrasound evidence of double contour sign or DECT demonstrating urate deposition	Absent or not done Present (either modality)	0 4
Imaging evidence of gout-related joint damage: conventional radiography of the hands and/or feet demonstrate at least one erosion	Absent or not done Present	0 4

Table 7.3 Causes of pseudopodagra

Cellulitis
Septic arthritis
Hallux rigidus
Hallux rigidus with bursitis or DJD
Bunion
Sesamoiditis
Morton's neuroma
Tarsal tunnel syndrome
Stress fracture
Reactive arthritis
Psoriatic arthritis
Rheumatoid arthritis
Inflammatory bowel disease arthritis
Palindromic arthritis
Calcium pyrophosphate crystal deposition disease
Basic calcium phosphate crystal deposition

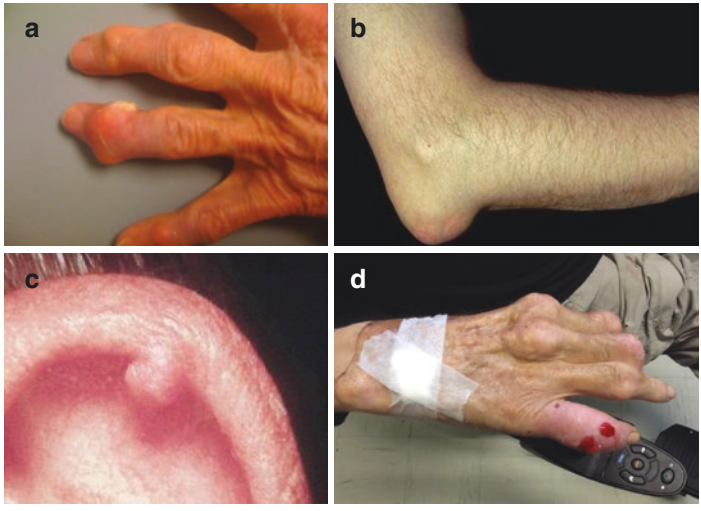

Fig. 7.2 Clinical presentation of gout. (**a**) Heberden's nodes in a patient with osteoarthritis (OA) with tophus fourth distal interphalangeal joint draining or chalk-like subcutaneous nodule under transparent skin. (**b**) Tophi in the ear. (**c**) The elbow (olecranon bursa). (**d**) Chronic tophaceous gout with draining tophus and bleeding from overlying vascularity

Case 1 A 69-year-old male fireman with a past medical history significant for hypertension, hypercholesterolemia, osteoarthritis presents with a 5-day history of acute erythema and swelling of the right toe. He denies any recent trauma to the foot or toe, although he states that he often "kicks the door" at the fire scenes. He was initially evaluated by this primary care physician and treated with colchicine, ibuprofen, and 40 mg of prednisone for 2 days with minimal improvements in his joint symptoms. Medications included valsartan, hydrochlorothiazide, atorvastatin, zolpidem, and omega-3-fatty acids. He drinks about 1–3 beers on the weekend. He denies any family history of gout or prior h/o gouty attacks. Rheumatology review of systems remains unremarkable. Physical exam showed swollen right 1st MTP with small effusion. No tophi on the ears, elbows (olecranon bursae), or elsewhere, no other swollen joint. Labs showed an elevated C-reactive protein of 47.2 mm/L (normal <8.0 mg/L), sedimentation rate of 37 mm/H (normal 0–17 mm/H), serum uric acid of 4.8 mg/dL, and normal white count and creatinine. His pain started all of a sudden in the middle of the night and is burning and exquisitely tender. He says he could not even stand or have the bed sheet touch his right toe. X-rays were unremarkable, and bedside ultrasound showed synovitis on gray scale and positive power-Doppler signals consistent with inflammatory monoarthritis (Fig. 7.3).

The best diagnostic course of action at this point is to perform a diagnostic arthrocentesis. Synovial fluid should be evaluated for cell count, Gram stain, and cultures. Evaluation of the synovial fluid for the presence of negative birefringent crystals on compensated polarized light microscopy is carried out to confirm the diagnosis of acute monoarticular gout (Fig. 7.1) [9]. In the above case, the patient failed to respond to the "*standard of care"* (SoC) of acute gout and combination therapy (Fig. 7.4), and one should consider alternative diagnosis as outlined in Table 7.3, including bacterial infection. A small amount of synovial fluid obtained from the first MTP examined under a compensated light polarized microscope showed needle-shaped and strongly negative birefringent crystals, consistent with MSU crystals, and mild-to-moderate polymorphonuclear leucocytes (PMNs) with intracellular crystals, con-

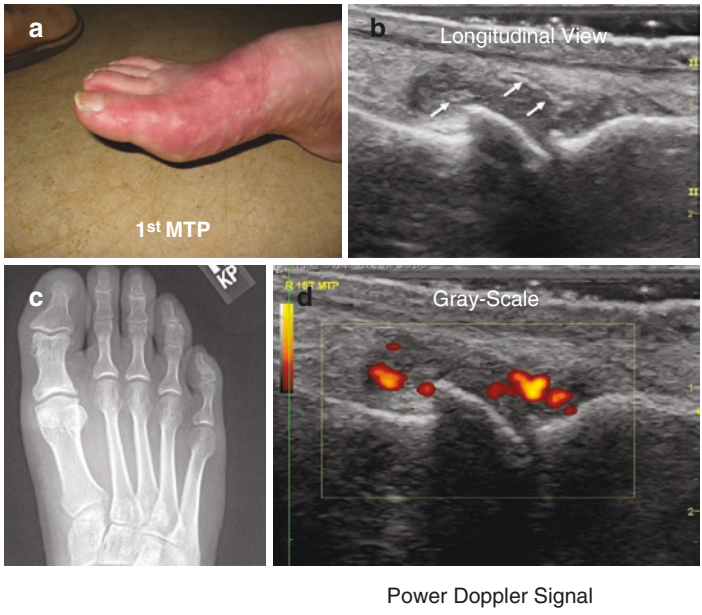

Fig. 7.3 Case 1. (**a**) Erythema over the first MTP in a patient with PODAGRA. (**b**) X-rays of the foot with minimal soft-tissue swelling. (**c**) Point-of-care ultrasound with a longitudinal view of the 1st MTP showing hyperechoic aggregates (arrows) within the joint capsule. (**d**) Inflammation with positive power-Doppler signal within the joint capsule consistent with inflammatory arthritis on ultrasound

sistent with the diagnosis of acute monoarticular gout. Only a small amount of synovial fluid was drained from the right MTP and sent for Gram stains and cultures. The Gram stain showed abundant neutrophils with moderate Gram-positive cocci in clusters; overnight cultures grew methicillin-sensitive *Staphylococcus aureus*. The patient was brought to the emergency room where orthopedic surgery performed a second diagnostic arthrocentesis to confirm the presence of septic arthritis in the background of podagra. The second arthrocentesis grew the same organisms with identical antibiotic sensitivities. The patient was later brought to the operating room for I&D and completed a course of antibiotics for septic arthritis. Septic arthritis of the first MTP is extremely uncommon;

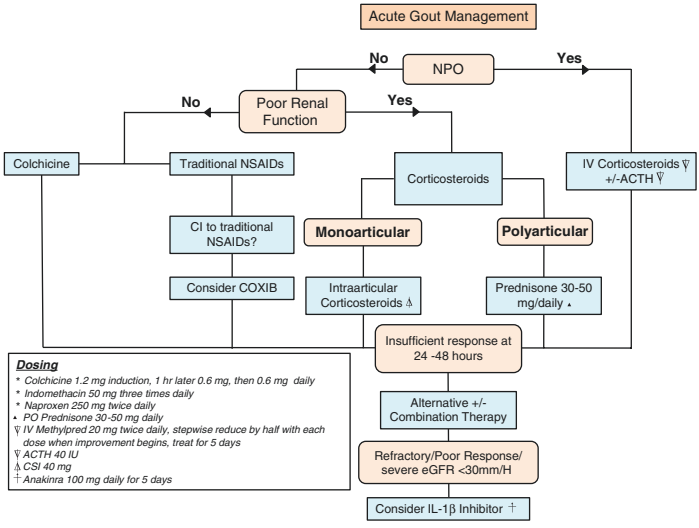

Fig. 7.4 Pharmacological strategies for management of acute gout based on 2020 American College of Rheumatology. CI contraindications, eGFR glomerular filtration rate, ACTH adrenocorticotropic hormone

however, failure to respond to the SoC (Fig. 7.4) should raise the suspicion of alternative diagnosis (Table 7.3).

Pitfalls and Pearls of Acute Monoarticular and Polyarticular Gout

- *Serum uric acid during an episode of acute attack may be normal or even low. sUA at the time of the attack* should not *be used to support or refute the diagnosis of acute gouty arthritis. Prior laboratory studies demonstrating hyperuricemia may provide much more reliable and useful information or alternatively rechecked 1–2 weeks after resolution of gout attack. Hyperuricemia is common in the general population.*
- *Triggers for gout include shellfish, red meat, beer, and other high purine foods. Despite diet being a trigger for gout, changing the patient's diet does not reliably reduce uric acid levels as it only accounts for about <1 mg/dL decrease of total sUA.*

- *In the absence of a gout flare or tophi, there is no indication for treating asymptomatic hyperuricemia for gout flare prevention.*
- *Other frequently involved joints in gout are knee, ankle, wrist, and elbow. The hips are very rarely involved, and similar considerations apply to the shoulder; these joints may occur in the context of polyarticular gout.*
- *Nodal gout represents gout superimposed in one or more Heberden nodes predominantly in older women who take diuretics. The visible tophi may precede the acute gout attacks and are often confused as rheumatoid arthritis* (Fig. 7.2a).
- *Polyarticular gout appears late in the course of the disease and occurs more frequently in women and patients with myeloproliferative disorders or cyclosporine-induced gout.*
- *Patients may present with a febrile episode, leukocytosis; the severity is proportional to the number of affected joints, which may raise the concern of underlying infection. Blood cultures and synovial fluid Gram stain and cultures are critical in these cases.*
- *Renal function, liver function, glucose, lipid profile, and full blood count should be checked to screen for chronic kidney diseases (CKDs), liver disease, diabetes, dyslipidemia, and myeloproliferative disorders. Joint aspiration is usually required to confirm gout (if gout is suspected), but mainly to exclude the alternative diagnosis, particularly bacterial infections as these may also coexist.*
- *The "gold standard" diagnosis of gout requires the identification of MSU crystals in the synovial fluid of an inflamed joint or aspirates of tophi. MSU crystals are usually easily found under compensated polarized light microscopy as long, needle-shaped, and highly birefringent (bright) crystals. These crystals demonstrate negative elongation, being yellow when aligned parallel to the direction of orientation of the red compensator and blue when aligned perpendicular to this direction* (Fig. 7.1).
- *Synovial fluid leukocytes counts in acute gout arthritis are usually greater than 2000/mm^3 and may be as high as 100,000/mm^3, with a predominance of neutrophils. Peripheral leukocy-*

tosis may be present, and other nonspecific indicators of inflammation such as the erythrocyte sedimentation rate and/or C-reactive protein may be elevated. These findings are not usually present in chronic gouty arthritis or tophaceous gout.

- *Application of* point-of-care ultrasound *is sensitive in detecting MSU crystals. The ultrasonographic findings of gout include "double contour sign" (MSU-crystal deposition on the surface of hyaline articular cartilage), intra-articular and/or intra-bursal tophi, and hyperechoic aggregates* (Fig. 7.5a, b).
- *Radiographs of the affected joint(s) usually show ONLY soft tissue during acute or tophaceous gout. Preserved joint space*

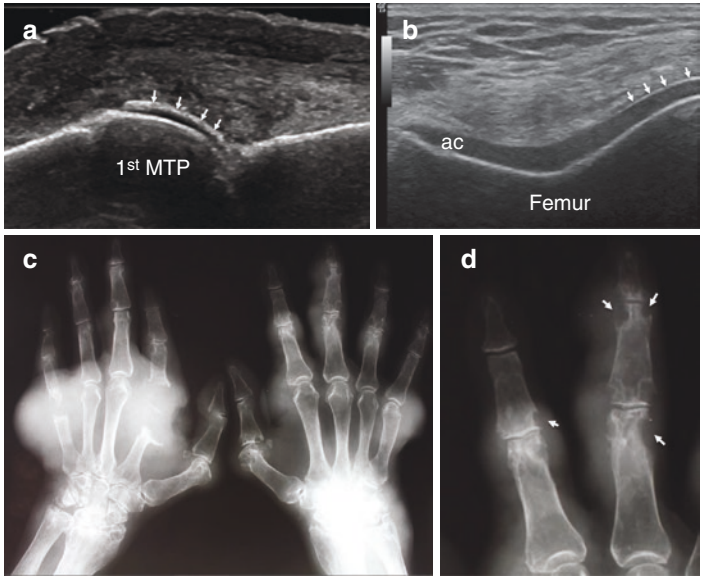

Fig. 7.5 Imaging modalities in gout. Point-of care ultrasound showing a "double-contour sign" (arrows) on the surface of articular cartilage (ac) on a longitudinal view of the 1st MTP (**a**) and knee (**b**) of the hyaline cartilage. (**c**) Conventional radiography of the hands showing erosive gouty arthropathy in a patient with tophaceous gout. (**d**) Higher magnification of the right second and third digit highlighting cortical break with sclerotic margin and overhanging edge (arrows) seen on conventional radiography. 1st MTP metatarsophalangeal joint, ac hyaline cartilage

until late in the disease. Increased soft tissue density/calcification in tophaceous gout is eccentric. Cortical described as well-defined erosions, marginal/intra-articular/away from the joint line, with sclerotic margins and overhanging edge and absence of bony proliferation are characteristic of erosive gout (Fig. 7.5c).

- *Acute cervical and lumbar spine gout is rare but cannot be crystal proven. The presence of concurrent involved joints and back with improvement on colchicine may preclude a presumptive diagnosis of axial gout. CT scan is helpful in the diagnostic evaluation of axial disease.*
- *Early onset of gout in the background of neurologic disorders in infancy or early childhood should call attention to possible rare genetic disorders such as PRPP (phosphoribosylpyrophosphate synthetase) hyperactivity or partial deficiency of HGPRT (hypoxanthine-guanine phosphoribosyl transferase).*

Natural History of Gout

Acute Gout

Acute attacks are characterized by typical features of acute crystal synovitis, such as rapid onset (symptoms peaking 12–24 hours after onset), excruciating pain, tenderness to touch, erythema, and articular/periarticular swelling [3, 4]. The attack usually resolved 1–2 weeks. Approximately 30–40% of patients with the first episode of podagra will not present with another flare within a year, and half of these will escape recurrence during the second year. In the remaining 60–70% of these patients, recurrences of acute flare require suppressive medications or prolonged use of urate-lowering therapy [3, 4].

Chronic Tophaceous Gout

Chronic tophaceous gout usually develops after many years of recurrent attacks; however, it can occasionally develop more quickly, over a few years, with relatively few attacks. Gouty tophi are nodular masses of MSU crystals and inflammatory tissues and

appear as white-to-yellow firm subcutaneous deposits with heterogeneous consistency, generally in the fingertips, feet, and olecranon and prepatellar bursae. Tophaceous gout presents with chronic joint pain, stiffness, and tenderness, with superimposed episodes of acute gout.

Transplant-Associated Gout

Immunosuppressed solid organ transplant recipients on low-dose prednisolone and calcineurin inhibitors, such as cyclosporine, can present with rapidly progressive tophaceous gout. Unlike patients with primary gout, where tophi typically take over 10 years to develop, transplant recipients can develop tophi within 3–5 years [3, 4].

Treatment of Acute Gout

The goal of therapy in an acute gout attack is prompt and safe termination of pain and inflammation (Fig. 7.4). Treatment of gout includes two separate issues: (1) treatment of the acute attacks and (2) treatment of the chronic hyperuricemic state to prevent recurrent attacks, tophus formation, articular cartilage damage, and bone erosions and to decrease the risk of gout nephropathy (Fig. 7.6). Management includes prompt use of nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, or corticosteroids [12]. Host factors such as age and/or comorbid disease(s) will largely dictate the treatment of acute gout (Fig. 7.4). These are most effective when started early, for example, within the first 12–24 hours of onset. Acute gout responds dramatically to colchicine, NSAIDs, with the exception of aspirin or other salicylates, and parenteral or oral corticosteroids. All these treatments are highly effective in an individual patient. Some of the other conservative modalities include the following: (1) joint aspiration by removing crystals will foster recovery; (2) temporary bed rest or splinting the joint improves pain by decreasing joint mobility; (3) ice packs are used, as heat increases crystal-induced inflammation, while decreasing joint temperature has anti-

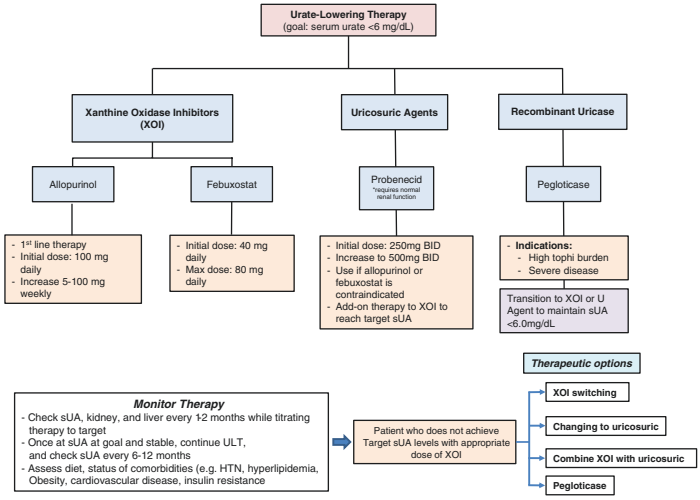

Fig. 7.6 Gout treatment algorithm for urate-lowering therapy (ULT) utilizing treat-to-target (sUA <6.0 mg/dL) approach. CI contraindications, eGFR glomerular filtration rate, ACTH adrenocorticotropic hormone

inflammatory properties; (4) acute gout is a self-limited condition that will resolve in a few days to weeks and may be used in patients intolerant to the *standard of care* (SoC). If medications cannot be used in a particular patient, then consider joint aspiration (exclude infection), immobilization, cooling the joint, and monitoring for spontaneous resolution of gout flare.

NSAIDs, Colchicine, and Glucocorticoids

Three first-line therapies are available: NSAIDs or COX-2 inhibitors, colchicine, and systemic glucocorticoids (Fig. 7.4). NSAIDs are the treatment of choice for healthy individuals with acute gout attacks with normal liver and renal function. The most important factor is not the choice of NSAIDs but rather the time at which the treatment is initiated and is generally best within the first 12 hours after the onset of pain. When used, treatment with NSAIDs or COX-2 inhibitors should be initiated at the fully approved dose and continued until the attack has completely resolved. In one study, 73% of patients had a pain reduction of ≥50% when taking

NSAIDs relative to only 27% of patients on placebo [13]. All available NSAIDs are considered effective, but only three NSAIDs are specifically approved for treatment of acute gout (naproxen, indomethacin, and sulindac). There is no evidence supporting one NSAID as being more effective than another, and the evidence that does exist fails to show a meaningful difference [13]. Limited evidence indicates that selective COX-2 inhibitors, including celecoxib, have efficacy similar to non-selective NSAIDs and may have fewer adverse events driven in part by fewer gastrointestinal events (6% versus 16% for GI events) [13]. NSAIDs should be used with caution or avoided in our elderly patients with renal insufficiency, poorly controlled congestive heart failure, gastric or peptic ulcer disease, anticoagulation therapy, or liver dysfunction.

Colchicine has long been used as prophylaxis for acute gout attacks and has been endorsed for the treatment of acute attacks. Evidence suggests that colchicine dosed at 1.2 mg initially followed by a single 0.6-mg dose 1 hour later is as effective with fewer side effects compared to a traditional regimen of 1.2 mg followed by 0.6 mg every hour for up to 6 hours [14]. Approximately 40% of patients have 50% pain reduction within 24 hours and a 40% absolute risk reduction in adverse events on this "low-dose" regimen. The efficacy of colchicine relative to other therapies is unknown, especially for patients presenting longer after the attack onset. The 2020 American College of Rheumatology (ACR) treatment guidelines recommend colchicine only if treatment is initiated within 36 hours of attack onset, but this is based solely on expert consensus [12]. Likewise, the above trial for "low-dose" colchicine did not provide information about dosing beyond the first 6 hours, leaving little guidance for follow-up treatment of residual pain beyond the 32 hours reported [12, 14]. In a recent randomized, prospective double-blind placebo-controlled trial, colchicine (0.6 mg twice a day) experienced fewer oral flares over 6 months compared to placebo [15]. The tolerability profile of colchicine is dose dependent, and clearance is reduced in patients with renal impairment with recommended dosage reduction in advance chronic kidney disease. It is well tolerated with diarrhea as one of the most common reported

adverse events. Rare cases of blood disorders (bone marrow suppression, aplastic anemia, and thrombocytopenia) have been reported at therapeutic doses. Serious toxicities, such as myopathy and neuropathy, have rarely been reported. Adverse events with the combination use of statin include acute myopathy and rhabdomyolysis [16].

Glucocorticoids are also commonly used in treating acute gout [17]. Their systemic use is available in various preparations, including oral, intravenous, intramuscular, or indirectly by administration of corticotropin (ACTH). Steroids are a good option in patients with relative contraindication to NSAIDs or colchicine, particularly in liver and kidney dysfunction, and those with polyarticular flare. In one clinical trial comparing 30 mg oral prednisolone daily for 5 days versus a combination of indomethacin for 5 days and an initial intramuscular injection of 75 mg diclofenac, there was a small pain reduction benefit for prednisolone, but the difference was not clinically significant [18]. The prednisolone group also had fewer patients with adverse events, including abdominal pain (0% versus 30%) and gastrointestinal bleeding (0% versus 11%). The lower incidence of short-term adverse events may be one of the primary benefits of systemic glucocorticoids [19]. Intra-articular glucocorticoids are not suggested first-line therapies but are commonly used by rheumatologists [17]. Intra-articular glucocorticoid injection helped to quickly resolve 20 out of 20 crystal-proven gout attacks in one uncontrolled study [20]. However, no randomized controlled trials have examined this. While seemingly efficacious, other considerations are important for this modality. Intra-articular glucocorticoids may not be preferred for polyarticular attacks or attacks in difficult-to-aspirate joints. Additionally, intra-articular glucocorticoids have been anecdotally associated with rebound attacks (i.e., attacks that occur shortly after resolution without other interventions). However, the aforementioned uncontrolled study had no such attacks occurring among participants [20]. Finally, septic arthritis must be ruled out as in any case of acute onset of monoarticular arthritis. There are no head-to-head clinical trials of colchicine versus NSAIDs or colchicine versus glucocorticoids. One trial comparing glucocorticoids to an NSAID showed no difference in

mean reduction of pain and no difference in adverse events [13]. Thus, without further study, treatment choices are often guided by factor(s) other than the existence of robust evidence.

Biologic Therapy

Biologic agents targeting interleukin IL-1β are not currently approved for gout, although there is burgeoning data suggesting that this strategy may have substantial merit [21, 22]. MSU crystals trigger IL-1β release via innate immune pathways and the NALP3 inflammasome complex (cryopyrin) [23]. Based on this rationale, anakinra (IL-1 inhibitor) has been successfully employed in the management of flares in refractory gout patients with complete treatment failure to other medications [24, 25]. Two other IL-1 inhibiting agents currently in the market have been evaluated in randomized controlled trials for management of gout [26, 27]. Canakinumab, a fully humanized immunoglobulin G1 (IgG1) monoclonal antibody, is specific for IL-1 with a half-life of around 28 days. Three randomized controlled trials (RCTs) have shown the efficacy of canakinumab compared to other drugs for the management of acute gout [27–29]. Rilonacept (or IL-1 Trap) is a fusion protein formed by the ligand-binding domain of the extracellular part of IL-1R1 and IL-1 receptor accessory protein (IL-1RAcP) linked to the Fc portion of human IgG1 (half-life of 9 days) [30]. Three different RCTs have shown their efficacy in chronic gouty arthritis [26], prevention of gout flares, and acute gout [30, 31]. Additionally, there is limited evidence that adrenocorticotropic hormone (ACTH) may provide rapid pain relief when other available therapies are ineffective or contraindicated. However, ACTH studies thus far have not provided robust trial designs and drug costs remain substantial, thus limiting its widespread use in acute gout [32, 33]. Anti-IL-1 agents or ACTH may both be considered as second-line options if first-line therapies are contraindicated or fail. Careful consideration should be given to their side effect profiles, patient preferences, and cost [34].

Case 2 A 62-year-old gentleman with a past medical history significant for obesity and hypertension presents to urgent care with a hot, red, painfully left first toe while on vacation in New England

during the summer. He does not take any medications and denies any recent trauma. He is not a diabetic. He arrived in New England 3 days ago for a family reunion in Cape Cod, and his symptoms started overnight after attending a family lobster and clambake, where he had several beers. He arrives at your office with one shoe off because he cannot let anything touch his toe because of the pain. He describes that last night he could not even have the sheet covering his toe. Bedside point of care ultrasound showed tophaceous deposits involving the right elbow and synovial aggregates in the 1st MTP. He had a history of hyperuricemia but never had a flare of gout. Treatment recommendations for hyperuricemia and gout were discussed given tophaceous deposits.

Treatment of the Hyperuricemic State

Long-term urate-lowering therapy (ULT) should be explained and discussed with all gout patients at diagnosis (Fig. 7.6 and Table 7.4). Current guidelines recommend ULT if a patient is getting regular attacks (>1 attack/year), has tophi, renal impairment, transplant-associated gout, or nephrolithiasis, or needs to continue on diuretics for heart failure [12]. Although most patients with gout exhibit renal underexcretion rather than overproduction of urate, the efficacy of and tolerability of xanthine oxidase inhibitors (XOIs) makes them the mainstay of ULT. Certain guidelines recommend that ULT should be started 1–2 weeks after the acute attack has subsided as a reduction in sUA may prolong the current episode or precipitate another attack. The 2020 American College of Rheumatology guidelines support ULT initiation during an acute attack of gout [12]. Patients on ULT who develop an acute attack should continue on it. ULT should be started at a low dose and gradually increased with monthly sUA measurements, aiming as sUA <6.0 mg/dL or <300 μmol/L [12].

Other day-to-day triggers such as alcohol, meat or seafood consumption, and dehydration exist for some gout sufferers. Patients should be informed of these inciting factors as they could potentially be avoided, reducing the risk of future gout attacks. It is important to recognize, however, that dietary or behavioral

Table 7.4 Prescribing and monitoring urate-lowering therapies

	Allopurinol	Febuxostat	Probenecid	Pegloticase
Dosing	50–900 mg daily (max is 800 mg daily, FDA-approved dose) dose should be titrated to sUA level	40–120 mg daily (max is 80 mg daily, FDA-approved dose) dose should be titrated to sUA level	500–1000 mg twice daily	8 mg IV every 2 weeks
Mechanism of action	Xanthine oxidase inhibitor: prevents urate production	Xanthine oxidase inhibitor: prevents urate production	Increases renal urate excretion	Recombinant uricase breaks down urate to water-soluble allantoin
Metabolism and excretion	Metabolized by aldehyde oxidase to oxypurinol, which is excreted primarily by the kidneys	Hepatic conjugation by uridine diphosphate glucoronysyl transferase enzymes and oxidation to active metabolites CYP1A2, CYP8C2, and CYP2C9; excreted via the kidneys	Oxidation of alkyl side chains and glucuronide conjugation; excreted via kidneys	Renal excretion
Monitoring	Serum uric acid, renal function, liver function	Serum uric acid, renal function, liver function	Serum uric acid, renal function	Serum uric acid

(continued)

Table 7.4 (continued)

	Allopurinol	Febuxostat	Probenecid	Pegloticase
Contraindications	Hypersensitivity to allopurinol	Use with caution in heart failure and ischemic heart disease (black box warning)	Blood dyscrasias, uric acid kidney stones	G6PD deficiency (hemolysis and methemoglobinemia) repeat infusions are contraindicated if serum urate response is lost
Clinically important drug interactions	Azathioprine increases 6-mercaptopurine concentrations, resulting in myelosuppression, warfarin (increased anticoagulant effect), diuretics (possible increased risk of allopurinol hypersensitivity syndrome)	Azathioprine increases 6-mercaptopurine concentrations, resulting in myelosuppression	Aspirin, methotrexate (can increase methotrexates' toxic effects)	Other urate-lowering drugs can mask lack of response to pegloticase and therefore increase the risk of infusion reaction; other PEGylated drugs
Special considerations	Dose escalation about 300 mg or above renal function to achieve sUA can be done taking careful consideration of renal and liver function and education about rash	Hypersensitivity may occur rarely in patients who have previously had allopurinol hypersensitivity	Advise about high fluid intake and consider urine alkalization to reduce the risk of kidney stones	Should not be used with other urate-lowering therapy

interventions have generally yielded only modest sUA reductions. For the vast majority of patients, therefore, reduction and maintenance of sUA ≤6.0 mg/dL requires ULT. As patients starting ULT are at risk of recurrent gout attacks called "mobilization flares," co-prescription of anti-inflammatory medication of colchicine or NSAIDs or COX-2 inhibitors or low dose prednisone (5–7.5 mg) for up to 6 months is required to prevent mobilization flares during the initiation of sUA-lowering therapy and maintained until treat-to-target sUA <6.0 mg/dL is achieved [12, 15]. Maintenance therapy includes chronic treatment with urate-lowering agents to control flares and ensure resorption of tophi. The most commonly used class of sUA-lowering drugs include (1) xanthine oxidase inhibitors (allopurinol and febuxostat), (2) uricosuric agents (probenecid, sulfinpyrazone, benzbromarone, and lesinurad), and (3) uricases (rasburicase and pegloticase) (Table 7.4 and Fig. 7.6).

Allopurinol

Allopurinol is a purine analog of hypoxanthine, and along with its active metabolite oxypurinol, it competitively inhibits xanthine oxidase, causing a decrease in the production of urate. The usual dose is 300 mg/day, generally starting at 100 mg/day and slowly increased over a period of weeks to achieve the target sUA level <6 mg/dL, which may require doses of up to 800 mg/day in some patients. Toxicities to allopurinol are not rare and include rash, pruritus, cytopenias, diarrhea, and fever with hypersensitivity syndrome (drug rash with eosinophilia and systemic (DRESS) syndrome, toxic epidermolysis, and Steven–Johnson syndrome), which remains a serious complication with mortality rates up to 20%, in those with renal failure and current diuretic use. HLA-B*5801 allele has a significant risk of severe allopurinol cutaneous reactions in Han Chinese, Korean, Thai, Japanese, European, and African American populations and may require testing [35]. Allopurinol dose adjustment to renal function is recommended by the recent ACR guidelines to avoid toxicity [12]. Allopurinol interferes with azathioprine metabolism through inhibition of xanthine oxidase, and co-administration results in higher serum levels of azathioprine associated with increased toxicity.

Febuxostat (Uloric)

Febuxostat, a thiazole carboxylic acid derivative that, unlike allopurinol, is a nonpurine selective inhibitor of xanthine oxidase, which is orally administered and undergoes hepatic metabolism. Febuxostat 40 mg/day is the recommended starting dose and increased to 80 mg/day if sUA level of <6 mg/dL is not achieved after 2 weeks. Febuxostat 80 mg was superior to allopurinol 300 mg in reducing sUA levels to <6 mg/dL in mild-to-moderate renally impaired subjects [36, 37]. Mobilization flares were very common, requiring concomitant anti-inflammatory prophylaxis as with allopurinol. During the phase 3 studies, mild transaminase elevations greater than 3 times the normal limit were observed in the febuxostat group [36]. Unfortunately, in 2017, the FDA issued a black box warning for febuxostat with an increased risk of death from heart-related deaths and all-cause mortality. Febuxostat still has a place in the treatment of gout in patients with mild-to-moderate chronic kidney disease and in those intolerant to allopurinol [12].

Uricosuric Drugs

The uricosuric agents (probenecid, sulfinpyrazone, benzbromarone, lesinurad) represent another class of sUA-lowering medications that act by inhibiting the urate transporter URAT1 at the tubules, thus raising the renal excretion of urate. In patients with a history of renal calculi, uricosuric drugs should be used with caution; alkalinization of urine and high urine volumes are required. Benzbromarone has been removed from the US and some European markets due to concerns of severe hepatotoxicity but is still available in some countries with restrictive use. Similarly, lesinurad is no longer produced in the United States. In difficult "allopurinol refractory" patients, the combined use of allopurinol, which decreases the local amount of urate formed, and a uricosuric drug, probenecid, by raising the renal urate clearance, may further decrease sUA levels effectively and is worth considering in refractory gout patients [12].

Fenofibrate and losartan have uricosuric effects and may be used as adjuncts to XOIs when otherwise indicated, although these drugs are not recommended by the ACR guidelines [12]. Of

these, fenofibrate 200–300 mg/day reduces sUA by approximately 100 μmol/L, while losartan 50 mg/day reduces sUA by 47 μmol/L with no further reduction at higher doses [38, 39].

Uricases (Rasburicase, Pegloticase)

The alternative approach to reduce sUA is the use of uricase, which mediates the conversion of uric acid into a more soluble molecule, allantoin, either in the form of rasburicase or pegloticase (PEGylated form) [40–42].

Rasburicase, a short-half-life uricase, has been used extensively for the prevention of tumor lysis syndrome and at a low dose of 0.15 mg/kg for compassionate use in patients with refractory gout. The largest series including five patients treated with monthly 0.2 mg/kg infusions [43] in the presence of severe renal function impairment showed sUA reduction.

Pegloticase is a recombinant porcine PEGylated uricase developed for the treatment of refractory gout [41, 42]. Pegloticase 8 mg administered IV every 2 weeks for 12–24 weeks showed the best results defined as sUA level <6 mg/dL for ≥80% of the time during 3–6 months and 45% of the patients had complete resolution of their target tophus compared with placebo (8%) during 6 months. The striking reduction of sUA level induced by pegloticase was associated with a high rate of gout flares (over 80% of patients) [41, 42], and the development of antibodies to pegloticase was associated with a lower rate of response and increased risk of adverse infusion reactions [44]. Knowledge of sUA preceding each pegloticase infusions and cessation of therapy when urate-lowering efficacy is lost (sUA is >6.0 mg/dL) provides a means of optimizing the safety of pegloticase in clinical practice [44]. The use of pegloticase infusions facilitates the debulking of chronic tophaceous gout in patients with chronic refractory gout with the objective of reducing the tophi burden carried by these patients [45].

Pitfalls and Pearls of Urate-Lowering Therapy (ULT)

- *Allopurinol is the preferred first-line agent for urate-lowering therapy in all patients, including those with moderate-to-*

severe CKD. Low-dose allopurinol (<100 mg per day and lower in patients with CKD 3) is recommended. Some patients require more than 300 mg allopurinol to reach treat-to-target sUA <6.0 mg/dL (Table 7.4 and Fig. 7.6).

- *Before prescribing allopurinol to patients of southeast Asian or African American heritage, check a HLA-B*5801 allele, as this allele is more common in these populations and has a strong association with allopurinol hypersensitivity syndrome.*
- *Febuxostat (<40 mg/day with subsequent dose titration) can also be used for gout in patients with CKD 3.*
- *When starting urate-lowering therapy, it is strongly recommended that concomitant anti-inflammatory prophylaxis with colchicine, NSAIDs, or prednisone is prescribed, and it should be continued for 3–6 months to reduce mobilization flares.*
- *Starting, stopping, and adjusting ULT can precipitate a "mobilization flare" or the need for bridge therapy when starting ULT.*
- *Mobilization flares reduce confidence in treatment effectiveness and decreases compliance with ULT.*
- *Treatment with urate-lowering therapy (ULT) is lifelong therapy.*
- *Educate patients that gout is "still there" between episodes of flares.*
- *Educate patients not to* stop *ULT therapy between flares as they feel better.*

Case 3 A 72-year-old woman with a past medical history significant for obesity, hypertension, and poorly controlled diabetes mellitus complicated by chronic kidney disease from diabetic nephropathy presents with an acutely red, hot, and swollen midfoot for which she cannot walk on. Her medications include Lantus, Humalog, Lisinopril, and a baby aspirin. She denies trauma to the midfoot. She had a diabetic foot infection 2 years ago, but she follows podiatry regularly and has no active wounds currently. A crystal diagnosis of gout was made; you are asked what treatment you can give her given her history of diabetic and chronic kidney disease.

For patients experiencing their first gout flare, initiating ULT is conditionally recommended against, but given that she has moderate-to-severe CKD (stage ≥3) in the setting of her diabetes, ULT should be started to prevent progression of gout and her renal disease. When initiating ULT, concomitant anti-inflammatory prophylaxis with either NSAIDs, prednisone, or colchicine should be prescribed and continued for 3–6 months. In diabetic gout sufferers, prednisone can still be used for acute attacks, along with closer blood sugar monitoring. Also, in patients who have CKD (CrCl <30), colchicine can be renally dosed, starting at 0.3 mg daily for prophylaxis and increasing the dose with close monitoring. For those gout patients on hemodialysis, colchicine at a dose of 0.3 mg two times a week with no supplement after dialysis is recommended.

Given monoarticular gout flare, diagnostic arthrocentesis was performed to exclude septic arthritis, and intra-articular steroid injections were administered to treat the pain and inflammation of the midfoot given diabetes.

Comorbidities, Contraindications, and Therapeutic Choice

Acute gout care, especially in the context of comorbidities, has been identified as a critical treatment concern by an international group of rheumatologists [12, 34]. However, frequently applied clinical trial exclusion criteria have limited data necessary to guide treatment when comorbidities are present. Therefore, acute gout treatment in the context of disease comorbidities represents a major unmet need in understanding and optimizing gout care.

Chronic Kidney Disease

Chronic kidney disease (CKD) is common in gout with 20% of gout sufferers having an estimated glomerular filtration rate (eGFR) of <30 mL/min [3, 4]. CKD is an important consideration when deciding on the best treatment modality for acute gout. The ACR recommendations do not provide specific guidance on

NSAID use in CKD but suggest the potential option of tapering the dose as the pain begins to resolve. There is mixed evidence that NSAIDs accelerate CKD progression with the best evidence for high-dose NSAID use [46]. The concomitant use of NSAIDs with other medications affecting kidney function is addressed below.

For colchicine, current labeling and evidence indicate that no dose adjustments are needed for stage 3 or better CKD (eGFR ≥60 mL/min), even among the elderly [47]. Though labeling indicates that a single unadjusted dose (0.6 mg) can be given once every 2 weeks for those with severe CKD (eGFR <30 mL/min) or on dialysis, alternative therapies should be considered as adverse events increase with decreasing renal function (92). Colchicine should not be used in those with eGFR <10 mL/min [48]. All CKD patients treated with colchicine should be informed of the side effects and closely observed for signs of toxicity, including blood dyscrasias, neuromyopathy, emesis, or diarrhea. Considering the potential complications for NSAIDs and colchicine, patients with CKD may be good candidates for glucocorticoid therapy, administered either systemically or as an intra-articular injection [12, 34]. Alternatively, second-line agents such as IL-1 inhibition, anakinra, may be considered in such patients [49].

Hypertension

Hypertension is one of the most common comorbidities among gout sufferers and is an important consideration when deciding on treatment. Poorly controlled hypertension is a relative contraindication for both NSAIDs and systemic glucocorticoids. Patients with hypertension in the absence of significant renal impairment may be good candidates for colchicine. The ACR 2020 gout guidelines recommend switching hydrochlorothiazide to alternate antihypertensive agents (preferably losartan) regardless of disease activity [12].

Diabetes Mellitus and Hyperlipidemia

Glucocorticoids should be avoided if possible in the setting of inadequately controlled diabetes mellitus or hyperlipidemia. Glucocorticoids exacerbate insulin resistance and stimulate glu-

cose secretion from the liver. This can create substantial and sometimes dangerous fluctuations in circulating glucose concentrations. Additionally, glucocorticoids may increase serum triglycerides and low-density lipoprotein (LDL) levels. Thus, patients with diabetes mellitus or hyperlipidemia may be good candidates for alternative treatments such as colchicine or NSAIDs. In regard to combined chronic management, per the ACR 2020 gout management guidelines, fenofibrate, despite its urate-lowering effects, should not be used instead of other cholesterol-lowering medications [12].

Cardiovascular Disease

COX-2 inhibitors have been shown to increase cardiovascular disease (CVD) risk, and this risk may be present for all NSAIDs. Current FDA labeling suggests limiting NSAID and COX-2 inhibitor use in patients with a history of myocardial infarction, congestive heart failure, or stroke, among others. Given the potential impact on cardiovascular risk factors, including hypertension, diabetes, and hyperlipidemia, glucocorticoids may not be ideal for patients with known CVD or those at high risk. Per ACR 2020 gout management guidelines, patients should also be maintained on low-dose aspirin if they have an indication for it. Recent evidence has shown that colchicine use is associated with a lower risk of myocardial infarction among gout patients [50]. These results, in addition to a proposed dual role of IL-1 in both gout and CVD [51], suggest that either colchicine or IL-1β inhibitors may be rational agents in the treatment of acute gout in the context of CVD. Recently, the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) has provided convincing evidence that an anti-inflammatory intervention reduces cardiovascular events and reduced the risk for incident gout flares across all levels of baseline sUA in well-treated CAD patients [52].

Hepatic Impairment and Gastrointestinal Bleeding

Patients with cirrhosis should avoid NSAID use due to the potential for increased bleeding risk from underlying coagulopathy. Additionally, colchicine clearance may be reduced in patients with severe liver impairment, mandating close surveillance when

this agent is used. If hepatic impairment is mild to moderate, judicious use of any of the first-line therapies may be appropriate. Patients with gastrointestinal bleeding or a history of peptic ulcer disease should avoid NSAIDs and may benefit from COX-2 inhibitors such as Celebrex. If an NSAID or Celebrex is used, proton-pump inhibitors may be used concomitantly to further decrease the risk of mucosal damage.

Drug Interactions

Colchicine is metabolized by CYP3A4 and is a substrate for p-glycoprotein. Therefore, concomitant use of colchicine with potent inhibitors of CYP3A4 or P-glycoprotein should be avoided when possible. These agents include macrolide antibiotics (clarithromycin), calcium channel blockers (verapamil and diltiazem), and cyclosporine (commonly used in transplant patients who are at high risk for gout). New evidence-based dosing recommendations indicate that no dose reduction is required with azithromycin [53].

NSAIDs are contraindicated with the concomitant use of ACE inhibitors and/or diuretics. NSAIDs decrease prostaglandin production resulting in increased constriction of afferent renal arterioles and decreased glomerular filtration pressure. This physiologic effect of NSAIDs can be exacerbated when used in combination with ACE inhibitors or diuretics, both of which can also reduce glomerular filtration pressures. Combination therapy increases the risk for NSAID-mediated acute kidney injury. Additionally, NSAID use should be avoided in patients taking anticoagulants such as warfarin or heparin due to increased bleeding risk.

When to Refer to the Rheumatologist

Patients with gout rarely need a rheumatologic referral. There are specific situations when a referral is justified: difficult to aspirate joints, gout with onset below the age of 30, therapeutic guidance in patients with organ failure, treatment of polyarticular gout, and treatment of chronic refractory gout are among the most common reasons for referral.

Pitfalls and Pearls of Comorbidities

- *Gout is associated with metabolic syndrome, and patients should always be screened for obesity, diabetes mellitus, hypertension, hyperlipidemia, and cardiovascular disease.*
- *Comorbidities that put patients at bigger risk for developing gout and also complicate treatment management.*
- *Some medications can worsen or cause hyperuricemia due to decreased renal excretion of urate. These medications include cyclosporin, nicotinic acid, thiazide diuretics, tacrolimus, loop diuretics, ethambutol, aspirin, pyrazinamide, and alcohol.*
- *When managing a patient with gout, it's important to make other medication choices wisely. It is recommended to switch hydrochlorothiazide to an alternate antihypertensive, preferably losartan in patients with gout regardless of disease activity. It is also recommended against using fenofibrate despite its urate-lowering effects as the risks and side effects outweigh the benefits.*
- *Patients on azathioprine or mercaptopurine should not be started on allopurinol, as this combination leads to life-threatening bone marrow toxicity.*

Calcium Pyrophosphate Deposition Disease (CPPD)

Calcium pyrophosphate deposition disease (CPPD) is characterized by acute attacks of pseudogout, unusually degenerative joint changes, plus the presence of systemic chondrocalcinosis on X-rays. Calcium pyrophosphate (CPP) crystals deposit in both articular tissues (predominantly hyaline cartilage and fibrocartilage) and periarticular soft tissues [54, 55]. CPPD may be asymptomatic or be associated with a spectrum of clinical syndromes including both acute and chronic inflammatory arthritis [55]. The European League Against Rheumatism (EULAR) suggested changes in CPPD terminology [55].

