BMJ Best Practice

Evaluation of inflamed joint

Straight to the point of care

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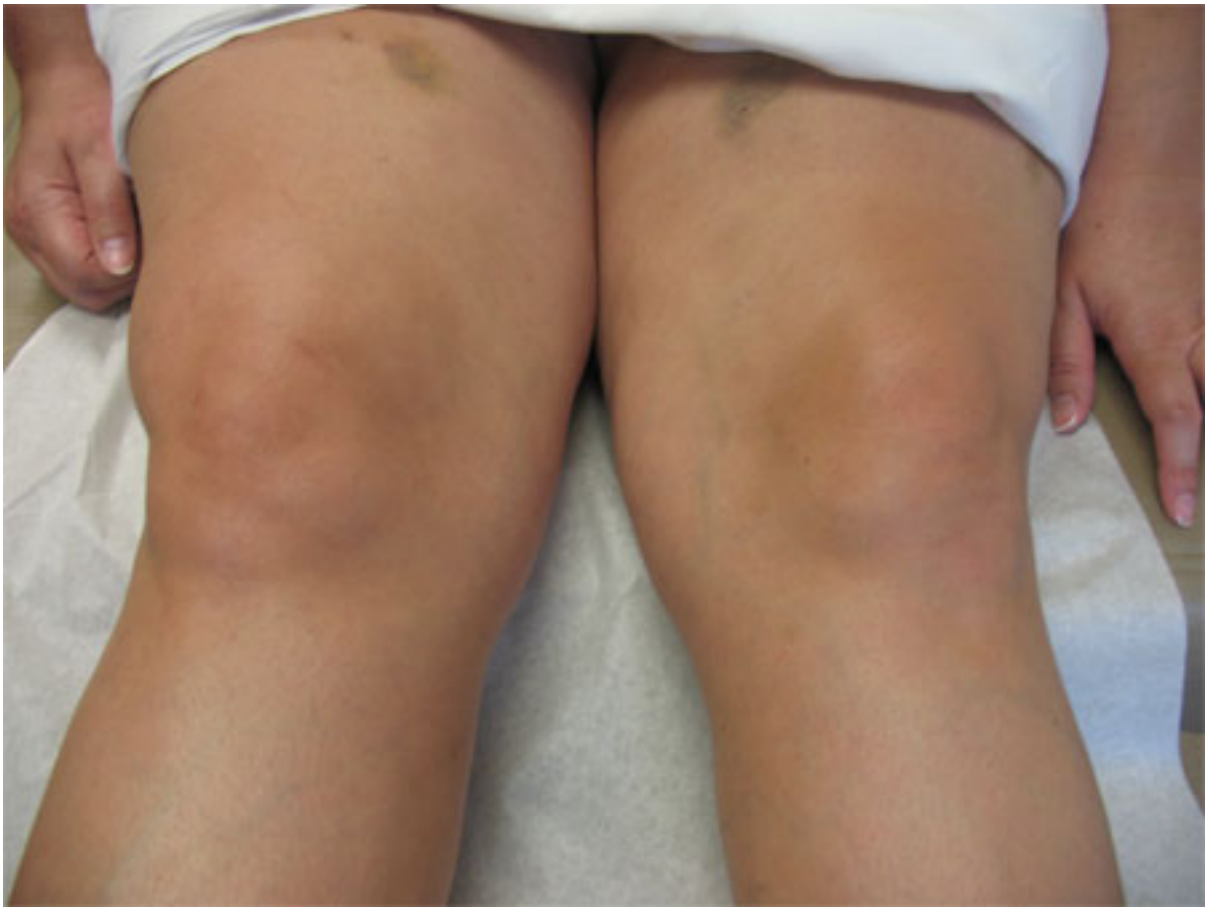
Summary

Inflammatory arthritis is a common term for several conditions that manifest as joint pain, swelling, and stiffness with varying degrees of functional impairment. These diseases can be broadly categorized as:

- Infectious arthritis
- Immune-mediated arthritis
- Noninfectious and nonimmune-mediated inflammatory arthritis
- Paraneoplastic arthritis
- Neoplastic arthritis.

In patients with pain and swelling in a single joint, acute infection is a relatively common cause - one that can result in rapid and irreversible damage. In contrast, the majority of patients with involvement of multiple joints tend to have disorders of chronic duration. The prognosis is good for those who remain unclassifiable, with nearly 50% of such patients undergoing remission requiring no pharmacologic therapy at follow-up at 1 year.



Acute monoarthritis of the right knee

From the collection of Dr Soumya Chatterjee

Differentiation of joint pain

In addition to inflammatory joint diseases, joint pain can also be due to:

- Joint damage (e.g., osteoarthritis, or trauma leading to a fracture or internal derangement)
- Referred pain

- Altered pain threshold (as is seen in central sensitization syndromes such as fibromyalgia).

Pain due to an intra-articular pathology needs to be differentiated from referred pain arising from adjacent soft tissues or juxta-articular bone. In the context of referred pain, the range of motion of the joint is usually unaffected, and joint motion does not aggravate pain, whereas palpation over a regional bursa, tendon, or ligament can elicit pain.

Characteristics of inflammation

The classic signs of inflammation generally also apply to inflammatory joint disease:

- Pain (aggravated by movement)
- Erythema
- Warmth
- Swelling
- Stiffness
- Limitation of range of motion.

It is usually not possible to detect all of the above features (especially swelling and erythema) in deep-seated joints such as the shoulders, hips, intervertebral joints, and sacroiliac joints.

Mono- versus poly- site arthritis

Most causes of oligoarthritis (involving 2-4 joints) or polyarthritis (involving ≥5 joints) can also be causes of monoarthritis, because almost any arthritic condition can initially affect a single joint. The most important and serious condition that needs to be considered in the workup of an acute monoarthritis is septic (pyogenic) nongonococcal arthritis. If the diagnosis is missed and appropriate antimicrobial therapy is not instituted early, rapid destruction of articular cartilage can lead to irreversible joint damage.

Etiology

The etiologies of inflammatory arthritis are varied, and can be grouped into the following broad categories:

- Infectious arthritis
- Immune-mediated arthritides
- Noninfectious and nonimmune-mediated inflammatory arthritis
- Paraneoplastic arthritides
- Neoplastic arthritis.

Infectious

For all practical purposes, an acute monoarthritis is due to septic arthritis until proven otherwise. It is by far the most serious cause of an acute "hot joint" and should always be excluded before other conditions are considered.

In disseminated gonococcal infection involving the joint, the acute symptoms of fever, urethritis, and joint pain are accompanied by tenosynovitis and a pustular or vesiculopustular rash.

Tuberculous, nontuberculous mycobacterial, brucellar, and fungal arthritides are much less common than acute pyogenic (septic) arthritis or gonococcal arthritis, and are often indolent. A high index of suspicion is necessary to establish the correct diagnosis, which may be confirmed by synovial biopsy. If the diagnosis is missed, or the wrong treatment is instituted, permanent joint damage can occur. In addition, the disease can disseminate and become life-threatening.

History of an antecedent tick bite in endemic areas (e.g., the northeastern states, the midwest, and the western coastal area of the United States, and in central European and Scandinavian countries) suggests Lyme disease. The rash at the site of the bite has a bull's-eye appearance, with central clearing and vesicular lesions (erythema migrans).

Parvovirus B19 is the same virus that causes erythema infectiosum (fifth disease) in children, and can cause an acute polyarthritis that may resemble rheumatoid arthritis (RA). It can affect people of any age but is most common in children ages 6 to 10 years.[1] There may also be an occupational risk for people working with young children such as daycare workers and elementary school teachers.[2] [3] The rash in adults is nonspecific. Circulating B19-specific IgM and IgG antibodies are useful in diagnosing acute infection in an immunocompetent host.[4] [5]

Inflammatory arthritis can occur in other viral infections such as rubella, infectious mononucleosis (Epstein Barr virus infection), hepatitis B and C, and HIV infection. It has also been described with coronavirus-19 (COVID-19).[6] [7] [8] [9]

Various arboviruses have been included in the list of emerging viral pathogens associated with acute or chronic inflammatory polyarthritis. An increase in worldwide prevalence of these arboviruses is largely attributable to international travel, and the increasing range of mosquito vectors due to trade, travel, and climate change. In some cases, these infections may lead to an inflammatory arthritis resembling RA. Nearly all symptomatic infections with chikungunya, Ross River virus, Zika, O'nyong nyong, and Mayaro result in significant arthralgia. Chikungunya infection has been reported in travelers returning to the United States, Europe, and Canada. It should be suspected in patients with inflammatory polyarthritis who have a history of travel to endemic areas.[10] A large-joint polyarthritis associated with Ebola virus disease has been

described.[11] Moreover, in a cross-sectional study detailing clinical sequelae among 277 survivors of Ebola virus disease, arthralgias were reported in about 76% of patients (predominantly oligoarthralgia pattern [1-4 joints], with bilateral involvement in most patients).[12]