According to the EULAR classification, pseudogout or CPPD has been reclassified based on new key terms that include several of the previously described disease phenotypes: asymptomatic CPPD; acute CPP-crystal arthritis (previously known as pseudogout); osteoarthritis (OA) with CPPD (previously, pseudo-OA) (Fig. 7.7b); and the chronic CPP-crystal inflammatory arthritis (previously, pseudo-rheumatoid arthritis) (Fig. 7.7a). Chondrocalcinosis (CC) refers to calcification of the fibrocartilage and/or hyaline cartilage identified by imaging or histological analysis. Although CC is most commonly seen in CPPD, it is not exclusive to this disease as can be seen in other crystal diseases (oxalosis, BCP) and appears as a casual finding or coexists with OA [55].

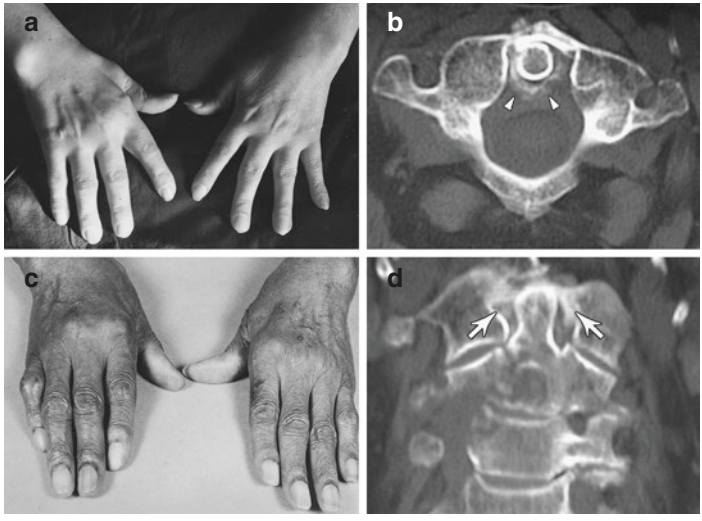

Fig. 7.7 Clinical presentations of CPPD. (**a**) Pseudo-rheumatoid arthritis with ulnar deviation, interosseous muscle atrophy, and metacarpophalangeal and wrist involvement. (**b**) Pseudo-arthritis. (**c, d**) Crowned dens syndrome with calcification around the dens. Axial (**c**) and reformatted coronal (**d**) CT scan images at C1–C2 level with calcification of transverse ligament (arrowheads) and surrounding odontoid process (arrows)

Presentation and Progression

Cause

The cause of CPPD is in most cases unknown. There are familial forms of the disease that may occur in isolation or with epiphyseal dysplasia. An association has been described with osteoarthritis (OA), hyperparathyroidism, renal insufficiency, hemochromatosis, and rare disorders such as Gitelman's syndrome and hypophosphatasia (Table 7.5). The incidence of chondrocalcinosis increases with various factors, such as trauma, but is most closely linked with advanced age and osteoarthritis (OA). Radiographic surveys of the knees, hands, wrists, and pelvis have demonstrated an age-related increase in the prevalence of calcium pyrophosphate deposition according to age: 15% prevalence between ages 65 and 74, 36% prevalence between ages 75 and 84, and 50% prevalence in patients greater than 84 years of age [56–59].

Presentation

In clinical practice, CPPD may present with several phenotypic forms. In asymptomatic CPPD, CC is a common radiographic finding without clinical symptoms. Acute CPP arthritis should always be suspected in any patient >65 years of age presenting with an acute monoarticular or oligoarticular arthritis, migratory

Table 7.5 Conditions associated with calcium pyrophosphate deposition disease

Aging
Familial/epiphyseal dysplasia
Osteoarthritis
Hyperparathyroidism
Hemochromatosis
Hypomagnesemia
Hypophosphatasia
Gitelman's syndrome
Familial hypocalciuric hypercalcemia
Neuropathic joints

or additive, symmetrical, or polyarticular arthritis [55, 60]. Acute CCP arthritis is characterized by self-limited acute or subacute attacks of arthritis involving one or several extremity joints (knees, wrists, ankles, and rarely affects the large toe). Typically, the acute attacks last 7–10 days. Several unusual sites (e.g., the hip joints, trochanteric bursa, and deep spinal joints) may also be affected. However, differences in the pattern of joint involvement are insufficient to permit definitive diagnosis without demonstration of the specific crystal type in the inflammatory joint fluid.

Pseudogout attacks closely resemble gouty arthritis; CPP arthritis presents as intermittent flares and often is asymptomatic between flares. Trauma, surgery, or severe medical illness frequently provokes attacks of monosodium urate (MSU) as well as acute CPP arthritis. Systemic findings such as fever, leukocytosis with a left shift in the differential count, elevated sedimentation rate (ESR), and C-reactive protein (CRP) can also occur, resembling pyogenic arthritis, osteomyelitis, and/or systemic sepsis in the elderly patient. Diagnosis must be confirmed with aspiration, Gram stain and cultures of the synovial fluid, and evaluation for the presence of CPP crystals under polarized light microscopy [9, 55]. The diagnosis can be difficult to confirm secondary to the weakly birefringent nature of CPP crystals making the diagnosis even more elusive (Fig. 7.1) [9]. Coexistence of MSU and CPP crystals in a single inflammatory effusion is neither uncommon nor unexplained given increased frequencies of both hyperuricemia/gout and chondrocalcinosis among elderly patients [61]. Chronic CPP crystal inflammatory arthritis may present as a chronic, symmetrical, bilateral, and deforming polyarthritis (Fig. 7.7a, b). It frequently affects the wrists and metacarpophalangeal joints and tendon sheaths. It may resemble rheumatoid arthritis (RA) and produce wrist tenosynovitis, which may manifest as carpal tunnel syndrome and/or cubital tunnel syndrome. Chronic CPP arthritis should always be on the differential diagnosis in the elderly patient presenting with a clinical picture that resembles “sero-negative” rheumatoid arthritis, with morning stiffness, synovial thickening, localized edema, and restricted motion due to active inflammation or flexion contracture of the hands/wrist (Fig. 7.7a). They may present with prominent sys-

temic features such as leukocytosis, fevers, mental confusion, and inflammatory oligo or polyarthritis. The diagnosis of chronic CPP arthritis may still be possible even if the rheumatoid factor (RF) is positive, given the increasing likelihood of elevated RF in the older population. In this setting, aspiration of joint fluid and radiography will assist in the clarification of the diagnosis. Furthermore, CPPD typically does not cause the type of erosive disease that is often seen in RA.

CPP arthritis can also mimic polymyalgia rheumatica (PMR). A direct comparison of a cohort of pseudo-PMR (PMR/CPPD) patients with actual PMR patients found that increased age at diagnosis, presence of knee osteoarthritis, tendinous calcifications, and ankle arthritis carried the highest predictive value in CPPD patients presenting with PMR-like symptoms [62]. However, the PMR/CPPD variant can be difficult to distinguish because both conditions can have elevated systemic inflammatory markers and both are steroid responsive.

CPPD involving a single joint can rarely lead to extensive destruction—as with neuropathic joints in the absence of any neurological deficits and is extremely debilitating. This presentation is not well understood and does not have good treatment alternatives. CPP crystals are often associated with manifestations of OA. Indeed, up to 20% of OA joints have been found to be positive for CPP crystals in various studies. Given the extensive evidence supporting treatment of OA, they are usually treated in a similar fashion with good results. Occasionally, these will have unusual manifestations for typical OA—such as involvement of wrists and MCP joints; however, the presentation is often indolent like OA (Fig. 7.7b).

CPP crystal deposition involving the spine has been associated with a number of clinical manifestations. Spine stiffness, sometimes associated with bony ankylosis, can resemble ankylosing spondylitis or diffuse idiopathic skeletal hyperostosis (DISH). Such symptoms are more commonly seen in familial CPPD deposition disease rather than in the elderly. However, crystal deposition in the ligamentum flavum at the cervical spine levels has been associated with a condition called crowned dens syndrome (Fig. 7.7c, d) [63]. Although mostly asymptomatic, it may be

present with acute neck pain, fever, and an increased ESR, sometimes mimicking PMR or giant cell arteritis (GCA) or neurological symptoms. Similarly, CPP crystal deposition in the posterior longitudinal ligament at the lower levels of the spine may lead to spinal cord compression syndromes or symptoms of either acute nerve compression or chronic spinal stenosis [64, 65]. CPP crystal deposition can also occur in other soft tissues such as bursae, ligaments, and tendons and may be sufficient to cause local nerve compressions, such as carpal or cubital tunnel syndrome [66–69].

Chronic hypomagnesemia, hypophosphatemia, hypothyroidism, and hemochromatosis have been linked to chondrocalcinosis and pseudogout (Table 7.5). In general, patients greater than age 55, newly diagnosed with CPPD, do not need extensive evaluation for alternate metabolic causes unless there are other indications to do so. On the other hand, hyperparathyroidism and hypothyroidism tend to occur in older populations, and it has been recommended that all patients with chondrocalcinosis should be screened despite age [66]. In addition to age, familial and metabolic syndromes provide a predisposition for CPPD disease. In the familial form, a gain-of-function mutation for the multipass transmembrane protein, ANKH, results in an increase in the transport of inorganic pyrophosphate from the cell. Patients with ANKH mutations are more likely to have early-onset CPPD disease [70]. Similarly, patients with Gitelman's disease, an inherited renal tubular disorder resulting in hypomagnesemia, hypokalemia with normal or high urinary potassium excretion, hypocalciuria, and normal blood pressure, may develop CPPD disease [66].

Osteoarthritis and CPPD Disease

CPPD and osteoarthritis are both prevalent in the elderly and may potentially be connected [71]. The exact role of CPPD in the pathogenesis of OA remains controversial. Thus far, it has been difficult to conclude if crystals preferentially form in damaged cartilage or if crystals cause changes that lead to osteoarthritis, or if the processes are unrelated.

Patients who received knee replacement surgery were found to have a 25–43% incidence of CPP crystals in synovial fluid [72–74]. Positive correlations between the presence of CPPD/chondrocalcinosis and osteophytes have been identified as well [73, 75]. Evaluation of the Boston Osteoarthritis Knee Study (BOK) and the Health, Aging, and Body Composition (Health ABC) Study suggested that there is a protective association between chondrocalcinosis and cartilage loss [76]. However, most studies claim that calcium crystals are linked to the cause of OA or that they worsen OA [72, 74]. Cadaveric evaluations of 7855 tali within 24 hours of death have linked joint destruction of the ankle to the presence of CPPD and BCP crystals. The ankle joint was evaluated because osteoarthritis of the ankle joint is relatively uncommon. This study also confirmed crystals to be more common with advanced age [77, 78]. Additional support between OA and CPPD disease has come from pyrophosphate arthropathy. In contrast to OA, pyrophosphate arthropathy involves atypical joints such as elbows, wrists, and shoulders. Patients with familial forms of CPPD have exemplified this relationship because they develop severe and premature degenerative arthritis in atypical joints not commonly involved in OA [79].

Precipitators of Acute Pseudogout in the Elderly

Diuretics are known to exacerbate gout, but they can also exacerbate pseudogout. Additionally, the incidence of chondrocalcinosis increases with chronic diuresis. It is hypothesized that both loop and thiazide diuretics inhibit magnesium reabsorption by the renal tubules and can lead to hypomagnesemia and subsequent CPPD disease [78]. This is of particular interest in the aging population as hydrochlorothiazide (HCTZ) is a common first-line antihypertensive agent and the elderly are more prone to congestive heart failure that requires chronic diuresis with loop diuretics.

In addition, multiple case reports have described pseudogout caused by bisphosphonate administration. Intravenous pamidronate, oral etidronate, and alendronate therapy have all been

described in the elderly [80–82]. The overall mechanism behind this link is not completely understood, but bisphosphonates are structurally similar to pyrophosphates. Clearly, the elderly population is more likely to require treatment with bisphosphonates for osteoporosis or diseases such as Paget's disease.

Isolated and recurrent episodes of acute pseudogout have been associated with joint injections of hyaluronate [83, 84]. The mechanism of action is unknown; it has been speculated that phosphate present in the hyaluronate preparation may lower calcium concentrations, leading to CPPD crystal shedding in patients with chondrocalcinosis. A similar phenomenon has been described with hypocalcemia following parathyroidectomy [85, 86]. Pseudogout attacks have also been described in neutropenic patients undergoing treatment with granulocyte colony-stimulating factor [87, 88].

In addition to pharmaceutical exacerbation of pseudogout, surgical procedures and trauma can precipitate attacks. Joint lavage has been described to increase the incidence of pseudogout [89]. They hypothesized that joint lavage with fluid induced "crystal shedding" from CPP crystals imbedded in the joint tissue. Patients who underwent meniscectomy of the knee 20 years ago had a 20% incidence of chondrocalcinosis in the knee that was operated compared to 4% chondrocalcinosis in the contralateral nonoperated knee [90]. Overall, the surgery most linked with an acute CPP arthritis attack is parathyroidectomy [78, 85]. However, the incidence of chondrocalcinosis or pseudogout attacks after parathyroidectomy has not been described.

Case 4 A 60-year-old female veteran presents with a 4-month history of pain in the right wrist, some bony changes of knuckles, and swelling in her right wrist. She has never had a diagnosis or gout or a red hot or swollen joint. Physical examination demonstrated OA of the hands, bony changes in the 2nd and 3rd MCPs, and positive grind test of the first left CMC. X-rays showed joint space narrowing of the 2nd and 3rd MCP and chondrocalcinosis of the right wrist. Bedside ultrasound showed hyperechoic signal within the right triangular fibrocartilage and synovitis of the left

wrist consistent with monoarticular inflammatory arthritis. The right wrist was aspirated, yielding a small amount of turbid fluid, which on examination under a light compensated polarized microscope showed poorly birefringent, rhomboid crystals consistent with CPP crystals (Fig. 7.8). The patient was admitted to the hospital and treated with 30 mg prednisone taper out over a two-week period and transition to colchicine 0.6 mg po BID. Metabolic workup failed to demonstrate hypomagnesemia, hyperparathyroidism, chronic kidney disease, and vitamin D deficiency. However, joint space narrowing of the 2nd and 3rd MCP raised the suspicion of hemochromatosis. She had normal iron and ferritin levels but was found to be heterozygous for H63D gene for hemochromatosis.

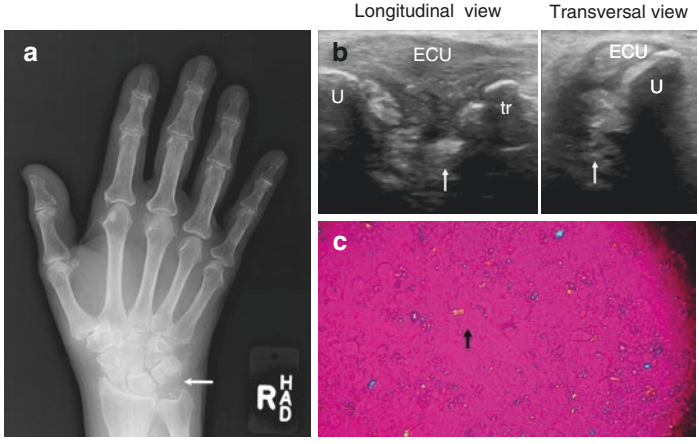

Fig. 7.8 Case 4. (**a**) X-rays of the right wrist showing joint space narrowing of the 2nd and 3rd MCP with chondrocalcinosis of the triangular fibrocartilage complex (TFCC) (arrow). (**b**) Ultrasound of the right wrist showing hyperechoic signal (arrows) within the TFCC consistent with chondrocalcinosis seen in both longitudinal and transverse views. (**c**) Synovial fluid from the right wrist confirming the presence of rhomboidal shape CPP crystals. (black arrow: direction of polarized light). ECU extensor carpi ulnaris, U ulna, tr triquetrum

Diagnosis

Demonstration of CPP crystals in synovial fluid or tissue by compensated polarized light microscopy is considered the "gold-standard" (Fig. 7.1) [9, 55]. The presence of chondrocalcinosis on radiographic evaluation of affected joint(s) (Fig. 7.9) is also highly suggestive of CPPD arthropathy. CPP crystals have a characteristic rhomboid shape that display weakly positive birefringence under polarized light microscopy obtained from tissue and/or synovial fluid. The sensitivity and specificity for CPP-crystal detection in the synovial fluid have been shown to be 95.9% and 86.5%, respectively [90]. However, the CPP crystal is more readily identified by rheumatologists rather than standard hospital laboratories, which miss 30% of CPP crystals [91].

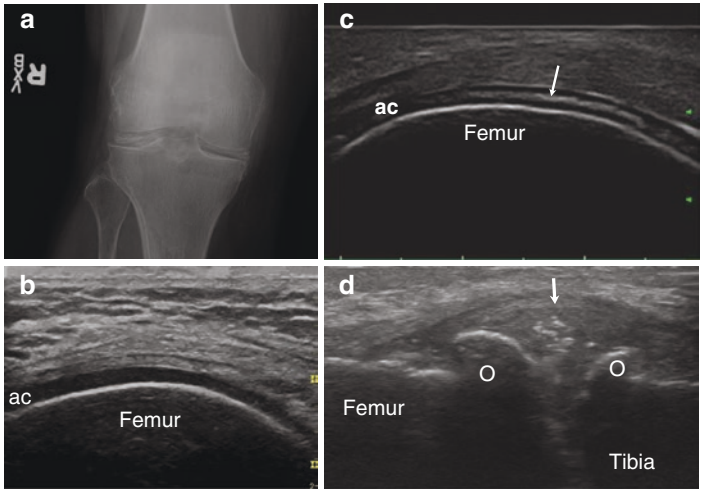

Fig. 7.9 Musculoskeletal images of pseudogout. (**a**) Chondrocalcinosis of the meniscus seen on conventional radiography of the knee. (**b**) Normal musculoskeletal ultrasound of the articular cartilage (ac) with characteristic anechoic signal within the cartilage. (**c**, **d**) Musculoskeletal ultrasound image of the knee. The presence of CPP crystals is seen as hyperechoic enhancement in the intermediate layer of the articular cartilage (arrows) with characteristic features as "beads in a rosary" (**c**) and hyperechoic aggregates of the medial meniscus (arrow) with osteophytes (o) (**d**) characteristic of CPPD disease. ac cartilage

Findings of CC on radiograph strengthens a CPPD diagnosis, but its absence does not rule it out [55]. More recently, the use of point-of-care ultrasound has improved the capacity to visualize CPP-crystal deposits within the joint structures, the hyaline cartilage, and/or fibrocartilage (Fig. 7.9) [92]. The presence of hyperechoic bands within the intermediate layer hyaline cartilage and hyperechoic spots in fibrocartilage (meniscus) is consistent with CPP-crystal deposits (Fig. 7.9c, d) [55, 92]. Deposition within the intermediate layer of the hyaline cartilage with hyperechoic enhancement resembles "beads in a rosary" [93]. These ultrasonographic changes seen in the intermediate hyaline cartilage precede the radiographic changes seen in chondrocalcinosis. Ultrasound may prove an alternative method for diagnosis of gout or pseudogout, and in some cases, it may preclude the need for synovial fluid analysis. However, the limitations of ultrasound are that it cannot differentiate the type of tophi deposition and/or exclude infection requiring diagnostic arthrocentesis. Studies have demonstrated the clinical usefulness of ultrasound in the diagnosis and management of gout or pseudogout; however, further long-term studies are needed to establish its role in crystal-induced arthropathies. The use of computed tomography is the gold-standard imaging modality for the identification of CPPD of the spine (Fig. 7.7c, d) [93]. There is limited evidence to support the use of MRI in the diagnosis of CPPD disease, but it may play a role in rare complications [55].

Natural History

The natural history of CPPD varies with the clinical form. Pseudogout attacks are self-limited. In some cases, attacks may recur in the same or other joints causing significant morbidity. In most cases, however, CPPD behaves as a slow progressive degenerative joint condition. Whether acute flares accelerate joint deterioration has not been determined. In the rare pseudo neuropathic forms, joint destruction is abrupt.

Treatment

The management of an acute pseudogout attack (Fig. 7.10) is quite similar to that of gout. The EULAR recently defined new guidelines for the management of CPPD [94], which state that asymptomatic CPPD needs no treatment. In other CPPD phenotypes, the goals are to attempt prompt resolution of the acute synovitis, reduction in chronic damage, and management of associated conditions. In acute attacks, treatment modalities used in gout are often required; however, data in CPPD treatment is limited (Fig. 7.10). Treatment relies on the use of colchicine and NSAIDs, but their use is limited by toxicity and comorbidities in the elderly. Given increased renal impairment, the loading dose of colchicine is not recommended [47, 48]. Colchicine has recently been shown to completely block crystal-induced maturation of

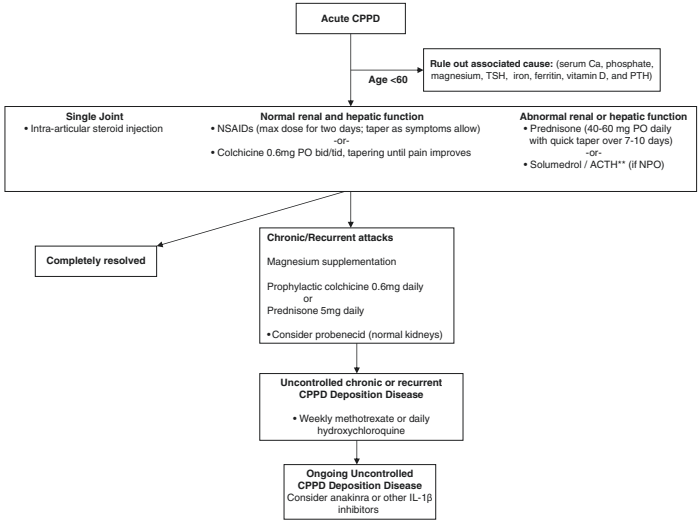

Fig. 7.10 Proposed algorithm for the management of pseudogout. ** Solumedrol, 100–150 mg/day; corticotropins, 25–40 USP units SC/IM or IV once. NSAIDs nonsteroidal anti-inflammatory drugs, PO by mouth, IV intravenous, IM intramuscular, USP United States Pharmacopedia, SC subcutaneous

IL-1β in vitro, indicating that the drug acts upstream of inflammasome activation [95]. This is in addition to the well-known role of colchicine in inhibition of microtubule formation, likely leading to prevention of the endocytosis of crystals and/or presentation to inflammasome. Intra-articular injection of corticosteroid is an efficient and well-tolerated treatment alternative for monoarticular CPP flares. Oral or parenteral corticosteroids are frequently used for polyarticular flares, in particular, those patients in whom NSAIDs and colchicine are contraindicated [47, 48]. Parenteral ACTH has been used in patients with congestive heart failure, renal insufficiency, gastrointestinal bleeding, or resistance to NSAIDs [87]. For prophylaxis of acute CPP crystal arthritis, a low dose of oral NSAIDs, oral colchicine, or prednisone may be used with good results [94]. In chronic CPP arthritis, continuous use of colchicine, NSAIDs, or low-dose prednisone is frequently appropriate. If these interventions are ineffective or contraindicated, hydroxychloroquine (HCQ) and methotrexate (MTX) have been successfully employed to control chronic CPP-crystal inflammation [96, 97]. Recent trials have raised questions about MTX [98], and further trials on HCQ usage are underway. Biological agents targeting IL-1 are not currently approved for the treatment of CPPD, but there are suggestions that it may be effective in refractory cases and induce rapid stable remissions after 3 days of therapy [99, 100].

In contrast to gout, there is no specific target therapy for lowering CPP-crystal load in the elderly. Crucial in the management of CPPD in the elderly is the search for associated diseases, such as hyperparathyroidism, hemochromatosis, hypomagnesemia [94], and hypophosphatemia, as well as avoidance of tacrolimus, which facilitates or causes chondrocalcinosis. Correction of the underlying metabolic disorder, especially when undertaken early, may reduce the severity of CPPD. However, there is little evidence to suggest that treatment of associated disease results in resolution of CPPD—most famously, while therapeutic phlebotomy does not help in hemochromatosis for prevention of crystal disease, chelating agents seem to be moderately effective [101]. Only oral administration of magnesium has shown a reduction in meniscal CC in a patient with chronic CPP arthropathy [102]. In addition,

this was in the setting of familial hypomagnesemia associated with CPPD. However, unlike uricosuric agents for gout, no pharmacological treatments can prevent CPP-crystal formation or dissolution in tissues.

Agents That May Prevent Crystal Formation and Deposition in CPPD

Magnesium

Magnesium is a cofactor for the activity of pyrophosphatases that converts inorganic pyrophosphates into orthophosphates. In addition, it can increase the solubility of CPP crystals. Early detection and management of hypomagnesemia are recommended because it occurs in patients who have well-defined conditions and situations: Gitelman's syndrome, thiazide and loop diuretics use, tacrolimus use, familial forms of renal magnesium wasting or use of proton pump inhibitors, short bowel syndrome, intestinal failure in patients receiving home parenteral nutrition, and chronic use of proton pump inhibitors [102–104]. Long-term administration of magnesium in some patients with chronic hypomagnesemia decreased meniscal calcification [101].

Dietary Calcium

Epidemiological studies showed a lower incidence of chondrocalcinosis in Chinese subjects. The authors speculated that this lower prevalence of CPPD could result from high levels of calcium found in the drinking water in Beijing, which may affect parathyroid hormone secretion. Further studies are needed to confirm this hypothesis, as it could be a cheaper approach to pseudogout prevention [105].

Probenecid

Probenecid is an in vitro inhibitor of transmembrane pyrophosphate transporter thought to possibly prevent extracellular pyrophosphate elaboration. However, this observation has not been confirmed by either case reports or clinical trials [106].

Phosphocitrate

Phosphocitrate acts directly on preventing crystal deposition in tissues in CPPD as well as BCP based on in vitro evidence as well as mouse models [107, 108].

Hyaluronan

Amelioration of pain and increased range of motion (ROM) were observed in radiographic CC with OA (168). However, it is associated with increased acute CPP arthritis [84, 109].

Radiosynovectomy

In one double-blind study of 15 patients with symmetrical CPPD arthropathy, the knee that underwent intra-articular injection of yttrium-90 (5 mCi) plus steroid had less pain, stiffness, joint line tenderness, and effusion compared to the contralateral control knee injected with saline and steroids [110].

When to Refer

Chondrocalcinosis is found serendipitously in an older individual, clinical OA is associated with chondrocalcinosis, and pseudogout should be handled by the primary care. Early-onset chondrocalcinosis and cases of recurrent pseudogout, OA with osteochondral bodies, pseudo-RA, pseudo-AS, and rare destructive arthropathy should require rheumatologic evaluation.

Pearls and Pitfalls of CPPD

- *Acute CPPD is called "pseudogout" and causes acute, red, hot, swollen, and painful joints. It is commonly mistaken for cellulitis. Also with the addition of fever and malaise to the patients' symptoms, CPPD can be mistaken for a septic joint.*
- *CPPD deposition usually only occurs after 50 years of age, and patients with CPPD who are younger than that should be worked up for metabolic diseases.*
- *If a patient presents with CPPD and is younger than 50 years old, it is recommended to check calcium, phosphorus, magnesium, ferritin, iron, TIBC, renal function, and ALP.*

- *CPPD is an important diagnosis to consider in older patients who present with headaches, neck pain, and PMR-like symptoms or seronegative RA.*
- *The biggest risk factors for CPPD are age and OA.*
- *For the diagnosis of CPPD, fluid analysis should show CPP crystals within cells under polarized light microscopy. Point-of-care ultrasound shows chondrocalcinosis in the TFCC and hyaline cartilage.*
- *Acute pseudogout in the wrist of an elderly person can cause carpal tunnel, and CPP crystal deposition in the cubital tunnel can cause cubital tunnel syndrome.*
- *Patients with CPPD classically do not have frequent flares and therefore do not require prophylaxis for pseudogout. They may require a low dose of colchicine (0.6 mg) once or twice a day to reduce CPPD flares.*

Basic Calcium Phosphate (BCP) Crystal Deposition Disease

Basic calcium phosphate crystal deposition disease has a predilection for tendons, ligaments, and fasciae. The crystal species involved are a rare heterogeneous group of calcium crystals, including carbonated substituted apatite, octacalcium phosphate, tricalcium phosphate or whitlockite, and dicalcium phosphate dihydrate (brushite).

Presentation and Progression

Cause

The cause of BCP crystal deposition is unknown, but trauma and overuse may be the ground for calcification. An additional cause may be ischemia since BCP crystals deposit preferentially in avascular, hypoperfused tendons. The inflammation occurs from crystal phagocytosis and IL-1β release. In cases of cortical bone

erosion, mononuclear cell phagocytosis of the apatite crystal may result in prostaglandin and metalloproteinases release, causing bone resorption.

Basic calcium phosphate (BCP) crystals are common but rarely diagnosed due to the cumbersome and expensive methods required to identify the crystals [111]. BCP crystals are unable to be identified by light microscopy unless they congregate into clumps that can appear as a stack of "shiny coins." Multiple techniques, including X-ray diffraction and electron microscopy with energy dispersive analysis, have been shown to be specific for BCP crystal identification; however, the expense and technical knowledge required to conduct these techniques are prohibitive. Similarly, BCP crystals can be identified with alizarin red S stain but are performed in only specialized rheumatological centers and has a high degree of false positives (Fig. 7.1) [112]. BCP and CPPD crystals may coexist in synovial fluid [111]. Similar to CPPD disease, BCP crystal disease is often concurrent with osteoarthritis and can cause calcification of articular cartilage [113]. BCP is more common than CPP crystals with an occurrence of 30–50% in OA synovial fluid [113]. Additionally, BCP crystal disease has been linked to increased severity of OA. BCP crystals in knee joints were found to have radiographically more severe arthritis with larger effusions [71, 113]. Similarly, BCP crystals in OA synovial fluid correlated with higher Kellgreen Lawrence grade scores by radiography [71].

Case 5 A 39-year-old male presents with acute, severe pain involving the right shoulder after playing tennis. He had X-rays of the right shoulder that showed calcific tendinopathy. Bedside ultrasound showed hyperechoic material with posterior acoustic shadowing on the supraspinatus tendon consistent with calcific tendinopathy. He failed a course of NSAIDs, physical therapy, and two courses of intra-articular corticosteroid injection of the right shoulder, and only needling and barbotage of the calcific tendon improved pain and ROM (Fig. 7.11).

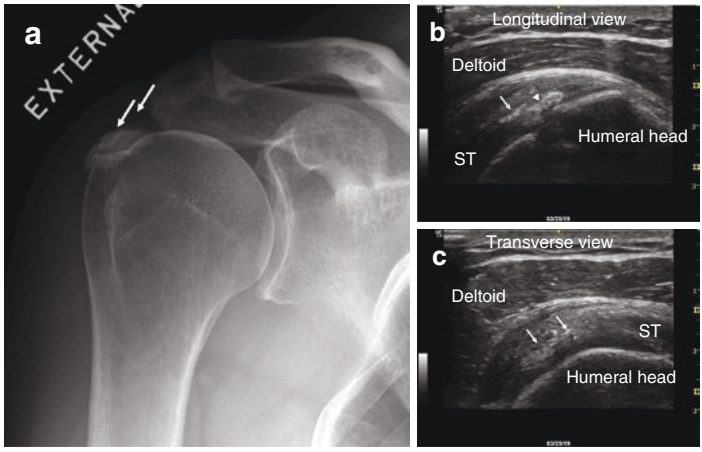

Fig. 7.11 Case 5. (**a**) Conventional radiography of the right shoulder showing calcific tendonitis. (**b**, **c**) Point-of-care ultrasound of the supraspinatus tendon on both longitudinal (**b**) and transverse (**c**) views showing hyperechoic aggregates (arrows) and thicker aggregates with posterior acoustic shadowing (arrowhead) consistent with calcific tendonitis of the rotator cuff tendon

Presentation

Acute calcific tendinitis is the usual presentation of BCP crystal deposition disease. Typically, involved areas include the rotator cuff tendon, extensor carpi ulnaris, flexor carpi radialis at the wrist, the iliopsoas tendon as it inserts in the lesser tuberosity, and toe tendons (young women's podagra). Acute calcific periarthritis of the hand presents similar to gout or pseudogout affecting the wrist, usually in postmenopausal women [114]. Paradiaphyseal deposits occur near the linea aspera of the femur. Milwaukee shoulder syndrome is an arthropathy associated with BCP crystals in the joint fluid and results in extensive destruction of shoulder articular cartilage and surrounding tissues. It is commonly bilateral and occurs in elderly women more than men [115]. Aspiration of the shoulder joint typically reveals a serosanguinous fluid. Fluid samples can be assessed for hydroxyapatite crystals by staining with alizarin red dye, which produces a characteristic

"halo" or orange-red stain by light microscopy (Fig. 7.1) [112]. Surgical treatment of Milwaukee shoulder is difficult due to the increased age of the population affected and the severity of the shoulder destruction. Usually, a conservative approach of analgesics, recurrent shoulder aspirations, and steroid injections are the best treatment option.

Diagnosis

Clinically, acute calcific tendinitis causes excruciating pain and pain-induced paralysis. Radiographically, there is amorphous calcification at the involved tendon or site and effusion, with or without calcium spillage in adjacent bursae. Similarly, point-of-care ultrasound shows hyperechoic aggregates in the affected tendon or site with or without posterior acoustic shadowing. Rarely, multicentric calcific tendinitis in which recurrent episodes of calcific periarthritis occur at various sites may have a familial predisposition. Polarized microscopy does not identify BCP crystals. Using alizarin red stain, BCP crystals may be identified in synovial fluid with an ordinary microscope [112].

Expected Outcome

Like all crystal-induced arthritis, it is a self-limited process, lasting from days to weeks before symptoms resolve. Rapid control of inflammation can be achieved with similar anti-inflammatory agents used for gout or pseudogout. Within months to years, most of the amorphous calcifications spontaneously dissolve. Bone erosions adjacent to paradiaphyseal calcifications eventually fill in. Large deposits may persist and chronically obstruct tendon functions (such as subacromial impingement) requiring surgery or tenotomy. Some cases of acute calcific tendinitis keep recurring, requiring a prolonged course of anti-inflammatory agents.

Treatment

Treatment of acute BCP tendinitis follows the lines of treatment of gout and pseudogout. Common treatments including NSAIDs, intra-articular steroids, ice, and splinting of affected joints do help [115]. Colchicine has received little use. Large obstructive calcific

masses are less likely to reabsorb spontaneously and may require other modalities for pain relief and recovery of function. High-energy extracorporeal shock wave therapy has been shown to be effective when used with conscious sedation [116, 117]. Needling or barbotage in association with lavage and steroid injections is also effective and has occasionally been shown to reduce the size of the calcium deposit as well, often in combination with an injection of drugs like EDTA (mesotherapy) [118–120]. The aspirated material is thick, resembling toothpaste.

Expected Response

Response of BCP tendinitis is rapid, usually 1–2 days. Disappearance of calcification takes months to years and may require needling and/or barbotage.

When to Refer

Calcific tendinitis is rarely a reason for referral. A rheumatologist should evaluate the rare multicentric cases, as they may need chronic colchicine. Large calcific masses should be evaluated by a rheumatologist and an orthopedic surgeon for possible aspiration, drainage, needling, or baronage.

Pearls and Pitfalls of BCP

- *The three crystals in BCP are hydroxyapatite, octacalcium phosphate, and tricalcium phosphate. Hydroxyapatite is the most abundant.*
- *BCP most commonly deposits in the shoulder, usually on the rotator cuff tendons. About 50% of cases are bilateral. But it is more common on the dominant side. Long-standing calcification can lead to adhesive capsulitis and sometimes tendon tears.*
- *BCP crystals are not visible on regular light or polarizing microscopy because they are amorphous and they lack birefringence. BCP requires alizarin red stain for microscopic identification.*

- *Shoulder impingement syndromes can result from calcific tendonitis from BCP. Management is usually conservative with PT and NSAIDs.*
- *BCP can be a cause of "pseudopodagra" in young women and is distinguished from gout by the women being premenopausal.*
- *Shockwave therapy has been used for calcific tendonitis secondary to BCP as well as pulsed ultrasound therapy.*
- *Barbotage refers to the use of needling with repetitive aspiration and lavage to break up local calcification.*

Summary

Primary care providers will encounter patients with crystal-induced arthritis in their practices and should feel empowered to treat this condition with some assistance from the rheumatologist. Following the ACR guidelines in gout with a "focus on treat-to-target" uric acid levels, use of ULT, and acute management, generalists should remember to make a definitive diagnosis and joint aspiration at some point in their patient's care and choose a medication based on the patients' comorbid conditions for better management of gout. Crystal arthropathies are a common presentation to a primary care office, and management of each type of crystal arthropathy has its own nuance (Table 7.6). By appropriately managing these arthropathies from the offset, one can prevent destructive joint damage and long-term disability and improve patients' quality of life. This chapter highlights key concepts in mind for the generalist to successfully diagnose, manage, and treat crystal-induced arthritis.

Table 7.6 Characteristics of crystal-induced arthritis

Characteristic	Gout	Pseudogout	BCP
Crystals	Monosodium urate crystals Negatively birefringent Needle shaped	Calcium pyrophosphate dihydrate Weakly positively birefringent Linear or rhomboidal	Carbonated substituted apatite Octacalcium phosphate, tricalcium phosphate (or Whitlock) Dicalcium phosphate dihydrate (brushite) "Shiny coins" in clumps on microscopy (not visible on microscopy as individual crystals) Alizarin red S stain
Prevalence	1.5–2.6 cases per 1000 individuals Increases with age in men and postmenopausal women	<1 case per 1000 individuals Increases with age	Equal gender distribution In almost 50% of patients 80–89 and >60 years old, prevalence doubles with each decade
Joint involvement and predilection	Monoarticular > oligoarticular Polyarticular <30% 1st MTP joint initially 50%, eventually 90% Ankles, knees, other	Monoarticular > oligoarticular Knee, wrist, other	Monoarticular and polyarticular (commonly bilateral) Shoulders, wrists, toes, femur

Table 7.6 (continued)

Characteristic	Gout	Pseudogout	BCP
Associated findings	Tophi (in chronic disorder) Hyperlipidemia	Chondrocalcinosis (increases with age, most will not have pseudogout)	OA
Conventional radiography	Overhanging edges	Chondrocalcinosis of hyaline cartilage or meniscus	Calcific tendonitis
Ultrasound findings (US)	Double contour sign	Hyperechoic signal within the intermediate layer of the hyaline cartilage	Hyperechoic signal within tendons and ligaments

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Overuse Injuries

8

Richard G. Chang, Lissa Hewan-Lowe, Elena Nehrbass, Aaron Bolds, Jonathan Sukumar, and Joseph E. Herrera

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Overuse Injuries

Overuse injuries are defined as injuries that occur with gradual onset over time and result from a mechanism of repetitive stress and cumulative trauma. Such injuries typically do not have a specific onset incident but instead progress with continued activity [1]. Tissues that are frequently injured by overuse include tendons, bone, periosteum, nerves, and bursa.

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Tendinopathy

Tendinopathy is a broad term that describes an overuse injury that is characterized by the delayed healing of stressed or damaged tissue in tendons due to altered biomechanics and/or abnormal loads. Injury or inflammation of the covering tendon sheath is referred to paratenonitis [2]. This injury may occur in the presence of inflammation after an acute initial injury. Though, in general, often chronic microtrauma and degeneration of tendon tissue leads to chronic tendinosis/tendinopathy, which manifests as persistent pain, swelling, with limited strength and function of associated joints, ligaments, and muscles [3].

Epidemiology

Tendinopathy is the most common overuse injury observed, particularly in competitive athletes. These injuries most often occur in the lower extremity, related to running and jumping activities [4].

Tendinopathy is also commonly found in individuals who perform physical labor, especially if such work involves high force, repetitive motion, or exposure to vibration [5].

Several risk factors are associated with developing tendinopathy. Some intrinsic risk factors include structural misalignment of bony structures, limb length discrepancies, and muscular imbalances. Extrinsic risk factors such as poor training education, improper technique, suboptimal environmental conditions, and low equipment integrity can also put one at greater risk of developing tendinopathy [6].

Lastly, preexisting medical conditions such as obesity and diabetes mellitus, as well as the presence of other inflammatory conditions, can also predispose one to tendinopathy [3].

Pathophysiology

The excessive loading of a tendon with a subsequent mechanical breakdown of the loaded tendon can cause micro-injuries to the tissue. The tendon may be able to heal such injuries; however, as repetitive loading of the tendon continues, the healing process is hampered and a sustained pattern of injury can occur. Histologically, this change is observed as collagen fibers losing

their normal tightly-bundled, parallel orientation. After being subject to chronic mechanical stress, collagen fibers themselves lose diameter and density and are found to have a loose and crimped organization with increased waviness [3].

Presentation/Symptoms

Tendinopathies present as a gradual onset of stiffness and activity-related pain in involved tendons. Sometimes localized swelling may be present. There can be decreased range of motion, with involved joints as well as reported weakness with involved muscles—an overall functional deficit can be perceived [5].

Symptom Classification

The following classification system, developed by Nirschl et al., can be used to guide a clinician's assessment of tendinopathy severity:

Pathologic stages:

Stage I: temporary irritation (chemical inflammation)

Stage II: permanent tendinosis—less than 50% tendon cross section.

Stage III: permanent tendinosis—greater than 50% tendon cross section.

Stage IV: partial or total rupture of tendon.

Phases of pain:

Phase I: mild pain after exercise activity, <24 hours

Phase II: pain after exercise activity, >48 hours, resolves with a warm-up.

Phase III: pain with exercise activity, does not alter activity.

Phase IV: pain with exercise activity that alters activity.

Phase V: pain caused by heavy activities of daily living.

Phase VI: intermittent pain at rest that does not disturb sleep; pain caused by light activities of daily living.

Phase VII: constant rest pain and pain that disturbs sleep [5].

Physical Exam

Pain can be elicited with stretching, isometric contractions, and palpation of the pathological area. Upon palpation, tendon thickening, crepitus, and tenderness can be observed. Tendon loading tests (e.g., pain on passive dorsiflexion, pain on single heel raise,

and pain on hopping for the Achilles tendon) can provide a dynamic testing aspect to physical exam assessment [3]. Impingement tests are useful for the contribution of irritation from bony anatomy (e.g., for rotator cuff tendinopathy) [5]. See Figs. 8.1 and 8.2.

Diagnosis

It is primarily made via history and physical exam. Plain radiography has a limited role in evaluating tendinopathy; however, it can be used to diagnose associated or incidental bony abnormalities [2].