Immune-mediated

RA typically manifests as morning stiffness and a symmetrically distributed swelling and tenderness of the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, although other joints can also be affected. Rheumatoid nodules are quite specific for RA but are seen in only about 30% of patients.[13]

Although more common in children, acute rheumatic fever (ARF) also occurs in adults. In a typical patient, the arthritis of rheumatic fever affects several joints in quick succession (migratory arthritis), each joint being involved for no more than a week.[14]

The polyarthritis of systemic lupus erythematosus (SLE), which is rarely deforming (Jaccoud arthropathy), causes moderate pain and stiffness. It is worse in the morning and associated with minimal joint swelling. Tenderness and painful range of motion are present in affected joints, but the joints are not typically hot or swollen (as in RA). Avascular necrosis of the epiphysis of long bones (hips, knees, shoulders) can occur in patients with lupus and antiphospholipid syndrome, and can mimic an inflammatory arthritis of the adjacent joint.[15]

Inflammatory arthritis can also develop in other autoimmune rheumatic diseases such as primary Sjögren syndrome, mixed connective tissue disease, systemic sclerosis (scleroderma), relapsing polychondritis, Behçet disease, Henoch-Schönlein purpura, systemic vasculitides (e.g., granulomatosis with polyangiitis [formerly, Wegener granulomatosis], microscopic polyangiitis, polyarteritis nodosa, and Kawasaki disease), antisynthetase syndrome, and MDA-5 dermatomyositis. Detailed discussion of these conditions is beyond the scope of this review.

Fever of at least 102°F (39°C) with rash, pharyngitis, and polyarthritis involving the wrists, knees, ankles, elbows, PIP joints, and shoulders are features of adult-onset Still disease (AOSD).

Spondyloarthropathy can develop in association with gastrointestinal conditions such as inflammatory bowel disease (Crohn disease and ulcerative colitis), enteric-infection-associated reactive arthritis (*Salmonella* , *Shigella* , *Yersinia* , *Campylobacter* , and *Clostridium difficile*), gastric bypass surgery, celiac disease, or Whipple disease. It is sometimes called enteropathic arthritis.

Juvenile-onset spondyloarthropathy causes asymmetric, mostly lower-extremity involvement that begins in boys aged 7 to 16 years. Spondyloarthropathy can also develop without specific characteristics (undifferentiated spondyloarthropathy).

The presence of an inflammatory arthritis, sacroiliitis, and spondylitis in a patient with psoriasis of skin and/or nails makes the diagnosis of psoriatic arthritis likely. Joint-line tenderness and effusions in the affected small and large joints, often in an asymmetric distribution, are typical findings.

Sternoclavicular joint arthritis, vertebral and sacroiliac joint involvement, palmoplantar pustulosis, and acne suggest SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome.

Reactive arthritis follows infection (*Chlamydia trachomatis* , *Chlamydia pneumoniae* , or certain gram-negative enteric bacteria such as *Salmonella* , *Shigella* , *Yersinia* , *Campylobacter* , and *Clostridium difficile*) and is accompanied by urethritis, conjunctivitis and anterior uveitis, oral ulcers, keratoderma

blennorrhagica (yellow-brown vesicopustular waxy lesions on palms and soles that may coalesce to form larger crusty plaques), nail changes similar to psoriasis, and circinate balanitis.

Involvement of the axial joints is an essential feature of ankylosing spondylitis (AS) and helps differentiate this condition from other forms of inflammatory arthritis. Sacroiliac joint tenderness (elicited by direct pressure over the sacroiliac joints), limited spinal mobility, and limited chest expansion are typical findings.

In acute sarcoidosis, polyarthritis, tendinitis, enthesopathy (inflammation of the entheses, the location where a bone has an insertion of a tendon or a ligament), and dactylitis (sausage digit) may manifest.[16]

Juvenile idiopathic arthritis (JIA) is the most common chronic arthropathy of children and includes several subtypes. Polyarticular JIA can progress to adult RA (especially if seropositive), and contrary to what was believed in the past, a substantial percentage of these patients can continue to have active disease as adults. Oligoarticular JIA affects 2 to 4 joints initially and is more common in young girls (toddlers).[17] Diagnosis is made clinically. Laboratory and radiographic testing provide classification and prognostic information, but are not diagnostic. Around 11% to 30% of children with JIA are at risk of developing anterior uveitis (especially if they have positive antinuclear antibodies), which requires regular ophthalmologic examinations to detect and manage.[18] [19] [20]

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome presents with acute-onset polyarthritis, with significant pitting edema of the dorsal surfaces of the hands and feet. It is more commonly seen in males, in older patients (≥50 years), and is usually nonerosive. As the name implies, rheumatoid factor is typically negative.[21] RS3PE syndrome could be a form of paraneoplastic arthritis, and an underlying malignancy should be looked for.

In the last few decades, various heritable autoinflammatory syndromes have been recognized both in children and in adults and have raised considerable interest in the scientific community. These conditions include periodic syndromes such as familial Mediterranean fever (FMF); hyper-IgD syndrome (HIDS); tumor necrosis factor receptor-associated periodic syndrome (TRAPS); cryopyrin-associated periodic syndromes (CAPS); Blau syndrome; pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome; periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome, and vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome. Inflammatory arthritis can be an important feature in some of these syndromes. Detailed description of these conditions is beyond the scope of this review.[22] [23] [24]

Various drug classes have been implicated in the induction of an immune-mediated inflammatory arthropathy. Procainamide, hydralazine, minocycline, isoniazid, propylthiouracil, and tumor necrosis factor inhibitors can induce SLE. Serum sickness-like reaction has been seen with oral and parenteral pharmacologic agents, including plasma-derived products and biologics (e.g. infliximab and rituximab). In addition, arthralgia, inflammatory arthritis, and tendinitis have also been associated with the use of aromatase inhibitors, clopidogrel, quinolone antibiotics, and statins. Sitagliptin and saxagliptin (oral hypoglycemics for type 2 diabetes) have been associated with severe, incapacitating polyarthralgia.[25]

Immune-related adverse events, including inflammatory arthritis, have been reported secondary to immune checkpoint inhibitor therapy for cancer.[26] [27] [28] [29] In one retrospective study of 1,293 patients on immune checkpoint inhibitor therapy, 43 had rheumatic immune-related adverse effects.[30] Clinical syndromes included inflammatory arthritis, myopathy, and other rheumatic syndromes.