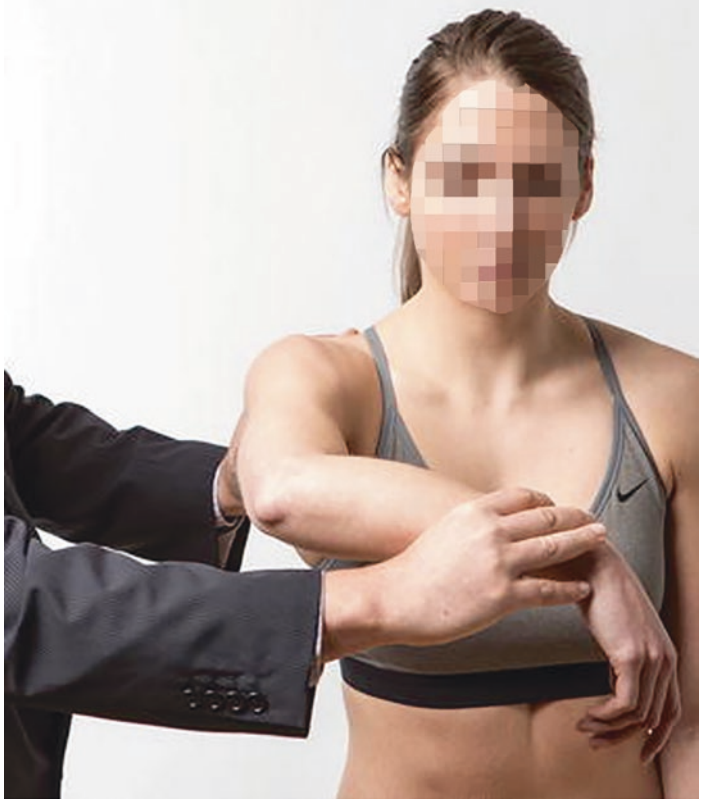


Fig. 8.1 Left image: Hawkins–Kennedy test, in which upper extremity is flexed and internally rotated

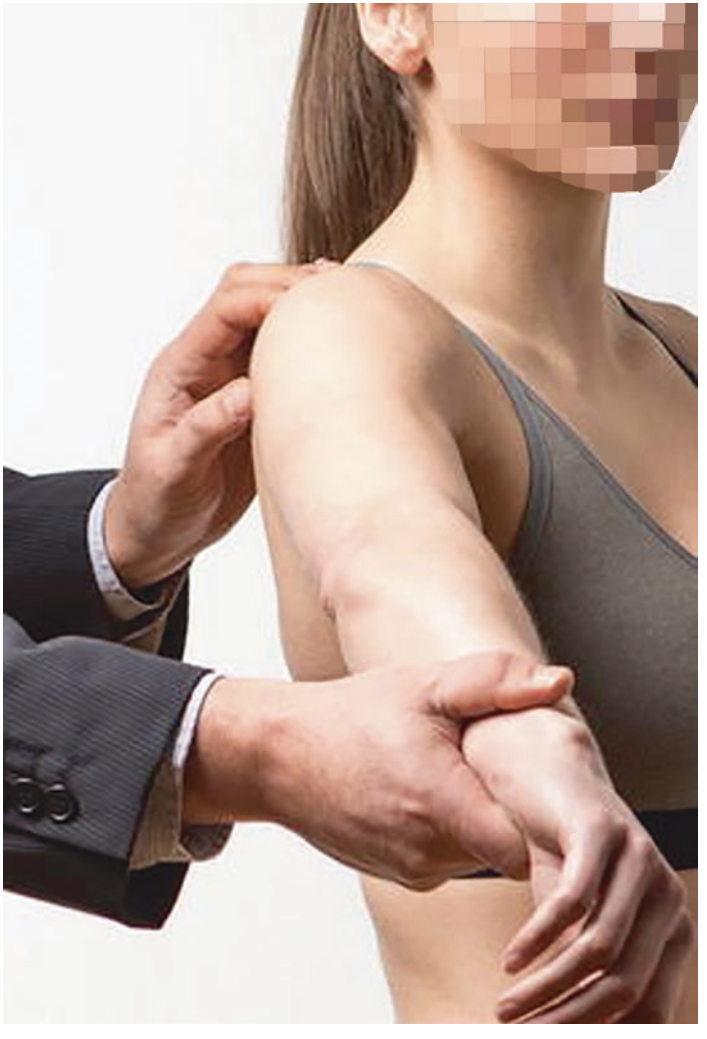


Fig. 8.2 Right image: Neer's sign, in which upper extremity is elevated and internally rotated; pain or discomfort with either of these provocative maneuvers may indicate rotator cuff tendinopathy or impingement. (Used with permission from: Baumann and Morgan [32])

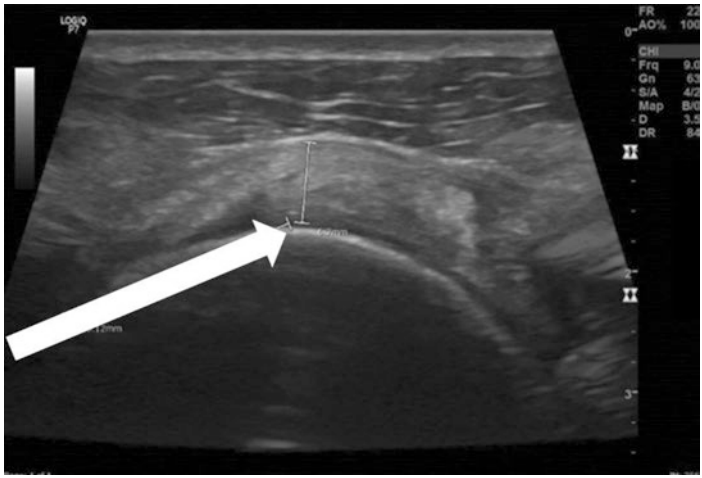


Fig. 8.3 Ultrasound imaging demonstrating diffuse supraspinatus tendon thickening and hypoechogenicity (white arrow), consistent with supraspinatus tendinopathy. (Used with permission from: Niazi et al. [33])

Diagnostic ultrasound is useful for visualizing structural changes or pathology to tendons. Demonstration of hypoechoic areas surrounding the tendon, tendon thickening, neovascularization, and blurring of anatomical borders between tendons and its sheath can all indicate the presence of tendinopathy (Fig. 8.3). Ultrasound evaluation of tendons is fast, dynamic, and cost-effective; however, the reliability of its results is operator-dependent [2].

MRI studies can be performed if ultrasound investigations prove equivocal. MRI imaging is advantageous in that it provides the best detail of soft tissue anatomy. Tendinopathy can present as high signal intensity in tissue. Effusions and adhesions can also be observed with this modality. T2-weighted images typically have greater sensitivity than T1-weighted sequences in highlighting pathology. Disadvantages of MRI include high cost and prolonged time for performing this procedure [2].

Treatment

Tendinopathy is a clinical diagnosis based on a patient's presentation and is supported by physical exam and objective imaging stud-

ies [5]. The first line of management for tendinopathy is conservative interventions such as rest and icing, short-term nonsteroidal anti-inflammatory drugs, and supervised physical therapy. The use of orthotics can also be explored at this time. Furthermore, passive modalities like ultrasound, iontophoresis, and deep transverse friction massage can be employed by physical therapists. Corticosteroid injections to decrease acute inflammation may also be considered as well but are not effective and be detrimental to overall tendon health integrity if exposed repeatedly to corticosteroids (no agreed-upon set number, but more than 3 within a 6 month to 1 year period may increase the risk for further tendon degeneration) [5].

When utilizing strengthening-based physical therapy approaches, eccentric exercise therapy has shown to be effective in treating chronic tendinopathy, particularly when incorporating slow speed, low intensity, and gradual intensification [5].

When conservative measures fail to alleviate symptoms, additional therapies to augment treatment and healing can be considered such as extracorporeal shockwave therapy, heat application, and cryotherapy. Higher-level procedures to treat tendinopathy include ultrasound-guided percutaneous needle tenotomies, platelet-rich plasma (PRP) injections, and high-volume image-guided injections (HVIGI), with promising support for these procedures found for treatment of refractory rotator cuff, patellar, and Achilles tendinopathies and lateral epicondylosis [3, 5].

Stress Fractures

A stress fracture is a partial or complete fracture resulting from repetitive stress loads lower than the threshold for single load fracture. It is typically categorized as either insufficiency or fatigue fractures. Insufficiency fractures result from repetitive stress on the bone that is abnormally weak or inelastic due to metabolic diseases, hormonal imbalances, and osteoporosis. Fatigue fractures result from failure of the normal bone secondary to repetitive stress load, including a sudden increase in activity, inappropriate footwear, improper technique, and changes in surface texture, that is, running on track versus street surface [7].

Epidemiology

Much of the published literature regarding stress fractures occurs within the military recruit population because of high incidence [7]. Also, 0.7% to 20% of sports medicine clinic patient presentations are secondary to stress fractures. Stress fractures most commonly occur in lower limbs. Running athletes have the highest incidence of stress fractures [8]. Track and field and distance runners predominantly present with navicular and tibial stress fractures, respectively. Upper extremity stress fractures can occur in throwing athletes and rowers but tend to be less common than lower extremity stress fractures [7]. It is important to note that military epidemiology studies do not directly translate across civilian athletes because of differences in training, equipment, and overall fitness level [8].

Pathophysiology

Bone responds to repetitive stress loads by increasing remodeling rate. Remodeling consists of lamellar bone resorption by osteoclasts and replacement of denser bone by osteoblasts. Weakened vulnerable bone occurs from a lag between increased activity of osteoclasts and osteoblasts. Repetitive loading prevents adequate recovery time and causes microdamage that accumulates and jeopardizes the integrity of the bone, which leads to a stress fracture. Sudden increases in activity during this lag period can also create a more vulnerable bone state. It is also believed that repetitive loading decreases oxygen delivery to the bone, leading to ischemia and weakened bone and stress fractures [8].

Presentation/Symptoms

Patients often report progressively worsening symptoms that are insidious onset and often activity related. Patients may also present with risk factors that often include previous stress, low bone density, menstrual irregularity, poor nutritional status, that is, low calcium, or increased alcohol consumption [8]. There are also structural risk factors such as arch deformities that increase stress and torsional forces on lower extremities [34]. See Figs. 8.4 and 8.5.

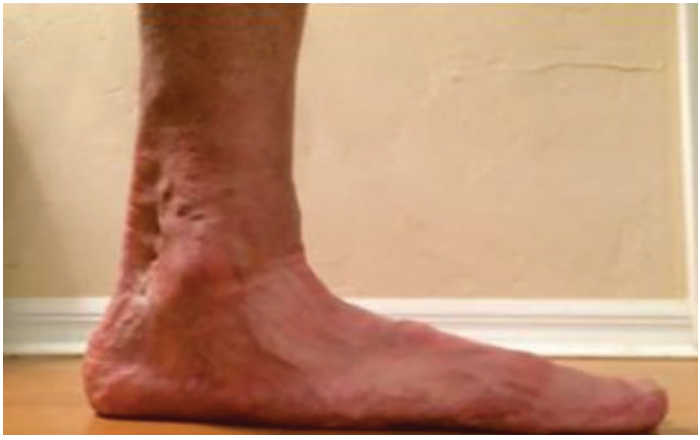


Fig. 8.4 Low-arched (pes planus) foot

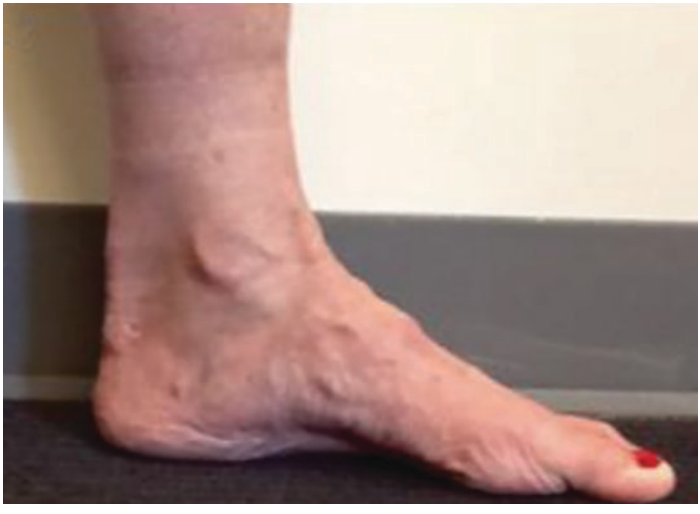


Fig. 8.5 High-arched (pes cavus) foot. (Used with permission from: Miller and Kaeding [34])

Physical Exam

Point tenderness is often elicited at the site of fracture. The patient has difficulty shifting weight or pivoting on the affected limb. There is increased pain and difficulty hoping on the affected limb. The patient may or may not report pain at rest. Inspection of the lower extremities may reveal leg length discrepancy, pes planus, or arch deformities.

Diagnosis

X-ray is the initial imaging study ordered for pain. Approximately 65% of symptomatic patients have negative initial radiographic findings. Focal periosteal bone formation is the most common sign in early stress fractures and usually appears two to four weeks after symptom onset. Figs. 8.6 and 8.7 show examples of radiographic progression of an early stress fracture of the third metatarsal shaft [30].

Bone scans can also confirm diagnosis within the first week of symptom onset. MRI has also proven to be a reliable imaging modality that can assess the severity of injury [8].

- Four-stage grading system used to assess severity using MRI [8]:
  - Grade 1: periosteal edema on fat-suppressed imaging.
  - Grade 2: increased signal intensity on fat-suppressed T-2 weighted images.
  - Grade 3: decreased signal intensity on T-1 weighted images.
  - Grade 4: evident fracture line on both T-1 and T2 weighted images.

Treatment

Early diagnosis is important to allow for effective conservative management. History taking should include determining risk factor exposure, training regimen, menstrual cycle changes in women, and timing of symptoms. Stress fractures need to be classified as noncritical and critical. Noncritical stress fractures in the lower extremity include medial tibia, fibula, and the second, third, and fourth metatarsals. Critical stress fractures have higher rates of nonunion, and locations include anterior tibia, medial malleolus, talus, navicular, fifth metatarsal, and sesamoids [8].

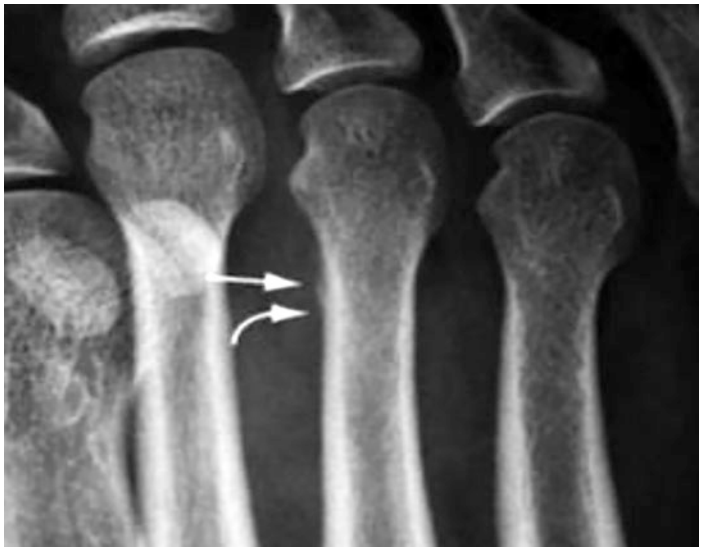


Fig. 8.6 Left image. Early periosteal changes of medical cortex of third metatarsal shaft

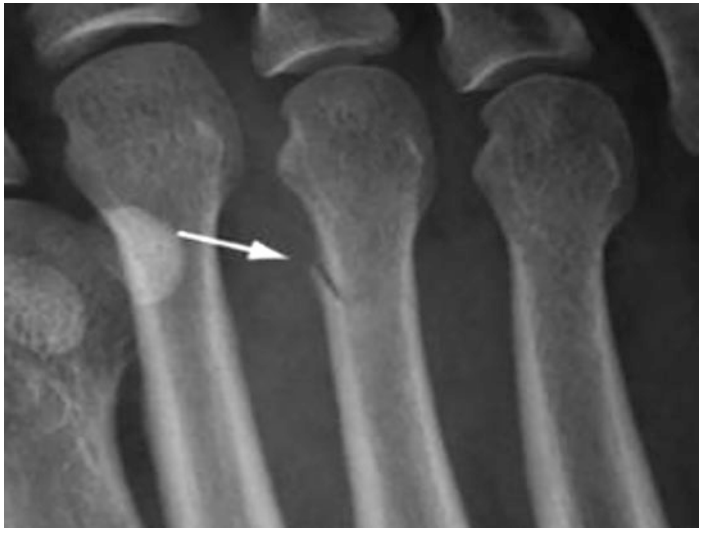


Fig. 8.7 Right image. There is evident cortical fracture 3 weeks later. (Used with permission from: Miller and Kaeding [34])

Bojanic Ivkovic developed an algorithm for nonoperative management of stress fractures that can generally be applied across various fracture sites [7]. Ivkovic recommended nonweight bearing for 3 weeks during the symptomatic phase followed by provocative pain tests such as the fulcrum test and hopping test. If the provocative tests are negative, the patient can progress to 3 weeks of cycling, light weights, and jogging. However, if provocative tests are positive, the patient should remain nonweight bearing. For noncritical stress fractures, return to full activity usually occurs within a 6- to 8-week time frame. Most nondisplaced fractures can be managed nonoperatively with the exception of femoral neck stress fractures that occur in the superior lateral cortex (*tension-sided femoral neck fractures*).

Critical stress fractures may fail conservative treatment and require surgical intervention due to increased tensile load at the specific fracture site and avascularity.

Periostitis and Periosteal-Muscle Junction

The most widely known disorder of this group of injuries is medial tibial stress syndrome (MTSS) or "shin splints." Patients often present with insidious onset of diffuse, vague pain over distal posteromedial tibia that is aggravated with exertion and exercise.

Epidemiology

Overall, MTSS is frequently reported among physically active individuals. In runners, the incidence has been reported to range anywhere from 13.6% to 20% in runners [9], while in military recruits, the reported incidence is from 7.2% to 35%. Risk factors for injury include increased BMI, female gender, prior lower extremity injury, and running or ballistic/cutting sports (football, soccer, dancing, and basketball). Anatomical risk factors include pes planus (or increased forefoot pronation and rearfoot eversion), increased navicular drop (associated with lower foot arch), decreased internal tibia rotation in runners, increased ankle plantarflexion ROM, and increased hip external ROM [10]. Core and pelvic weakness has also been identified as a risk factor [11].

Pathophysiology

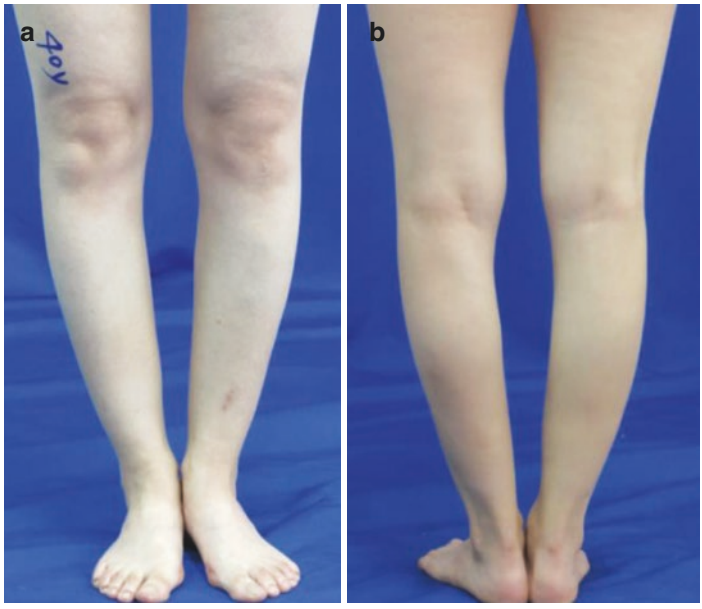
Etiology is unclear, but it is hypothesized to be multifactorial. This syndrome is considered possibly a precursor in a spectrum of repetitive stress conditions that may lead to bony stress reactions and stress fractures [12]. Traction periostitis of the tibia along with inflammation and/or microtrauma of the inserting tibialis posterior and soleus muscles is believed to be caused by repetitive, abnormal loading of the tibia from periosteal remodeling and dysfunction and tendinopathy of the tibialis anterior, tibialis posterior, and soleus muscles. Kinetic chain deficiencies and improper sports training techniques (e.g., sudden increase in intensity of training or running greater than 20 miles per week) are other important contributing factors [10, 11, 13].

Presentation/Symptoms

Patients often complain of dull and achy pain over the distal posteromedial tibia. The symptoms are usually worse at the beginning of activity and improve during the end of training. More severe cases may present with pain with less exertion and may occur at rest. Historical details regarding weekly running mileage, terrain/surface, footwear, and orthotic use are important for determining possible changes in an exercise routine that may have led to the injury. Runners may commonly ramp up too quickly. For female patients and/or when considering female athlete triad syndrome, getting a history of diet, nutrition, weight change, and menstrual cycle abnormalities is important for diagnosis.

Physical Exam

A complete musculoskeletal exam should be completed, with special attention to the hip, lumbar spine, and lower extremities. Look for any biomechanical abnormalities and/or asymmetries on the exam. Gait abnormalities, asymmetrical joint involvement (e.g., genu valgum or varum; see Figs. 8.8 and 8.9), leg length discrepancies, forefoot or subtalar pronation (usually associated with rearfoot eversion), and dropped navicular and lower foot arch are important to consider when inspecting the patient. Range of motion evaluation of the hip, knee, and ankle/foot is used to assess for proximal quadriceps/hip flexor tightness, hamstring, or



Figs. 8.8 and 8.9 Mild genu varum. (Used with permission from: Qin et al. [35])

distal gastrocsoleus complex tightness; femoral retro/anteversion may also guide treatment. Core and pelvic hip muscle weakness may be assessed with the ability to maintain a single leg stance and/or pelvic bridge position. Examination of patients' running shoes (e.g., assessing medial or lateral wear along soles) is also performed.

Example Images

Diagnosis

Clinical impression is formed mainly based on history and physical exam. If needed, imaging is completed if symptoms persist and/or to exclude other similarly presenting diagnoses. In the differential for exertional leg pain, besides MTSS, stress reaction/fracture of the tibia (more commonly found in the anterior tibia), compartment syndrome, and vascular conditions must be consid-

ered if a patient does not improve with conservative treatment within a month's time.

X-rays of the tibia are generally negative within the first 3 weeks of presentation [12, 13]. If a stress fracture is suspected, it will demonstrate the dreaded "black line" along the tibia. See Fig. 8.10. Chronic MTSS may show periosteal exostoses.

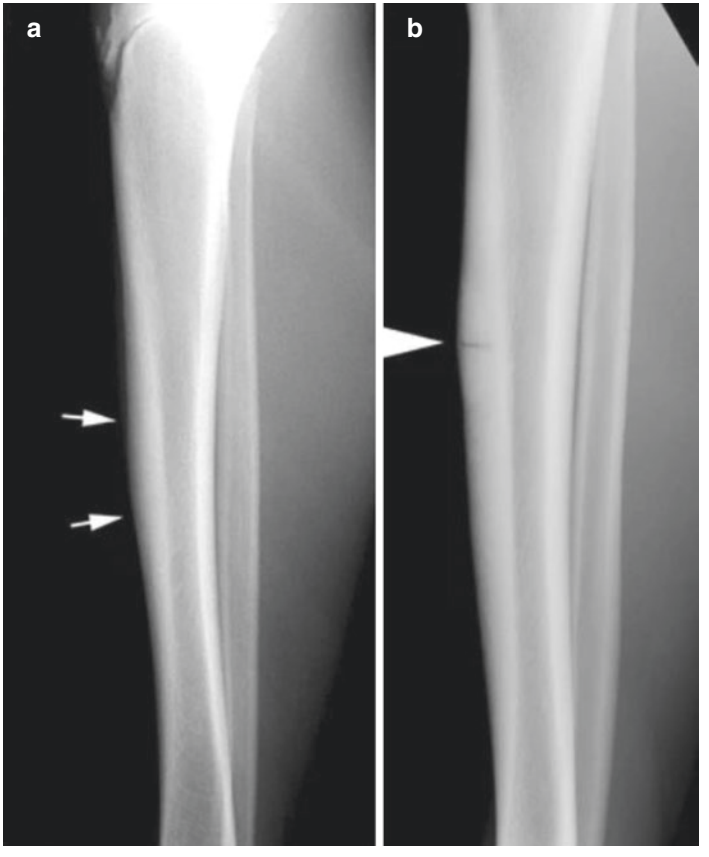


Fig. 8.10 Plain films: bony changes. (**a**) In this patient, only focal thickening of the anterior cortex (arrows) is seen. (**b**) In this patient, in addition to such thickening, an actual transverse stress fracture. (Used with permission from: Swischuk and Jadhav [36])

A triple-phase bone scan may also be performed to rule out a stress fracture. Typical findings consistent with a stress fracture will show diffuse, longitudinal uptake along the posterior tibia in the delayed phase of the scan.

MRI is the preferred imaging modality because it will better assess soft tissue injuries and demonstrate progression and severity of an injury from initial periosteal edema and inflammation (grade 1, shin splints) on MRI fat suppression images to periosteal and bone marrow edema (grades 2–3) to finally cortical stress fracture (grade 4) [14].

Treatment

Nonpharmacologic treatment includes orthotics, footwear change (shock-absorbing soles/insoles with stable heel counter; change after every 250–400 miles in runners), weight-loss counseling (if overweight/obese), and cool compress in acute phases. Physical therapy is important for strengthening of core, hip, tibial, and gastrocsoleus muscle groups. It is also important for improving overall biomechanical and kinetic chain.

Pharmacologically, acetaminophen, as needed for analgesia, is the first line of treatment. Cautious use of NSAIDs is recommended due to possible stress reaction/fracture; otherwise, NSAIDs may be used as needed for anti-inflammatory effect and analgesia [15].

Refractory cases may require an orthopedic referral for possible compartment release.

Peripheral Nerve Entrapment

Nerve injury from overuse is a common cause of pain experienced by athletes and the weekend warrior to office workers. Overuse of specific muscle groups and/or repetitive motion at joints increases pressure on nerves causing compression and subsequent damage [16].

Epidemiology

Peripheral nerve entrapment occurs at various sites in the extremities. The most common nerves include the median, ulnar, and peroneal nerves. Other nerves that are also affected but less common include the suprascapular nerve, radial nerve, lateral femoral cutaneous nerve, and posterior tibial nerve. The most common site of compression occurs at the wrist and causes median nerve compressive neuropathy affecting up to 6% of adults in the United States [17].

Pathophysiology

Peripheral nerve entrapment is seen in subacute to chronic overuse injury due to repetitive microtrauma related to soft-tissue injury, which leads to entrapment as nerves can no longer glide normally with adjacent tissue and with proper joint function. The use of vibrating tools such as a jackhammer can also cause repetitive trauma to nerves [18]. The repetitive motion and vibration can cause swelling of the tendons that run with the nerve through the sheath, which leads to the compression of the nerve [17]. Injured muscles around nerves undergo regeneration causing adhesions to the nerve's outer layer, or epineurium, leading to tension and ischemia within the nerve, and epineural scarring. Prognosis is influenced by the amount of demyelination, axon loss, and distance to muscle [16].

Presentation/Symptoms

The onset of symptoms is insidious. Patients often complain of a constellation of symptoms, which include pain, numbness, tingling, paresthesias, and weakness in the distribution of the injured nerve. Patients with mild-to-moderate injury complain of symptoms that are exacerbated by specific activities such as typing, using a jackhammer, or throwing a ball. Patients with severe nerve injury may complain of the symptoms at rest and may also complain of nocturnal wakening.

Physical Exam

A thorough musculoskeletal exam of the symptomatic extremity is crucial to the diagnosis. Evaluation for any atrophy, weakness, and sensory loss is important in determining which nerve is affected. Most patients present with one of the above physical exam findings.

Provocative maneuvers such as the median nerve compression test, the nerve percussion test, also known as Tinel's test, and the scratch collapse test provide additional clues to which nerve is affected [19]. Level II evidence shows that the scratch collapse test (sensitivity 64%, 69% for CTS, cubital tunnel) has higher sensitivity than Tinel's test (sensitivity 32%, 54% for CTS, cubital tunnel), with accuracy being 82% and 89% for carpal tunnel syndrome and cubital tunnel syndrome, respectively [20]. See Figs. 8.11, 8.12, and 8.13.

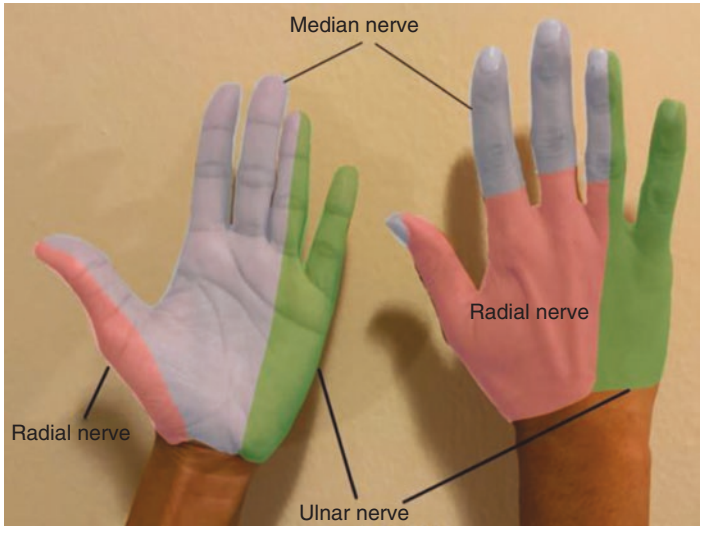


Fig. 8.11 Hand peripheral nerve distribution

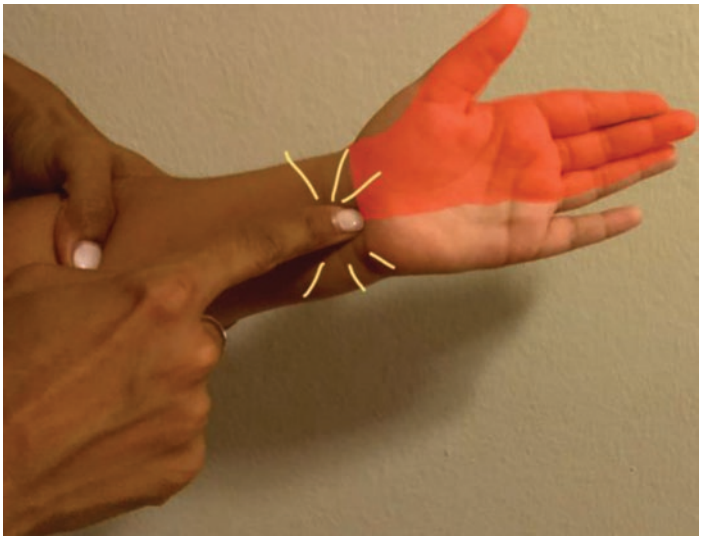


Fig. 8.12 Tinel's over carpal tunnel

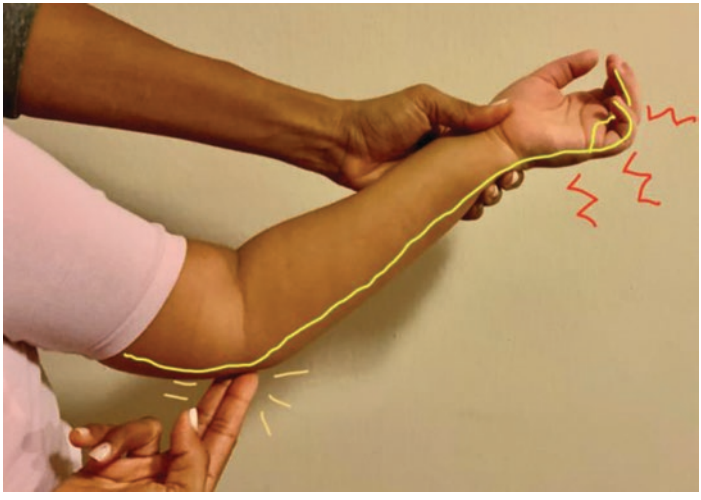


Fig. 8.13 Tinel's over cubital tunnel. (Original images, used with permission from Anna Di Franco and Viola Di Franco)

Diagnosis

Peripheral nerve entrapment is primarily a clinical diagnosis. Physical exam, provocative maneuvers, and electrodiagnostic studies (not more sensitive or specific than physical exam) are performed. MRI and ultrasound have limited evidence for diagnosis but may help provide support to the clinical diagnosis [17]. MRI and ultrasound are often used to rule out other pathologies such as central or other musculoskeletal causes.

Treatment

For example, a cock-up splint for median nerve neuropathy due to carpal tunnel syndrome and tendon gliding exercises can decrease symptoms significantly; however, there is limited evidence in the literature to suggest the efficacy of neural gliding [21]. There is limited evidence of nighttime splinting as a more effective short-term treatment versus no treatment in CTS. There is also a lack of evidence to suggest one type of splint or splint regimen over another [22].

Surgical referral is usually considered when symptoms return or persist despite conservative treatments. In the case of carpal tunnel syndrome, about 25% of patients will not experience post-surgical relief [4].

Bursitis/Bursopathies

Bursitis is the inflammation of bursae. Bursae are the fluid-filled, synovium-lined, sac-like structures found throughout the body near bony prominences and between bones, muscles, tendons, and ligaments that serve as cushions during musculoskeletal movement.

The etiology may be due to chronic issues such as prolonged pressure, repetitive overuse, strenuous activity, or inflammatory conditions (i.e., rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, scleroderma, spondyloarthropathy, gout). It may also occur due to acute causes such as direct injury or trauma, crystal-induced arthropathy (i.e., gout), infection, or superinfection (*Staphylococcus aureus* septic bursitis due to transcutaneous or hematogenous spread of bacteria).

Figures 8.14, 8.15, 8.16, 8.17, 8.18, 8.19, and 8.20 show some anatomical locations of bursae and sites of bursitis.

Epidemiology

The anatomical location of bursitis appears to have a strong correlation with the patient's occupation. Students resting their elbows on the desks as well as people performing manual labor for a living (typically males [21] working in plumbing, construction, and gardening) are more often affected by olecranon bursitis. People performing cleaning services are predisposed to prepatellar bursitis—formerly known as "housemaid's knee." Dancers and figure skaters often present with calcaneal bursitis after wearing tight or poorly fitted shoes. Infrapatellar bursitis (also known as "clergyman's knee") is frequently encountered in people who kneel and crawl without appropriate padding. Individuals with a

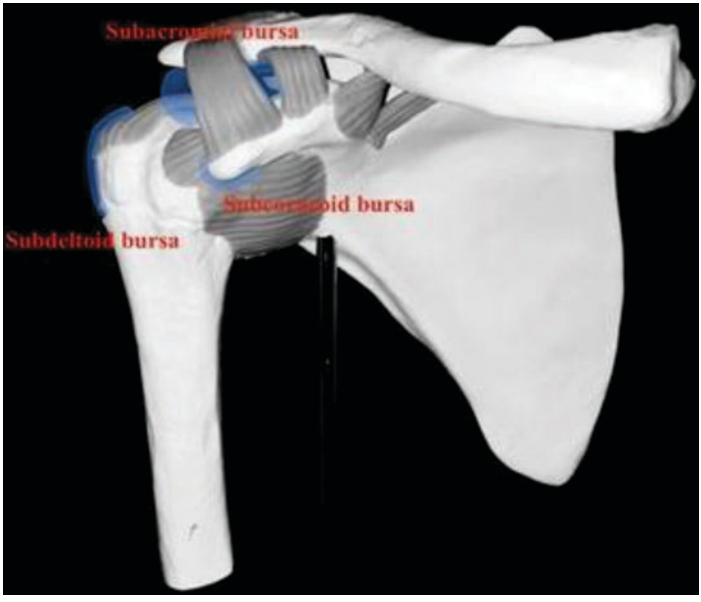


Fig. 8.14 Bursae around the shoulder. (Used with permission from: Kancherla and Cortez [37])

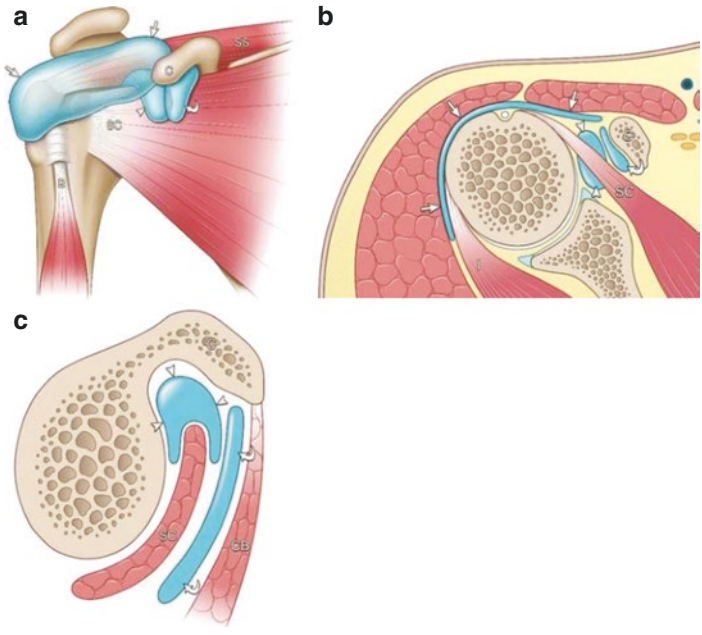


Fig. 8.15 Shoulder bursae. Illustrations of (**a**) coronal section of the anterior shoulder, (**b**) a transverse section at the level of the subscapularis (*SC*), and (**c**) a sagittal section at the level of the coracoid process (*C*) show the subacromial–subdeltoid bursa (*arrows*), subscapularis recess (*arrowheads*), and subcoracoid bursa (*curved arrow*). *SS*, supraspinatus; *B*, biceps brachii long head tendon; *CB*, coracobrachialis. (Used with permission from: Ruangchaijatuporn et al. [38])

sedentary lifestyle may get ischial bursitis ("weaver's bottom"), which occurs from prolonged sitting on hard surfaces that press against the bones of the bottom or mid-buttocks and irritating bursa between the ischial tuberosity and proximal hamstring tendons. The most common etiology of bursitis is prolonged pressure by hard surface over bony prominences. Obesity is often an exacerbating factor in weight-bearing forms of bursitis. Osteoarthritis and other chronic diseases are more prevalent in the elderly, hence increased risk of bursitis in this patient population. Immunocompromised patients with HIV, alcoholism, diabetes,

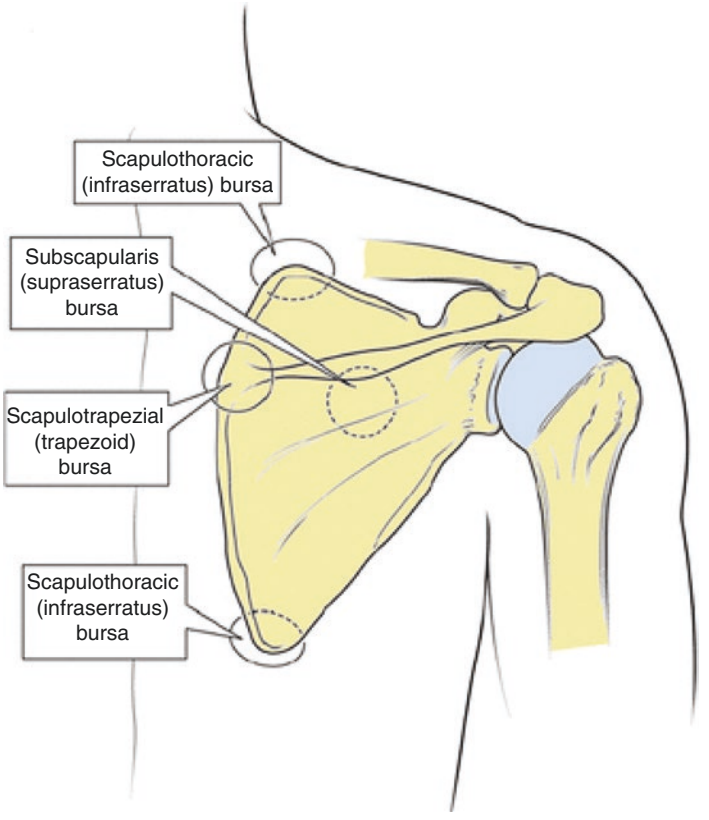


Fig. 8.16 Multiple named bursae around the shoulder, AP view. (Used with permission from: Diercks [39])

and rheumatologic disorders are at increased risk of septic bursitis. Females have a documented predilection for pes anserine and trochanteric bursitis.

Pathophysiology

Bursitis occurs when a trigger such as overuse or direct pressure aggravates the bursa and causes it to fill with synovial fluid. Some bursal fluid studies have revealed increased inflammatory media-

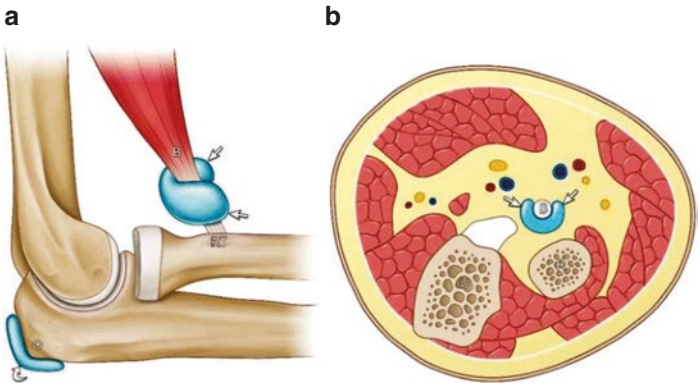


Fig. 8.17 Elbow bursae. (**a**) Lateral elbow and (**b**) transverse section distal to the elbow joint show bicipitoradial bursa (*arrows*) and olecranon bursa (*curved arrow*). Note the brachialis (*white* area anterior to ulna). *B*, biceps brachii; *O*, olecranon; *RT*, radial tuberosity; *U*, ulna; *R*, radius. (Used with permission from: Ruangchaijatuporn et al. [38])

tors such as tumor necrosis factor-alpha, cyclooxygenases, and specific interleukins. However, not all bursitis is associated with an overt inflammatory process [24].

Presentation/Symptoms

Patients often report progressively worsening symptoms that are insidious in onset and often activity related.

Traumatic bursitis puts the patient at risk for septic bursitis, which is most often caused by direct penetration of the bursa through the skin (via trauma or instrumentation). Septic bursitis can also be provoked through the hematogenous spread; however, due to the relatively poor blood supply to the bursa, this is rare. *Staphylococcus aureus* causes the majority of septic bursitis [24].

Bursitis can frequently occur in conjunction with or secondary to pathology in adjacent or remote structures. Greater trochanteric pain syndrome often involves trochanteric bursitis that is secondary and concurrent with gluteus medius tendinosis or partial tears. It can result from chronic back pain, core muscle deconditioning, or contralateral knee pathology. Similarly, pes planus can predispose to pes anserine knee pain.

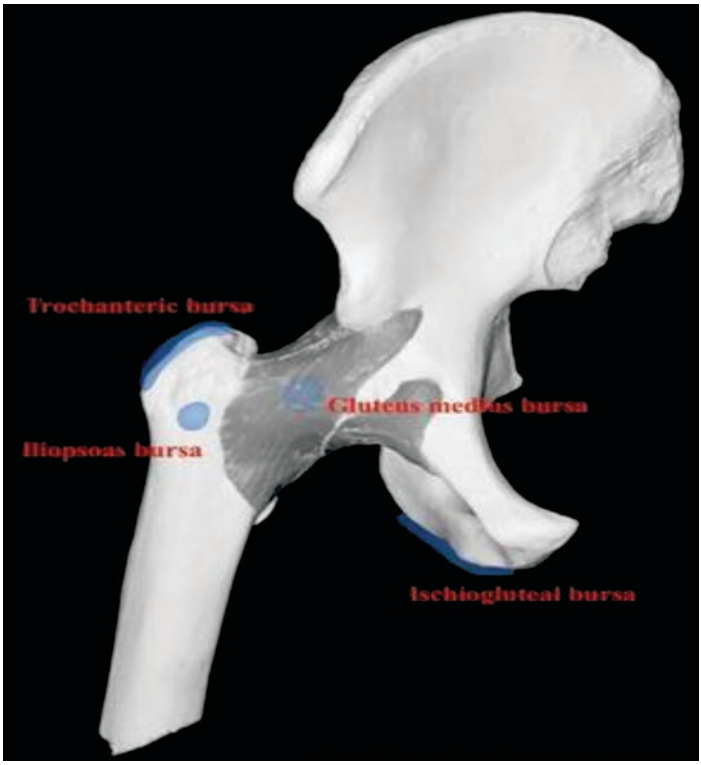


Fig. 8.18 Bursae in the pelvis. (Used with permission from: Kancherla and Cortez [37])

Physical Exam

Acute bursitis manifests as tenderness to palpation of the bursa, pain with active motion of the affected joint due to an increase in intrabursal pressure. Thus, patients with acute olecranon bursitis can fully extend their elbow, but full flexion of the elbow is often uncomfortable. Similarly, patients with acute prepatellar bursitis are typically most comfortable with their knee in full extension, whereas knee flexion is uncomfortable. Superficial and septic bursitis may reveal abrasions, puncture wounds, surrounding areas of cellulitis. The skin should always be examined for signs of trauma, erythema, and warmth [23, 24].

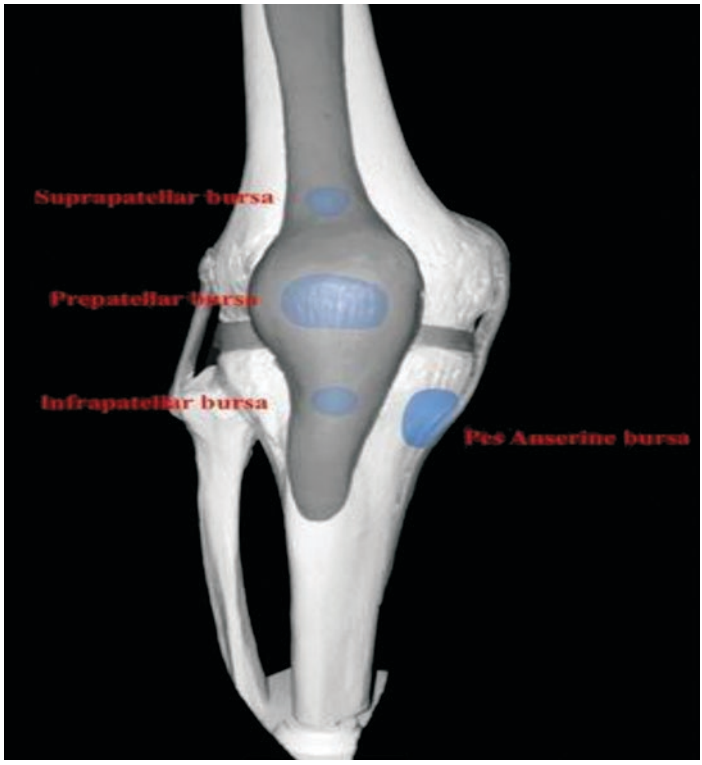


Fig. 8.19 Bursae surrounding the knee. (Used with permission from: Kancherla and Cortez [37])

In chronic bursitis, pain is often minimal. However, there is increased swelling and thickening of superficial bursae because it has had time to expand and accommodate the increased intrabursal pressure. This may lead to immobility, which can result in contracture and muscle atrophy. This is the pathophysiology behind the development of adhesive capsulitis, which can develop in as little as 1 week [25]. Olecranon bursa is a common site for the formation of rheumatoid nodules and gouty tophi.

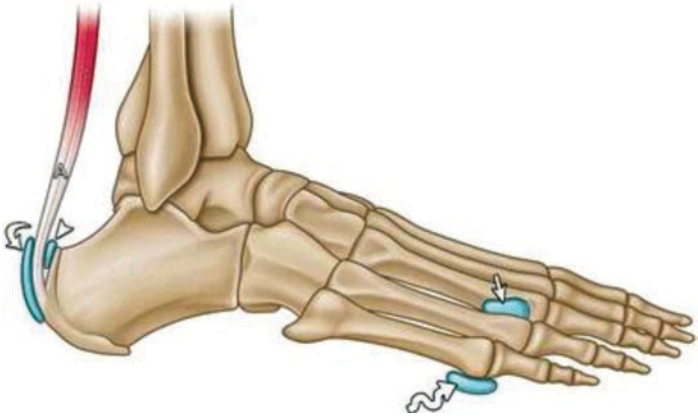


Fig. 8.20 Ankle and foot bursae. Lateral foot and ankle show retrocalcaneal (*arrowhead*), retro-Achilles (*curved arrow*), intermetatarsal (*arrow*), and adventitious (*squiggly arrow*) bursae. *A*, Achilles tendon. (From: Ruangchaijatuporn et al. [38])

Diagnosis

Imaging is typically not warranted, especially when involving superficial bursitis. Imaging is utilized to rule out other pathologies and typically includes plain radiographs, ultrasonography, and MRI. A plain film is taken to exclude a fracture, the presence of a foreign body, or calcifications in the region of a bursa (although there is no evidence of correlation with the clinical course of bursitis). A plain film, however, will not reveal the condition of the bursae as they are radiolucent on this type of imaging [26, 27].

Ultrasonography is preferable as it can be used to guide needle aspiration of the bursa and permits for dynamic assessment of the bursa and adjacent structures, visualizing cobblestoning of the fat overlying a bursa, while color Doppler is good for showing signs of infection, such as hyperemia.

MRI is used to rule out labral tears and other soft tissue pathologies. A definitive diagnosis of bursitis can also be elicited from the MRI [28].

Bursal fluid aspiration and analysis serve to rule out infection and to aid in the diagnosis of a microcrystalline arthropathy. Deeper bursa typically requires image-assisted needle placement using ultrasonography or computed tomography (CT) guidance only if there is a suspicion for septic arthritis (i.e., patient also presents with systemic toxicity).

Bursal fluid can be classified as clear, hemorrhagic, cloudy, or purulent; there may be chalk-like sediment visualized in gouty olecranon bursitis. A white blood cell count of under 500/mm^3 from the aspirated bursal fluid is consistent with the noninfectious and noncrystalline etiology of bursitis. Synovial fluid can be aspirated when suspecting systemic, crystalline, or infectious etiology. Etiology is considered noninflammatory if the white blood cell count is less than 2000 per mm^3 (2.0 × 109 per L), typically with less than 75% polymorphonuclear leukocytes. Infection is confirmed and best treated with a positive Gram stain with confirmed growth of bacteria or other pathogens on culture. Gout is confirmed by findings of intracellular negatively birefringent crystals on polarized microscopy, whereas pseudogout or calcium deposition disease is confirmed with positively birefringent crystals [29].

Treatment

With the exception of septic etiology, bursitis is self-limited. The management goals are thus directed to relieve the immediate symptoms. This includes joint protection program, analgesia typically with ice packs alternating with heat, oral NSAIDs, or topical NSAIDs [30].

Physical and occupational therapy is a treatment option that improves biomechanics, prevents complications of immobilization, and maintains a range of motion [31].

Utilizing braces such as kneeling pads can help prevent mechanical injury to the prepatellar bursa. Cutting a “V” groove into the back of footwear reduces pressure on the area of Achilles-region bursitis. Removable concave orthosis firmly affixed to the elbow with a velcro strap can provide pressure to prevent fluid re-accumulation in the bursa.

Glucocorticoid injections are often utilized for refractory cases that have failed conservative treatment [30].

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9 Systemic and Localized Inflammatory Diseases of Older Adults

Seema Malkana and Leslie D. Kerr

Inflammatory Arthritis

Epidemiology, History, and Diagnosis

Arthralgias in older adults are most commonly due to osteoarthritis, a degenerative, noninflammatory condition. However, when joint pain is accompanied the hallmarks of synovitis—stiffness, tenderness, effusion, or warmth—inflammatory arthritis should be considered.

Rheumatoid arthritis (RA) is the most prevalent inflammatory arthritis in adults, affecting 1–2% overall and 2–2.3% of the geriatric population [1]. While many older adults with RA have long-standing disease, including classic hand deformities and erosive changes on X-rays, there is a separate cohort who develop new-onset disease as older adults.

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As described by Ehrlich [2], 10–20% of RA patients may present after age 60. Elderly-onset rheumatoid arthritis (EORA) includes a greater proportion of men, more often has insidious onset, and is less likely to be complicated by extra-articular disease manifestations, such as rheumatoid nodules on the forearms. It is more frequently large joint-predominant (particularly the shoulder girdle) and is often associated with systemic complaints (e.g., fatigue, malaise, weight loss, generalized stiffness, depression) that sometimes precede the onset of articular disease. Patients describe overwhelming generalized morning stiffness and have marked symmetric synovitis of the small joints of the hands (wrist, metacarpal phalangeal, and proximal interphalangeal joints) and shoulder. As in patients diagnosed at a younger age, symptoms are persistent and must be present for at least 6 weeks to reliably exclude other etiologies of inflammatory polyarthritis.

Laboratory testing may reveal a marked inflammatory response (e.g., elevated erythrocyte sedimentation rate [ESR]) and mild anemia of chronic disease [3]. The rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies are usually absent. X-rays generally show a lack of erosive changes and reveal only soft tissue swelling and periarticular osteoporosis [4].

Differential Diagnosis

The differential diagnosis for elderly-onset RA includes polymyalgia rheumatic (PMR), the pseudo-rheumatoid pattern of pseudogout, gout, complex regional pain syndrome (CRPS), remitting seronegative symmetrical synovitis with pitting edema (RS3PE), and osteoarthritis [5].

While both PMR and EORA may present with aching pain and stiffness in the upper extremities, patients with PMR lack the objective synovitis seen in RA. They may also have signs or symptoms related to overlapping giant cell arteritis.

Gout and pseudogout flares are episodic and self-limited, while RA synovitis is persistent and lasts for at least 6 weeks. The gold

standard for diagnosis of crystal arthritis is synovial fluid analysis under polarized microscopy. It will show intracellular monosodium urate or calcium pyrophosphate crystals that are not seen in patients with RA. A newer imaging modality, dual-energy CT (DECT), demonstrates good sensitivity and specificity for detection of monosodium urate crystals when gout is suspected but cannot be confirmed with joint aspiration [6]. Risk factors for gout include low-dose aspirin therapy, diuretic use, renal insufficiency, acute on chronic congestive heart failure, and dietary intake of purines commonly found in red meat, shellfish, and alcohol [7]. A serum uric acid level may be spuriously low during the acute gout attack.

Calcium pyrophosphate deposition disease (CPPD), or pseudogout, is associated with hypothyroidism, diabetes mellitus, hyperparathyroidism, hypomagnesemia, advanced age, and acute illness [8]. The linear stippled deposition of these CPP crystals into fibrous or hyaline cartilage can be seen on plain X-rays of the knee or wrist and is called chondrocalcinosis [9]. "Pseudorheumatoid pseudogout" refers to a chronic symmetric polyarthritis affecting the small joints that closely mimics RA. The diagnostic distinction is important and frequently missed. Identifying chondrocalcinosis is key in the absence of synovial fluid aspiration as the treatment of pseudorheumatoid pseudogout differs from the treatment of RA.

Milwaukee shoulder syndrome is another crystal deposition disease to which older adults are predisposed. This is a destructive arthritis caused by periarticular or intra-articular deposition of calcium hydroxyapatite crystals [10]. Patients are more commonly female and present with sudden joint effusion with a limited range of motion of one or both shoulders. Synovial fluid is typically hemorrhagic and noninflammatory, and hydroxyapatite crystals are seen with the alizarin red S stain [11]. With recurrent episodes, rotator cuff tears develop and there is a rapid decline in joint function. X-rays will show calcific tendinitis and loss of the normal glenohumeral and subacromial spaces, sometimes with erosions of the articular surfaces. Rotator cuff repair and/or total shoulder replacement may be required.

Complex regional pain syndrome (CRPS) is unlikely to be bilateral, whereas symmetric involvement is a key characteristic of RA. Although marked upper extremity swelling may be present in CRPS, painful dysesthesias, temperature differences, and trophic changes occur in between joint areas, which are not seen in RA [5].

Remitting seronegative symmetrical synovitis (RS3PE) is marked by pitting edema of the hands, wrists, and feet. Flexor and extensor tenosynovitis commonly develop. It remits in 6–15 months with low doses of steroids. RS3PE was originally described as a variant of elderly-onset RA, but the RA-associated HLA-DRB1 genotype is absent, synovitis is milder than the pitting edema and tenosynovitis, and it generally responds to lower doses of prednisone than EORA and does not require DMARDs [12].

Osteoarthritis involving the hands affects the distal and proximal interphalangeal joints. The hypertrophic bone found in osteoarthritis results in enlarged bony nodules of these joint areas known as Heberden's nodes and Bouchard's nodes, respectively. The basal or carpometacarpal joint of the thumb is another classic site for osteoarthritis. MCP and wrist synovitis are not seen in osteoarthritis but are commonly seen in patients with rheumatoid arthritis. Therefore, although pinch strength may be impaired in patients with osteoarthritis, grip strength, which reflects proximal hand joint integrity, will be preserved [5]. Generalized diffuse morning stiffness, constitutional symptoms, and elevated sedimentation rates are not seen in osteoarthritis. Fluid obtained from an osteoarthritic joint is typically noninflammatory, and X-rays show productive rather than erosive changes [4].

Treatment

It is important to distinguish older patients with RA from those with osteoarthritis and other differential diagnostic possibilities because the symptoms, although debilitating, can either improve remarkably or remit with pharmacologic treatment [5]. In long-standing RA, inflammation may be "burned out" leaving ana-

tomic and functional limitations mainly due to superimposed osteoarthritis. But patients with long-standing RA may also have undergone joint replacement or failed multiple trials of disease-modifying therapy. In these cases, systemic manifestations including rheumatoid lung, vasculitic ulcers, peripheral neuropathy, and secondary amyloid (complications of long-standing inflammation) may be seen [4]. Functional status and independence can be maintained in older adults with RA if the disease is recognized and treatment strategies are carefully considered [5].

Pain caused by inflammatory synovitis should be addressed with anti-inflammatory medications. Unfortunately, the first-line treatments for younger RA patients (salicylates and NSAIDs) cause toxicity in older adults at therapeutic doses and may be insufficient to induce remission. Risks include renal insufficiency, hypertension, edema, exacerbation of congestive heart failure, bleeding, and mental status changes [13]. Instead, since patients with EORA are extremely responsive to low-dose steroids (e.g., prednisone ≤5 mg/day) [14], the risk–benefit ratio favors steroids as first-line agents in all older RA patients.

Disease-modifying antirheumatic drugs (DMARDs) are indicated for older patients who have the pattern of disease seen in younger patients or who are unable to be tapered off of steroids after de novo onset [15]. In older adults, hydroxychloroquine sulfate (Plaquenil) and sulfasalazine (Azulfidine) are well-tolerated DMARDs that do not require extensive monitoring [16], although patients should be counseled that their therapeutic effects can take up to 6 months. All patients requiring treatment with DMARDs should be referred to a rheumatologist due to the potential toxicity of these agents.

Of the biologic DMARDs for long-standing RA, while tumor necrosis factor (TNF) alpha inhibitors (e.g., adalimumab, infliximab, etanercept) are generally first-line therapies, potential adverse effects include severe infections (particularly tuberculosis) [17, 18], congestive heart failure, and malignancies (particularly lymphomas) to which older adults are more susceptible [5]. Oral Janus kinase (JAK) inhibitors are known to carry an increased risk of herpes zoster, and there is recent evidence associating tofacitinib with an increased risk of cardiovascular disease in

patients over 50 years old [19]. The anti-CD20 monoclonal antibody rituximab (Rituxan) has been well-studied in older adults. It can be used in patients with prior malignancy or congestive heart failure and is not associated with a higher risk of tuberculosis reactivation [20].

High-dose NSAIDs are first-line therapy for acute attacks of crystal arthritis, but these must be avoided in older adult patients. Similar to EORA, crystal arthritis in older adults are best treated with intra-articular or systemic steroids for palliation and to prevent debility and functional impairment [21]. Colchicine can be used to treat an acute flare if <48 hours from the onset and for prophylaxis against recurrent attacks. Renal dosing is indicated for chronic kidney disease, and patients should be counseled to stop colchicine immediately if they develop abdominal cramping, nausea, or diarrhea [22]. Patients with recurrent gouty attacks, tophi, history of nephrolithiasis, or chronic kidney disease should be offered urate-lowering therapy with concurrent colchicine prophylaxis.

Polymyalgia Rheumatica and Giant Cell Arteritis

Polymyalgia Rheumatica

Acute onset of severe pain and stiffness of the shoulder and hip girdles in patients >60 years old should raise suspicion for polymyalgia rheumatica (PMR), which was first described by Dr. Harry Spiera at the Mount Sinai Hospital [23]. Pain and stiffness may also extend from the shoulder to the neck and from the hip girdle and buttocks to the proximal thighs. Imaging studies have shown inflammation of the periarticular structures, including tendons and bursae [24]. Patients with PMR may therefore have a painful active and passive range of motion [25], but they should not be truly weak unless prolonged symptoms have led to disuse atrophy.

Ninety percentage of cases of PMR show marked elevation of the ESR and a moderate degree of anemia. Fever, malaise, anorexia, and weight loss are also common. A dramatic and com-

plete clinical response to prednisone ≤15 mg/day is essential for diagnosis [26]. Once at 10 mg/day, a slow taper of 1 mg every 4 weeks is recommended to prevent flares [27].

The differential diagnosis for PMR includes malignancy, neurologic disease, thyroid disease, depression, polymyositis (which should display elevated muscle enzyme and proximal weakness more than pain), EORA, adhesive capsulitis, and fibromyalgia (though there is a low incidence of de novo onset fibromyalgia in older adults unless a physiologic or psychologic trauma has occurred) [25]. Due to epidemiologic, pathophysiologic, and clinical features overlapping between the two conditions, patients with a new diagnosis of PMR should be screened for signs and symptoms of giant cell arteritis [28].

Giant Cell Arteritis

Giant cell arteritis (GCA) is commonly called temporal arteritis due to the classic presentation of swollen or tender temporal arteries along with new-onset headache, diplopia, and jaw claudication [29]. Fifteen to twenty percentage of patients with GCA will have an overlap with PMR symptoms [26]. GCA is also exclusively a disease of older adults >50 years old and is characterized by a marked increase in ESR (sometimes >100 mm/h). Constitutional symptoms, fatigue, malaise, anemia, and thrombocytosis may also be seen. Extracranial manifestations of GCA are varied but may include dissection, aneurysm, or stenotic lesions of the great vessels and carotids; cough; hoarseness; tongue or limb claudication; and acute hearing loss. High-dose glucocorticoid (prednisone 40–60 mg/day) should be started immediately due to the risk of permanent ischemic vision loss, even while work-up continues.

The gold standard for diagnosis is a temporal artery biopsy, but sensitivity is only 77% due to skip lesions and sample processing. Sensitivity can be improved with bilateral biopsies and ensuring a segment of ≥2 cm [30]. Jaw claudication has a high positive predictive value for biopsy findings on the ipsilateral side. Histopathology reveals intimal thickening or necrosis with obstruction of the arterial lumen. Multinucleated giant cells in a

granulomatous infiltrate may be seen between the media and intima but are not required for the diagnosis [26]. Special attention should be made to the elastic Van Gieson stain addendum, which may reveal evidence of vasculitis with a disrupted internal elastic lamina.

Treatment of GCA requires continuing high-dose steroids for 1 month to induce remission. Following this, steroids should be tapered to a target dose of 15–20 mg/day within 2–3 months and to ≤5 mg/day after 1 year [31]. There is conflicting evidence as to the association of PMR and/or GCA with malignancy [32–35]. Age-appropriate cancer screening should be performed at minimum.

Patients should be counseled that relapse and recurrence are common in both PMR and GCA [29]. Because of this, prospective management should include bone-protective therapy. Gastroduodenal protection and *P. jirovecii* prophylaxis may also be considered [26]. Consultation with a rheumatologist is recommended due to the expected need for a steroid-sparing immunosuppressive medication such as Tocilizumab

Drug-Induced Lupus

Patients presenting with new-onset joint pain, serositis, autoimmune hemolytic anemia or thrombocytopenia, and/or constitutional symptoms should raise suspicion for drug-induced lupus erythematosus (DILE) [36]. Idiopathic SLE is extremely rare in older adults, but this cohort has a higher frequency of medication exposure that may trigger new inflammatory symptoms. Carefully review the medication list, particularly for drugs started in the past year. Associations have been reported with isoniazid, procainamide, hydralazine, D-penicillamine, minocycline, sulfa-based drugs, sulfonylureas, anticonvulsant agents, beta-blockers, proton pump inhibitors, and antifungal agents [37].

Compared to systemic lupus erythematosus (SLE), DILE affects males and females equally and renal and CNS diseases are rare. DILE is characterized serologically by a positive antinuclear

antibody (ANA) and anti-histone antibody but is overall a clinical diagnosis [36]. Symptoms typically resolves within days or weeks of stopping the inciting medication. Topical steroids may be used to treat rashes, which are very similar to subacute cutaneous lupus erythematosus. Severe disease may require low doses of systemic glucocorticoids.

TNF-inhibitor-induced lupus is a special case of DILE, which represents a growing proportion of cases as these agents reach widespread use [37]. Infliximab is most commonly implicated [38]. The ANA is positive, but instead of an anti-histone antibody, these patients more commonly have antibodies against double-stranded DNA. Patients with DILE due to TNFα-inhibitors are more likely to have classic lupus symptoms, including rash, hypocomplementemia, and renal disease [39]. They may require oral glucocorticoids and additional immunosuppressive therapy.

Localized Musculoskeletal Disorders

Bursitis

The bursae are fluid-filled sacs that cushion opposing surfaces between muscles, tendons, ligaments, and bony prominences and are lined by a synovial membrane. Superficial bursae such as the olecranon, prepatellar, and retrocalcaneal bursae may show characteristic signs of inflammation; deeper ones must be carefully targeted on a physical exam for tenderness. Marked inflammation, warmth, and swelling in the superficial bursae should prompt evaluation for septic bursitis [40].

Subacromial and subdeltoid bursitis commonly occur with other rotator cuff pathology, including tears, impingement syndrome, and PMR. Pain may be present even at rest and will be exacerbated by overhead activities. Patients may also complain of pain when lying on the affected side [41]. Active abduction of the arm beyond 80 degrees will produce pain as the bursa is compressed under the acromion, but patients will not be weak unless there is a concomitant muscle tear. Prolonged disuse allows for

contracture and muscle atrophy, which can lead to frozen shoulder or adhesive capsulitis. Patients should be counseled on the importance of physical therapy once therapeutic glucocorticoid injection takes effect.

Olecranon bursitis may occur from acute trauma or chronic impact forces if the patient leans frequently on the elbow. As the bursa is extra-articular, passive elbow extension is unaffected. However, the patient may experience pain upon maximal flexion of the elbow due to compressive forces, which increase the intrabursal pressure. Gouty bursitis can be indistinguishable from or occur concurrently with septic bursitis, which is commonly due to staphylococcus or streptococcus infection [36]. Tophus may be appreciated within the distended bursa sac.

Trochanteric bursitis is a common cause of hip pain when patients point directly to the lateral hip area [42]. Pain may refer down the iliotibial band and may be worse when lying on the affected side at night. It is usually exacerbated by extending the leg during walking. Patients who reference pain in the groin should be evaluated for true hip joint pathology.

In the lower extremities, pre-patellar and pes anserine bursitis are extra-articular mimics of knee osteoarthritis [36]. Pre-patellar bursitis is also known as carpenter's or housemaid's knee due to repetitive forces from kneeling in these occupations [43]. Active and passive knee extension will be normal, but maximal flexion may be painful. The pes anserine bursa lies medial and distal to the knee joint line where the sartorius, gracilis, and semitendinosus muscles insert. Patients have comorbid osteoarthritis and may complain of pain when crossing one leg over the other, lying on the side at night, or rising from a chair, or ascending or descending stairs.

Treatment of bursitis involves rest, ice, bracing or joint protection, and anti-inflammatory medications. Due to the risk of infection or creating a draining sinus tract, superficial lesions such as olecranon, prepatellar, and retrocalcaneal bursitis should not be injected. NSAIDs or a short course of prednisone may be prescribed if topical therapies do not provide relief [44]. For deeper bursae, local corticosteroid injection is preferable to NSAIDs in older adults.

Spontaneous Osteonecrosis of the Knee (SONK)

SONK is a unique form of avascular necrosis encountered only in older adults. The typical patient is an elderly woman who presents with the hyperacute onset of severe knee pain in the medial aspect of the medial femoral condyle, which is a weight-bearing segment [36, 45]. Plain films are insensitive for the diagnosis of SONK. MRI or bone scan is diagnostic and can also provide prognostic information regarding lesions that will resolve without surgical intervention [46]. Additional investigation is needed regarding the use of bisphosphonates for the nonsurgical management of SONK [47].

Diffuse Idiopathic Skeletal Hyperostosis (DISH)

Widespread calcification and ossification of the paravertebral ligaments and entheses are known as DISH, ankylosing hyperostosis, or Forestier's disease [48]. It is more common in men than women and is rare under age 40. Pain and reduced motion in the neck and back are common, but some are asymptomatic and diagnosed only by characteristic changes on radiographic imaging such as CT [49]. Spinal morning stiffness can occur along with functional impairment [50]. Compared to inflammatory spondyloarthropathies in a younger cohort, laboratory markers in patients with DISH are reassuringly normal and the HLA-B27 antigen is negative. Mechanical factors associated with advanced age are suspected of contributing in part. Multimodality physical therapy, acetaminophen, and NSAIDs may be used for treatment.

Discussion

This chapter has delineated multisystem and localized inflammatory diseases that commonly affect older adults. Recognition of these conditions as distinct from age-related osteoarthritis is important as timely diagnosis and treatment can be lifesaving and improve quality of life.

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10 Interpretation of Rheumatological Tests

Shane Murray and Yousaf Ali

Case Scenario

A 68-year-old woman presents with worsening pain in her left wrist and right knee over several years. She has a past medical history of obesity and type 2 diabetes mellitus. Past surgical history is notable for the repair of a right anterior cruciate ligament rupture. Her pain is exacerbated by activities such as walking or holding objects with her left hand. The review of systems is otherwise negative. On examination, she has a mildly decreased range of motion of her left wrist and right knee. Crepitus is appreciated on passive movement of the right knee. No tenderness, erythema, or warmth is appreciated on the complete joint examination. Testing reveals a weakly positive 1:160 antinuclear antibody (ANA) titer. What diagnostic tests, if any, should be ordered next?

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Testing for Connective Tissue Diseases

Connective tissue diseases (CTDs) are characterized by an autoimmune response leading to systemic inflammation and musculoskeletal pain as a result. They share many overlapping features with primary musculoskeletal disorders. Unlike musculoskeletal disorders, CTDs have additional specific features and serological test results that characterize each one (Table 10.1) [1, 2].

Table 10.1 Tests for suspected connective tissue disorders

Connective tissue disorder	Screening test	Follow-up tests
Systemic lupus erythematosus	ANA	Anti-double-stranded DNA antibodies, anticardiolipin antibodies, anti-Smith antibodies, anti-ribonucleoprotein U1 antibodies, lupus anticoagulant, Sjögren antibodies
Rheumatoid arthritis	Rheumatoid factor	Anticyclic citrullinated antibodies
Mixed connective tissue disease	ANA	Anticardiolipin antibodies, anticyclic citrullinated peptide antibodies, anti-Jo-1 antibodies, anti-ribonucleoprotein antibodies, anti-Scl 70 antibodies, rheumatoid factor
Dermatomyositis/ polymyositis	ANA, creatine kinase	Myositis-specific-antibodies, including anti-Jo-1 antibodies
Sjögren syndrome	ANA	Sjögren antibodies
Vasculitis	Antineutrophil cytoplasmic antibodies	Antiproteinase 3 antibodies, antimyeloperoxidase antibodies

Information from Refs. [1, 2]
ANA antinuclear antibody

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic, recurrent, multisystem autoimmune disease characterized by the production of autoantibodies resulting in end-organ inflammation. The multisystem nature of the disease leads to a range of clinical manifestations. The diagnosis of SLE is based on a combination of clinical features and serological evidence [3].

SLE affects women and black populations most commonly. The highest estimates of incidence and prevalence geographically are in North America [4]. It should be suspected in patients with a photosensitive rash, mucositis, arthritis, renal, hematologic, CNS, and serosal involvement [3]. ANA is the classic hallmark for SLE, found in more than 95% of patients [5]. In addition to ANA testing, in suspected cases of SLE, it is also important to screen for end-organ complications of disease. A complete blood count (CBC) with white cell differential can be ordered to evaluate for anemia (which can be secondary to chronic inflammation or autoimmune hemolysis), neutropenia, leukopenia, lymphopenia, and thrombocytopenia. A basic metabolic panel (BMP) can screen for renal injury with urea and creatinine and establish baseline renal function. Urinalysis with microscopy checking for red cells, white cells, cellular casts, and protein can identify early signs of kidney disease, which may be silent clinically [6].

Antinuclear Antibodies

The term ANA refers to antibodies directed at various cellular compartments. It is a highly sensitive screening test for SLE; a positive test result is found in nearly all affected patients [7]. The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) now recommend that a positive ANA be used as an “entry criterion” required for SLE classification [3]. Nevertheless, due to the high prevalence of autoantibodies in the community and lack of specificity, the majority of patients with a positive ANA, however, do not have SLE. Up to

32% of normal individuals can have a positive result at a 1/40 titer [8]. The prevalence varies according to age and sex, with older patients, particularly women over 65 years, having a positive result [9].

ANA is detected in most other connective tissue diseases, including Sjögren's, mixed connective tissue disease (MCTD), rheumatoid arthritis (RA), and scleroderma (SSc). It is also observed in organ-specific autoimmune diseases, including Hashimoto thyroiditis, type 1 diabetes mellitus, autoimmune liver disease, and pulmonary fibrosis. Finally, it is important to remember that ANA can be positive in malignancy or in chronic infections such as tuberculosis, mononucleosis, HIV, and hepatitis C.

ANA results are reported using a titer of varying dilutions. A higher ANA titer generally means that the patient is more likely to have a connective tissue disorder. The titer indicates how many times the patient's serum was diluted before the antibodies could no longer be detected. The titer is therefore a measure of the amount of ANA in the blood. A higher titer indicates more autoantibodies. ANA levels can fluctuate over time. The changes, however, have not been shown to provide useful clinical information and do not reflect disease activity [10]. If the test is positive once, it does not need to be repeated. Although a negative ANA test can become positive over time, the positive result is rarely associated with a new diagnosis. Therefore, repeat testing after a negative result is not recommended and results in high costs [11].

The results of ANA testing are also reported as the staining pattern produced by the antibodies. In SLE, the ANA pattern will commonly be reported as homogeneous or rim; in Sjögren's disease, a speckled pattern is often reported. A nucleolar pattern is most common in systemic sclerosis (SSc), reported in 15–40% of patients [12]. In limited SSc, a pattern of centromere staining is seen in approximately 30% of patients.

ANA titers are frequently false positive as a result of diseases capable of nonspecific autoantibody generation. Hence, the performance of an ANA test depends on the pretest probability of the disease. When an ANA test results positive and clinical suspicion remains, it should be followed with a more specific assay to confirm the diagnosis. These assays also detect antibodies to cellular

antigens. If SLE is suspected, anti-double-stranded DNA (anti-dsDNA) and anti-Smith (anti-Sm) antibodies are key markers for the diagnosis and should be tested [13, 14]. Testing for lupus anticoagulant, anti-β2 glycoprotein, anticardiolipin, complement levels, and direct Coombs is also recommended [3, 15].

Anti-Double-Stranded DNA Antibodies

Anti-dsDNA antibodies are important in the evaluation and management of patients with SLE. The test has a sensitivity of 70% and a specificity of 95% [10]. The high specificity can help distinguish patients with SLE from patients with other autoimmune diseases. Fluctuations in levels can be useful in monitoring and predicting exacerbations; increasing levels correlate with disease activity in some patients [16, 17]. The antibodies have been shown to form immune complexes that are deposited in the glomeruli leading to glomerulonephritis [18]. In this subset of patients, high levels of anti-dsDNA antibodies correlate with active glomerulonephritis [17].

Anti-Smith Antibodies

Anti-Sm antibodies are insensitive markers but have the greatest specificity for SLE (98.6%) [19]. The antibodies are detected in only 10–50% of patients with SLE, contributing to the low sensitivity of the test (39.7%). Levels of the antibody do not fluctuate unlike anti-dsDNA antibodies, which may return to a normal range when the disease is inactive.

Drug-Induced Lupus

Certain medications can induce the expression of autoantibodies. If produced in high enough quantities, a syndrome with clinical features similar to SLE termed drug-induced lupus (DIL) can develop. Medications classically associated with the disorder

include diltiazem, hydralazine, procainamide, isoniazid, and anti-tumor necrosis factor (TNF) alpha therapy (most commonly infliximab and etanercept) [20, 21]. Typically, DIL will present as a milder version of SLE. Symptoms of arthralgia, myalgia, and fever in a patient taking one or more associated medications should raise suspicion for DIL. Pleurisy and pericarditis are other characteristic signs [22], but DIL rarely involves the renal or nervous system.

Anti-histone antibodies are classically associated with DIL; however, they can also present in idiopathic lupus, rheumatoid arthritis, Sjögren's disease, systemic sclerosis, and primary biliary cirrhosis [23]. The vast majority of patients with drug-induced autoantibodies will never develop signs of DIL [24]. Hence, testing should be restricted to patients with features of SLE taking one of the medications listed above. An ANA titer should be obtained, and if positive, a follow-up anti-histone antibody test is recommended. Anti-histone antibodies are sensitive but nonspecific for DIL. They are found in 95% of patients with DIL; fortunately, most patients who produce the antibodies rarely develop clinical disease [25].

Sjögren Syndrome

Sjögren syndrome (SS) is a chronic autoimmune disease characterized by lymphocytic infiltration of exocrine glands. It classically involves the lacrimal and salivary glands resulting in dryness of the eyes and mouth (sicca and xerostomia). In addition, other organs can be involved leading to a variety of clinical manifestations. SS can occur in isolation (primary SS) or can complicate another CTD (secondary SS). Diagnostic criteria include objective findings of oral and ocular dryness in a patient with symptoms, focal lymphocytic sialadenitis on salivary gland biopsy, and positive autoantibody titers, including ANA [26, 27].

The classic antibodies associated with SS are anti-Ro/SSA and anti-La/SSB. They can be detected in 70–100% and 40–90%,

respectively, of patients with primary SS [28]. Anti-Ro/SSA can be positive independent of anti-La/SSB, but the contrary is rare. Anti-Ro/SSA antibodies are prevalent in several autoimmune diseases, including SLE, SSc, rheumatoid arthritis (RA), and primary biliary cirrhosis, whereas anti-La/SSB antibodies are more specific for SS [29]. When positive in patients with RA, the risk for secondary SS is increased. In the context of SLE, anti-Ro/SSA and anti-La/SSB are produced earlier than other SLE-related autoantibodies; anti-Ro/SSA increases the risk for interstitial pneumonitis, cytopenia, subacute cutaneous lupus, and nonerosive deforming arthritis (Jaccoud's arthropathy) [30]. Additionally, both antibodies are capable of crossing the placenta leading to neonatal complications such as neonatal lupus. A positive test can help identify pregnant women at risk. The most serious complication is congenital heart block, which occurs in about 2% of newborns from women known to be anti-Ro/SSA positive and with known CTD [31].

Mixed Connective Tissue Disease

MCTD is an overlap syndrome of SSc, SLE, and polymyositis. Making a diagnosis is complicated, typically taking years as the characteristic overlapping features of each disease tend to occur sequentially. Patients can initially present with nonspecific symptoms; low-grade fevers, myalgias, arthralgias, and fatigue are common. The characteristic clinical features include the Raynaud phenomenon, hand edema, puffy fingers, arthritis, and myositis. Patients are also at risk for pulmonary hypertension. Obtaining an ANA titer is the best initial screening test, and staining is typically positive in a high titer speckled pattern. A positive ANA should be followed by testing for anti-ribonucleoprotein (RNP) antibodies (RNP). Although positive in other autoimmune diseases, their sensitivity for diagnosing MCTD is 71–100% and specificity is 84–100% [14].

Systemic Sclerosis (Scleroderma)

SSc is a clinical syndrome characterized by chronic widespread vascular dysfunction, alterations of humoral and cellular immunity, and abnormal collagen deposition. This results in fibrosis of the skin and internal organs, pulmonary hypertension, and interstitial lung disease. The disease is classified based on the extent of skin involvement and pattern of organ involvement. The two major categories are limited cutaneous SSc and diffuse cutaneous SSc. Diagnosis is dependent on the presence of specific clinical findings and autoantibodies. In patients with clinical features of SSc, antibody testing should be performed. ANA is positive in 95% of patients with Scc and is the best initial test. Positive ANA titers should be followed up with anti-centromere and anti-Scl 70 antibody tests, which are present in limited SSc and diffuse SSc, respectively. Anti-Scl 70 is also associated with a higher risk of severe interstitial lung disease and increased mortality [12]. When comparing patients with SSc to healthy controls, both tests have relatively low sensitivity, 33% and 43%; however, their specificity is extremely high, 99.9% and 100%, respectively [32]. Other autoantibodies found in SSc but outside the scope of this text include anti-RNA polymerase III and anti-PM/Scl and have prognostic significance for certain complications such as renal crisis and lung involvement, respectively.

Dermatomyositis and Polymyositis

The inflammatory muscle diseases dermatomyositis (DM) and polymyositis (PM) are characterized by immune-mediated muscle inflammation and destruction. They should be suspected in patients with symmetric proximal muscle weakness, elevated levels of muscle enzymes such creatine kinase, absence of nerve involvement on EMG, and characteristic muscle pathology. In DM, the pattern of muscle involvement is similar to PM but is almost always accompanied by specific skin findings affecting the hands (Gottron papules), eyelids (heliotrope rash), chest (V sign

neck), and back of the neck (shawl sign). ANA may be positive in up to 80% of patients with DM or PM [33]. Autoantibodies can be categorized into myositis associated, which can be found in other autoimmune diseases, and myositis specific, which are mainly positive in patients with inflammatory myositis.

Anti-Jo-1 antibody is the most common myositis-specific antibody in patients with DM and PM. The antibody is also associated with antisynthetase syndrome, seen in one-third of patients with PM and DM. in addition to myositis, antisynthetase syndrome is characterized by the presence of Raynaud phenomenon, nonerosive arthritis, interstitial lung disease, and skin fissuring on the lateral aspects of the distal fingertips and palms termed "mechanic's hands." Anti-Jo-1 makes up part of a group of autoantibodies that target aminoacyl-tRNA synthetases (anti-synthetase). These autoantibodies are found in about 20% of patients with inflammatory myositis, and anti-Jo-1 accounts for 80% of all antisynthetases [33]. Due to their low prevalence, these antibodies are not routinely measured in patients with myalgia.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, symmetric, peripheral polyarthropathy affecting large and small joints with a predilection for the hands, wrist, and feet. The ACR/EULAR classification criteria for diagnosis uses a combination of clinical findings and laboratory testing. The criteria include number of small joints involved, the presence of autoantibodies (rheumatoid factor and anticyclic citrullinated peptide antibodies), acute phase reactants, and duration of symptoms [34].

Rheumatoid Factor

Rheumatoid factor (RF) is an autoantibody, produced from polyclonal β cell activation and directed against the Fc portion of IgG immunoglobulin (Ig). While classically associated with RA, a positive RF can be positive in a variety of rheumatic diseases,

nonrheumatic diseases, and in healthy subjects (Table 10.2) [35]. In patients presenting with distal symmetrical polyarthritis, a positive RF increases the probability of RA but does not provide a definite diagnosis. RF is reported as a titer; a higher titer increases the likelihood of RA. RF-positive patients are more likely to develop erosive joint disease and extraarticular manifestations than those with RF negative RA [36]. The overall sensitivity and specificity are 69% and 85%, respectively; the positive likelihood ratio (LR+) is 4.9, and the negative likelihood ratio (LR−) is 0.41 [37]. The utility of RF testing therefore depends on the pretest

Table 10.2 Conditions associated with a positive rheumatoid factor

Connective tissue disorder (rate of positive titer)
Cryoglobulinemia (40–100%)
Mixed connective tissue disease (50–60%)
Rheumatoid arthritis (50–90%)
Sjögren syndrome (75–95%)
Systemic lupus erythematosus (75–95%)
Systemic sclerosis (20–30%)
Nonrheumatic conditions
Aging
Infections
Bacterial endocarditis
Liver disease
Tuberculosis
Syphilis
Parasitic infections
Viral infections (especially rubella, mumps, and influenza)
Pulmonary diseases
Sarcoidosis
Asbestosis
Silicosis
Interstitial pulmonary fibrosis
Other conditions
Cancers (especially leukemias and colon cancer)
Primary biliary cirrhosis

Adapted with permission from Shmerling and Delbanco [49]

probability of RA. In areas of low disease prevalence and in patients with a few clinical signs of RA, the positive predictive value of the test is low. Hence, RF should not be used as a screening test in patients with joint pain.

Anticyclic Citrullinated Peptide Antibodies

The relatively low sensitivity and specificity of RF led to the development of the anticyclic citrullinated peptide (CCP) antibody test. Measurement of Anti-CCP antibodies by enzyme-linked immunosorbent assay (ELISA) is useful in patients presenting with polyarthritis because of the high specificity of the test for RA. The pooled sensitivity and specificity are 57% and 96%, respectively; LR+ is 12.7 and LR− is 0.45 [38]. Anti-CCP antibodies may provide information on prognosis and are more predictive of erosive joint disease than RF [37].

Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis

ANCA-associated vasculitis includes three diseases characterized by the presence of ANCA: granulomatosis with polyangiitis, formerly known as Wegener's granulomatosis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA or Churg–Strauss syndrome). All three diseases are characterized by vasculitis of small and medium blood vessels and can be classified by typical patterns of vascular involvement, clinical features, and laboratory testing.

ANCA

There are two forms of autoantibodies associated with ANCA: p-ANCA (perinuclear, directed against the neutrophil enzyme myeloperoxidase) and c-ANCA (cytoplasmic directed against

the neutrophil proteinase 3). Cytoplasmic and perinuclear refer to the patterns of immunofluorescent staining; ELISA is used to confirm antibody positivity. Although biopsy with characteristic vascular histology is the preferred diagnostic test for each disease, ANCA testing has clinical utility as a diagnostic marker. ANCA is associated with all three conditions as either targeting proteinase-3 (c-ANCA) or myeloperoxidase (p-ANCA), but almost never both.

In GPA, approximately 90% of patients with active, generalized disease are c-ANCA positive. ANCA can be negative in patients with inactive disease and in those with limited forms of the disease. The pooled sensitivity and specificity of c-ANCA for GPA are 66% and 98%, respectively [39]. GPA is a rare condition with a low prevalence in the general population; a positive c-ANCA test is more likely to be false positive in this situation if not applied to patients with a high pretest probability of disease. For example, patients presenting with isolated sinus disease and a positive ANCA have a low probability of having GPA. However, in patients with combined sinus and pulmonary disease, a positive ANCA test is strongly suggestive of disease. Therefore, ANCA testing should be reserved for patients with clinical features of active disease, such as rapidly progressive renal failure, alveolar hemorrhage, pulmonary–renal syndrome, and mononeuritis multiplex [40].

Like GPA, microscopic polyangiitis (MPA) characteristically affects the lungs and kidneys along with other organ systems. Close to 90% of patients are ANCA positive, with the majority having p-ANCA. Because c-ANCA and p-ANCA can occur in both GPA and MPA, they cannot be distinguished on the basis of ANCA specificity. MPA is distinguished from GPA by the absence of granulomatous vasculitis on biopsy.

In eosinophilic granulomatosis with polyangiitis (EGPA), approximately 50% of patients are ANCA positive. Both c-ANCA and p-ANCA can be detected, with p-ANCA occurring more frequently in ANCA-positive patients. ANCA-positive EGPA may have clinical differences to ANCA-negative disease [41].

Other Tests

Erythrocyte Sedimentation Rate

Erythrocyte sedimentation rate (ESR) measures the rate (expressed as mm/h) at which erythrocytes fall through anticoagulated plasma. Proteins in the plasma, such as acute phase reactants, can interact with and neutralize charges on the erythrocyte surface, promoting their ability to settle at a faster rate. Therefore, ESR functions as an indirect marker of inflammation. ESR elevation can be seen in many rheumatological diseases but is of particular importance in polymyalgia rheumatica (PMR) and giant cell arteritis (GCA), where it is also used to measure response to treatment. ESR is included in the ACR classification criteria for PMR along with C-reactive protein [42].

The normal ESR increases with age due to changes in blood fibrinogen levels affecting the fall or erythrocytes. ESR is also typically higher in women. An accepted rule of thumb to calculate the age-adjusted upper limit of normal ESR is age/2 in men and (age + 10)/2 in women. The ESR can be influenced by factors unrelated to inflammation such as low fibrinogen levels as seen in liver disease or heart failure, other constituents of blood such as immunoglobulins, erythrocyte shape, size, and number, and technical factors (Table 10.3). A markedly elevated ESR (>100 mm/h)

Table 10.3 Factors that may influence erythrocyte sedimentation rate

Increased ESR	Decreased ESR
Age/female sex	Polycythemia
Pregnancy	RBC abnormality (e.g., spherocytosis)
Anemia	Technical factors
RBC abnormality	Clotted sample
Macrocytosis	Short ESR tube
Hyperfibrinogenemia	Vibration during testing
Infection	Hypofibrinogenemia
Inflammation	Hypogammaglobulinemia
Malignancy	Dysproteinemia

should raise concern for conditions such as malignancy, overwhelming infection, active CTD, and giant cell arteritis [43].