THEORY

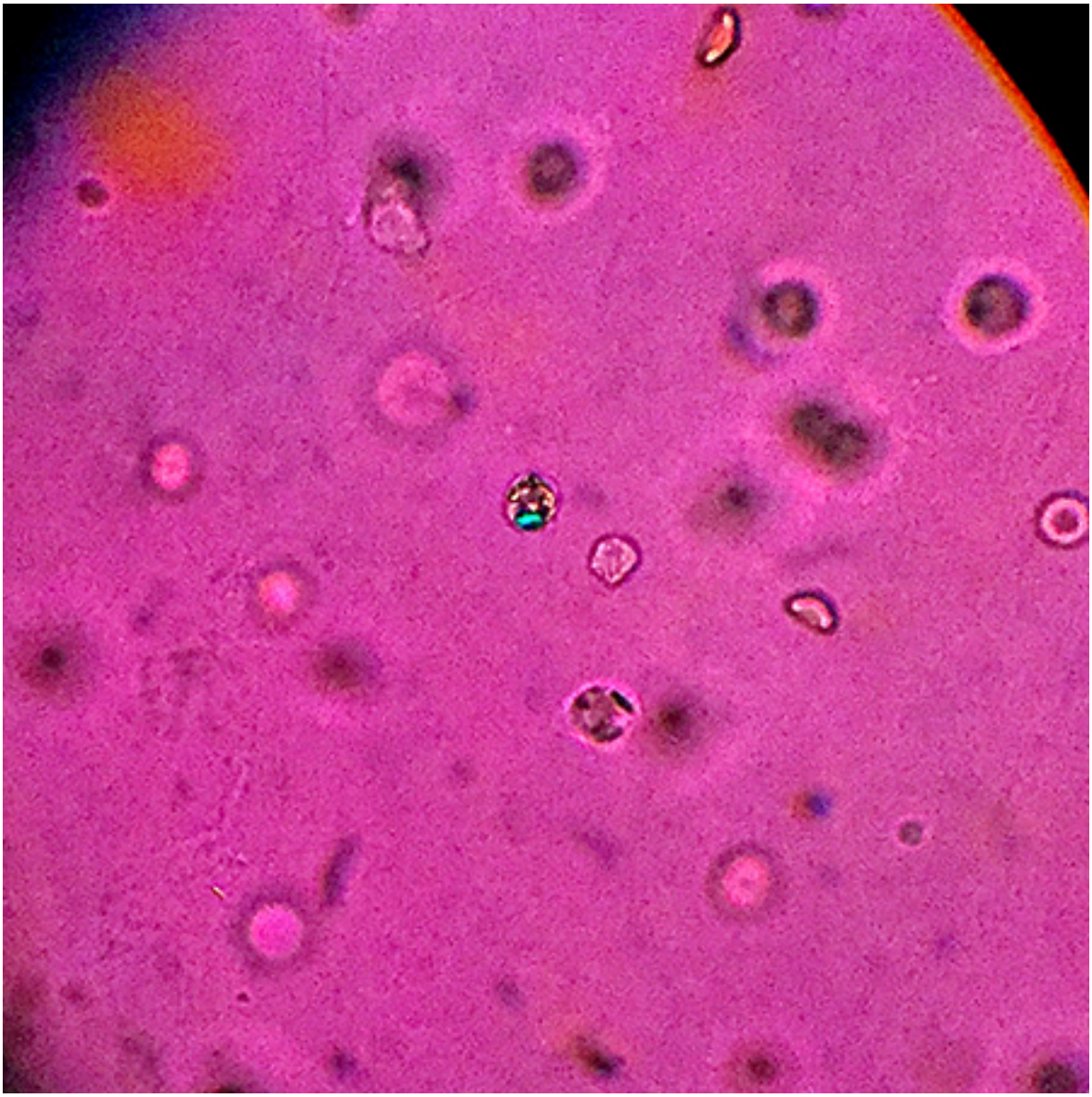
Noninfectious and nonimmune-mediated inflammatory arthritis

Osteoarthritis is a degenerative joint disorder. The prevalence increases with age. Although this is predominantly a degenerative rather than an inflammatory process, clinically sometimes it can be difficult to differentiate from the latter, hence its inclusion in the differential diagnosis. The most commonly affected joints are the knee, hip, finger joints (proximal and distal interphalangeal and first carpometacarpal joints), and lumbar and cervical spine. Patients present with joint pain and stiffness that is typically worse with activity. Erosive osteoarthritis, sometimes referred to as inflammatory osteoarthritis, is characterized by a more severe, aggressive type of hand arthritis that may become acutely symptomatic, similar to inflammatory arthritis.

Joint pain and swelling in a patient with a recent history of trauma to the affected joint always raises the possibility of fracture, dislocation, or internal derangement. Occasionally (e.g., with drug overdose, alcohol intoxication, or a history of seizure or concussion), the history of joint injury may not be available; hence, if there is any suspicion of trauma to a joint, immobilization and appropriate imaging studies are necessary to rule out a fracture or other anatomic derangement.

Acute gout is more common in men, often affecting the foot with intense pain localized to the great toe.[31]

Pseudogout involves acute attacks of crystal precipitation of calcium pyrophosphate dihydrate (CPPD) that produce symptoms very similar to those of acute gout. In this case, the typically affected joint is the knee. However, it can also affect the wrist, elbow, shoulder, ankle, metacarpophalangeal joints, and symphysis pubis.



Calcium pyrophosphate dihydrate (CPPD) crystals in synovial fluid under compensated polarized light microscopy

From the collection of Dr Soumya Chatterjee

In addition to gout and pseudogout, other crystal-induced arthropathies (such as those associated with deposition of calcium hydroxyapatite, basic calcium phosphate, calcium oxalate, etc.) rarely occur, and can be missed unless specifically considered and investigated.

The hemarthrotic joint is swollen and warm, and has a very painful and restricted range of motion. Superficial bruising and ecchymoses can be seen. Possible underlying causes to consider include fracture of an adjacent bone, a bleeding disorder (e.g., hemophilia A or B, acquired factor VIII inhibitor, or over-anticoagulation), scurvy, or a tenosynovial giant cell tumor (formerly, pigmented villonodular synovitis.