C-Reactive Protein

C-reactive protein (CRP) is produced by the liver in response to interleukin-6 generated by leukocytes during inflammation. Compared to ESR, CRP is more sensitive to subtle changes in the acute-phase response and correlated better with disease activity [44].

Although acute phase reactants (APRs) typically follow a similar pattern, there are exceptions to this; ESR and CRP levels can be discrepant. CRP levels rise and fall more rapidly than other acute phase reactants in response to inflammation. Characteristics of the inflammatory stimulus and response can also lead to the production of different APRs. In SLE, ESR is typically elevated, often markedly, while the CRP response is blunted. Those with serositis can show a marked CRP response, but its absence should raise suspicion for infection [45].

Human Leukocyte B27 Antigen

HLA B27 is a MHC class I surface antigen involved in presenting antigenic peptides to T cells. It has a high association with ankylosing spondylitis and is present in up to 90% of patients with the disease [46]. It is implicated in the other types of seronegative spondyloarthropathies, such as psoriatic arthritis, reactive arthritis, and enterohepatic arthritis. HLAB-27 is also present in up to 6% of healthy persons in the United States [47]. The predictive value of testing for HLA-B27 therefore depends on the pretest probability of ankylosing spondylitis or related spondyloarthropathy. The test should not be ordered in patients routinely presenting with back pain; however, if ankylosing spondylitis is suspected but further evidence is needed, the test can be helpful. Testing for HLA-B27 can also help differentiate alternative etiologies of aortic regurgitation, iritis, and oligoarticular arthritis [48].

Final Comment

The patient described in the clinical scenario does not have symptoms of a connective tissue disease. Her clinical presentation is typical of osteoarthritis (OA), the most common form of arthritis in her age group. Her examination is also consistent with a noninflammatory etiology of joint pain with the absence of erythema, pain, or swelling. She has several risk factors for OA, including obesity, gender, age, and prior joint injury. The positive ANA test is not helpful in this situation. As previously mentioned, ANA results are frequently false positive, and positive results at a titer of 1:40 are commonly found in women over the age of 65 [7, 10]. Hence, as this patient has no clinical evidence of clinical signs of a connective tissue disorder, no further immunologic tests are warranted.

Tests for connective tissue disorders should be performed selectively in the correct clinical context. Inappropriate testing can lead to unnecessary costs, misdiagnosis, and even inappropriate treatment. Serologic testing is one aspect of diagnostic testing and should be reserved for patients with a high clinical likelihood of a specific rheumatological disease.

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Infectious Arthritis

11

Daniel Bunker and Gayle Phadungchai Balba

Septic Arthritis

A 72-year-old male with diabetes presents with 1 day of left knee pain and swelling. His symptoms began suddenly and have been worsening. He describes severe pain throughout the entire knee; he is unable to bear weight. He reports feeling hot, but he is unsure if he has had a fever. On exam, he has a warm and palpable effusion in the left knee. What is the most important next step in diagnosis?

The history and exam are concerning for septic arthritis, which is typically due to a bacterial infection. Many different bacteria can cause osteoarticular infections (Table 11.1). The most common is *Staphylococcus aureus*, though Streptoccocal species are also frequently reported [1]. Gram-negative bacteria

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Table 11.1 Bacteria causing septic arthritis

Bacteria	Comment
Staphylococcus aureus	Most common
Streptococcus pneumonia	Do not need to have a concurrent pneumonia
Neisseria gonorrhea	Common in younger patients, two phenotypes: purulent arthritis or triad of tenosynovitis, dermatitis, and polyarthralgias (discussed later)
Gram negative (e.g., *E. coli*)	Usually seen in immunocompromised patients
Lyme	Can migrate and self-resolve (discussed later)

are less common but can be seen in immunocompromised patients. Additionally, *Neisseria gonorrhea* deserves special mention as it is the most common cause of septic arthritis in younger sexually active adults. In addition to bacterial infections, mycobacterial and fungal organisms should be considered in the immunocompromised patient with an indolent progressive arthritis (discussed later). The knee is by far the most common joint affected (~50% of cases); other common involved joints include hip, ankle, elbow, wrist, and shoulder [2]. Septic arthritis is typically monoarticular, but polyarticular disease can be seen in 10–20% of cases [3]. Major risk factors for septic arthritis include age (both very young and elderly), immunosuppression, diabetes, intravenous drug use, dialysis dependence, and importantly, a history of joint prosthesis; however, it should be noted that approximately 20% of patients do not have any identifiable risk factors. The overall incidence of septic arthritis is increasing, especially among the elderly [4].

Bacterial joint infections can cause significant joint destruction within 24–48 hours; early identification and initiation of appropriate therapy is crucial to joint preservation as well as patient survival. Of note, there are no vital signs or serum lab values that can appropriately diagnose septic arthritis; fever and leukocytosis, for example, are seen in only about half of patients with septic arthritis [5]. Elevated inflammatory markers are expected, but this does

not distinguish septic arthritis from the most common mimickers, notably crystalline arthropathies (gout or acute calcium pyrophosphate deposition disease arthropathy). Importantly, although almost all joints are seeded hematogenously, blood cultures are positive in only about 50% of cases.

In contrast to peripheral blood tests, a joint aspiration is indispensable for the diagnosis of septic arthritis and is the most important next step in the workup of the above patient. If this cannot be done in the office, the patient should be sent urgently to the Emergency Room. The likelihood of septic arthritis increases with a higher synovial fluid white blood cell count [6], but the diagnosis is only confirmed by culture of the organism from the joint fluid.

Septic arthritis is treated initially in the hospital setting with IV antibiotics for 4–6 weeks. Additionally, as the infection can be considered a closed-space infection like an abscess, drainage of the affected joint—most commonly with surgical arthroscopy—is also necessary [7]. The overall mortality of septic arthritis is about 10–15%, and about a third of patients will have poor joint outcomes [8]. Age greater than 65 is a major risk factor for both mortality and lasting joint damage in septic arthritis [5].

Disseminated Gonococcal Infection

A 22-year-old female presents with 1 week of migratory polyarticular joint pain and fevers. She first noticed pain and swelling of the right knee, such that it limited her ambulation. There was a minimal response to ibuprofen. A few days later, she noticed swelling and pain in the left wrist and hand; at that time, it was difficult to get dressed in the morning and open doorknobs. She has felt febrile. She denies any sore throat. On exam, she has warmth of the right knee and left wrist, as well as pain in the fingers with passive flexion. You also note purpuric pustular skin lesions around the ankles and on the volar fingers. What is the most likely diagnosis?

This patient is presenting with an acute asymmetric polyarthritis. The differential includes autoimmune, crystalline, or infectious causes, as well as serum sickness due to a new medication. As in the previous case, a joint aspiration would be the best next step. However, the symptoms of an acute migratory polyarthritis, with notable tenosynovitis (as represented by pain with passive ROM of the fingers), and purpuric pustular skin lesions, in a younger patient, is most consistent with disseminated gonococcal infection (DGI). DGI can occur phenotypically in two ways [9]. The first, as described above, is with fever, tenosynovitis, and dermatitis. Characteristic cutaneous lesions are small purpuric macules on the hands and feet [10]. DGI can also present with a more classic monoarticular septic arthritis. Less than 5% of primary gonococcal infections will disseminate [11]; however, the primary infection is often asymptomatic so the lack of mucosal symptoms (e.g., urethritis) cannot be used to rule out the disease. Patients with inherited complement deficits are at high risk for DGI, while menstruating, pregnant and recently post-partum women are also at increased risk. The incidence of gonococcal infections has been decreasing but remains high in certain populations such as men who have sex with men (MSM).

The diagnosis of DGI is made by finding evidence of gonorrhea in a patient with a compatible clinical picture. Blood cultures processed on Thayer-Martin media should be obtained; nucleic acid amplification testing (NAAT) from specimens from all three mucosal sites (pharyngeal, urogenital, and rectal) should also be performed. Importantly, patients with DGI can have evidence of gonorrhea even at asymptomatic sites; so, it is crucial to sample all potential sites of mucosal infection. Synovial fluid should be sent for cell count, differential, gram stain and culture as well as NAAT.

Treatment of DGI is typically intramuscular or intravenous ceftriaxone daily for 7–14 days with a single dose of azithromycin 1000 mg. Drug resistance among gonococcal isolates is growing, and treatment with tetracyclines and especially fluoroquinolones is no longer recommended [12].

Acute Rheumatic Fever

A 33-year-old female patient originally from Brazil presents with 1 week of fevers, pain, and swelling of multiple joints. Originally, she endorsed pain in the right ankle; subsequently the pain spread to her left knee and left wrist, and her right ankle spontaneously improved. She has been taking naproxen with some improvement in symptoms. She notes a history of "rheumatism" for which she has had to see a cardiologist in the past, and a low pitch diastolic murmur is heard at the apex on exam today. She endorses a sore throat in the weeks prior to her joint symptoms. You are concerned about acute rheumatic fever; however, a rapid strep test in the office is negative. What are the appropriate next diagnostic steps?

Acute rheumatic fever (ARF) is an immunological reaction to group A strep (GAS) pharyngitis; symptoms typically occur 2–4 weeks following the primary infection and can consist of fevers, arthritis, carditis, erythema marginatum (an evanescent, annular pink/red rash with slightly raised red border, most common on the trunk and limbs), chorea, and subcutaneous nodules. Importantly, not all patients—especially children—recall a preceding sore throat [13]. At presentation throat cultures and rapid strep tests are usually negative as in the above patient, so evidence of a recent GAS infection is typically made serologically with positive antistreptolysin or anti-DNase titers [14]. ARF is very uncommon in the United States but can be seen in patients immigrating from other counties. It is also more common in patients with previous episodes of rheumatic fever, as in the patient above.

The arthritis of ARF is described as migratory or additive as it spreads from joint to joint. Large/medium size joints such as the knee, ankle, elbow, and wrist are most commonly affected; each individual joint will have symptoms for a few days to a week. It typically responds well to aspirin or NSAIDs [15].

The diagnosis ARF is made using the Jones Criteria, which were updated in 2015 and now distinguish between patients from high and low prevalence countries [16]. Evidence of a recent GAS infection (typically made via serology) is required for diagnosis.

Eradication of GAS with antibiotics is recommended, even if the patient has no current evidence of pharyngitis, as well as screening and treatment of household contacts with group A streptococcus positive throat cultures. The arthritis of ARF is treated symptomatically, typically with aspirin or NSAIDs, and should resolve within 4 weeks without any sequalae [15].

The most problematic complication of ARF by far is rheumatic heart disease (RHD). Although the carditis of rheumatic fever can affect any structure in the heart, valvular disease is typically the most clinically relevant; RHD is the most common cause of acquired valvular disease in the world and causes 275,000 deaths per year [17]. Thus, patients with a history of ARF should receive prophylaxis against future strep infections at least until age 21 (and even longer if there is a history of RHD), since these patients at high risk for recurrent ARF attacks upon re-exposure to GAS, and each subsequent attack typically worsens RHD.

Lyme Arthritis

A 52-year-old male presents with 1 week of swelling, redness, and pain of the right knee. There was no precipitating trauma. The pain and swelling have been gradually increasing, to the point that it is difficult to fully flex his knee. He can ambulate but with difficulty. He denies any fevers or chills, night sweats, unintentional weight loss, or rashes. Other than a history of hypertension, he has no significant medical history; however, he notes that a few weeks prior he had similar symptoms of pain and swelling in the left knee that self-resolved after 5 days. He goes hunting frequently but denies any known tick bites. Bedside ultrasound shows a large right knee effusion with an associated Baker's cyst. How should he be evaluated and treated?

Lyme borreliosis is caused by the spirochete bacteria *Borrelia burgdorferi* and is transmitted to humans by *Ixodes* ticks. Lyme disease is the most common tick-borne illness in the United

States, and it is estimated that reported cases are only approximately 10% of actual cases. Currently, the vast majority of Lyme cases are seen in only a few states, mostly in the Northeast but also in the Upper Midwest [18]. The incidence of Lyme is expected to rise due to changes in habitats favorable to *Ixodes* expansion [19].

Lyme borreliosis has well-defined clinical stages: early localized, early disseminated, and late disseminated. Approximately 80% of patients with Lyme borreliosis develop the characteristic centrifugally expanding erythematous rash known as erythema migrans at the site of the tick bite (usually days afterward). EM rashes are typically minimally painful or pruritic, and thus the rash may not be recognized; it can be accompanied by fevers, myalgias, and arthralgias. EM rashes self-resolve after about 30 days. Days to weeks after the initial infection in the skin, the bacteria will disseminate and can cause further cutaneous, neurologic, or cardiovascular symptoms.

Weeks to months after the initial infection, Lyme arthritis can occur. Notably this phase is characterized by a true inflammatory arthritis, with redness and swelling of the affected joint (not just joint pain). It is estimated that 60% of patients with early Lyme disease will progress to Lyme arthritis in the absence of antibiotic treatment [20]. Interestingly, in the current era, many patients with Lyme arthritis do *not* report a history of erythema migrans since most patients with EM are diagnosed quickly and cured with antibiotic therapy; thus, the absence of a rash consistent with EM cannot rule out the diagnosis. Lyme arthritis typically presents with intermittent episodes of joint swelling primarily of the large joints (especially the knee), often self-resolving [21].

Lyme borreliosis is diagnosed serologically in patients with compatible clinical symptoms. A two-step algorithm is recommended by the Centers for Disease Control (CDC); traditionally this has been an initial enzyme-linked immunosorbent assay (ELISA) follow by confirmatory Western blot [18]. Patients with Lyme arthritis, as in the patient above, are universally found to have almost all ten tested IgG bands on the Western blot (testing

joint fluid for Lyme DNA via polymerase chain reaction (PCR) is not recommended). In 2019, the CDC updated its recommendation to include tests with ELISA for both the screening and confirmatory testing [22], with the goal to increase the sensitivity in early infection. There is a significant rate of overdiagnosis of Lyme driven by the use of serologic testing in patients without compatible clinical features of the disease [23].

Lyme disease is treated with antibiotic therapy. Isolated erythema migrans is treated with oral antibiotics: typically doxycycline for 10 days; or amoxicillin (if pregnant) for 14 days, whereas neurologic or cardiac disease is treated for 4 weeks, usually with intravenous ceftriaxone. Lyme arthritis is treated with 4 weeks of antibiotics, though notably almost half of patients require another round of treatment [21]. Of note, about 10% of patients with Lyme arthritis are antibiotic refractory, in that they continue to have evidence of joint inflammation despite appropriate antibiotic therapy. In those patients, evidence does not suggest a persistent infection but rather the triggering of local autoimmunity [24], and they are treated with anti-inflammatory and immunosuppressive therapy.

There are several misconceptions about Lyme borreliosis. The most pernicious is that Lyme disease can cause persistent infection requiring long-term antibiotic therapy. A small percentage of patients who have been appropriately treated for Lyme disease will develop nonspecific symptoms of fatigue, headache, joint and muscle pain, in the absence of objective markers of inflammation (e.g., joint swelling). This is known as Post-Lyme Disease Syndrome, though it is unclear if these symptoms occur at a higher rate than the background risk in the general population [25]. What is clear is that chronic antibiotic therapy is not more effective than placebo in ameliorating these symptoms [26]. Unfortunately, a large industry has sprouted to inappropriately diagnose patients with “chronic Lyme” and offer unproven and potentially harmful therapies [27]. The American College of Rheumatology does not recommend testing for Lyme disease in patients without objective evidence of joint inflammation [28].

Chikungunya Virus Infection

A 27-year-old female presents with severe polyarticular pain in the axial and peripheral joints over the last 24 hours, with associated high fevers and a diffuse maculopapular rash. The pain is severe enough that it is difficult to even get out of bed. She has never had anything like this before. Two days ago, she returned from a vacation in Turks and Caicos. What lab tests should be sent?

The patient's incapacitating joint pain, along with systemic symptoms and an appropriate exposure history, is characteristic of chikungunya virus infection. Chikungunya virus is an alphavirus spread by the *Aedes* mosquitos. Although chikungunya was first identified in the 1950s in Tanzania ("Chikungunya" means "that which bends up" in the Makonde language, describing the contorted position of the affected patients) [29], the disease was limited to sporadic outbreaks in sub-Saharan Africa until 2004, when a large-scale epidemic developed on islands on the Indian ocean, India, Southeast Asia, and China. Chikungunya was thought to be limited to the tropics until an outbreak in Italy in 2007. The disease subsequently spread to the Americas in 2013, and has since exploded in incidence, infecting millions of people in virtually all South American, Central American, and Caribbean countries [30]. Local transmission has been reported in the United States, but the majority of cases are seen in returning travelers as in the patient above [31]. The incubation period is usually 2–4 days but can be as long as 2 weeks.

Most patients infected with chikungunya become acutely symptomatic, with a high fever, maculopapular rash, and debilitating joint pain affecting both the peripheral and axial skeleton. Chikungunya can be difficult to differentiate from Dengue fever, though joint symptoms are typically more prominent in chikungunya and thrombocytopenia is more common with Dengue [32]. The diagnosis is made with serum PCR when testing is performed with symptoms between 1 and 7 days and positive serologies in those with symptoms for 8 or more days. Acute therapy is supportive with NSAIDs and hydration.

Although most symptoms of chikungunya resolve in 1–2 weeks, and the mortality rate appears to be lower than other alphaviruses like Dengue, importantly joint pain and swelling can persist for months or even years in a up to 40% of patients [33]. In those patients, evidence suggests that the persistent inflammation is related to triggering of immunologic abnormalities, and not persistent viral infection [34]; patients can even develop erosions mimicking rheumatoid arthritis [35]. These patients are therefore treated like rheumatoid arthritis, using disease-modifying agents like methotrexate [36], and even TNF-alpha inhibitors.

Parvovirus Infection

A 45-year-old female presents with 7 days of pain and stiffness in the small joints of her hands. There is associated swelling most prominent in the metacarpal phalangeal joints (MCPs). Upon waking, she is stiff for about 2 hours and has difficulty with morning tasks like buttoning her clothes or squeezing toothpaste. She has never had any similar symptoms in the past. Prior to the development of these symptoms, she described a few days of low-grade fevers, malaise, and coryza. She denies a rash. On exam, she has swelling and tenderness of the MCPs and PIPs. What is the most likely diagnosis?

Although many viruses can cause diffuse arthralgias, typically in the setting of fevers and myalgias (e.g., influenza, Epstein-Barr virus, or Cytomegalovirus), it is uncommon for viruses to cause a true arthritis (characterized by joint swelling and redness) in which the joint involvement dominates the clinical picture. SARS-Cov-2, the virus that causes COVID-19, is also not thought to cause a true inflammatory arthritis. An exception to this is the single-stranded DNA virus parvovirus B19, which in adults can cause an acute small joint arthritis resembling rheumatoid arthritis. Adults with exposure to young children, for example preschool teachers, are at highest risk of infection, especially in the winter months. As in the scenario above, patients usually have prodromal flu-like symptoms and then present with symmetric pain and stiffness in the small joints of the hands and wrist, but

large joints such as knees, shoulders, and elbows can also be affected [37]. Of note, while the "slapped cheek" rash (erythema infectiosum) is a characteristic feature of acute parvovirus infection in children (in which case it is also called Fifth disease), this rash is uncommon in adults.

Many cases of parvovirus are asymptomatic, and most adults typically have serologic evidence of previous infection with positive IgG levels. The diagnosis of acute parvovirus infection is made with positive IgM serologies. The joint symptoms can be managed with NSAIDs and are typically short-lived, resolving over a few weeks. Unlike with chikungunya infection as above, there is no evidence linking parvovirus to the development of a chronic inflammatory arthritis [38]. Of note, parvovirus infection can transiently elevate rheumatoid factor, which can make the distinction between acute parvovirus and early rheumatoid arthritis difficult. Persistent arthritis beyond 6 weeks as well as a positive test for antibodies to citrullinated proteins (CCP antibody test) would suggest rheumatoid arthritis.

Osteoarticular Tuberculosis

A 45-year-old HIV positive male comes to your office for 4 months of right knee pain. The pain began gradually but has been worsening. He has noticed swelling and difficulty bending his knee. He is able to ambulate but with difficulty, and you notice a limp as he walks into the exam room. He denies any fevers, night sweats, cough, or unintentional weight loss. The patient admits to noncompliance with his HIV regimen; he is unsure of his last CD4 count and has not seen his infectious disease doctor in a few years. On exam, the knee is swollen but minimally red and tender; the range of motion is preserved. What diagnosis should be considered?

Given his immunocompromised state, this patient is at risk for uncommon opportunistic osteoarticular infections, including fungal and mycobacterial infections. All can present with a subacute to chronic inflammatory arthritis. In this case, synovial biopsy eventually grew mycobacterium tuberculosis (MTB). According

to the WHO, about 1/3 of persons living with HIV are co-infected with MTB [39].

The spine is the most common site for osteoarticular tuberculosis infections, but peripheral arthritic involvement is also a frequent complication [40]. Unlike pyogenic bacteria (e.g., staphylococcal) that present acutely, peripheral joint infections of mycobacteria will develop indolently over months. Notably, only about half of patients with peripheral joint tuberculosis will have fevers, and only a quarter will have night sweats or weight loss [40]; thus, the absence of these symptoms cannot be used to rule out the diagnosis.

Serum blood tests are unlikely to be helpful in this case. A positive interferon-gamma release assay does not distinguish between latent and active tuberculosis infection. Additionally, a negative test cannot rule out active MTB. The diagnosis can be established by culturing MTB from another site in the setting of compatible osteoarticular features, or by synovial culture. Synovial fluid aspiration would be expected to show inflammatory fluid (e.g. 15–30,000 WBCs), but the sensitivity of AFB staining for diagnosis of joint MTB is very poor [41]. Culture of synovial fluid is more sensitive, but often a synovial biopsy and tissue culture is needed for definitive diagnosis. Nucleic acid amplification testing can add in the diagnosis of TB but do not have FDA approval for testing in synovial fluid. Osteoarticular tuberculosis is treated similarly to pulmonary tuberculosis, with multiple drug therapy over 6–9 months [42].

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Autoinflammatory Disease

12

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Abbreviations

AID	Autoinflammatory disease
CANDLE	Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
CAPS	Cryopyrin-associated periodic fever syndrome
CINCA	Chronic infantile neurologic cutaneous articular syndrome
DADA2	Adenosine deaminase 2 deficiency
DAMPs	Damage-associated molecular patterns
DIRA	Deficiency of the interleukin-1 receptor antagonist
FMF	Familial Mediterranean fever
HIDS	Hyper-IgD with periodic fever syndrome
MVK	Mevalonate kinase deficiency
NLR	NOD-like receptor proteins
NLRs	NOD-like receptors

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NOD	Nucleotide-binding oligomerization domain
NOD2	Nucleotide-binding oligomerization domain-containing protein 2
NOMID	Neonatal-onset multisystem inflammatory disease
PAMPs	Pathogen-associated molecular patterns
PFAPA	Periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis
PLAID	PLCG2-associated antibody deficiency and immune dysregulation
PRRs	Pattern recognition receptors
SAVI	STING-associated vasculopathy with onset in infancy
SIFD	Sideroblastic anemia, immunodeficiency, fevers, and developmental delay
TLR	Toll-like receptors
TRAPS	TNF receptor-associated periodic syndrome
YAOS	Yao syndrome

Introduction

Autoinflammatory diseases (AIDs) are a heterogeneous group of disorders characterized by dysregulation of innate immunity. The term was coined by Kastner et al. to describe a group of monogenic periodic fever syndromes that are clinically and immunologically distinct from the classic systemic autoimmune diseases where adaptive immunity plays a critical role [1]. Typically, monogenic AIDs clinically present with protean manifestations such as seemingly unprovoked recurrent episodes of fever and systemic inflammation, which lack autoantibodies and antigen-specific T cells. These disorders can be clinically distinguished based on the characteristic phenotypes and genetic mutations. Classically, hereditary monogenic periodic fever syndromes include familial Mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), hyper-IgD syndrome (HIDS)/mevalonate kinase deficiency (MKD), and cryopyrin-associated periodic syndrome (CAPS) [2, 3].

The AID spectrum is rapidly expanding to include new monogenic autoinflammatory diseases, such as STING-associated vasculopathy with onset in infancy (SAVI), adenosine deaminase 2 deficiency (DADA2), chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), sideroblastic anemia, immunodeficiency, fevers, and developmental delay (SIFD), PLCG2-associated antibody deficiency and immune dysregulation (PLAID), and deficiency of the interleukin-1 receptor antagonist (DIRA), among others [4]. Some genetically complex diseases are also included in AIDs; examples are Behçet disease, Still/adult-onset Still's disease, Schnitzler syndrome, periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA), and Crohn disease [5]. Due to space limitations, herein we will focus on hereditary periodic fever syndromes and NOD2-associated diseases.

General Pathophysiology

Central to the pathogenesis of AID are perturbations of innate immune pathways that have naturally evolved to provide the first line of defense against microbial and metabolic stimuli. Innate immunity is rapid and nonspecific and does not confer immune memory as opposed to adaptive immunity, which is slower and antigen-specific and induces immunologic memory [6]. Innate immune cells harboring surface and intracellular pattern recognition receptors (PRRs) are primed to respond to triggers containing usually highly conserved pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) [7]. Examples of cell surface PRRs are the Toll-like receptors (TLR), whereas NOD-like receptors (NLRs) are cytoplasmic. This host–environment molecular interaction via PRR-PAMPs and DAMPs results in the initiation of intracellular signaling cascades. Ultimately, cytokine production ensues to contain the noxious trigger. Common cytokines fulfilling that purpose and also known to be mediating AID manifestations include IL1, IL-6, IL-18, TNFα, and type I interferons (IFNα, IFNβ) [8].

In classic monogenic AIDs, nosology occurs in the presence of aberrant cytokine production due to mutations in genes encoding proteins critical in the cascade of innate immune defense. One of the well-characterized mechanisms of IL-1-mediated pathology in the context of AID is gain-of-function mutations in the NLRP3, which cause CAPS [9]. NLRP3 or cryopyrin is a structural component of the NLRP3 inflammasome. Inflammasomes are multiprotein cytoplasmic complexes, which are assembled upon stimulation in a two-step fashion. They are composed of sensor proteins, such as the nucleotide-binding oligomerization domain (NOD) protein and NLR proteins, the adaptor protein ASC, and the proteolytic enzyme caspase 1, which cleaves precursor forms of IL-1 and IL-18 to their active moieties.

Specifically, NLRP3 consists of an N-terminal pyrin domain, a central NOD/NACHT domain, and a C-terminal leucine-rich repeat (LRR) domain, which along with the adaptor protein ASC and caspase-1 form the NLRP3 inflammasome. Pyrin inflammasome is different in that it lacks a NOD/NLR protein [10]. Pyrin, which is encoded by the *MEFV* gene, has a C-terminal B30.2 domain, which plays a role in regulatory responses from bacteria such as *Burkholderia*, *Clostridium difficile*, and *C. botulinum*. This causes dephosphorylation of pyrin and enables inflammasome assembly [11]. Pyrin encoded by MEFV gene mutations in FMF provides insight into the potential evolutionary advantage they confer in Mediterranean populations against such environmental pathogens.

Another pathway deciphering the pathophysiology of AID such as TRAPS includes the endoplasmic reticulum stress response accompanied by the unfolded protein response (UPR) [12]. Mutations in genes encoding for proteins involved in innate immune responses cause conformational changes rendering the protein dysfunctional and misfolded [12]. A classic example is TRAPS, where the misfolded receptor TNFA encoded by *TNFRSF1* accumulates in the ER activating pathways leading to IL-1, IL-6, and TNFα production [13].

Diagnostic Clues for AIDs

Monogenic AIDs can be molecularly classified based on the causative genetic mutation of the respective disease. While molecular genetics has revolutionized the diagnosis of AIDs, there is a lot of genotypic and phenotypic heterogeneity, suggestive of environmental factors that contribute to the disease expression [14]. In clinical practice, there are geographic and ethnic elements that may help assist with the diagnosis of and raise suspicion for AIDs. For example, FMF is more prevalent in populations in the Mediterranean basin as opposed to other AIDs with no ethnic predilection. TRAPS, although initially described in patients of Irish descent, is currently known to afflict people of all ethnic backgrounds. Genetic inheritance patterns are very important, particularly in hereditary periodic fever syndromes. For example, TRAPS is an autosomal dominant disease as opposed to HIDS, which is autosomal recessive. Recent progress in molecular genetics is enlightening in many ways. For example, FMF has traditionally been thought to be an autosomal recessive disease; it is currently thought to be autosomal dominant in some cases as patients with a single copy variant may present with signs and symptoms, especially in adults [15]. Duration and frequency of fever and flares are distinguishing factors along with associated symptoms. Erysipeloid rashes on the lower extremities are seen in FMF, whereas maculopapular rashes involving the hands and feet are described in HIDS [16]. TRAPS rashes can be migratory and centrifugal with underlying myalgia. Cold-induced urticaria-like rashes are more suggestive of CAPS and NLRP12 inflammatory disease [17].

Familial Mediterranean Fever [18–20]

Familial Mediterranean fever (FMF) is prototypic of monogenic autoinflammatory diseases worldwide and most commonly affects the population of the Mediterranean basin. The disease is presented in an autosomal recessive pattern; however, up to 30% of

patients carry heterozygous gene mutations, and up to 20% of patients have no detectable mutations.

FMF presents with attacks that typically begin in childhood, which include fevers, serosal inflammation including abdominal pain and chest pain, and mono- or oligoarthritis in the lower extremities. Peritonitis occurs with 90% of attacks and can be so severe that it can mimic acute abdomen and patients can end up with unnecessary surgical intervention. Peritoneal adhesions from recurrent inflammation can also lead to small bowel obstruction. Patients can develop pleural or pericardial effusions. Skin manifestations include tender erysipelas-like eruptions on the distal lower extremities, often involving the ankles and feet (Fig. 12.1b).

The MEFV gene encodes pyrin, which leads to an inflammatory response via excessive secretion of cytokines, including IL1β. During attacks, laboratory evaluation will reveal leukocytosis and elevated acute phase reactants, including ESR, CRP, and

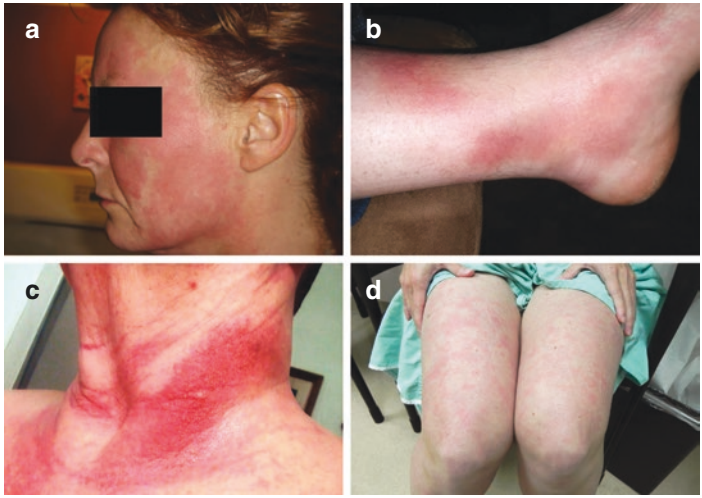

Fig. 12.1 Rashes in autoinflammatory diseases. Erythematous patches on the face in Yao syndrome (**a**), erysipelas-like rash on the distal lower extremity in FMF (**b**), plaques on the neck in TRAPS (**c**), and urticaria in CAPS (**d**). (Reprinted with permission from Yao et al. [37, 42])

serum amyloid protein A. Patients should be monitored for proteinuria due to amyloidosis.

The diagnosis of FMF is based on clinical presentation, supported by genetic testing. The diagnostic criteria listed below have a sensitivity and specificity of >95% (Table 12.1). Diagnosis is suspected if a patient has any of the following:

- ≥1 major criteria
- ≥2 minor criteria
- 1 minor plus 5 supportive criteria
- 1 minor criterion plus ≥4 of the first five supportive criteria

Table 12.1 Diagnostic criteria for FMF

Major criteria: *Typical attacks*: 1. Peritonitis (generalized) 2. Pleuritis (unilateral) or pericarditis 3. Monoarthritis (hip, knee, ankle) 4. Fever alone (≥38 °C)
Minor criteria: 1–3. *Incomplete attacks* involving one or more of the following sites: 1. Abdomen 2. Chest 3. Joint 4. Exertional leg pain 5. Favorable response to colchicine
Supportive criteria: 1–4. Features of attacks: 1. Severe, requiring bed rest 2. Spontaneous remission 3. Symptom-free interval 4. Transient inflammatory response, with one or more abnormal test result(s) for leukocyte count, ESR, serum amyloid protein A, and/or fibrinogen 5. Family history of FMF 6. Appropriate ethnic origin (North African Jews, Armenians, Turks, Arabs, Greeks, and Italians; in the United States, seen in Ashkenazi Jewish population) 7. Age < 20 at disease onset 8. Episodic proteinuria/hematuria 9. Negative laparotomy or removal of normal appendix 10. Consanguinity of parents

The presence of biallelic pathogenic mutations in the MEFV gene is highly diagnostic. The MEFV gene mutations, M694V, M694I, M6801, and V726A, account for most of the mutations.

The initial therapy is a short-term use of colchicine 1–2 mg/day to prevent acute attacks, and a long-term maintenance therapy can decrease amyloidosis. For patients who are deemed colchicine resistant, IL-1 blockade with canakinumab, anakinra, or rilonacept can be used.

Cryopyrin-Associated Periodic Syndrome [21–24]

Cryopyrin-associated periodic syndrome (CAPS) consists of three overlapping disorders of increased severity, including familial cold autoinflammatory syndrome (FCAS1), Muckle–Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurologic cutaneous articular (CINCA) syndrome. Each of these is caused by mutations in the NLRP3 gene, which encodes cryopyrin (also known as NALP3, CIAS1, or PYPAF1).

Cryopyrin is an intracellular protein in the NLR family that senses molecular danger signals and participates in the assembly of the NLRP3 inflammasome. Mutations in NLRP3 lead to the aberrant formation of the inflammasome, which increases the production of IL1β, leading to inappropriate inflammation.

FCAS1 is the mildest, with symptoms typically occurring in childhood. Flares begin within hours of cold exposure, including urticarial rash (Fig. 12.1d), polyarthralgia, and fever. Patients may also have conjunctivitis, fatigue, dizziness, headaches, and nausea. FCAS1 can rarely lead to secondary amyloidosis. Muckle–Wells syndrome (MWS) manifests similarly with the addition of progressive sensorineural hearing loss due to inner ear inflammation and a higher possibility of secondary amyloidosis. Febrile episodes may last several hours to days. NOMID/CINCA is the most severe in the spectrum, which includes a similar presentation to FCAS and MWS in addition to characteristic physical examination abnormalities including frontal bossing, protruding eyes, saddle-shaped nose, and joint deformities. It typically manifests

at or near the time of birth. Patients can also exhibit aseptic meningitis, which may be chronic and cause increased intracranial pressure, papilledema, and seizures.

Laboratory findings include leukocytosis with neutrophilia, thrombocytosis, and elevated acute phase reactants. A skin biopsy shows a marked perivascular infiltration of neutrophils. Cerebrospinal fluid analysis may show neutrophilic leukocytosis and protein elevation.

The diagnostic criteria include raised inflammatory markers plus at least two of the six typical CAPS manifestations:

- Urticarial-like rash
- Cold-triggered episodes
- Sensorineural hearing loss
- Musculoskeletal symptoms
- Chronic aseptic meningitis
- Skeletal abnormalities

The diagnosis of CAPS is confirmed by genetic testing for *NLRP3* mutations. However, some patients may be clinically diagnosed with CAPS in the absence of a genetic mutation due to mosaicism or epistasis. Mosaicism refers to the presence of more than one cell population with different genetic make-ups. FCAS2, also called NLRP12-induced autoinflammatory disease, is similar to FCAS1 in phenotype, but genotype is different between the two diseases [17]. Treatment includes IL-1-blockade with canakinumab, anakinra, or rilonacept, which can lead to complete resolution of symptoms.

TNF Receptor-Associated Periodic Syndrome [16, 25, 26]

TNF receptor-associated periodic syndrome (TRAPS) is caused by mutations in the TNFRSF1A gene, which encodes TNF receptor 1. Clinical manifestations usually present in childhood and adolescence but may present in adulthood in about 20% of

patients. Flares are prolonged, with a mean length of 14 days but sometimes lasting up to 4 weeks. Presenting features originate from multiple system involvement and include recurrent fever, migratory and centrifugal rash (Fig. 12.1c), localized myalgia underlying rash, peritonitis, pleuritis, arthralgias, and conjunctivitis. Monocytic fasciitis can also be present. Neurological manifestations include headaches, aseptic meningitis, optic neuritis, and behavioral alterations. Therapy for TRAPS depends on the frequency and severity of the disease flares. Nonsteroidal anti-inflammatory drugs (NSAIDs) and short-term glucocorticoids can be beneficial. IL-1 blockers are FDA approved for the treatment of TRAPS. TNFα inhibition using etanercept is effective in some cases.

Hyper-IgD Syndrome/Mevalonate Kinase Deficiency [27–29]

Hyper-IgD syndrome (HIDS), or mevalonate kinase deficiency, is caused by mutations in the MVK gene. Most patients experience their first disease attack before 1 year of age. Episodes last 3–7 days and occur every 4–6 weeks. Patients present with recurrent fevers, rash, gastrointestinal symptoms, polyarthralgia, and cervical lymphadenopathy. Rash may be maculopapular, urticarial, nodular, and purpuric. Hepatosplenomegaly can occur. Molecular analysis of MVK gene mutations is diagnostic in a proper clinical scenario. Serum IgD levels can be elevated but not diagnostic. Treatment includes NSAIDs and glucocorticoids. Short-term IL-1 blockade or maintenance therapy may be tried.

NOD2-Associated Diseases

Nucleotide-binding oligomerization domain-containing protein 2 (*NOD2*) is a cytosolic NOD-like receptor. *NOD2* protein consists of three regions: six leucine-rich repeats (LRRs) at the C-terminal, central NOD/NBD, and two caspase recruitment domains

(CARDs) at the N-terminal [30]. *NOD2* is important in defense against microorganisms, mediating inflammatory response and maintaining homeostasis. NOD2 gene mutations/variants are associated with certain diseases [31, 32]. NOD2 variants are present in approximately 28% of Caucasian patients with Crohn's disease in North America and Europe and commonly include 1007fs, G908R, and R702W that are on exons 8 and 11 with loss-of-function [33, 34]. NOD2 mutations are also linked to Blau syndrome and Yao syndrome.

Blau Syndrome

Blau syndrome is an autosomal dominant disease and typically manifests as a triad of granulomatous dermatitis, uveitis, and inflammatory arthritis. It primarily occurs in children, and adult-onset disease is extremely rare [35]. Dermatitis usually presents as erythematous papular scaly rashes. Arthritis mainly affects the wrist, knee, ankle, and proximal interphalangeal joints, leading to camptodactyly and rheumatoid arthritis-like/cystic articular changes [36]. Fever, abdominal pain, and diarrhea are unusual in Blau syndrome [36]. The disease is associated with high penetrant NOD2 mutations on exon 4. Therapy includes NSAIDs, glucocorticoids, and infliximab.

Yao Syndrome [37–40]

Yao syndrome (YAOS), formerly called NOD2-associated autoinflammatory disease, is characterized by recurrent episodes of fever, dermatitis, arthralgia, and gastrointestinal and sicca-like symptoms. The disease is associated with specific NOD2 gene variants. The disease can start at any ages but is mostly reported in Caucasian adults. Female patients are more affected than males with a ratio of 2:1.

Common manifestations include intermittent fever, rash/dermatitis, arthralgia (more common in lower extremities), distal

lower extremity swelling, gastrointestinal and sicca-like symptoms, and fatigue. Fevers can last for several hours to days and occur weeks or months apart. Rashes occur in 90% of cases and include nonpruritic erythematous patches most commonly on the face, chest, and back (Fig. 12.1a). Histopathology often reveals spongiotic dermatitis. Gastrointestinal symptoms include abdominal pain, bloating, cramping, and nonbloody diarrhea, and pathology is not consistent with inflammatory bowel disease; however, nonspecific colitis can be seen occasionally. Sicca-like symptoms can occur, and patients may have a positive Schirmer test but no serological or pathological evidence of primary Sjogren syndrome. Other symptoms include eyelid swelling, mouth ulcerations, chest pain, and lymphadenopathy.

Laboratory evaluation yields mild leukocytosis, normal hemoglobin or mild anemia, and elevated ESR/CRP in 50% of cases. YAOS results likely from a combination of genetic and environmental factors. NOD2 variants are detected in all patients; nearly all patients carry the NOD2 variant IVS8+158 with concurrent variant R702W in 30% of patients. Other NOD2 variants can be seen in the disease. To detect the gene variants, NOD2 whole gene sequencing is performed by targeted DNA and/or next-generation sequencing. It is important to note that the presence of a NOD2 variant does not mean the patient has the disease.

A diagnosis of YAOS is made based on characteristic phenotype and positive genetic testing for NOD2. Proposed diagnostic criteria include two major criteria, one or more minor criteria and the molecular and exclusion criteria (Table 12.2).

Treatment of YAOS includes glucocorticoids, sulfasalazine, and IL-1/IL-6 inhibitors. Canakinumab is effective [41]. A choice of a drug may depend on the frequency and severity of the disease flares, as well as the patient's response and tolerance to a particular medication.

In summary, AIDs are usually devoid of detectable autoantibodies and are often associated with genetic mutations/variants. These diseases share overlapping clinical phenotypes, which pose diagnostic challenges. However, there are differences in clinical manifestations and genetic markers between these disorders (Table 12.3). If any individual patient presents with autoinflam-

Table 12.2 Diagnostic criteria for Yao syndrome

Major criteria: 1. Periodic occurrence ≥twice 2. Recurrent fever or dermatitis or both
Minor criteria: 1. Oligo- or polyarthralgia/inflammatory arthritis, or distal extremity swelling 2. Abdominal pain or diarrhea or both 3. Sicca-like symptoms 4. Pericarditis or pleuritis or both
Molecular criterion: NOD2 IVS8+158 or R702W or both, or other rare variants
Exclusion criteria: High titer antinuclear antibodies, inflammatory bowel disease, Blau syndrome, adult sarcoidosis, primary Sjogren syndrome, and monogenic autoinflammatory diseases

Table 12.3 Phenotypic and genotypic features of YAOS and relevant SAIDs

	YAOS	FMF	CD	BS
OMIM	617321	249100	266600	186580
Age at onset	Adult and children	<20 years	15–40 years	<5 years
Gender	F/M: 2/1	F = M	F slightly>M	F/M: 12/19
Ethnicity	Caucasian, Asian	Caucasian, Asian	Any ethnic groups	Caucasian, Asian
Fever	63%	>80%	24%; irregular	Rare
Serositis	Yes	Yes, more frequent	Yes, less frequent	No
Joints	Oligo- or polyarthritis, distal leg swelling	Oligo- or monoarthritis	Mono- or oligoarthritis	Polyarthritis, granulomatous, camptodactyly
Skin	Spongiotic dermatitis, primarily erythematous patches/ plaques	Erysipeloid rash on the lower extremities	Erythema nodosa, pyoderma gangrenosum	Granulomatous dermatitis, mostly papulonodular rash and subcutaneous plaques

(continued)

Table 12.3 (continued)

	YAOS	FMF	CD	BS
GI	Mild to moderate, abdominal pain, bloating, and diarrhea	Peritonitis-related, acute abdomen, tenderness and rebound, constipation, rarely diarrhea	Ileitis, ileocolitis, colitis, granulomas, transmural inflammation, segmental distribution	Hepatomegaly
Sicca	Yes, eyelid swelling	No	Rare	Yes
Uveitis	No	No	<5%	80%
Oral ulcer	20%	3.3%	Yes	No
Inheritance	Genetically complex, mostly sporadic	Recessive	Genetically complex	Dominant
Gene mutations	*NOD2*: IVS8+158 plus R702W or other variants	*MEFV*	*NOD2*: 1007 fs, G908R, R702W	*NOD2*: NOD, R334Q, R334W
Therapy	GC, sulfasalazine, IL-1 inhibitors, IL-6 inhibitors	Colchicine, IL-1 inhibitors, TNFα inhibitors	Sulfasalazine, mesalamine, GC, purine analog, methotrexate, TNFα inhibitors, integrin inhibitors, IL-12/IL-23 inhibitors	NSAID, GC, infliximab

Adapted with some modification from Yao et al. [43]
OMIM Online Mendelian Inheritance in Man, *YAOS* Yao syndrome, *CD* Crohn's disease, *BS* Blau's syndrome, *FMF* familial Mediterranean fever, *GI* gastrointestinal, *Sicca* dry eyes and/or mouth, *LRR* leucin-rich repeat, *NOD* nucleotide-binding domain, *MEFV* Mediterranean fever, *GCs* glucocorticoids, *SAIDs* systemic autoinflammatory diseases

matory symptoms in the absence of autoantibodies, AIDs should be contemplated. Periodic fever syndrome gene panel may be tested to arrive at a correct diagnosis.