Rare conditions affecting the synovium include tenosynovial giant cell tumor (formerly, pigmented villonodular synovitis, characterized by inflammation and synovial overgrowth due to an unknown trigger) and synovial osteochondromatosis (where multiple osteochondral loose bodies form inside a joint, causing pain, swelling, and repeated episodes of locking).

Fibroblastic rheumatism is a rare disorder characterized by development of an erosive polyarthritis with multiple cutaneous nodules. Skin and synovial biopsy reveal proliferation of myofibroblast-like cells within a background matrix of collagen.[32]

Paraneoplastic

Hypertrophic osteoarthropathy (HOA) is a clinical syndrome of clubbing of the fingers and toes, enlargement of the extremities, and painful, swollen joints. HOA is characterized by symmetric periostitis involving the radius and fibula and, to a lesser extent, the femur, humerus, metacarpals, and metatarsals. The syndrome can be primary or secondary with associated malignancy.

Other paraneoplastic articular syndromes include: palmar fasciitis with polyarthritis syndrome (PFPAS); paraneoplastic arthritis; paraneoplastic RS3PE syndrome; amyloid arthritis (seen in multiple myeloma); pancreatitis, polyarthritis, and panniculitis (PPP) syndrome (occasionally seen in pancreatic cancer); and multicentric reticulohistiocytosis.[21] [33] [34] Detailed description of these conditions is beyond the scope of this review.

Neoplastic

Lipoma arborescens is a very rare primary benign synovial neoplasm that can involve one or more joints. Involvement of the knees, ankles, hips, shoulders, and elbows has been described.[35]

Synovial sarcoma is a rare malignancy that affects young adults between 20 and 40 years old, with a median age of 35 years at the time of diagnosis. The lower-extremity joints are the most common sites affected. With early diagnosis, a cure can be achieved in those patients with localized disease; however, missed diagnosis can lead to local joint destruction and incurable metastatic disease.

Intra-articular metastasis may be the first manifestation of a malignancy in which the primary source is unknown. A high index of suspicion is necessary in patients with known malignancy. It is difficult to establish the correct diagnosis without synovial fluid cytology and a synovial biopsy.

Urgent considerations

(See **Differentials** for more details)

Septic nongonococcal arthritis

By far the most serious cause of an inflamed joint. Patients at risk include:[36] [37]

- Older people
- Intravenous drug users
- Those with recent bacteremia
- People with diabetes
- Immunocompromised patients (e.g., those with HIV disease, on immunosuppressive agents, or with other immunocompromised states)
- Patients with sickle cell disease or other hemoglobinopathies
- People with rheumatoid arthritis
- Those with prosthetic joints
- Those who have had recent arthroscopy or arthrocentesis.

If the diagnosis is missed and treatment with appropriate antibiotics is not instituted early, septic nongonococcal arthritis can lead to permanent joint damage and be life-threatening.

Definitive diagnosis of a septic joint requires joint aspiration and synovial fluid analysis (including Gram stain and culture). In all patients with suspected joint sepsis, empiric antibiotic therapy should be started once appropriate specimens (i.e., blood and synovial fluid) have been obtained for culture.[38] Empiric antibiotic coverage must include coverage for *Staphylococcus aureus* (including MRSA), *Streptococcus pyogenes*, and Gram negative and anerobic bacteria in vulnerable patients.

Antibiotics are often given intravenously for 2 weeks, followed by a further 4-6 weeks of oral therapy. Prosthetic joint infections are treated more aggressively and often warrant removal of the prosthesis, treating aggressive antibiotic treatment, and eventually replacing the old prosthesis with a new prosthesis one once the infection has been eradicated.

Gonococcal arthritis

Gonococcal arthritis is a manifestation of disseminated gonococcal infection (DGI). DGI is much more common in women, especially during the perimenstrual period, due to endometrial disruption enabling *Neisseria gonorrhoeae* to enter the bloodstream. Patients present initially with polyarthralgia, tenosynovitis (typically of the wrists and/or ankles), and sparse, painful vesiculopustular skin lesions. Later, the condition presents as mono- or oligoarthritis (involving <5 joints).

Diagnosis can be established by Gram stain and culture of urethral, cervical, rectal, or oropharyngeal swabs or by DNA probe of fluid from the affected joint. Skin pustules can also be cultured, though the yield is very low. Concomitant infection with *Chlamydia trachomatis*, syphilis, and HIV is frequent and should be tested for. Bacteremia and arthritis should be treated with ceftriaxone or similar antibiotics, depending on local policy and sensitivities.