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Scleroderma

13

Margrit Wiesendanger

Patient Case

Ms. D. is a 32-year-old woman with a chief concern of progressive shortness of breath, which started very gradually a few months ago, but which has become increasingly bothersome and is associated with unusual fatigue. For several years, she has had bluish discoloration and pain in the fingers and toes in cold weather but manages this by making sure to use warm boots and mittens. She is otherwise healthy and has no other chronic medical problems. On exam, she has difficulty opening her mouth wide because the skin on her face is tight. There is also tight, thickened skin on her hands and feet. Her PCP has checked an ANA serology, which is positive in titer 1:1280 with a speckled pattern. She is concerned and would like to know more about her diagnosis and what she can do to manage her symptoms.

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Introduction

Scleroderma is a rare autoimmune condition, whose defining clinical feature is fibrosis of the skin (from the Greek "skleros," hard; and "derma," skin), but that can more ominously result in severe, irreversible damage to internal organs. Because early recognition and management of fibrosis of the lungs, gastrointestinal, heart, and kidneys are essential in optimizing a patient's clinical outcome, the term "systemic sclerosis" is finding increasing acceptance as a descriptor of the disease. While multiple distinct subtypes of scleroderma have been described, based on the distribution of skin sclerosis ("limited" vs. "diffuse") and autoantibody specificity, several key features are highly specific and recognizable and thus can greatly aid in diagnosis. Many excellent reviews have already provided in-depth explanations of the epidemiology, pathophysiology, diagnostic features, and management strategies in this complex disease [1–3]. In this chapter, the aim is to guide PCPs in the early recognition of this multifaceted illness and in screening for potential internal organ involvement by emphasizing specific and high-yield clinical indicators.

Epidemiology

Scleroderma has an overall low prevalence, with estimates ranging from fewer than 15 cases/100,000 (Northern Europe, Japan) to up to 40 cases/100,000 (North America, Australia) [4]. In comparison, prevalence estimates for systemic lupus range from 0.04% to 0.16% of the population, and for rheumatoid arthritis, up to 0.5%. The peak age at the onset of systemic sclerosis is between 20 and 50 years, though the disease has been described in younger and older patients. Scleroderma affects women more often than men, but the prognosis tends to be worse in men, including the extent of skin fibrosis, the risk of pulmonary hypertension, and mortality [5]. African American patients develop symptoms at an earlier age and tend to have an increased burden of morbidity and mortality compared to Caucasian patients. Overlap with a distinct

autoimmune disease, such as Sjögren's syndrome or inflammatory myopathy, occurs in about 25% of cases of scleroderma [6].

Mechanisms/Pathophysiology

Although the etiology of scleroderma is unknown, genetic susceptibility factors and epigenetic modifications have been identified. Each of these plays a relatively modest effect, too low to provide useful criteria for diagnosis. Similarly, there is no convincing data to implicate individual chemical exposures or infectious agents in the pathogenesis of scleroderma. Nonetheless, the disease is characterized by a unique combination of immune dysregulation, vascular changes, and fibrosis. Numerous cell types have been implicated in this chronic, self-perpetuating process, including lymphocytes, macrophages, dendritic cells, endothelial cells, platelets, smooth muscle cells, and fibroblasts [1].

Inflammation and Autoimmunity

Nearly all patients with scleroderma have circulating autoantibodies, including antinuclear antibodies (ANAs). Patients also frequently test positive for one of several specific, mutually exclusive antibodies, targeting nuclear antigens such as topoisomerase and centromere B. Several of these antibodies can be detected in clinical laboratories and are thus useful to confirm the diagnosis and help predict major organ manifestations (Table 13.1) [7]. Additional autoantibodies have been more recently discovered to target nonnuclear proteins, including endothelial cell antigens, chemokine receptors, matrix metalloproteinases, and fibrillin-1. However, conclusive evidence that these antibodies are directly implicated in tissue damage is still lacking [8]. There is also a prominent cellular immune response, characterized by increased numbers of monocytes, macrophages, dendritic cells, T cells, and B cells in the affected tissues, and an increased expression of type I interferon-regulated genes. Other cytokines of special interest

Table 13.1 Proposed classification of scleroderma using autoantibodies and skin subset as criteria: cumulative incidence of specific complications at 15 years

	ACA+ limited	Topo+ limited	Topo+ diffuse	RNAP+	U3 RNP+	Other Ab limited	Other Ab diffuse
Pulmonary fibrosis	9	86	84	45	22	54	54
Pulmonary hypertension	14	7	13	15	34	19	11
Cardiac scleroderma	2	5	13	2	13	2	8
Scleroderma renal crisis	0.3	4	8	28	11	3	16
Survival	79	74	48	63	66	72	48

Adapted with permission from Table 4, published in Ref. [7]. Values are the percentage of patients in each group
ACA centromere antibody, *Topo* topoisomerase I/Scl-70 antibody, *RNAP* RNA polymerase III antibody, *U3 RNP* U3 ribonucleoprotein antibody, *Other Ab* includes U1 RNP, Th/To, SSA, SSB, *limited* limited cutaneous involvement, *diffuse* diffuse cutaneous involvement

include transforming growth factor-β and interleukin-6 because of their prominent pro-fibrotic signature [1].

Vasculopathy

Endothelial cell activation initiates a cascade of microvascular injury, the end result of which is tissue ischemia. This includes a reduction in the number of capillaries, as well as endothelial and smooth muscle cell proliferation with thickening of the vessel wall and narrowing of the lumen. Activated endothelial cells also recruit inflammatory cells, which in turn express pro-fibrotic cytokines and amplify the vascular and tissue damage [1]. Important vascular complications of scleroderma vary by the affected organ: in the skin, cutaneous ulcers and Raynaud's phenomenon; in the kidney, scleroderma renal crisis; in the gastrointestinal tract, vascular ectasias; and in the heart and lungs, pulmonary arterial hypertension.

Fibrosis

Scleroderma is distinguished by the progressive accumulation of fibrotic connective tissue (collagen, elastin, glycosaminoglycan, and fibronectin) in several body areas, thus replacing normal blood vessels, glands, muscle, and fat with rigid and permanent scar tissue. Myofibroblasts are key connective tissue cells that have features of both fibroblasts and smooth muscle cells; thus, their role in normal tissue repair after an injury includes producing fibrotic matrix and contraction of the wound. In scleroderma, myofibroblasts are highly activated and produce excessive amounts of connective tissue matrix, as well as additional profibrotic cytokines that amplify the process. There is also enhanced cross-linking of collagen and defective breakdown of scar tissue, and the increasing tissue stiffness in turn induces a mechanical stress, which further exacerbates fibroblast activation and recruitment [1]. Clinically, the major manifestations of tissue fibrosis also vary by organ system: in the skin, tightening and thickening of the dermis; in the gastrointestinal tract, dysmotility; in the lungs, interstitial lung disease; and in the heart, arrhythmias or pericarditis.

Diagnosis and Screening

Scleroderma is challenging to diagnose because it shares some features with other, unrelated conditions, because several different organs may be affected in an individual patient, and because the constellation of signs and symptoms may vary between patients and over time. However, certain key features have been recognized as uniquely characteristic of systemic sclerosis so that even if they are not the most common manifestations, they are helpful in differentiating scleroderma from mimics. In 2013, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) published a joint update of the classification criteria for scleroderma (Table 13.2). Although this criterion set, like its predecessor, is designed primarily to

Table 13.2 The 2013 ACR/EULAR criteria for the classification of systemic sclerosis

Item	Subitem(s)	Score
Skin thickening of the fingers of both hands, proximal to MCP joints		9
Skin thickening of the fingers	Puffy fingers Sclerodactyly of the fingers	2 4
Fingertip lesions	Digital tip ulcers Fingertip pitting scars	2 3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial disease and/or interstitial lung disease	Pulmonary arterial disease Interstitial lung disease	2 2
Raynaud's phenomenon		3
Scleroderma-related autoantibodies	Anti-centromere Anti-topoisomerase I/Scl-70 Anti-RNA polymerase III	3 3 3

Adapted with permission from Ref. [9]
If more than 1 subitem is present, only the higher score is counted
Sclerodactyly: skin thickening proximal to the proximal interphalangeal joints and distal to the metacarpophalangeal joints

ensure an accurate case definition for inclusion of patients in research trials, the 2013 update is more sensitive for the detection of early disease and features modern diagnostic measures [9]. A number score is assigned to each clinical feature; if the total is equal to or greater than 9, then this is considered "definite systemic sclerosis." Because these classification criteria highlight specific features of scleroderma, they also have diagnostic utility but must be interpreted with caution. For example, the criteria are not applicable to patients who lack skin thickening of the fingers or who have fibrosis due to a different condition (e.g., diabetes, exposure to gadolinium contrast).

Identifying Specific Clinical Features of Scleroderma

Skin Sclerosis

Measuring the extent and severity of skin fibrosis is useful for classification and for following the progression of the illness, as patients with scleroderma have traditionally been categorized as "limited cutaneous" or "diffuse cutaneous." The limited cutaneous distribution is defined as thickening of the skin distal to the elbows and knees, whereas diffuse cutaneous skin disease includes the distal limbs as well as thickening proximal to the elbows and knees. While thickening of the facial skin can occur in either subset, the torso is only involved in the diffuse cutaneous type.

Skin thickness is determined using a palpation technique, with the patient in a comfortable seated or supine position, to avoid artifacts from tense underlying muscle. Using the thumb and index finger, the examiner attempts to create a skin fold by gently pinching the patient's skin [10]. The thickness and appearance of the skin fold may vary according to the amount of subcutaneous fat and muscle so that even in normal subjects, the skin fold is thinner over the dorsum of the hands compared to the upper arm. To perform the standardized modified Rodnan skin score (mRSS), skin thickness is assigned a value of 0 (normal) to 3 (severe) and measured in 17 distinct body areas for a maximum of 51 points. However, for the purpose of establishing a diagnosis of scleroderma, it is not necessary to perform a complete mRSS, and I would recommend focusing the skin assessments on the hands and feet, which are expected to show skin thickening in the vast majority of cases of scleroderma (both limited and diffuse cutaneous).

Skin score definitions:

0 = normal, no increase in thickness, and fine wrinkles are appreciated with the pinching maneuver.

1 = mild increase in thickness, but a fold of skin remains easy to elicit.

2 = moderate skin thickness with difficulty making a skin fold, and no wrinkles.

3 = severe skin thickness, and the examiner is unable to create a skin fold.

Of note, over time, the dermal thickening of the hands and fingers can progress from an "early puffy" edematous phenotype, in which the patient will note soft tissue discomfort and itching, to a sclerodactyly appearance, in which there is severe skin thickening, resulting in pigment changes and loss of hair and of subcutaneous fat [2]. Deep fibrosis leads to tendon friction rubs that can be auscultated and eventually, to joint contracture (Fig. 13.1).

Raynaud's Phenomenon

Raynaud's phenomenon is present in all subsets of scleroderma and is often the first symptom, preceding the onset of other manifestations by several years. It is a vasospastic disorder triggered by cold or stress, in which occlusion of the digital arteries in the hands and feet produce distinctive skin color changes. In classic triphasic Raynaud's phenomenon, one or several distal digits will first become pale (ischemia), then cyanotic (deoxygenation), followed by redness in the reperfusion stage. However, Raynaud's

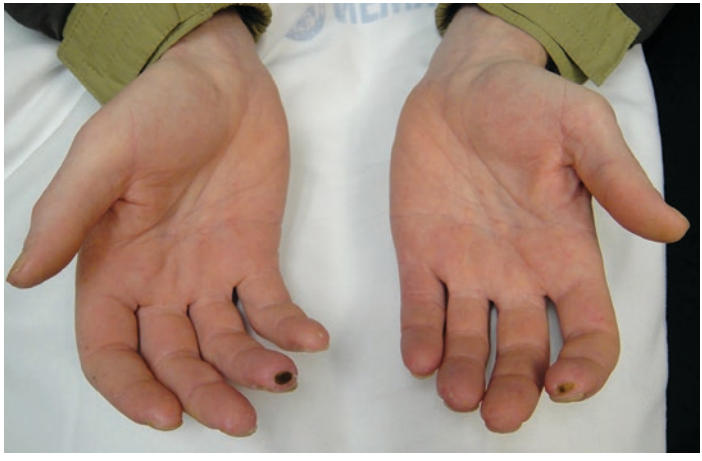

Fig. 13.1 Sclerodactyly. Progressive skin thickening of the fingers results in sclerodactyly and joint contracture. Note the fingertip ulcers, with overlying eschar, and the superficial pitting scars

phenomenon may also be mono- or biphasic (Fig. 13.2a, b). When seen in the context of scleroderma, Raynaud's phenomenon is considered secondary and tends to be associated with more permanent signs of digital ischemia, including abnormal nailfold capillaries and fingertip ulcers. This is in contrast to primary Raynaud's ("Raynaud's disease"), which is commonly encountered in general clinical practice, has an excellent prognosis, and has no association with systemic disease nor with local signs of digital ischemia.

Abnormal Nailfold Capillaries

The thin skin just proximal to each nail allows visualization of the nailfold capillaries, using a magnifying method and appropriate lighting. Normal capillaries are arrayed side by side, each forming a hairpin pattern, with the terminal loop positioned just proximal to the nail. In contrast, giant capillaries, microhemorrhages, and loss of capillaries ("dropout") are visible signs of scleroderma vasculopathy and are commonly (but not exclusively) associated with symptomatic Raynaud's phenomenon. Examination of the nailfold capillaries can be accomplished in several ways, the most advanced of which uses video microscopy and generates highly

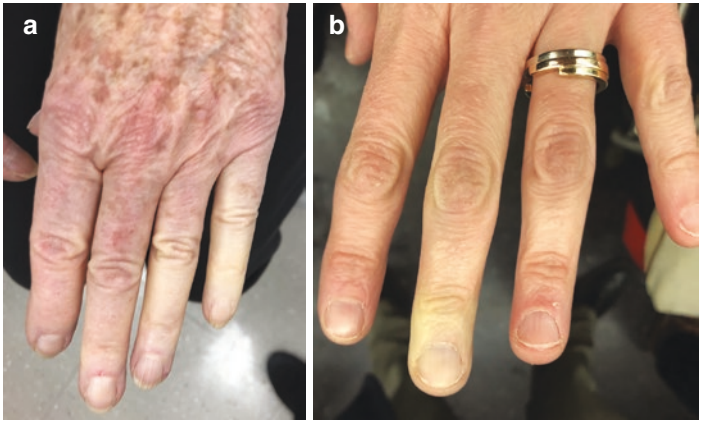

Fig. 13.2 (**a**, **b**) Raynaud's phenomenon. Pallor of selected distal fingers is shown in these two examples

magnified images [11]. However, in general practice, a dermatoscope readily provides sufficient visualization of abnormal capillaries (Fig. 13.3a, b). These clinical photos were taken with a smartphone camera, overlaid on the magnifying lens of the dermatoscope.

Fingertip Lesions: Cutaneous Ulcers

Digital ischemic ulcers occur in approximately 40% of patients with scleroderma as a consequence of vascular insufficiency and can be categorized according to severity. Superficial digital ulcers involve loss of the epidermis and may appear as an abrasion, a blister, or a small crater. Intermediate digital ulcers have full-thickness skin loss and include damage to subcutaneous tissue up to the underlying fascia; these are typically deep craters (Fig. 13.4). Finally, deep digital ulcers also have full-thickness loss of the skin, in addition to extensive damage to muscle, tendon, and bone, leading to gangrene and autoamputation of the fingertips in the most severe cases [12]. A significant reduction in quality of life and hand function can result from digital ulcers, which are typically very painful, difficult to treat, and vulnerable to superinfection.

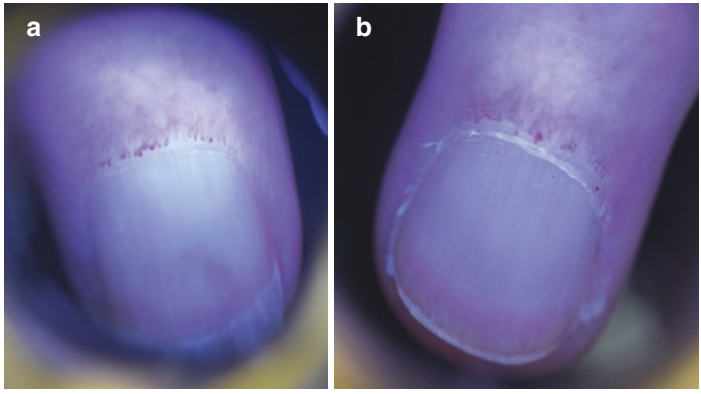

Fig. 13.3 (**a**, **b**) Abnormal nailfold capillaries. Giant capillaries and loss of capillaries at the nailfold are shown, magnified by the dermatoscope. In Fig. 13.3b, there is also a microhemorrhage

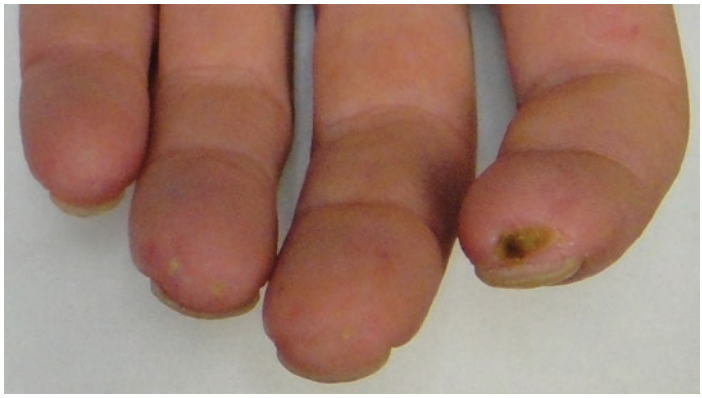

Fig. 13.4 Fingertip lesions: digital tip ulcers and fingertip pitting scars. This image is a closer view of Fig. 13.1, highlighting the fingertip ulcer on the second digit, with overlying eschar, and the numerous superficial pitting scars on the other digits

Telangiectasia

Telangiectasia are dilated blood vessels in the skin, which are not typically symptomatic or prone to hemorrhage but can be a cause of significant disfigurement (Fig. 13.5). They are helpful diagnostically because they represent a visible form of systemic vasculopathy that is characteristic of scleroderma. Ectatic blood vessels can also form in the gastric antrum, giving the endoscopic appearance of gastric antral vascular ectasia (GAVE), and lead to gastrointestinal hemorrhage. Microcytic anemia in a patient with suspected or known scleroderma should prompt an evaluation for GAVE.

Pulmonary Hypertension

Pulmonary hypertension is defined as a mean pulmonary artery pressure greater than 25 mmHg. It is a manifestation of systemic vasculopathy that is typically caused by dysfunction of the small pulmonary arteries, although there are frequent contributions from concomitant interstitial lung disease, myocardial fibrosis, and pulmonary veno-occlusive disease [13]. As such, pulmonary hypertension is a potentially lethal manifestation of systemic

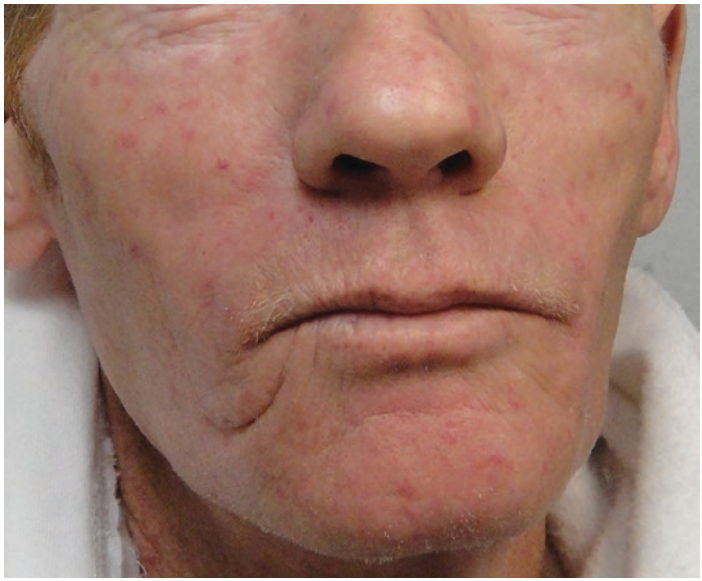

Fig. 13.5 Telangiectasia. Several telangiectasia lesions are seen distributed on the face. Also shown is the pursed lips appearance, resulting from skin thickening of the face in scleroderma

sclerosis, occurring in about 5–12% of patients with scleroderma, and with variable risk according to the clinical subset (Table 13.1). Because symptoms of dyspnea and exercise limitation may be subtle at the onset, early detection by screening tests is crucial. Echocardiography provides an estimate of right ventricular systolic pressure using the tricuspid regurgitant jet, and diffusion capacity for carbon monoxide will be typically reduced to a greater extent than would be predicted based on the spirometry results. Diagnosis is formally established with selective coronary angiography. In addition, since echocardiography may underestimate the severity of pulmonary hypertension, referral for right heart catheterization is appropriate when the clinical suspicion is high. In severe cases, pulmonary hypertension will eventually lead to disabling exertional dyspnea and heart failure.

Interstitial Lung Disease

Interstitial lung disease is defined as progressive pulmonary interstitial fibrosis, which leads to alveolar dysfunction, a decrease in the diffusion capacity, and eventually restrictive lung disease and hypoxemia [14]. It has surpassed renal crisis as the leading cause of mortality in patients with scleroderma, occurring in about 30% of patients (Table 13.1). Typical presenting symptoms are a dry cough and exertional dyspnea, which can then progress to shortness of breath at rest and severe fatigue. Clinically, fine dry crackles can be auscultated in the basolateral lung fields. The diagnosis is established by high-resolution computed tomography (CT) of the chest without the use of intravenous contrast, which classically shows a pattern of nonspecific interstitial pneumonia with peripheral ground-glass opacities. Of note, CT imaging of the thorax is usually performed with the patient lying in a supine position, in which case opacities resulting from lung collapse (atelectasis) may mimic the appearance of interstitial lung disease. To assess for this potential confounder, the patient may be imaged in the prone position: dependent opacities will resolve during prone imaging, while opacities due to interstitial lung disease will persist. Additional radiographic features include reticulation and traction bronchiectasis; honeycombing is more unusual (Fig. 13.6). The presence of a dilated esophagus provides a clue to scleroderma-related dysmotility and increases the risk for aspiration. As for establishing the presence of interstitial lung disease, supporting evidence may be gleaned from pulmonary function tests showing restrictive physiology (decreased forced vital capacity and forced expiratory volume at 1 second) and a decreased diffusion capacity for carbon monoxide (DLCO).

Scleroderma-Related Autoantibodies

The majority of patients with scleroderma test positive for antinuclear antibodies by immunofluorescence, typically in a speckled pattern (nucleolar or centromere pattern). However, these antibodies are nonspecific and a search for additional antibodies is useful, both for diagnostic purposes and to help

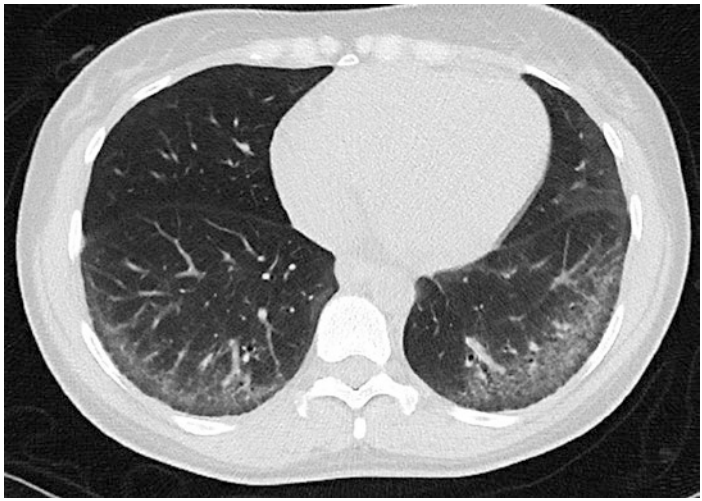

Fig. 13.6 Pulmonary fibrosis. Computed tomography of the chest, highlighting the basolateral ground glass opacities with pleural sparing. This is the nonspecific interstitial pneumonia pattern that is typical of pulmonary fibrosis in scleroderma

predict major organ manifestations. The most common specific antibodies are available for testing in clinical laboratories, recognize nuclear antigens, and are included in the classification criteria (Table 13.2): topoisomerase I (also known as Scl-70), centromere, and RNA polymerase III. In addition, several autoantibodies can be detected in patients with scleroderma but are not strictly specific for this condition. For example, the U1 ribonucleoprotein (U1 RNP) antibody may be associated with scleroderma, systemic lupus, inflammatory myopathy and mixed connective tissue disease. The SSA/SSB antibodies are associated with scleroderma, systemic lupus, and Sjögren's syndrome. The PM/Scl antibody is seen in the overlap syndrome of scleroderma with polymyositis.

Identifying Other Important Signs and Symptoms of Scleroderma (Not Included in the 2013 ACR/EULAR Classification Criteria)

In addition to the aforementioned classification criteria, there are several other important manifestations of scleroderma that warrant detection. These may provide important clues to the diagnosis of scleroderma (calcinosis of the skin, gastric antral vascular ectasia), or they may have significant adverse consequences if unrecognized (renal crisis, cardiac disease, gastrointestinal dysmotility). In this section, a brief description of each of these follows.

Gastrointestinal Dysmotility and Vasculopathy

Gastrointestinal involvement in the setting of scleroderma may affect any portion of the intestinal tract. Skin fibrosis around the mouth may cause a reduced oral aperture and resultant periodontal disease and tooth loss. There is decreased or absent peristalsis in the distal portion of the esophagus and a dysfunctional lower esophageal sphincter, which results in dysmotility, dysphagia, and gastroesophageal reflux (Fig. 13.7). This can be compounded by delayed gastric emptying, which additionally may cause anorexia and bloating. Gastric antral vascular ectasia (GAVE) is an infrequent cause of chronic bleeding or iron deficiency anemia that is diagnosed endoscopically. Small bowel transit is delayed in patients with scleroderma and can lead to bacterial overgrowth and pseudo-obstruction. Symptoms of this include nausea, bloating, abdominal pain, and diarrhea, and in the most severe cases, there can be persistent vomiting and regurgitation that requires parenteral nutrition. Because the lactulose hydrogen breath test has not been consistently reliable, the diagnosis of small intestinal bacterial overgrowth is usually made based on symptoms and responsiveness to cyclic antibiotic therapy [3]. Finally, large bowel dysmotility presents as bloating and constipation, and in rare cases, it can lead to toxic megacolon. Treatment is aimed at decreasing symptoms and complications, improving motility, and providing adequate nutrition.

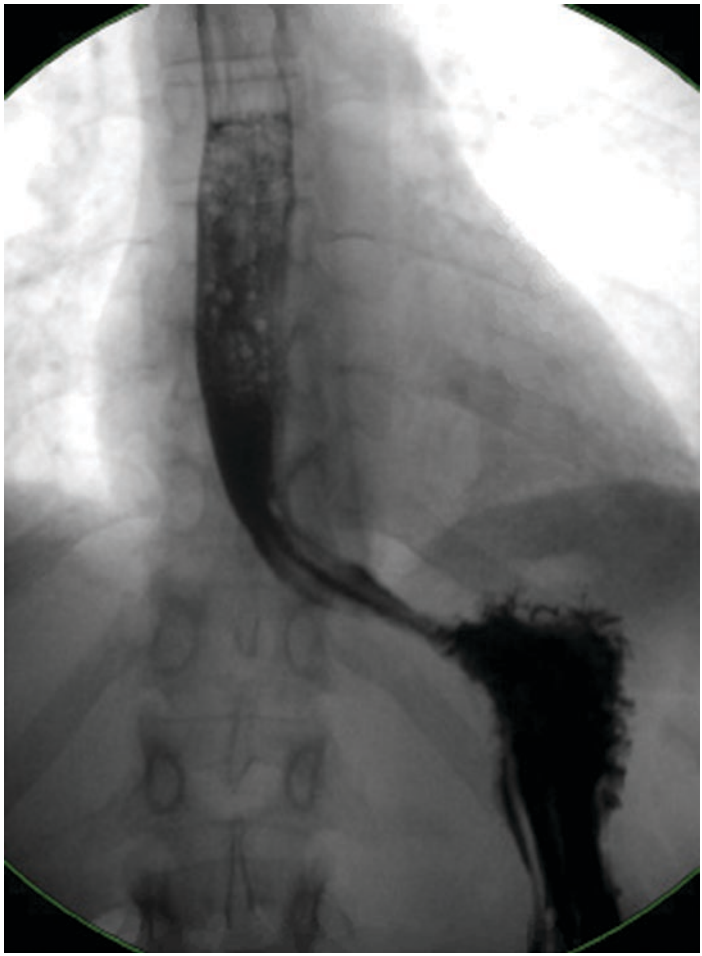

Fig. 13.7 Esophageal dysmotility. Barium esophagram demonstrating an overall decrease in peristaltic contractions, with retention of contrast in the thoracic esophagus. The esophagus is otherwise normal in caliber without narrowing or perforation

Cardiac Involvement

Cardiac disease is frequent in scleroderma and can affect the pericardium, myocardium, conduction system, and vasculature. In the majority of cases, cardiac fibrosis is clinically silent but can nonetheless be an important adverse prognostic sign [15]. Pericardial disease is the most frequent, typically causing effusions and less commonly, pericarditis that can lead to restrictive cardiomyopathy. Myocarditis begins with microvascular disease, leading to ischemia, reperfusion injury, and eventually fibrosis. Either echocardiography or magnetic resonance imaging can be used to detect diastolic dysfunction of both ventricles, which may progress to heart failure with a preserved ejection fraction. Arrhythmias are also common, likely as a result of myocardial fibrosis and microvascular injury, and the most common findings on electrocardiography include premature ventricular contractions, PR segment prolongation, left anterior fascicular block, and intraventricular conduction defects (reviewed in Ref. [15]).

Scleroderma Renal Crisis

Scleroderma renal crisis is a vasculopathic phenomenon, whereby renal interlobular and arcuate arteries become severely narrowed, leading to glomerular ischemia and rapid renal failure. The process begins with endothelial cell injury, which leads to thickening of the intima and smooth muscle layer, fibrosis of the adventitia, and narrowing of the lumen. There is a classic "onion skin" appearance on pathologic examination of the arteries. Although the diagnosis of renal crisis is typically made on clinical grounds, it may be necessary to perform a renal biopsy to exclude other causes of renal failure. Clinically, the onset of renal crisis is heralded by an abrupt increase in blood pressure, progressive renal insufficiency, proteinuria, and evidence of microangiopathy [1]. Rapid identification of this unusual manifestation of scleroderma is key because ACE inhibition has been shown efficacious in reversing the renal disease in its early stages and in decreasing mortality. It is also important to avoid the use of corticosteroids in doses exceeding 10 mg of prednisolone per day because of the risk of precipitating scleroderma renal crisis [16].

Skin Calcinosis

Calcinosis cutis consists of deposits of calcium in the skin and occurs in up to 25% of patients with scleroderma as a result of local tissue damage and hypoxia. The deposits can form at any site but are more troublesome when they are close to a joint and interfere with function; the calcinosis can also be painful due to local inflammation [3]. The deposits are firm subcutaneous calcific nodules that can be palpated clinically or detected on plain radiographs of the affected area (Fig. 13.8). Anti-resorptive treatment options are limited, but bulky calcium deposits can be mechanically removed. It is important to note that calcinosis also occurs in dermatomyositis, especially the juvenile form, and can be triggered by metabolic disorders including chronic renal failure, hypervitaminosis D, mild-alkali syndrome, and malignancy causing bone

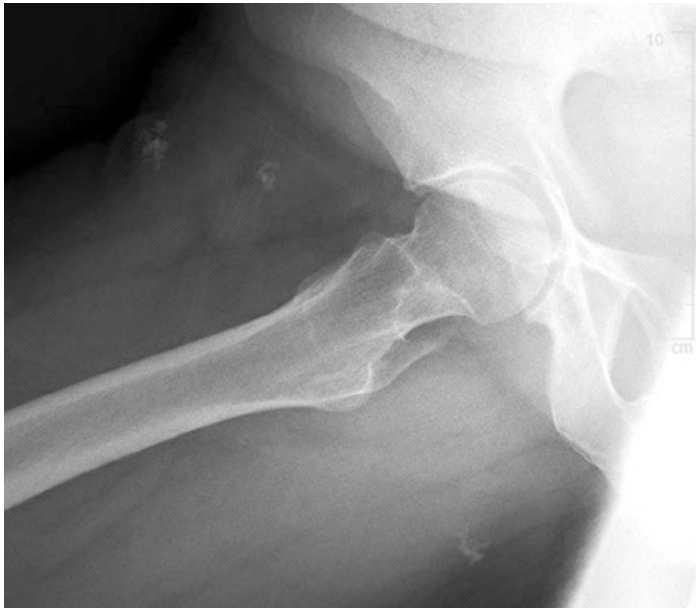

Fig. 13.8 Cutaneous calcinosis. On this plain radiograph of the right hip, several foci of soft tissue calcifications are demonstrated at the right lateral hip and posterior aspect of the proximal thigh

destruction. In addition, the clinical appearance of tophaceous deposits in gout may mimic that of calcinosis cutis; however, these two conditions can be distinguished from each other based on the radiographic appearance that would be quite distinctive. The calcific nodules may also resemble gouty tophi clinically, but plain radiographs could assist in making this distinction, as monosodium urate depositis are typically not calcified.

An Algorithmic Approach to the Diagnosis of Scleroderma

Given the pleiotropic nature of the symptom complex in scleroderma, an algorithmic, sequenced approach to the diagnosis is suggested (Fig. 13.9). Starting with a clinical suspicion and targeted review of systems, important features such as Raynaud's phenomenon and cardiopulmonary dysfunction can be elicited. The clinical exam, focusing on the skin, cardiopulmonary, and musculoskeletal systems, can then offer further clues. Once a hypothesis is formulated, additional diagnostic testing with laboratory, imaging and functional tests can

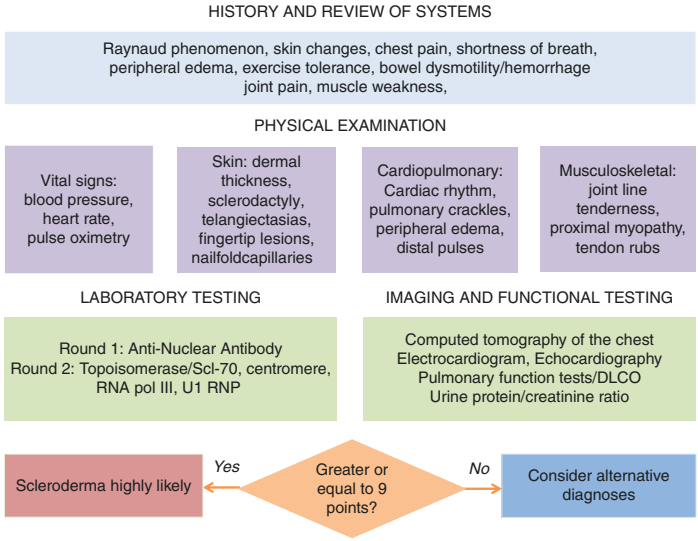

Fig. 13.9 Algorithm for the diagnosis of scleroderma

confirm or exclude the presence of specific antibodies, interstitial lung disease, and pulmonary arterial hypertension.

Staging and Management

Because scleroderma is a complex disease that can have protean manifestations and serious, irreversible complications, it is appropriate to involve a rheumatologist early in the care of such patients. Once the diagnosis is suspected, the first step is to define the clinical phenotype with as much precision as possible, using a combination of clinical examination and targeted diagnostic testing (Fig. 13.9). This should include screening for specific organ involvement, even in the absence of typical symptoms, and attempts to determine whether the disease is currently active, specifically, the frequency of Raynaud attacks and extent of complications (digital ulcers), the extent and progression of skin thickening, whether interstitial lung disease or pulmonary hypertension are present, and the severity of gastrointestinal dysmotility.

A flexible approach to the management strategy is needed because the disease can evolve over time, but broadly speaking, there are two approaches that are not mutually exclusive. The first is targeted to mitigate the dysfunction of specific organs, while the second seeks to slow down disease progression overall by using systemic immunosuppressive therapy. Because scleroderma is a rare disease, there is a paucity of treatment data from randomized controlled trials.

Skin Sclerosis

Patients with mild skin disease do not typically require treatment, but in patients with extensive or progressive skin fibrosis who lack internal organ manifestations, low dose methotrexate, with or without mycophenolate mofetil, has been recommended based on uncontrolled trials. Methotrexate is also useful in patients with inflammatory arthritis or myositis. In more severe cases,

intravenous immunoglobulin or low-dose cyclophosphamide has also been used, and studies of hematopoietic stem cell transplant (HSCT) are in progress [2]. Many of these therapies carry the risk of severe infection or bone marrow suppression, which must be monitored and factored into the decision.

Raynaud's Phenomenon

The severity of Raynaud's phenomenon is variable and can be graded based on the frequency, duration, pain, numbness, and effect on daily functioning. In mild cases where there is no digital ulceration, preventive measures may suffice to manage the symptoms and prevent complications. This includes avoidance of vasospasm with appropriate warming and relaxation techniques. The presence of digital ulcers or loss of digital pulp is an adverse prognostic factor that requires vasodilator therapy. First-line vasodilators are extended-release dihydropyridine calcium channel blockers, though the dose may be limited by hypotension and should be given at nighttime. A second vasodilator, such as topical nitroglycerin, an oral phosphodiesterase type 5 inhibitor, or infused prostacyclin may be added. In more severe cases of recurrent digital ulceration, an endothelin receptor antagonist may be used (reviewed in Ref. [2]).

Pulmonary Hypertension

Even with significant elevations in pulmonary arterial pressure, symptoms may not become manifest until the disease has progressed to right heart failure; hence, it is imperative to screen patients for this condition with echocardiography and pulmonary function testing, and in high-risk patients, establish the diagnosis with angiography. Early diagnosis and treatment are more likely to meet the goal of improving the patient's function, defined by the WHO class. Oral phosphodiesterase type 5 inhibitors or endothelin receptor antagonists are recommended for moderate-to-severe pulmonary hypertension, and therapy may be escalated to

infused prostacyclin in severe or refractory cases. Aerosolized prostaglandins may also be considered for severe pulmonary hypertension. Immunosuppression with biologic agents and the use of antifibrotic agents are being tested with the goal of preventing disease progression (reviewed in Ref. [2]).

Interstitial Lung Disease

Interstitial lung disease may begin at any stage of scleroderma; thus, screening by annual pulmonary function testing is recommended, along with high-resolution computed tomography of the chest in high-risk patients. More invasive diagnostic techniques, including bronchoscopy with lavage and surgical lung biopsy, have limited prognostic utility. Instead, disease severity is assessed based upon serial monitoring of the forced vital capacity, diffusing capacity, and extent of radiographic fibrosis. Various treatment options have been tested. Mycophenolate mofetil may be used as an immunosuppressive strategy, as it is less toxic than cyclophosphamide, and biologic therapy (rituximab, tocilizumab) is under investigation, as well as HSCT. The antifibrotic nintedanib was recently approved for this indication [17]. This therapy is generally well tolerated but may cause dose-limiting gastrointestinal side effects.

Gastrointestinal Dysmotility

A complete assessment of each patient's gastrointestinal symptoms should start from the oropharynx with the assistance of a dentist. Esophageal dysmotility is very common and is managed with proton pump inhibition to avoid esophagitis and stricture formation. Either endoscopy or cine-esophagram can be used to assess disease severity, which is often worse than initially suspected based on symptoms alone. Delayed gastric emptying is managed with prokinetic agents such as metoclopramide or domperidone, with monitoring of the cardiac conduction intervals.

GAVE responds to endoscopic interventions, such as argon plasma coagulation therapy or cryotherapy. Dysmotility in the small and large bowel may cause recurrent pseudo-obstruction, for which octreotide may be helpful, but this is relatively rare and milder cases can be managed by optimizing bowel transit and avoiding cycles of constipation and diarrhea. Cycles of antibiotic treatment may improve small intestinal bacterial overgrowth. In the most refractory cases of malabsorption and malnutrition, parenteral nutrition may be required (reviewed in Ref. [2]).

Scleroderma Renal Crisis

Scleroderma renal crisis typically manifests with the abrupt onset of hypertension, oliguric renal failure, and proteinuria, at which point urgent initiation of an ACE inhibitor, titrated to the maximum tolerated dose, is required. This therapy results in a good outcome in the majority of cases, such that renal crisis is no longer the leading cause of death in patients with scleroderma. Other therapies, including immunosuppressives and vasodilators, have not been proven effective, and prednisone in particular has been associated with new-onset cases of renal crisis. In addition, particularly in patients outside of the typical RNA polymerase III-positive diffuse cutaneous scleroderma subset, other causes of renal disease need to be considered. This can include immune complex glomerulonephritis or thrombotic microangiopathy (reviewed in Ref. [2]).

Quality of Life in Scleroderma

Because of the potential severity of internal organ manifestations in scleroderma, it is easy to overlook other aspects that can have a significant impact on a patient's quality of life and functioning. This includes depression, anxiety, fear of complications, fatigue, and poor self-image due to disfigurement (facial telangiectasias, purse-string appearance around the mouth). Hand contractures

can be disfiguring and may lead to functional disability. Recognizing and addressing these manifestations with psychosocial interventions, appropriate cosmetic procedures, and graded musculoskeletal exercises are most helpful when used in tandem with the management of the underlying disease process [2].

Risk of Malignancy and Associated Autoimmune Conditions

Scleroderma may be associated with other autoimmune conditions, most commonly Sjögren's syndrome, primary biliary cirrhosis, autoimmune hepatitis, and thyroid disease, as well as with neuropathy and audiovestibular disease. Screening for autoantibodies is most useful at disease onset to establish the phenotypic subset and prognosis; repeated testing of antibodies is not generally helpful. However, monitoring of standard laboratory measures, including complete blood count, comprehensive metabolic panel, and urinalysis, is important. Annual echocardiography and pulmonary function testing with diffusing capacity (DLCO) is recommended.

Because there is an increased risk of many types of cancer in patients with scleroderma, age-appropriate screening should be performed. In particular, meta-analyses have shown a higher risk of cancer of the lung, bladder, hematologic system, liver, skin (nonmelanoma), oropharynx, and esophagus in patients with scleroderma compared to the general population. Patients with scleroderma onset at an older age, diffuse cutaneous involvement, interstitial lung disease, and/or RNA polymerase III serology have been shown in some studies to have a higher risk of malignancy (reviewed in Ref. [18]). Although further studies are needed to guide cancer screening in patients with scleroderma, current recommendations emphasize the following:

1. A comprehensive physical examination including the lymphatic system, skin, oral cavity, and thyroid.
2. Cervical cancer screening and mammography for women.
3. Updated colonoscopy for all.

4. In selected high-risk patients: computed tomography imaging of the chest, abdomen and pelvis, esophagogastroduodenoscopy, serum and urine protein electrophoresis, peripheral blood flow cytometry, serum tumor markers [18].

Referral Guidelines and Outlook

Early referral to a rheumatologist is recommended in the following situations: when the diagnosis is uncertain, for assistance with the staging of the disease, selecting a treatment strategy, identifying complications and treatment goals, and with managing adverse effects of the therapy. The natural history of systemic sclerosis is highly variable, with some patients progressing to severe organ damage and others seeing spontaneous improvements in skin fibrosis. For this reason, the primary care physician plays a crucial role in coordinating a team of specialists, which may include a rheumatologist, pulmonologist, cardiologist, gastroenterologist, and nephrologist, depending on the patient's unique clinical circumstance. Because of the pleiotropic nature of the disease process, it is also critical to ascertain new or ongoing signs and symptoms accurately, as not all symptoms are necessarily attributable to the underlying autoimmune disease. In general, early identification and timely implementation of management strategies lead to better clinical outcomes, and new therapies are currently being investigated, with the goal of reducing disease progression and reversing established fibrosis.

Conclusion/Case Summary

Ms. D's case illustrates some key features of the approach to scleroderma. She has nonspecific symptoms that can be ascertained in detail using a combination of clinical assessments, diagnostic laboratory testing, functional assays, and three-dimensional imaging. Once accurate staging for her unique scleroderma subset has been accomplished, a personalized strategy that combines symptom-directed management with immunosuppression, as

appropriate, may be selected based on the available evidence. Thus, a multispecialty team of physicians, with the primary care physician as its quarterback, is best suited to care for the many potentially distressing aspects of a complex disease like scleroderma.

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Vasculitis

14

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Abbreviations

AAV	ANCA-associated vasculitis
ADA2	Adenosine deaminase 2
AION	Acute ischemic optic neuropathy
ANCA	Antineutrophil cytoplasmic antibody
BS	Behcet's syndrome
c-ANCA	cytoplasmic ANCA
CNS	Central nervous system
CRP	C-reactive protein
CTA	Computed tomography angiography
CTD	Connective tissue diseases
CV	Cryoglobulinemic vasculitis
DAH	Diffuse alveolar hemorrhage
ECG	Electrocardiogram

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EGPA	Eosinophilic granulomatosis with polyangiitis
ESR	Erythrocyte sedimentation rate
FDG-PET	18-fluorodeoxyglucose-positron tomography
GBM	Anti-glomerular basement membrane
GCA	Giant cell arteritis
GCs	Glucocorticoids
GI	Gastrointestinal
GPA	Granulomatosis with polyangiitis
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HLA	Human leukocyte antigen
ICI	Immune-checkpoint inhibitors
IRAE	Immune-related adverse event
LVV	Large-vessel vasculitis
MPA	Microscopic polyangiitis
MPO	Myeloperoxidase
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
PAN	Polyarteritis nodosa
p-ANCA	peripheral ANCA
PFAPA	Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy
PMR	Polymyalgia rheumatica
PR3	Proteinase 3
RPGN	Rapidly progressive glomerulonephritis
SGS	Subglottic stenosis
TA	Temporal artery
TAK	Takayasu's arteritis

Introduction

Vasculitis refers to a group of heterogeneous disorders characterized by the presence of inflammation (presence of leukocytes) in vessel walls. Vessel wall injury can result in compromise of lumen and blood flow, leading to ischemia and necrosis, as well as disruption of the vessel wall integrity, increasing risk of rupture and bleeding. Historically, the major forms of primary systemic vas-

culitis have been classified by the size of the vessel involved (Table 14.1) following the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides [1]. In some vasculitis, however, there can be an overlap in the size of blood vessel involvement.

Vasculitis can also occur in the context of other rheumatic conditions such as rheumatoid arthritis or connective tissue diseases (CTDs) (i.e., systemic lupus erythematosus), infections (i.e., subacute bacterial endocarditis), and reaction to medications. This chapter covers the main primary systemic vasculitides, including clinical presentation, diagnosis, and some aspects of treatment. As a general recommendation, patients with vasculitis should always

Table 14.1 Classification of primary systemic vasculitides based on the size of blood vessel involvement

Large-vessel vasculitis	Medium-vessel vasculitis	Small-vessel vasculitis
Giant cell arteritis (temporal arteritis)	Polyarteritis nodosa[b]	ANCA-associated vasculitis
Takayasu's arteritis	Buerger disease (thromboangiitis obliterans)	Granulomatosis with polyangiitis (Wegener's granulomatosis)[b]
	Primary angiitis of the central nervous system	Microscopic polyangiitis[b]
		Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)[b]
		Behcet's syndrome[a]
		Immune-complex mediated
		Cryoglobulinemia
		Henoch–Schönlein purpura[b]
		Hypersensitivity vasculitis
		Paraneoplastic small-vessel vasculitis

[a]Behcet's syndrome may involve large-, medium-, and small-sized vessels
[b]Commonly involve both medium- and small-sized blood vessels

be referred for evaluation by a rheumatologist and other relevant specialists (in some instances nephrologist or pulmonologist) to adequately care for these multisystem disorders. Ideally, they should be managed at a center with expertise in the treatment of these uncommon conditions.

Large-Vessel Vasculitis

Giant Cell Arteritis

Giant cell arteritis (GCA), also called temporal arteritis, is the most common vasculitis in individuals over the age of 50 and the most common large-vessel vasculitis (LVV). GCA can have overlapping symptoms with polymyalgia rheumatica (PMR), and these conditions are usually thought of as within the spectrum of the same disease. GCA is one of the main rheumatologic emergencies since delayed treatment can lead to severe ischemic complications such as irreversible sight loss.

Epidemiology

GCA occurs exclusively in individuals over age 50, with a peak between 70 and 80 years. The incidence of GCA significantly increased by each additional decade after 50 years [2]. GCA is more common in women than men (2–3:1). In the United States, the lifetime risk of GCA in women is 1% and 0.5% in men [3]. GCA is more common in white people, particularly in individuals with Nordic or North European descent. GCA in Black, Asian, or Hispanic individuals is less common. With regard to environmental risk factors, history of or current smoking has been identified as a risk factor for GCA in some studies. Despite some interest in the potential role of viral infections such as varicella-zoster virus, that association with GCA has not been confirmed.

Clinical Features and Findings

The onset of symptoms is usually insidious over weeks to months but can occur abruptly. Constitutional symptoms include fever, fatigue, malaise, weight loss, and anorexia. Fever is typically low

grade, but in some cases can be the most prominent symptom and GCA needs to be considered in the differential diagnosis of fever of unknown origin in individuals older than 50 years. Up to 50% of patients with GCA exhibit PMR symptoms such as myalgias and stiffness affecting the shoulder and pelvic girdle. PMR symptoms can precede GCA or can manifest later in the course of the disease.

The most common manifestations secondary to vascular injury include headache, scalp tenderness, and jaw claudication (ischemia of the masticatory muscles). Headache is usually described as constant and located in the temporal region but can vary in intensity and location; however, headache is not present in all patients. Scalp tenderness can be a feature and often noticed with hair brushing or while resting the head on the pillow at night. Physical exam should include palpation of the temporal artery (TA), assessing for erythema, tenderness, thickening, and decreasing palpation (compared to the unaffected artery). Visual manifestations such as partial or complete vision loss, amaurosis fugax, and diplopia occur less frequently but represent a medical emergency. Blindness occurs most frequently due to occlusion of the ophthalmic posterior ciliary arteries, leading to acute ischemic optic neuropathy (AION), or less frequently central retinal artery involvement. Other ischemic manifestations such as stroke, tongue claudication, tissue gangrene (i.e., scalp, tongue) are rare.

LVV is observed in many GCA patients at autopsy or 18-fluorodeoxyglucose-positron tomography (FDG-PET) studies. However, it is usually subclinical, and symptoms such as arm claudication, heart failure symptoms due to aortic insufficiency, asymmetric blood pressure readings, or aortic aneurysm are uncommon early in the disease course. Chest as well as carotid and subclavian auscultation should be part of the physical exam.

Diagnosis

The differential diagnosis for GCA includes migraine, atherosclerosis, malignancy, infectious aortitis (syphilis), and other rheumatic conditions. TA involvement has also been reported in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and polyarteritis nodosa (PAN).

Marked elevations in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are seen in over 90% of patients. Elevation in both carries a high sensitivity [4]. However, GCA cases with normal inflammatory markers have been reported, and these are usually associated with acute ischemic complications such as blindness. Inflammatory markers tend to normalize quickly after treatment. Other laboratory findings include hypochromic or normochromic normocytic anemia and thrombocytosis. Elevated liver transaminases, including alkaline phosphatase, can be observed.

TA biopsy remains the gold standard for diagnosis and should be ideally performed in all patients. Typical histologic findings include mononuclear cell infiltrates (lymphocytes, monocytes, dendritic cells, giant cells) causing arterial wall inflammation, internal elastic lamina fragmentation, and intimal thickening. Biopsy should be done on the symptomatic side, securing a biopsy length of at least 1 cm. The sensitivity for a biopsy is approximately 77% [5]. Biopsy should not delay initiation of treatment, as pathology findings can be observed in up to 2 weeks after starting glucocorticoids. Bilateral biopsies can increase the diagnostic yield, particularly when ischemic symptoms or TA exam findings do not strongly localize to one side, and many experts advocate for doing so.

Several imaging studies have been used for the assessment of GCA. Studies have shown good sensitivity and specificity for the use of TA ultrasound, and the finding of the "halo sign" (hypoechoic circumferential halo representing the edematous vessel wall) is felt to have good specificity. However, ultrasound is very operator dependent, and it is not advisable to rely on that diagnostically at a center without adequate expertise. Contrast-enhanced computed tomography angiography (CTA), magnetic resonance imaging (MRI), and magnetic resonance angiography (MRA) can be used to identify structural changes and even inflammation of thoracic and abdominal vessels. MRI/MRA is preferred over CTA for these purposes. Finally, whole-body FDG-PET is now being widely used for the assessment of acute inflammation (i.e., increased uptake) in large vessels. Increased uptake rapidly decreases after initiation of glucocorticoids (GCs), and athero-

sclerosis can sometimes be difficult to differentiate from actual inflammation.

Treatment

GCs remain the main treatment in patients with GCA, and due to the risk of vision loss, it should be started in patients with high diagnostic suspicion. Initially, oral prednisone should be started at 40–60 mg daily. For patients with visual symptoms or blindness, IV methylprednisolone pulses (1000 mg/d for 3 days) have been advocated for although there are no studies comparing this to high-dose oral GC. High-dose steroids should be continued for 2–4 weeks, and in the absence of symptoms, dose reduction of 10 mg should be done every 1–2 weeks. When reaching a total daily dose of 20 mg and later 10 mg, weekly dose reductions should be of 2.5 mg and 1 mg, respectively. However, there is no uniformly accepted algorithm for steroid taper, and these decisions must consider patient risk factors for GC toxicity and observed GC tolerability in defining the taper in individual patients. Inflammatory markers should be trended during follow-up but should only aid but not drive therapeutic decisions.

Tocilizumab, an IL-6 inhibitor, is the first FDA drug approved for the treatment of GCA. Tocilizumab enables a faster tapering of GC, reducing GC-related toxicity, and has shown improvements in long-term outcomes such as health-related quality of life [6]. Other steroid-sparring agents such as methotrexate and leflunomide are occasionally used, but evidence of their efficacy is less clear. It is important to remember that inflammatory markers will normalize in patients on IL-6 inhibitors, irrespective of true disease activity. Low-dose aspirin should be considered in GCA since retrospective studies suggest a potential benefit for stroke and blindness prevention.

Takayasu's Arteritis

Takayasu's arteritis (TAK) is another LVV, far less common than GCA. Although they both present some similarities, there are key

Table 14.2 Characteristics of giant cell arteritis and Takayasu's arteritis

Feature	Giant cell arteritis	Takayasu's arteritis
Age	>50 years	<40 years
Sex	Female > male	
Ethnicity	Northern European	Asian
Constitutional symptoms	Present	
PMR symptoms	Present	None
Vascular symptoms/ findings	Cranial manifestations (i.e., headaches) more common Vision loss	Limb claudication (especially lower extremities) more common Vascular abnormalities on exam more common
Elevation of inflammatory markers[a]	Present	
Imaging findings	More extensive involvement of aorta, including abdominal aorta Stenotic lesions more common	Aneurysmal lesions of thoracic aorta and subclavian arteries more common
Response to GC	Yes	
Steroid-sparing agents	Tocilizumab, methotrexate	TNF-α inhibitors, tocilizumab, methotrexate, mycophenolate mofetil, cyclophosphamide

GC glucocorticoids, *TNF-α* inhibitors, tumor necrosis factor-alpha inhibitors (i.e., infliximab, adalimumab), *PMR* polymyalgia rheumatica
[a]Elevated erythrocyte sedimentation rate, C-reactive protein

characteristic features that differentiate these two conditions (Table 14.2).

Epidemiology

The onset of TAK is reported at a younger age, peaking between 15 and 29 years. TAK is also more common in females but has a higher preponderance with a female to male ratio of 9:1. TAK prevalence depends significantly on the region and is mostly reported in patients of Asian descent and Turkey. There are no clear environmental factors reported, although several case reports

and series mention a concomitant diagnosis of TAK and tuberculosis. A causal relationship between these has not been clarified. The coexistence of TAK and inflammatory bowel disease has been reported.

Clinical Features and Findings

Constitutional symptoms such as low-grade fever, malaise, fatigue, and weight loss can occur at the time of presentation or during flares. Arthralgias can also occur, although actual synovitis is uncommon.

Vascular inflammation can be manifested as carotidynia (tenderness elicited on palpation). Damage later leads to stenosis and ischemia, which manifests as absent or weak peripheral pulses, limb claudication (upper and lower extremities), unequal blood pressure in extremities, and hypertension. Respiratory symptoms such as dyspnea and hemoptysis can occur due to the involvement of pulmonary arteries, which eventually lead to pulmonary hypertension. Neurologic symptoms such as vertigo, headaches, and syncope occur due to the involvement of carotid or vertebral arteries. Abdominal symptoms such as postprandial abdominal pain and bleeding (melena or hematochezia) can be observed with the involvement of the mesenteric artery. Although symptoms related to distal ischemia are common, tissue gangrene is rare in this disorder.

In a patient with suspicion of TAK, a physical exam should include blood pressure measurement of all four extremities, auscultation for bruits over the bilateral carotids, and subclavian, axillary, abdominal aorta, renal, and femoral arteries. Pulses should be evaluated as well. A cardiac exam should be done to observe for any signs of aortic insufficiency.

Diagnosis

Differential diagnosis includes other forms of LVV (including Bechet's), infectious aortitis (i.e., syphilis), fibromuscular dysplasia, and other genetic causes of connective tissue disorders.

Inflammatory markers are commonly elevated at presentation or during flares of disease. There are no other specific laboratory abnormalities. Imaging is the main diagnostic modality for diag-

nosis and evaluation in TAK. MRA and CTA have replaced conventional angiography as the gold standard for diagnosis. Conventional angiography might be required prior to surgical interventions. MRA is preferred for follow-up to minimize radiation exposure. FDG-PET can also be used for assessment, although its efficacy for follow-up is still limited.

Treatment

GC remains the most effective treatment, starting at 1 mg/kg of prednisone and then tapering over several months. Relapses are common during GC taper, and other steroid-sparring agents are generally employed, including methotrexate, azathioprine, leflunomide, mycophenolate mofetil, and much less commonly, cyclophosphamide. There is growing evidence regarding the use of tumor necrosis factor (TNF)-α inhibitors and tocilizumab, and these can be used in refractory cases.

Surgical interventions are sometimes required in patients with TAK. Ideally, active inflammatory disease should be controlled or in remission to improve the chances of surgical success anatomically (less friable tissue) and to minimize immunosuppression (i.e., lower doses of steroids) and avoid complications such as infections. There is a high failure rate for both vascular surgery and endovascular interventions.

Special considerations related to pregnancy are relevant in patients with TAK. Studies have shown an increased risk of both maternal complications (pre-eclampsia, stroke, heart failure) and fetal complications (intrauterine death) in patients with TAK. Medications, both antihypertensives and immunosuppressive agents, might require changes during pregnancy.

Medium-Vessel Vasculitis

Polyarteritis Nodosa

PAN is a necrotizing vasculitis that usually affects medium-sized muscular arteries, although occasional small arteries can be involved as well. PAN has been historically associated with

concomitant hepatitis B virus (HBV) infection, and with vaccination and treatment of HBV, the incidence of PAN has decreased.

Epidemiology

Although this varies depending on the region, the prevalence of PAN has been reported up to 31 per million. PAN presents most commonly in middle-aged or older adults, with a peak incidence between 50 and 60 years old, and more frequently in males than females. PAN associated with HBV has decreased significantly. No other infections or environmental factors have been clearly associated. A familiar form of early-onset PAN has been recently described in patients with mutations in the gene for adenosine deaminase 2 (ADA2) [7].

Clinical Features and Findings

Symptoms can evolve over weeks to months. Constitutional symptoms including fever, fatigue, weight loss are common. PAN can have a diverse spectrum of end-organ manifestations; however, lung involvement, in the form of capillaritis or parenchymal involvement, is not a feature of PAN and can help differentiate from other vasculitides such as ANCA-associated vasculitis (AAV) (Fig. 14.1). There are rare reports of bronchial artery involvement due to PAN.

Skin findings are a prominent feature of PAN and include subcutaneous nodules, skin ulcerations (particularly in lower extremities), and livedo reticularis. Palpable purpura can also be seen, which is a feature of small-vessel involvement (i.e., leukocytoclastic vasculitis). Peripheral edema can be associated with these lesions. Peripheral nervous system manifestations such as mononeuritis multiplex (i.e., foot or wrist drop) are common. Symmetrical polyneuropathy, sensory and/or motor, can occur. Gastrointestinal (GI) symptoms include nausea, vomiting, postprandial abdominal pain (due to mesenteric involvement). Tissue infarction can occur leading to acalculous cholecystitis or appendicitis, and these reported forms of single organ vasculitis due to PAN. Acute surgical abdomen due to intestinal perforation or rupture of microaneurysms (hepatic, renal, intestinal) is also a

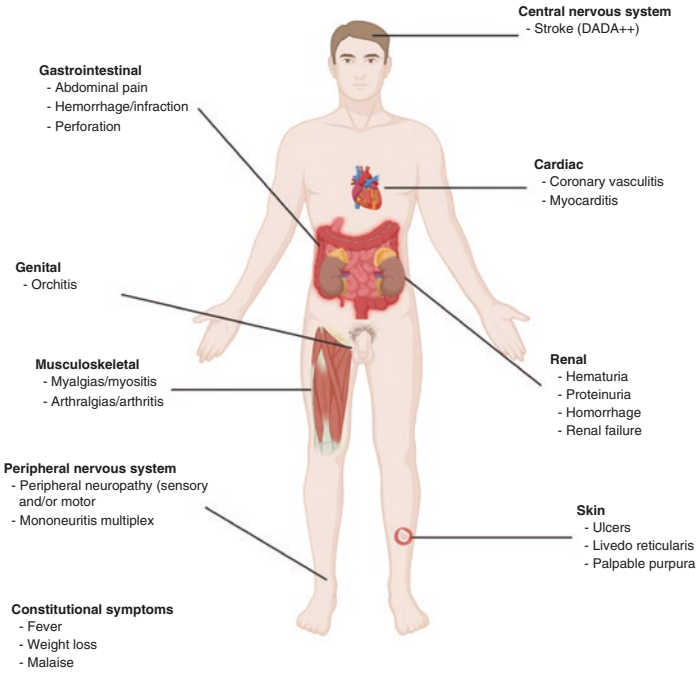

Fig. 14.1 Clinical manifestations in patients with polyarteritis nodosa (PAN). DADA, deficiency of adenosine deaminase 2

presentation of PAN. Renal involvement in PAN is not secondary to glomerulonephritis, but rather infarcts or hematomas. Hypertension in the context of PAN is secondary to renal artery involvement.

Other manifestations including cardiac involvement (coronary vasculitis, cardiomyopathy), central nervous system (CNS) involvement, testicular pain due to orchitis, and hearing loss are less commonly seen but can be clues to the diagnosis. Early-onset hemorrhagic and ischemic strokes, associated with hypogammaglobulinemia and immunodeficiency, have been reported in an inherited genetic auto-inflammatory form of PAN called deficiency of ADA2 or DADA2.

Diagnosis

Differential diagnosis includes other vasculitides such as AAV, cryoglobulinemia, IgA vasculitis, and vasculitis secondary to other connective tissue diseases. Infections such as infective endocarditis, HIV, and other viral hepatitis also need to be considered. Other disorders that can mimic PAN include antiphospholipid syndrome, embolic conditions such as left atrial myxoma, fibromuscular dysplasia, and segmental arterial mediolysis.

Elevated inflammatory markers and anemia are commonly found. There is no specific serologic testing, although if hepatitis B and C testing should be done in all individuals. Children or adolescent patients, if there is a family history of similar symptoms, should be tested for mutations in the gene for ADA2. ANCA, ANA antibodies, complement levels, and cryoglobulins should also be tested as part of workup and typically would be absent in primary PAN.

Noninvasive angiography (CTA, MRA) can be used to identify areas of ischemia or microaneurysms. Conventional angiography, although not required, is better for the visualization of microaneurysms and stenosis. Ideally, a biopsy confirming the diagnosis is needed. Renal and skin biopsies are higher yield and show the pathognomonic inflammation of medium-sized arteries. GI biopsy is lower yield.

Treatment

PAN often runs a monophasic course as opposed to some of the other vasculitides, which are more chronic (such as TAK) or relapsing (such as AAV). In the presence of end-organ damage, high-dose GC (i.e., 1 mg/kg) is used, and pulse IV GC can be considered. For severe manifestations (i.e., renal, GI disease), treatment with cyclophosphamide is often recommended and other steroid-sparring agents such as methotrexate and azathioprine during maintenance phase. Poor prognosis factors include renal disease with a serum creatinine higher than 1.6 mg/dl or nephrotic range proteinuria, GI infarction, cardiomyopathy, and central nervous system involvement [8]. For patients with HBV-associated PAN, anti-HBV therapy is recommended alongside a

short course of GC. TNF-α is the first-line agent for patients with DADA2.

Small-Vessel Vasculitis

ANCA-Associated Vasculitis

AAVs are a group of systemic necrotizing vasculitides that affect small-sized blood vessels and occasionally medium-sized vessels and are associated with detectable circulating ANCA. The major clinicopathological variants described include granulomatosis with polyangiitis (GPA, previously referred to as Wegener's granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA, previously called Churg–Strauss vasculitis), and microscopic polyangiitis (MPA). These conditions have a wide spectrum of manifestations; however, there are typical clinical manifestations associated with these conditions.

Granulomatosis with Polyangiitis

GPA is characterized by necrotizing granulomatous inflammation of small blood vessels that usually involve the upper and lower airway as well as the kidneys.

Epidemiology

GPA has an estimated prevalence of up to 21.8 per 100,000 cases. There is no sex predominance, and it occurs more often in Caucasian individuals. The peak incidence of GPA is between 40 and 70 years, and although GPA can occur in children and adolescents, it is rare. There are no clear environmental factors associated with GPA, although a recent study reported an increased risk associated with the history of smoking [9].

Clinical Features and Findings

The onset of symptoms usually follows a subacute to chronic course. Constitutional symptoms such as fevers, weight loss, fatigue, and malaise are common (Fig. 14.2). Nonerosive arthritis

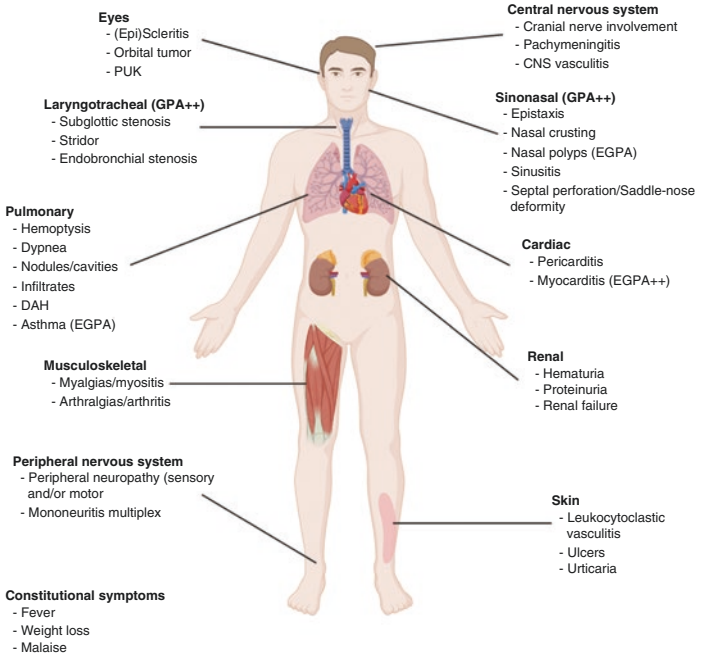

Fig. 14.2 Clinical manifestations in patients with ANCA-associated vasculitis. GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; MPA, microscopic polyangiitis; PUK, peripheral ulcerative keratitis; DAH, diffuse alveolar hemorrhage; CNS, central nervous system. ++ indicate clinical manifestation is more common in the specific form of ANCA vasculitis. Nasal polyps are characteristic of EGPA

is observed in several patients, usually in the context of systemic disease but can precede other more specific manifestations. Skin involvement occurs in up to half of the patients, and manifestations include palpable purpura, papules, petechiae, ulcers, and subcutaneous nodules. Leukocytoclastic vasculitis is the most common biopsy finding.

Sinonasal disease is the most common manifestation and occurs in up to 90% of patients with GPA. Although rhinosinusitis usually happens associated with other systemic manifestations, isolated localized disease can occur. Sinonasal disease includes

chronic rhinosinusitis, crusting rhinitis, and recurrent epistaxis and can lead to nasal septum perforation and saddle-nose deformity. Superimposed infections due to *Staphylococcus aureus* are common and can also trigger disease flares. Ocular disease including episcleritis, scleritis, keratitis, and uveitis can be seen. Orbital pseudotumor is another reported manifestation and manifests as proptosis, diplopia, and decreased vision. Involvement is most commonly unilateral. Recurrent otitis media with serous effusions, conductive and sensorineural hearing loss, and chronic mastoiditis can also occur as a complication of contiguous sinonasal disease. Subglottic stenosis (SGS) can present as stridor, cough, and dysphonia and can occur even during remission of other systemic manifestations. SGS is more likely in females and younger patients at the time of disease onset and is commonly associated with other upper airway manifestations such as nasal septum perforation and endobronchial involvement [10].

Renal involvement, manifested as proteinuria, microhematuria, and renal insufficiency, can occur in up to 85% of patients and can be rapidly progressive. Pulmonary disease manifested as cough, dyspnea, and hemoptysis occurs due to infiltrates, nodules and cavitary lesions, and diffuse alveolar hemorrhage (DAH), which can be fatal. Fibrosis and interstitial lung disease are less common. GPA is a cause of pulmonary-renal syndrome. Neurologic involvement includes either CNS involvement, such as CNS vasculitis and granulomatous meningitis (pachymeningitis), or peripheral nerve involvement, such as mononeuritis multiplex (i.e., foot drop) and sensorimotor polyneuritis, can be seen. Cardiac (i.e., myocarditis, pericarditis) and GI involvement are rare.

Diagnosis

Differential diagnosis includes other forms of AAV, antiglomerular basement membrane (GBM) disease, PAN, IgG4 disease, or vasculitis secondary to CTD. It is important to note that cases of concomitant anti-GBM or IgG4 disease have been reported. Levamisole, a substance present in cocaine, can also

cause vasculitis and present with nasal perforation. These patients present commonly with necrotic skin ulcers and have ANCA positivity (sometimes both c- and p-ANCA), but very rarely cause pulmonary and renal disease. Hepatitis serologies also need to be checked.

Elevated inflammatory markers are a common finding. Anemia and leukocytosis can be seen. Urinalysis looking for proteinuria, hematuria, and red blood cell casts needs to be done in all patients since renal involvement is often indolent initially but can then rapidly progress. ANCA testing is vital for diagnosis. The cytoplasmic pattern in immunofluorescence (c-ANCA) is usually secondary to antibodies directed toward proteinase 3 (PR3-ANCA), which are observed in 90% of patients with GPA. The remainder of patients with GPA have antibodies directed toward myeloperoxidase (MPO-ANCA) or no detectable ANCA serologies. This last scenario is observed more often in patients with localized disease (i.e., sinonasal, upper airway). ANCA levels can correlate with disease activity; however, they can persist even during remission in up to 40% of patients and flares of disease can occur in the context of negative ANCA titers.

CT imaging is important for diagnosis and monitoring of sinonasal and pulmonary disease. Evaluation by an experienced otorhinolaryngologist is crucial for the assessment and management of patients with sinonasal disease. Biopsy diagnosis is often warranted, although not always pursued if the presentation is classic clinically and serologies are strongly supportive. Skin and renal biopsy are higher yield, with the first most commonly showing findings consistent with leukocytoclastic vasculitis and the second showing crescentic pauci-immune (absence of complement or immunoglobulins) glomerulonephritis. Lung biopsies reveal granulomatous inflammation but generally require substantial tissue. It is uncommon to be able to establish a histologic diagnosis by bronchoscopic or needle biopsy, with those procedures more helpful to exclude other diagnoses such as infection or malignancy. Sinonasal biopsies are accessible but of low yield.

Treatment

Treatment of GPA is based on the severity of the manifestations. Generalized and severe disease, such as renal disease, pulmonary hemorrhage, mononeuritis, or organ ischemia usually is treated with rituximab (B-cell-depleting antibody) and less commonly cyclophosphamide, as well as high-dose corticosteroids. Treatment of localized disease (upper airway or sinonasal disease) has usually included lower dose corticosteroids and methotrexate, although other agents including azathioprine, mycophenolate, and leflunomide have been used. Rituximab has also been helpful in limited disease and is increasingly being utilized in these patients. Several new agents for AAV are currently being studied, including avacopan, a C5a receptor inhibitor, that has been shown in trials to reduce disease flares and cumulative GC exposure in patients with AAV.

The treatment approach involves a "remission-induction" phase, aimed at achieving clinical remission, and a "remission-maintenance" phase, aimed at maintaining disease control and prevention of flares. In the remission-induction phase, high-dose GC (1 mg/kg) is used in combination with either rituximab or cyclophosphamide in severe disease. The latter can be given either orally (higher incidence of side effects) or intravenously (higher risk of relapse). Rituximab has been shown to be as effective as cyclophosphamide and has a better safety profile [11]. Risk of infection is high during this phase of treatment, and prophylaxis for *Pneumocystis jirovecii* is essential. A recent study showed no significant benefit of the use of plasmapheresis in patients with severe AAV; however, potential benefit in specific subgroups is still to be determined [12]. The remission-maintenance phase usually involves the use of either oral steroid-sparing agents (methotrexate, azathioprine) or lower doses of rituximab [13].

Microscopic Polyangiitis

MPA is a systemic vasculitis that usually affects the kidneys and lungs and is one of the most common causes of pulmonary-renal syndrome. MPA is characterized by necrotizing vasculitis without granulomatous inflammation, which differentiates it from GPA and EGPA.

Epidemiology

Prevalence of MPA has been reported in up to 42.1 per 100,000, with variations depending on geographical region. MPA is the most prevalent form of AAV in Asia, compared to the higher prevalence of GPA in Europe. MPA has a mild male predominance and an average age of onset between 50 and 60 years. A systemic vasculitis with features of MPA (i.e., elevated p-ANCA) has been reported with medications including hydralazine, penicillamine, minocycline, propylthiouracil, and allopurinol.

Clinical Features and Findings

Constitutional symptoms such as low-grade fever, weight loss, and malaise can occur, but less frequently than in GPA. Arthralgia and myalgia are also reported (Fig. 14.2). Cutaneous lesions include palpable purpura, ulcers, and livedo and are a common manifestation.

Renal involvement is the hallmark lesion in MPA, reported in over 90% of patients. The clinical course can be slow or fulminant in the form of a rapidly progressive glomerulonephritis (RPGN). RPGN manifests as nonnephrotic proteinuria, microhematuria, and rapid decline in renal function. Patients with a slow indolent course can present without any other systemic manifestations (renal limited form). Pulmonary disease manifests as cough, dyspnea, and hemoptysis. This occurs due to pulmonary infiltrates or DAH. ILD and fibrotic lung disease can be a result or even precede other manifestations, and it occurs more often than in GPA. Peripheral neuropathy such as mononeuritis multiplex or distal polyneuropathy can occur in up to 50% of patients. Cardiac and gastrointestinal manifestations are rare. Sinonasal and ocular involvement is rare.

Diagnosis

Differential diagnosis for MPA is similar to that of GPA, and granulomatous manifestations such as sinonasal involvement are the main way to differentiate between both. Even though treatment might not be different between both, there are certainly different prognostic implications since PR3-ANCA, and

granulomatous manifestations of GPA tend to be associated with a higher risk of relapse.

Elevated inflammatory markers and anemia are reported. Urine sediment abnormalities include proteinuria, hematuria, and red blood cell casts. ANCA is positive in up to 90% of patients with MPA, usually showing a perinuclear (p-ANCA) pattern, usually MPO-ANCA. Less than 20% of patients with MPA can have PR3-ANCA, and ANCA-negative patients have been reported. Biopsy is often necessary and, in the case of renal disease, has prognostic implications as well. MPA patients tend to have a higher incidence of sclerotic changes in renal biopsies, which provide information regarding the long-term risk of end-stage renal disease. CT chest is also useful since, besides the acute findings, fibrosis can be detected in these patients.

Treatment

Treatment of MPA also follows a remission-induction and a remission-maintenance phase similar to GPA, with the use of similar agents during both phases. In cases of drug-induced MPO-AAV, the offending medications must be discontinued.

Eosinophilic Granulomatosis with Polyangiitis

EGPA is the most rare of AAV, and it is characterized by eosinophilia and granulomatous necrotizing vasculitis. Although it does maintain certain common features with other forms of AAV, EGPA has specific manifestations secondary to the presence of eosinophils.

Epidemiology

Prevalence of EGPA has been reported between 14 and 18 per 100,000, and there is no geographical variation. The mean age of onset is between 40 and 50 years old, and it rarely happens in children and adolescents. A few studies have reported a mild female predominance. An association between leukotriene-modifying agents has been reported; however, causality has been proven and it is currently thought that these agents lead to unmasking of EGPA in the context of GC withdrawal.

Clinical Features and Findings

The clinical course of EGPA has usually been described in three different phases: a prodromal, an eosinophilic, and a vasculitic phase. Overlap of these phases can occur, and sometimes patients may not present either the eosinophilic or vasculitic phase. Prodromal phase symptoms include allergic rhinitis and asthma and can precede the eosinophilic phase for up to 10 years. Asthma is an almost universal symptom in all EGPA patients. Recurrent rhinitis and sinusitis are commonly reported, and unlike patients with GPA, EGPA patients present polyposis.

The eosinophilic phase is characterized by worsening shortness of breath due to migratory lung infiltrates. Cough is common, with the persistence of wheezing. Hemoptysis secondary to DAH can occur. Cardiac symptoms including heart failure symptoms can occur secondary to myocarditis, which is the most common form of cardiac involvement and occurs more often than in other forms of AAV. Electrocardiogram (ECG) abnormalities can occur in these patients. GI involvement, although less common, can occur in this phase and is characterized by abdominal pain, diarrhea, and bleeding secondary to eosinophilic gastroenteritis. The vasculitic phase of disease is characterized by the skin involvement in the form of palpable purpura or nodules in extensor surfaces that occur in half of the patients. Peripheral neuropathy manifesting as pain, numbness, or weakness can be seen, and mononeuritis multiplex can be seen in up to 75% of patients. Renal disease is less frequent than in other forms of AAV, and a small percentage of patients present with RPGN.

Diagnosis

Differential diagnosis for EGPA includes other AAV, vasculitis associated with CTD, eosinophilic pulmonary diseases such as chronic eosinophilic pneumonia and allergic bronchopulmonary aspergillosis, and hypereosinophilic syndrome. Parasitic infections causing eosinophilia such as strongyloidiasis, toxocariasis, and HIV need to be considered.

Eosinophilia is present in all patients and correlates with disease activity. Inflammatory markers are commonly elevated during active disease. ANCA are positive in up to 40% of patients

and mostly specific for MPO-ANCA. The presence of ANCA correlated with two distinct disease phenotypes: ANCA-positive patients tend to present vasculitic manifestations more commonly while ANCA-negative patients usually have more eosinophilic complications. ANCA titers can correlate with disease activity.

CT chest imaging should be considered in all patients for evaluation of pulmonary disease. If suspicion of cardiac involvement, cardiac MRI is the preferred form of imaging. Given significant obstructive airway symptoms, pulmonary function tests should be done in EGPA patients. The biopsy usually confirms granulomatous vasculitis with eosinophilic infiltration, and ideally the least invasive site should be pursued (i.e., skin, peripheral nerve).

Treatment

The presence of either cardiomyopathy, severe gastrointestinal manifestations, central nervous system involvement, renal insufficiency, and proteinuria >1 g/day are poor prognostic factors and indicate the needs for high-dose GC (1 mg/kg) as well as an additional steroid sparring-agent [8]. Cyclophosphamide, either intravenous or oral, has been usually the preferred agent. Although the increasing use of rituximab has also extended into the treatment of EGPA, cyclophosphamide use is recommended in severe forms of EGPA including cardiomyopathy. Unlike other forms of AAV, the level of evidence for treatment in EGPA is lower. Azathioprine and methotrexate can be considered as steroid-sparring agents in nonsevere forms of EGPA. The benefit of agents such as rituximab in the treatment of these chronic manifestations is not clear, and persistent sinopulmonary symptoms usually lead to increased exposure to GC and related side effects. Mepolizumab, an IL-5 inhibitor, has been approved for the treatment of EGPA and is most relevant to sinopulmonary symptoms [14].

Cryoglobulinemic Vasculitis

Cryoglobulinemia refers to the presence of cryoglobulins (antibodies that precipitate with temperatures less than 37 °C), and

Table 14.3 Types of cryoglobulinemia

Type and frequency	Cryoglobulin	Causes	Manifestations
I (10–15%)	Single type monoclonal Ig (IgM or IgG)	Lymphoproliferative disorders (Waldenstrom macroglobulinemia, multiple myeloma, lymphoma, CLL)	Hyperviscosity (i.e., Raynaud's, livedo reticularis, gangrene)
II (50–60%)	IgG and monoclonal IgM	Infections (HCV, HBV, HIV, endocarditis), autoimmune conditions (Sjogren's, SLE, RA), malignancy (lymphoma), idiopathic	Immune-complex mediated vasculitis
III (30–40%)	IgG and polyclonal IgM		

Ig immunoglobulin, *CLL* chronic lymphocytic leukemia, *HCV* hepatitis C virus, *HBV* hepatitis B virus, *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis

although most patients remain asymptomatic, a few patients developed symptoms. This is called cryoglobulinemic vasculitis (CV). Different types of cryoglobulinemia exist (Table 14.3), and we will be mostly discussing types II and III, which are the ones associated with a clinical presentation of vasculitis and are called mixed cryoglobulinemia.

Epidemiology

CV is a rare condition, and its prevalence is usually associated with the endemic presence of hepatitis C virus (HCV). Cryoglobulinemia has been reported in a significant proportion of patients with conditions like HBV, HCV, and HIV. The prevalence of CV seems to be higher in males than females.

Clinical Features and Findings

Constitutional symptoms such as fatigue and myalgias are commonly reported. Nonerosive symmetric arthritis, commonly involving hands and knees, is commonly reported. Palpable purpura is the most common manifestation in up to 90% of patients and typically involves the lower extremities. Ulcers may develop.

Neuropathy can be seen, including mononeuritis multiplex (i.e., foot drop) or sensory-motor manifestations such as numbness, pain, and weakness. Renal involvement can be observed including proteinuria, hematuria, and renal failure in the context of nephritic syndrome. Pulmonary involvement, including DAH or interstitial lung disease, is rare and occurs in less than 5% of patients.

Diagnosis

Differential diagnosis includes other types of vasculitis such as AAV, vasculitis associated with connective tissue disorders, thrombotic disorders such as antiphospholipid syndrome, and infections such as bacterial endocarditis and rickettsia infections.

Inflammatory markers are usually elevated. Urine abnormalities such as microhematuria and proteinuria can be observed, and elevated hepatic transaminases can be seen. Hepatitis C, as well hepatitis B and HIV, serology testing should be considered in all patients with a potential diagnosis of CV. Cryoglobulins, following standard procedures, should be tested. False negatives can occur due to inadequate sample collection or laboratory processing, and concentrations can fluctuate. Immunofixation will show monoclonal or polyclonal spikes. Rheumatoid factor is commonly positive in these patients, and complement consumption (low C4 and CH50, normal C3) is typical. Biopsies from the skin will reveal leukocytoclastic vasculitis, and renal biopsies will commonly show membranoproliferative glomerulonephritis.

Treatment

Treatment of the underlying condition is as important as the treatment for CV. First-line therapy, which does not include interferon agents, for HCV is needed and can be the sole treatment if there are no severe or life-threatening manifestations. In the case of severe CV, high doses of GC (1 mg/kg) are used and plasma exchange should be considered. Rituximab and, less commonly, cyclophosphamide are immunosuppressives used in its management.

Behcet's Syndrome

Behcet's syndrome (BS) is a complex multisystem disease characterized by inflammation of small, medium, and large blood vessels both in the arterial and venous territory.

Epidemiology

The prevalence of BS varies depending on the region, with a pooled global prevalence of 10.3 per 100,000 and the highest prevalence reported in Turkey, 119.8 per 100,000. Prevalence is higher in the Mediterranean, Middle East, and Far East, the reason why it has been referred to as the "Silk Road Disease." Familial forms of BS have been recognized, and there is an association with human leukocyte antigen (HLA)-B51, although its presence is not necessary for disease. The onset of BS commonly occurs between 20 and 30 years old and has an equal male–female distribution. Male patients seem to have a higher incidence of severe forms of BS.

Clinical Features and Findings

Constitutional symptoms such as fever and malaise can be reported. Asymmetric nonerosive arthritis is in a mono-, oligo-, or polyarticular pattern and most commonly involves knees, ankles, and wrists. Lower back pain, including sacroiliitis and enthesopathy, is also reported.

Mucocutaneous manifestations are the most common manifestations. Oral painful aphthous ulcers occur in up to 95% of patients, and unlike other manifestations whose frequency decrease with time, these occur throughout all course of the disease. Ulcers are short lasting, appear in lips, gingiva, cheeks, and tongue, and leave no scar. Patients usually report triggers such as stress, fatigue, menstruation, or specific foods. Genital ulcers, occurring in the scrotum or major or minor labia, are also common but take longer to heal than oral ulcers and do form scars. Cutaneous manifestations include papulopustular lesions, which are commonly found in patients. Erythema nodosum is also observed. Patients should be queried about pathergy and the

formation of sterile pustules at a site where a needle has been inserted.

Ocular involvement occurs in up to 75% of patients and occurs more frequently and severely in males. This manifestation usually presents earlier in the disease course and, if untreated, can lead to blindness. Posterior or panuveitis is the most common manifestation. Retinal vasculitis, anterior uveitis, conjunctival ulceration, and secondary cataracts also occur, but less frequently. In particular, in males, evaluation by ophthalmology should be considered.

Vascular disease, including thrombosis and aneurysm formation, along with neurological disease constitutes a major cause of morbidity and mortality in patients with BS. Venous disease leading to recurrent thrombosis is more common than arterial disease. Superficial or deep vein thrombosis of extremities is the most common presentation, but atypical sites such as portal vein, Budd–Chiari syndrome (hepatic veins), cerebral venous sinus, and superior or inferior vena cava can occur. Arterial disease is uncommon, and pulmonary artery aneurysms are the most common arterial lesions in BS. Patients can present with hemoptysis, cough, and dyspnea. Presentation of this rare complication can be catastrophic and worsened if confused with pulmonary embolism and anticoagulation is instituted.

Neurological involvement is usually divided into nonparenchymal (i.e., cerebral venous sinus thrombosis) and parenchymal involvement. The latter is a rare but severe manifestation, is also more frequently reported in males, and presents later in the disease course. Symptoms are usually subacute and include headaches, dysarthria, ataxia, hemiparesis, and cranial nerve palsies, reflecting the structure involved (brain stem, basal ganglia, periventricular white matter). GI symptoms include abdominal pain, hemorrhage, and perforation. Cardiac involvements such as pericarditis, myocarditis, and coronary arteritis leading to infarction are uncommon, and renal involvement is rarely seen.

Diagnosis

Differential diagnosis depends on clinical symptoms and should include SLE, seronegative spondyloarthritis, inflammatory

bowel disease, autoinflammatory syndromes such as periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) syndrome, and viral infections such as herpes virus or HIV. Multiple sclerosis is the main differential diagnosis in patients with parenchymal neurological involvement.

There are no specific laboratory studies for BS, and like other vasculitis, elevation of inflammatory markers can be observed. HLA-B51 testing is not necessary for the diagnosis of BS, and this should be mostly guided by clinical presentation. Brain MRI for diagnosis of parenchymal neurological involvement can reveal the extensive lesions and brainstem atrophy that are typical for BS.

Treatment

Colchicine and thalidomide have been historically used for the treatment of mucocutaneous disease. More recently, apremilast, a phosphodiesterase-4 inhibitor, has been approved for the treatment of oral ulcers, and studies have shown improvement of genital ulcers as well [15]. TNF-α inhibitors have also been used for the treatment of arthritis symptoms and have an effect as well for mucocutaneous disease. Oral steroid-sparing agent drugs such as methotrexate and azathioprine have also been used, and combination with biologic agents could be considered extrapolating experience with other rheumatic conditions.

For severe manifestations, high-dose GC (1 mg/kg) should be considered, including pulse GC in severe presentation such as acute sight-threatening ocular disease or neurological involvement. TNF-α inhibitors, interferon-α or cyclosporin-A, can be used in ocular disease, and interferon-α and cyclophosphamide can be used in parenchymal neurological involvement. For the treatment of vascular disease, GC and immunosuppressive agents should be used. The role of anticoagulation is controversial and should be considered in refractory cases or extensive thrombosis. Evaluation for coexistent pulmonary artery aneurysm should be considered due to the risk of fatal bleeding.

Paraneoplastic Vasculitis

Vasculitic syndromes have been reported both with hematologic, such as lymphoma and myelodysplastic syndrome, and chronic lymphocytic leukemia and solid malignancies (i.e., genitourinary, pulmonary). Most cases are usually cutaneous vasculitis (i.e., leukocytoclastic vasculitis), although other forms such as GCA, GPA, and PAN have been reported. In these cases, treatment of both the underlying malignancy and the vasculitic syndrome is needed.

Although not strictly paraneoplastic, vasculitis associated with immune-checkpoint inhibitors (ICIs) is also part of the immune-related adverse events (IRAEs) associated with the use of new agents. Vasculitic syndromes are rare in frequency compared to ICI-associated inflammatory arthritis, one of the most common manifestations. LVV and CNS vasculitis are some of the forms of vasculitis reported to ICIs [16]. It is important to note that ICI-associated PMR is one of the common forms of IRAEs. CV and renal small-vessel vasculitis have also been reported (Table 14.4).

Relevant Comorbidities

Either as a complication of the underlying disease or treatment, patients with vasculitis are at an increased risk of morbidity. Although the data is limited for some forms of vasculitis, risks such as infection, cardiovascular disease, and thrombosis are common not only in patients with vasculitis but also in patients with other rheumatic conditions (Table 14.3). It is therefore important that attention to those comorbidities and comprehensive general care be part of the management approach to patients with vasculitis.

In the case of AAV, mortality has decreased in the last years due to the availability of new therapies and better understanding of the disease [17]. However, patients with AAV continue to have an increased risk of mortality compared with non-AAV population, and cardiovascular disease, infections, malignancy, and renal death are the main causes [18]. Infections continue to be the main cause of excess mortality.

Table 14.4 Comorbidities in patients with vasculitis

Relevant comorbidities	Comment
Infections	As a result of immunosuppression, patients with vasculitis such as GCA and AAV are at a higher risk for infections. PJP prophylaxis with TMP-SMX should be initiated in all patients on moderate-to-high doses of prednisone (≥10–20 mg/day). Patients with concomitant lung disease are at a higher risk for PJP or other respiratory infections. Infections can occasionally trigger flares of underlying disease. Long-term use of RTX can lead to hypogammaglobulinemia and increased risk of infections.
Cardiovascular disease	When compared to the general population, increased rates of ischemic heart disease and cerebrovascular diseases have been reported in patients with AAV and GCA. In patients with AAV, this risk seems to be higher during the initial years after diagnosis. Management of traditional cardiovascular risk factors is imperative and should be assessed at baseline.
Thromboembolic disease	Patients with GCA and AAV have been shown to have increased rates for venous thromboembolic events. These tend to occur during episodes of high disease activity.
Malignancy	Increased risk of genitourinary and hematologic malignancies has been reported in patients with AAV, usually attributed to the use of CYC. With improvement in CYC protocols and availability of newer agents, recent studies have shown that malignancy risk is now comparable to that of the general population.
Bone metabolic disease	As a result of GC use and advanced age in some patients, there is higher risk of osteoporosis and subsequently fractures. Measures for prevention of GIOP should be taken including calcium and vitamin D supplementation, as well as the use of metabolic agents such as bisphosphonates and recommendations for weight-bearing physical activity.

GCA giant cell arteritis, *AAV* ANCA-associated vasculitis, *PJP* pneumocystis jirovecii pneumonia, *TMP-SMX* trimethoprim-sulfamethoxazole, *RTX* rituximab, *CYC* cyclophosphamide

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Ankylosing Spondylitis

15

Ira Khanna and Ioannis Tassiulas

"Being seriously affected by a rheumatic disease at the age of 16 seems a catastrophe that somehow must be learned to manage. And the challenges that come up when the illness worsens in the life course have to be coped with." Dieter Weik, an 86-year-old retired teacher talks about living with ankylosing spondylitis in a recent patient perspective article [1].

Axial spondyloarthritis (axSpA) is a debilitating inflammatory disease of the spine commonly presenting as chronic back pain in young adults (<45 years). It may also be associated with periarticular/extra-spinal features (enthesitis, dactylitis) or extra-articular manifestations (uveitis, psoriasis, inflammatory bowel disease). AxSpA includes ankylosing spondylitis (AS), with evidence of sacroiliitis on plain X-rays and nonradiographic axSpA, without definite radiographic evidence of sacroiliitis (Fig. 15.1).

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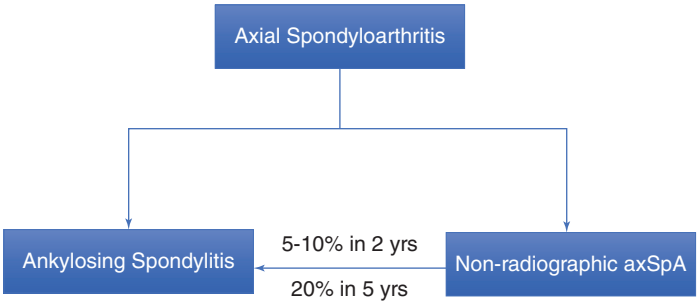

Fig. 15.1 Nomenclature and classification of axial spondylarthritis. Around 5–10% of nonradiographic axSpA develop radiographic sacroiliitis of AS in 2 years, 20% develop it in 5 years [2]

Epidemiology

The prevalence of AS is closely linked to human leukocyte antigen (HLA)-B27 in a given population, with the prevalence of AS being 5–6% among HLA-B27-positive individuals [3]. In the United States, the prevalence of HLA-B27 varies among different ethnicities: 7.5%, 4.6%, and 1.1% in non-Hispanic Caucasians, Mexican-Americans, and non-Hispanic African-Americans, respectively [4]. Estimates of the prevalence of AS in various countries range from 0.7 to 49 per 10,000: 31.9 in North America, 23.8 in Europe, 16.7 in Asia, 10.2 in Latin America, and 7.4 in Africa (per 10,000) [5]. AS affects men more than women with a ratio of 2–3:1, whereas they are equally affected in nonradiographic axSpA [6]. However, women tend to have higher disease activity and decreased response to tumor necrosis factor inhibitors (TNFi) therapy. Having an affected relative increases the risk of AS by 63% in monozygotic twins, 8.2% in first-degree relatives, and 1% in second-degree relatives [7].

Smoking and SpA: Cigarette smoking has been associated with an increased risk of psoriasis, psoriatic arthritis, and possibly also uveitis flares in patients with axSpA. Therefore, these additional risks of smoking in axSpA patients must be emphasized as additional motivation to promote smoking cessation [8].

Etiology and Pathogenesis

Genetic Factors

HLA-B27 is strongly associated with AS. The exact pathogenesis is not well defined; however, multiple hypotheses exist such as the presentation of cross-reactive bacterial antigens by HLA-B27, as well as HLA-B27 homodimers or misfolded HLA-B27 proteins triggering the innate immune system and autophagy [9]. More than 100 risk loci for AS have been identified, including genes coding for various cytokines, cytokine receptors, and endoplasmic reticulum aminopeptidases, which explain 27.8% of the heritability of AS, HLA-B27 contributing 20.4% [10].

Intestinal Dysbiosis

There is tremendous ongoing research exploring the role of the gut microbiome in various inflammatory arthritides including SpA. The composition of the gut microbiome, which is likely governed by genetic and other environmental factors, has been shown to differ among inflammatory diseases. A large study of gut microbiota including patients with SpA and rheumatoid arthritis (RA) and healthy controls discovered that the microbiota composition of each was different from the other. Even among healthy controls, the gut microbiota of HLA-B27-positive individuals differed from that of HLA-B27-negative individuals. These SpA-specific bacteria may have an increased capacity to generate breakdown in the epithelial and vascular integrity of the gut [11]. A large proportion of SpA patients have subclinical inflammatory lesions of the intestinal mucosa on endoscopic biopsy specimens, which correlate with disease activity [12, 13]. This breach in the intestinal barrier due to intestinal dysbiosis then leads to overexpression of the interleukin 17A (IL-17A)/interleukin 23 (IL-23) axis, which leads to target organ inflammation, causing synovitis, enthesitis, colitis, bone erosion, and proliferation. This inflammation is apparent

as bone marrow edema on magnetic resonance imaging (MRI), which is followed by reparative processes leading to granulation tissue and finally syndesmophyte formation at the periosteum–cartilage junction leading to vertebral fusion or "bamboo spine" (Figs. 15.2, 15.3, and 15.4).

Clinical Features

Ankylosing spondylitis primarily presents as low back pain associated with stiffness after periods of prolonged inactivity (inflammatory back pain). The insidious onset of a highly prevalent symptom like low back pain coupled with the slow radiographic progression of the disease leads to a delay in diagnosis that has been estimated to range from 5 to 10 years from the onset of the first symptoms [14–16].

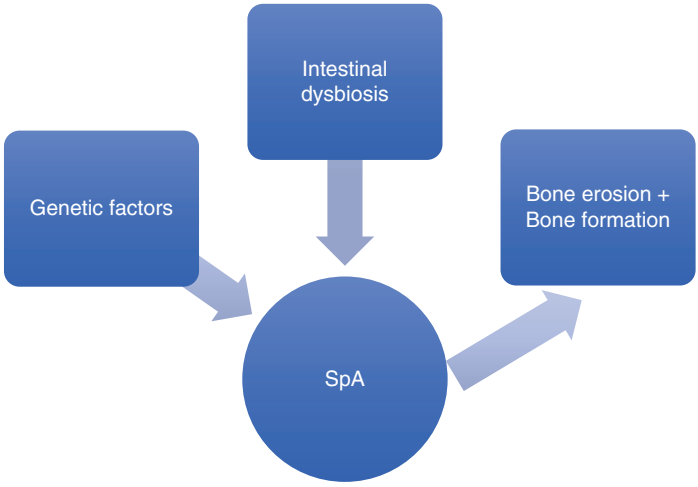

Fig. 15.2 Pathogenesis of SpA includes genetic predisposition, IL-17-mediated inflammation triggered by gut microbiome leading to paradoxical simultaneous bone erosions and bone formation

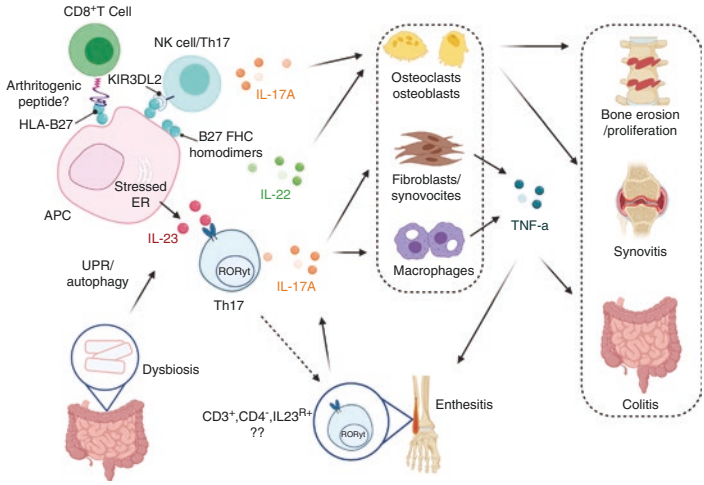

Fig. 15.3 SpA pathogenesis: effect of HLA-B27, intestinal dysbiosis on IL-17A/IL-23 axis-mediated inflammation on various target organs leading to synovitis, enthesitis, colitis, and bone erosion/proliferation

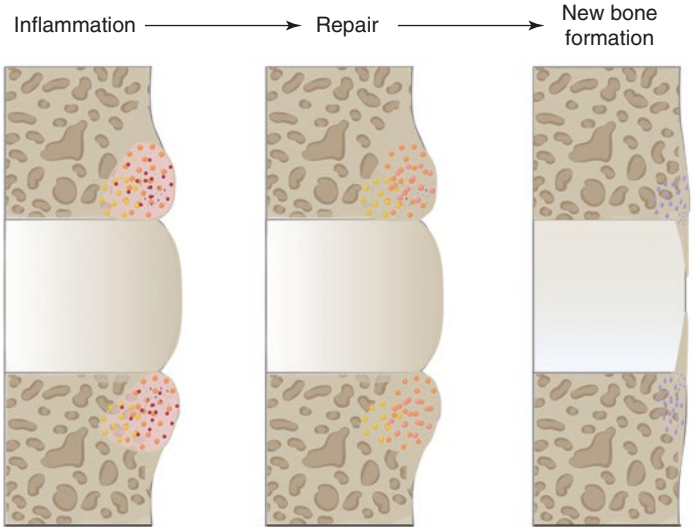

Fig. 15.4 Inflammation followed by reparative processes mediated by IL-17, TNF alpha, and IL-17, IL-22, respectively, leading to bone marrow edema, granulation tissue formation, and finally syndesmophyte formation resulting in the typical "bamboo spine" appearance of AS

Musculoskeletal Manifestations

As per the Assessment of SpondyloArthritis international Society (ASAS) criteria [17], "Inflammatory back pain" exhibits four out of the following five features:

- Age of onset <40 years.
- Insidious onset.
- Improvement with exercise.
- No improvement with rest.
- Pain at night (with improvement upon arising).

In advanced disease, progressive spinal fusion can lead to significant limitations in spinal mobility and chest expansion.

Other musculoskeletal manifestations include unilateral or alternating buttock pain from sacroiliac joint involvement, hip pain due to hip joint involvement in up to 25–35% of patients, peripheral joint involvement (ankles, knees, shoulders, sternoclavicular joint), and dactylitis (sausage digits). Enthesitis, that is, inflammation of the region of attachment of tendons and ligaments to bones, is a classic feature of axial SpA. It manifests as pain, stiffness, and tenderness without significant swelling.

Extra-Articular Manifestations

Acute anterior uveitis (AAU) typically presents as unilateral pain, photophobia, and blurred vision. It is the most common extra-articular manifestation of AS, present in 50% of patients [18]. The risk of developing AAU increases with disease duration [19]. HLA-B27-associated AAU has been found to be more severe and recurrent, which leads to complications such as posterior synechiae, glaucoma, cataract, and macular edema [20].

Inflammatory bowel disease (IBD) has been found in 6.4% of patients with nonradiographic axSpA and 4.1% of patients with AS [21]. However, ileal and colonic inflammation can be detected on pathology in up to 50% of patients with axial SpA [22, 23].

Psoriasis is present in 10% of axial SpA patients [21]. This subset of patients has more severe axial disease and frequent peripheral joint involvement [24].

Cardiovascular disease manifestations in AS are likely the result of aortic root inflammation (aortitis). This inflammation leads to aortic regurgitation (AR) in 6–10% of patients and conduction abnormalities in 3–33% of patients [25, 26]. As with other systemic inflammatory diseases, there is also an increased risk of myocardial ischemia, strokes, and thromboembolic events in patients with AS, although less so compared to RA [27].

Pulmonary disease in AS usually presents as a restrictive lung disease due to reduced chest wall and spinal mobility. A small proportion of patients also develop intrapulmonary diseases such as apical fibrosis, interstitial fibrosis, and subpleural nodules [28, 29].

The *psychological impact* of a disease like AS on patients' lives is inevitable. As with other patients suffering from chronic pain, AS patients are prone to anxiety and depression. A recent meta-analysis revealed an increased incidence of depression (relative risk 1.51; CI 1.28–1.79) and anxiety (hazard ratio 1.85; CI 1.37–2.49) [30].

Complications

Osteopenia is usually evident within the first 10 years of the disease [31]. However, in advanced disease, dual photon absorptiometry (DEXA) may measure false high values of bone density due to the presence of syndesmophytes. Lateral lumbar DEXA scans or dual-energy quantitative computed tomography scans may be more accurate in these cases; however, as these have not been validated for clinical use with age-matched controls, DEXA still remains the screening method of choice.

Fragility fractures of the vertebrae are twice as common in AS patients compared with controls [32]. This is likely due to a combination of osteopenia and vertebral rigidity.

Neurologic manifestations include spinal cord injury due to vertebral fragility fractures, atlantoaxial subluxation, and cauda equina syndrome.

Diagnosis

Ankylosing spondylitis should be considered in patients <45 years of age presenting with *inflammatory back pain*. Primary care physicians play a key role in decreasing the time to diagnosis and thereby preventing a delay in treatment (Fig. 15.5).

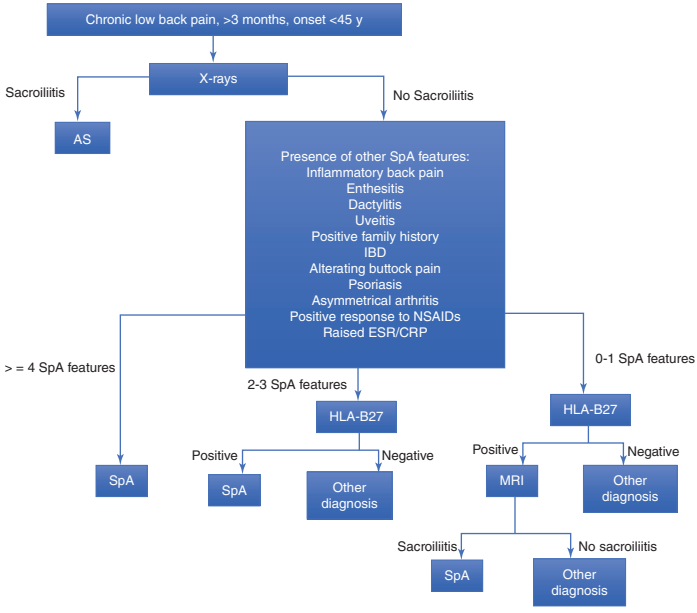

Fig. 15.5 2013 ASAS modification of the Berlin algorithm for diagnosis of axSpA [37]

History

Apart from the ASAS criteria for inflammatory back pain, it is important to consider the other features of SpA while taking a detailed *history*:

- Alternating buttock pain, caused by alternating sacroiliitis.
- Heel pain, caused by enthesitis of Achilles tendon.
- Swelling of toes/fingers "sausage digits," from dactylitis.
- Good response to NSAIDs, marked improvement in pain within 24–48 hours.
- Oligoarticular, asymmetric peripheral arthritis of lower extremities.
- Anterior uveitis/iritis.
- Inflammatory bowel disease.
- Psoriasis.
- Family history of SpA, presence of first- or second-degree relatives with a diagnosis of SpA, uveitis, reactive arthritis, psoriasis, or inflammatory bowel disease.

Physical Exam

A thorough joint exam and evaluation of spinal mobility are imperative in the diagnosis and are more important in monitoring disease activity.

Spinal Mobility

- *Occiput to wall distance:* To measure the degree of flexion deformity of the cervical spine, ask the patient to stand erect with heels and buttocks against a wall while keeping the mandible horizontal. Normally occiput should touch the wall.
- *Chest expansion:* To measure a range of motion at thoracic costovertebral joints, ask the patient to raise their arms above their heads and exert a maximal forced expiration followed by a maximal inspiration. Normal expansion is >2 cm at the fourth intercostal level.

- *Schober test:* To measure forward flexion of the lumbar spine, ask the patient to stand erect with feet shoulder length apart; place a mark in the midpoint of an imaginary line joining the two posterior superior iliac spines and a second mark in an imaginary vertical line 10 cm above the first; ask the patient to bend forward as much as possible keeping the knees straight. Measure the difference between the upper two marks in the erect and forward bent position. A measurement of ≥5 cm is considered normal (Fig. 15.6).
- *Lateral spinal flexion:* To measure lateral flexion of the lumbar spine, ask the patient to stand erect with heels and back against a wall with knees and hands extended, and measure the distance between the tip of the middle finger and the floor. Then ask the patient to bend sideways without bending knees or lifting the heels, measure the same distance in this new position, and record the difference between the two. Normal difference is >10 cm.

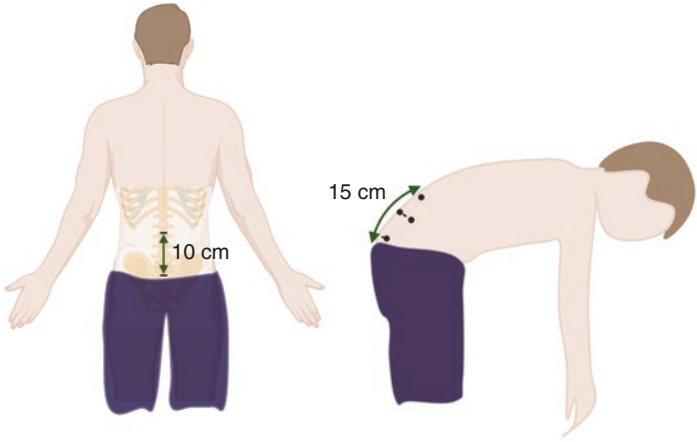

Fig. 15.6 Schober's test: A mark is made at the level of the lumbosacral junction and a second mark at about 10 cm above this mark. The patient is then instructed to touch his toes. If the increase in distance between the two marks on the patient's spine is less than 5 cm, then this is indicative of a limitation of lumbar flexion

Peripheral joint involvement: Determine the number of swollen and/or tender joints (hands, wrists, elbows, shoulders, hips, knees, ankles, feet).

Enthesitis: Tenderness and swelling at the insertions of plantar fascia and Achilles tendon into the calcaneus.

Dactylitis: Diffuse swelling of toes or fingers giving them a "sausage digit" appearance.

Skin: Examine the skin, scalp, and nails for signs of psoriasis.

Eyes: Patients with symptoms suggestive of uveitis should be examined by an ophthalmologist using a slit lamp for confirmation.

Laboratory Tests

No laboratory test is diagnostic of axSpA; however, the following may support the diagnosis in the right clinical setting:

- *HLA-B27*: If HLA-B27 is positive, the probability of axSpA goes up from 5% to 30% in patients with chronic back pain and from 14% to 60% in patients with inflammatory back pain [33]. A two-phase strategy in the primary care setting performed well in a 2013 study in identifying AS patients, wherein if a <45-year-old patient presents with chronic LBP and if they meet two-thirds of the following criteria: (1) bilateral buttock pain, (2) improvement by movement, and (3) psoriasis, they should directly be referred to a rheumatologist without HLA-B27 testing. But if they meet one-third of the criteria, then a positive HLA-B27 test should be referred to a rheumatologist [34].
- *ESR, CRP*: CRP is elevated in 40% of patients with axSpA and an even higher percentage of patients with AS compared with nonradiographic axSpA [35]. Although a normal CRP does not exclude a diagnosis of axSpA, CRP levels are used as a component of composite measures of disease activity [36].

Imaging

Imaging provides important objective data in the diagnosis of axSpA.

- *Plain X-rays*: All suspected patients of axSpA should have an anteroposterior (AP) plain X-ray of the pelvis to visualize sacroiliac (SI) joint abnormalities (Fig. 15.7).
  - *Grade 0:* Normal.
  - *Grade 1:* Suspicious changes.
  - *Grade 2:* Minimal abnormality; small localized erosions/sclerosis.
  - *Grade 3:* Unequivocal abnormality; moderate or advanced sacroiliitis with ≥1 of the following: erosions, sclerosis, joint space widening, narrowing, or partial ankylosis.
  - *Grade 4:* Total ankylosis of joints.

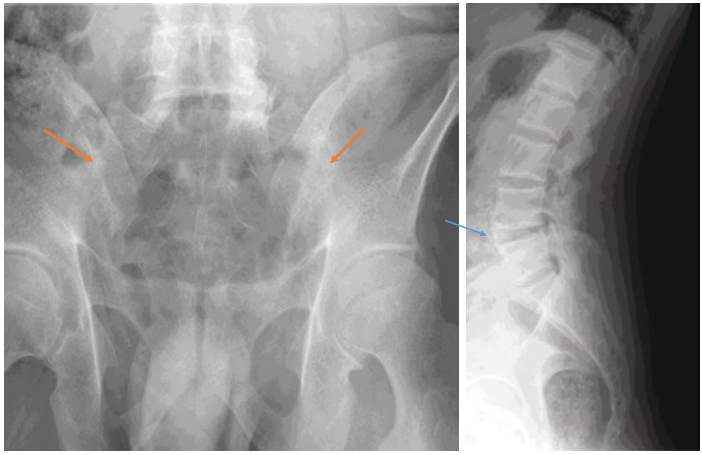

Fig. 15.7 AP view of the sacroiliac joints shows ankylosis of the sacroiliac joints (orange arrows). Lateral view of the lumbar spine shows syndesmophytes that extend from L2-S1, most prominent at L4-L5 (blue arrow). Note that the syndesmophytes are thin and vertical forming in the annulus

It is also important to distinguish AS from diffuse idiopathic skeletal hyperostosis (DISH) (Fig. 15.8).

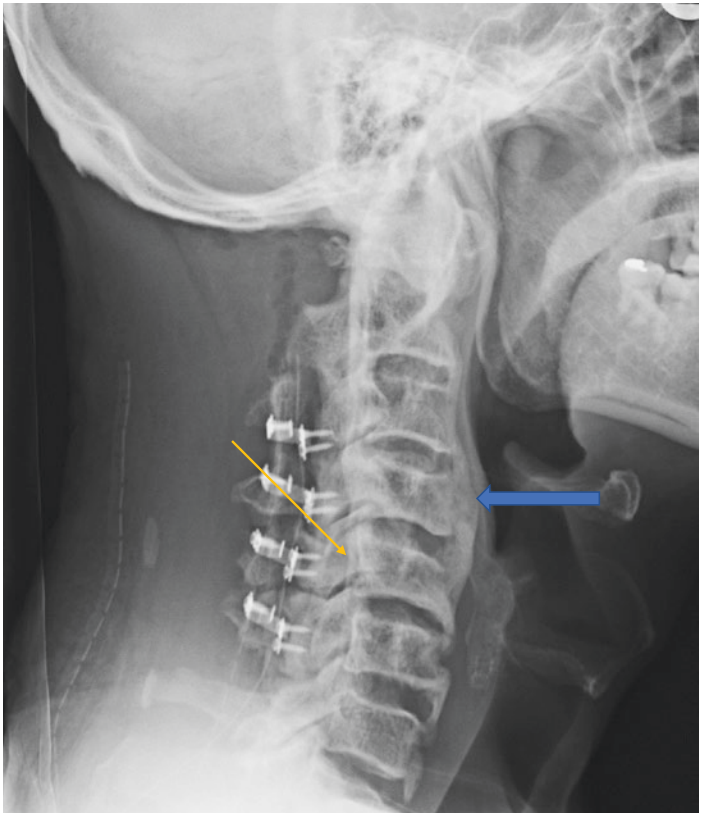

Fig. 15.8 Diffuse idiopathic skeletal hyperostosis (DISH) with concomitant ossification of posterior longitudinal ligament (OPLL). It is important to distinguish AS from DISH which is defined by the presence of nonmarginal syndesmophytes at three successive levels (involving four contiguous vertebrae). Lateral view of the cervical spine shows the effects of a recent cervical laminoplasty at C3 to C6. There is flowing ossification along the anterior longitudinal ligament in keeping with diffuse idiopathic skeletal hyperostosis (blue arrow). There is also ossification of the posterior longitudinal ligament (yellow arrow). Disc space heights are relatively preserved

- *MRI*: MRI of SI joints is indicated in patients without evidence of sacroiliitis on X-rays who have high suspicion for axSpA. ASAS definition of active sacroiliitis is as follows:
  - *Active inflammatory lesions of SI joints:* Appear as "osteitis" or bone marrow edema (BME) on STIR or on T2-weighted images in subchondral regions or periarticular bone marrow.
  - *Positive MRI:* At least two BME lesions on the same slice or one lesion in the same quadrant on at least two consecutive slices.

Treatment

The goal of treatment in axSpA is to improve the quality of life of patients by minimizing symptoms such as pain and stiffness; maintain the best possible functional capacity; prevent complications such as flexion contractures causing dorsal kyphosis; minimize extra-articular manifestations such as uveitis; and preserve the patient's active role in society.

A treat-to-target trial, the TICOSPA (The Tight Control for AxSpA), is a European randomized controlled trial (RCT) underway comparing tight disease control with monthly assessments to usual care with the primary outcome being change in ASAS HI (Assessment of SpondyloArthritis international Society Health Index; 17 item questionnaire) over 1 year and secondary outcome measures including ASDAS (Ankylosing Spondylitis Disease Activity Score), BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), quality of life, and resource utilization [38]. The 2017 revised recommendations included the use of the treat-to-target strategy of clinical remission for both musculoskeletal disease and extra-articular manifestations based on low evidence and expert opinion [39]. However, the latest update in axSpA treatment guidelines published by the American College of Rheumatology (ACR) in collaboration with the Spondylitis Association of America and the Spondyloarthritis Research and Treatment Network in 2019 conditionally recommends against using a treat-

to-target strategy in axSpA due to lack of direct evidence and concern for cost-effectiveness [40] (Tables 15.1 and 15.2).

AxSpA patients benefit from being cared for by a rheumatologist in the monitoring and management of their disease.

Initial Therapy

Initial treatment strategies include nonpharmacologic interventions and use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Nonpharmacologic Interventions

- *Counseling on smoking cessation* as smoking has seen to have an adverse effect on SpA and its extra-articular manifestations [8].
- *Screening for depression,* as these patients are more prone to developing anxiety and depression [30].
- *Physical therapy* is one of the major pillars of management of axial SpA patients regardless of pharmacologic therapy. The

Table 15.1 The BASDAI is the gold standard in assessing and following disease activity in axSpA. Calculated as (sum of values of question 1–4 + mean of questions 5 and 6) divided by 5; score ≥4 is indicative of active disease that warrants consideration of biologic therapy. Clinically significant improvement is defined as 50% improvement of BASDAI or absolute change of >=2

BASDAI questionnaire	Degree
How would you describe the overall level of fatigue/tiredness you have experienced?	1–10
How would you describe the overall level of AS neck, back, or hip pain you have had?	1–10
How would you describe the overall level of pain/swelling you have had in joints other than neck, back, or hips?	1–10
How would you describe the level of discomfort you have had from an area tender to touch or pressure?	1–10
How would you describe the level of morning stiffness you have had from the time you wake up?	1–10
How long does your morning stiffness last from the time you wake up?	1–10

Table 15.2 The ASDAS is a composite tool to measure disease activity including levels of inflammatory markers apart from clinical parameters. Disease activity is categorized as inactive, low, high, or very high; if ≥2.1, it warrants consideration of biologic therapy. Clinically significant improvement is defined as a change of ≥1.1

ASDAS-CRP
$0.121 \times \underset{\text{back pain}}{\text{Total}} + 0.110 \times \underset{\text{global}}{\text{Patient}} + 0.073 \times \underset{\text{pain / swelling}}{\text{Peripheral}} + 0.058 \times \underset{\text{morning stiffness}}{\text{Duration of}} + 0.579 \times \text{Ln}(\text{CRP} + 1)$

main goals of exercise programs are to increase spinal mobility, improve posture, relieve pain, decrease disease activity, and enhance physical function. This may include stretching, strengthening, and cardiopulmonary exercises [41]. A recent Cochrane review found that there is moderate-to-low-quality evidence that exercise programs, compared to no intervention, in AS patients, may provide clinically important pain reduction, likely improve physical function, and decrease patient global assessment of disease activity slightly when measured at the end of the intervention. There is, however, uncertainty regarding the effect of exercise programs on spinal mobility and fatigue [42]. A meta-analysis comparing the efficacy of home-based and supervised exercise programs in AS revealed that both home-based and supervised exercise programs can benefit to reduce Bath Ankylosing Spondylitis Metrology Index (BASMI), BASDAI, and Bath Ankylosing Spondylitis Functional Index (BASFI) scores. However, a short-term supervised exercise program may be more effective than home-based exercises at decreasing AS disease activity [43].

Pharmacologic Therapy

- *NSAIDs* can provide substantial relief of back pain and stiffness in 70–80% of patients [44]. They are usually effective within 2–4 weeks and are then to be used as needed to avoid adverse effects from continuous use. It remains unclear if continuous NSAID therapy has any effect on the radiologic progression of the disease. A RCT with celecoxib reported decreased radiographic progression in the spine at 2 years in patients on continuous therapy and elevated inflammatory markers before the start of treatment [45, 46]. In contrast, a RCT with diclofenac found no evidence for reduced radiographic change at 2 years in patients on continuous therapy [47].
  - *Naproxen 500 mg BID.*
  - *Celecoxib 200 mg BID.*
  - *Ibuprofen 800 mg TID.*

NSAID Nonresponders

In axSpA patients with an inadequate response to initial therapy with two different NSAIDs used consecutively in an adequate dose for at least 2–4 weeks each or in patients with BASDAI >4 or ASDAS >2.1 after at least 3 to 6 months of treatment, the addition of a tumor necrosis factor-alpha inhibitor (TNFi) is indicated.

- *TNFi.*
- A 2015 systematic review and meta-analysis of TNFi RCTs found significant improvements in disease activity and function compared to placebo [48]. Patients usually respond to treatment fairly quickly, within 6 weeks. TNFi are also found to be effective in patients with symptomatic nonradiographic axSpA who failed treatment with NSAIDs [49, 50]. A systematic review and meta-analysis of all phase 2/3 RCTs of interest for AS patients found infliximab and golimumab ranked highest for efficacy in AS [51].

TNFi are contraindicated in patients with active infections (should be held during an active infection), latent tuberculosis (TB), multiple sclerosis/optic neuritis, heart failure, and malignancy. Certolizumab is safe to use for the entire duration of pregnancy, whereas other TNFi should be discontinued in the late second or early third trimester [52]. All TNFi can be safely used during lactation.

- *Interleukin-17 (IL-17) inhibitors.*
  - *Secukinumab* has been shown to be efficacious in axSpA both in TNFi naïve and in patients with prior TNFi exposure [53, 54]. It is also the preferred biologic in patients who are at high risk of TB, as there are no reports of latent TB reactivation with this medication, although patients must still be screened and treated for latent TB prior to initiation. However, both the 2016 ASAS EULAR and the 2019 American College of Rheumatology guidelines recommend starting with a TNFi, given our long-term experience with these agents. However, in primary nonresponse

to TNFi, guidelines recommend switching to an IL-17 inhibitor [40, 55].
  - *Ixekizumab* is similar to secukinumab in safety and efficacy for axSpA patients [56, 57].

When to Consider Tapering Biologic Therapy

Considering the side effects and cost of therapy with biologics, the 2016 ASAS-EULAR recommend that patients who have maintained remission or low disease activity for 1 year could be considered for therapy reduction [55]. There is, however, a lack of a standardized tapering strategy: dosage reduction versus prolonged dosage intervals. It also remains unclear what level of reduction should be attempted. Multiple RCTs and observational studies have shown that with a 30–50% reduction in TNFi dosage or with prolonging dosage interval in stable AS patients, they were still able to maintain adequate disease control [58–60].

When to Consider Switching a Biologic Agent

- *Primary failure to initial TNFi:* Patients with inadequate response to a TNFi after 3 months of therapy should be switched to an IL-17 inhibitor.
- *Secondary failure to initial TNFi:* Patients with loss of efficacy to TNFi after initial response should be switched to a second TNFi.

Resistant to Standard Therapies

For patients with treatment failure to standard therapy, the efficacy of various other medications has been explored.

- *Tofacitinib* is a Janus kinase (JAK) 1 and 3 inhibitor, which has shown efficacy in AS in a phase II study [61]. Tofacitinib was the top-ranked therapy for ASAS20 response (≥20% improvement in the Assessment of Spondyloarthritis International Society Criteria) in a recent study comparing currently approved and investigational therapies for AS [51].

- *Upadacitinib* is a JAK 1 inhibitor, which was also found effective in AS in a phase II/III trial [62].
- *Filgotinib* is a JAK 1 inhibitor, which has also shown promise for the treatment of AS patients [63, 64].
- *Other IL-17 inhibitors under investigation include* brodalumab, netakimab, and bimekizumab.

Management of Extra-Articular Manifestations

Extra-articular manifestations (EAMs) may cause significant morbidity in axSpA patients. Given the variety of EAMs and differing efficacy of the various treatment options, it is important to individualize treatment strategies.

Acute anterior uveitis (AAU): Usually presents as an acute unilateral uveitis (90%) and is recurrent in up to 50% of AS patients [65]. It usually responds well to topical steroids; hence, timely referral to an ophthalmologist and prompt treatment can prevent further complications. In the case of recurrent attacks, TNFi should be considered, if not already started, for AS management. Infliximab, adalimumab, golimumab, and certolizumab have been shown to reduce the risk of AAU flares (40–80% reduction in flares compared to placebo) [66–70]. Results have been contradictory in various studies on efficacy of etanercept on preventing AAU, with some studies suggesting that it may in fact increase the risk of AAU; hence in patients with highly recurrent AAU, a monoclonal antibody TNFi is preferred over etanercept [66, 71, 72].

Psoriasis: 5–10% of axSpA patients develop psoriasis [73, 74]. Skin lesions usually respond to topical steroids or psoralen and ultraviolet A (UV-A) light therapy. However, in severe disease, systemic therapy with methotrexate, apremilast, or biologics (TNFi, anti-IL-17, anti-IL-12/IL-23) is indicated [75, 76]. Peripheral joint involvement responds well to NSAIDs, intra-articular steroid injections, methotrexate, leflunomide, or biologics [77].

Inflammatory bowel disease (IBD): 4–10% of axSpA patients go on to develop IBD, with a prevalence of 4.1% in radiographic and 6.4% in nonradiographic axSpA as per a recent meta-analysis

[73, 74]. It is important to refer these patients to a gastroenterologist to coordinate management. NSAID use must be minimized in these patients as they can worsen bowel inflammation and increase the risk of IBD complications [78, 79]. Sulfasalazine is known to reduce inflammatory activity in IBD as well as peripheral arthritis [80]. When considering biologics, the ASAS-EULAR and ACR guidelines recommend the use of TNFi in patients with axSpA and IBD [40, 55]. Infliximab, adalimumab, and certolizumab are approved for the treatment of Crohn's disease, whereas infliximab, adalimumab, and golimumab are approved for ulcerative colitis [40]. However, etanercept and IL17 inhibitors have been shown to paradoxically increase the risk of IBD exacerbations and should be avoided [81–84]. Ustekinumab (IL-23 inhibitor) is effective in the treatment of IBD; however, it does not seem to work for axSpA symptoms [85].

Surgery

Indications for surgery include the following:

- Severe hip involvement with persistent pain and severe limitation of mobility may warrant a total hip arthroplasty (THA); however, AS patients are at higher risk of developing heterotopic ossification (bone formation outside the skeleton) following joint replacement [86].
- Atlantoaxial subluxation with neurologic impairment requires a cervical fusion surgery.
- Severe flexion deformities are treated with corrective wedge osteotomies.

Considerations in Preoperative Clearance of AS Patients

There is a substantial risk of operative and perioperative complications in AS patients with clinically significant spinal involvement.

- The PCP must order flexion-extension radiographs of the cervical spine to evaluate for atlantoaxial subluxation.
- Endotracheal intubation may be difficult due to decreased spinal mobility; patients may require flexible scope intubation.
- Extensive calcification of spinal ligaments may make regional anesthesia difficult.
- Postoperative heterotopic calcification may limit THA success; preoperative prophylactic NSAIDs may reduce its incidence.
- Positioning for surgery must be planned preoperatively for patients with severe kyphosis.
- Consider the possibility of restrictive lung disease due to reduced chest wall and spinal mobility.
- Consider the risk of aortic regurgitation in these patients.

Risk of COVID-19 in AS Patients

In a New York case series of patients with immune-mediated inflammatory diseases (including AS) who were diagnosed with definite or presumed COVID-19, patients receiving biologic agents at baseline were no more likely to require hospitalization for COVID-19 than patients receiving nonbiologic conventional immunosuppressive agents. Therefore, these patients should be continued on their biologics [87].

Prognosis

Like any other chronic disease, patients with axSpA must learn how to attain the best quality of life possible, understanding their limitations. The prognosis of axSpA seems to have improved with the advent of TNFi.

A small number of studies have provided evidence of a decrease in radiographic progression of disease in patients on TNFi therapy. The Swiss Clinical Quality Management study demonstrated a reduction in radiographic progression as well as

disease activity. The benefit seemed to improve the longer the patient was on a TNFi (≥4 years of treatment showed 70% lower estimate in radiographic progression compared to 45% in ≤4 years of treatment) [88, 89]. However, contradictory studies failed to demonstrate that treatment with infliximab, adalimumab, etanercept, or golimumab could halt the radiographic progression of the disease despite clinical improvement and reduced spinal inflammation [90–93].

Prognostic Indicators

The following features are associated with increased disease severity [94]:

- Hip arthritis.
- Dactylitis.
- Poor response to NSAIDs.
- High ESR (>30 mm/h).
- Limitation of range of motion of the lumbar spine.
- Oligoarthritis.
- Onset <16 years of age.

The following features have been found to be associated with a good response to TNFi [95]:

- Increased acute phase reactants.
- Higher disease activity.
- Higher functional status.
- Younger age.
- HLA-B27 positivity.

The 12-year prospective Outcome in Ankylosing Spondylitis International Study (OASIS) found that progressive radiographic changes occurred significantly faster in men, HLA-B27-positive patients, and those with greater radiographic change at baseline [96].

Conclusions

The PCP has a crucial role in the early diagnosis and treatment of AS:

- Identify the patients with inflammatory back pain (IBP) among the multitude of patients presenting with mechanical back pain.
- Look for signs of enthesitis and dactylitis in patients with IBP.
- Evaluate IBP patients by checking levels of inflammatory markers and consider HLA-B27 testing and plain radiography of the sacroiliac joint.
- Start NSAID therapy and refer to a rheumatologist for further management.
- Be cognizant of extra-articular manifestations in axSpA patients and the need for referral to ophthalmology, gastroenterology, or dermatology when required.
- Counsel on smoking cessation.
- Screen for depression and anxiety.
- Screen for osteoporosis, understanding the possibility of falsely high bone densities on DEXA in severe disease; have a low threshold to consider fragility fractures.
- Screen for side effects of biologic agents, ask the patient to hold biologic in the setting of an active infection, and immunize with all appropriate inactivated vaccines including influenza, Pnemovax, and shingles.
- Consider specific risks of surgery in these patients while giving preoperative clearance.

From recognizing the early signs and symptoms of the disease, starting early treatment to coordinating with the rheumatologist and other specialists in the case of medication side effects or disease complications, the PCP is a critical member of the healthcare team caring for AS patients, with the common goal of improving their quality of life and helping them maintain their independence—their role as an active member of society.

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