Indolent infections

Tuberculous, nontuberculous mycobacterial, brucellar, and fungal arthritides are much less common than acute pyogenic (septic) arthritis or gonococcal arthritis, and are often indolent. A high index of suspicion

is necessary, and it is often difficult to establish the correct diagnosis. Some radiologic clues can suggest tuberculous arthritis, such as juxta-articular osteopenia, peripheral bone erosions, and gradual narrowing of the joint space (Phemister triad). Synovial biopsy and culture in special media are necessary if joint aspiration does not provide a definitive diagnosis. If the diagnosis is missed or the wrong treatment is instituted, permanent joint damage can occur, and the disease can disseminate and become life-threatening. Antibiotics and antifungal agents, specific for the causative organism, are often given for 6 to 18 months. Open joint drainage and debridement may be necessary if an abscess develops.

Joint trauma

In a patient with a recent history of joint trauma, pain and swelling of the involved joint always raises the possibility of a fracture, dislocation, internal derangement, traumatic effusion, or hemarthrosis. On occasion (e.g., with drug overdose, alcohol intoxication, or a history of seizure or concussion), the history of joint injury may not be available; hence, if there is any suspicion of trauma to a joint, immobilization and appropriate imaging studies are necessary to rule out a fracture or other anatomic derangement.

Acute hemarthrosis

This condition should be considered particularly in:

- Patients with a known history of a bleeding disorder (e.g., hemophilia A or B, or acquired factor VIII inhibitor)
- Patients on anticoagulation
- People with a history of recent injury to the affected joint (e.g., torn cruciate ligament).

Arthrocentesis reveals blood in the synovial cavity, which triggers an intense inflammatory reaction. If therapeutic arthrocentesis (sometimes repeated) is not done promptly, lysosomal enzymes liberated from inflammatory cells can destroy cartilage and cause permanent joint damage. Further investigations such as plain x-rays and magnetic resonance imaging of the affected joint may be required if there is suspected trauma to a joint.

Intra-articular metastatic cancer

Although extremely rare, metastasis may be the first manifestation of a malignancy in which the primary source is unknown. A high index of suspicion is necessary in patients with a known malignancy. Conservation of joint function may be achieved through minimally invasive surgery.

Synovial sarcoma

This rare malignancy affects young adults, with a median age of 35 years at the time of diagnosis. The lower-extremity joints are the most commonly affected sites. With early diagnosis, cure can be achieved in patients with localized disease; however, missed diagnosis can lead to local joint destruction and incurable metastatic disease. The most common treatment is surgery to remove the entire tumor with negative margins (i.e., no cancer cells are found at the edge or border of the tissue removed during surgery). If the first surgery does not obtain negative tissue margins, a second surgery may be needed.[39]

Approach

A focused, problem-oriented history and a thorough physical examination are essential to narrow down the differential diagnoses, streamline appropriate investigations, and establish the cause of the joint inflammation in a given patient. It is important to ascertain the correct diagnosis before initiating definitive treatment, as the wrong diagnosis and incorrect treatment can lead to irreversible joint damage.

A significant number of people have undifferentiated peripheral inflammatory arthritis (UPIA) for which no underlying cause can be found on initial investigation.[40] [41] [42] Over time, UPIA may either persist in these patients, or may progress to a specific diagnosis or even enter remission. It is important to monitor disease activity in these patients.[4] [40] [41]

History and physical exam

The differential diagnosis of joint inflammation will depend on whether the inflammation is acute and confined to a single joint, or whether it involves multiple joints. The physician should keep in mind the caveat that most causes of oligo- or polyarthritis can also be causes of monoarthritis, because almost any arthritic condition can initially affect a single joint.

Acute monoarthropathy

When a patient presents with an acute hot monoarthropathy, one must consider and exclude septic (pyogenic) arthritis. Septic (pyogenic) nongonococcal arthritis most commonly affects:

- Older people
- Intravenous drug users
- Those with recent bacteremia
- People with diabetes
- Immunocompromised patients (e.g., those with HIV disease, on chemotherapy or other immunosuppressive drugs, or immunodeficient states)
- Patients with sickle cell disease or other hemoglobinopathies
- People with rheumatoid arthritis (RA)
- Those with prosthetic joints.

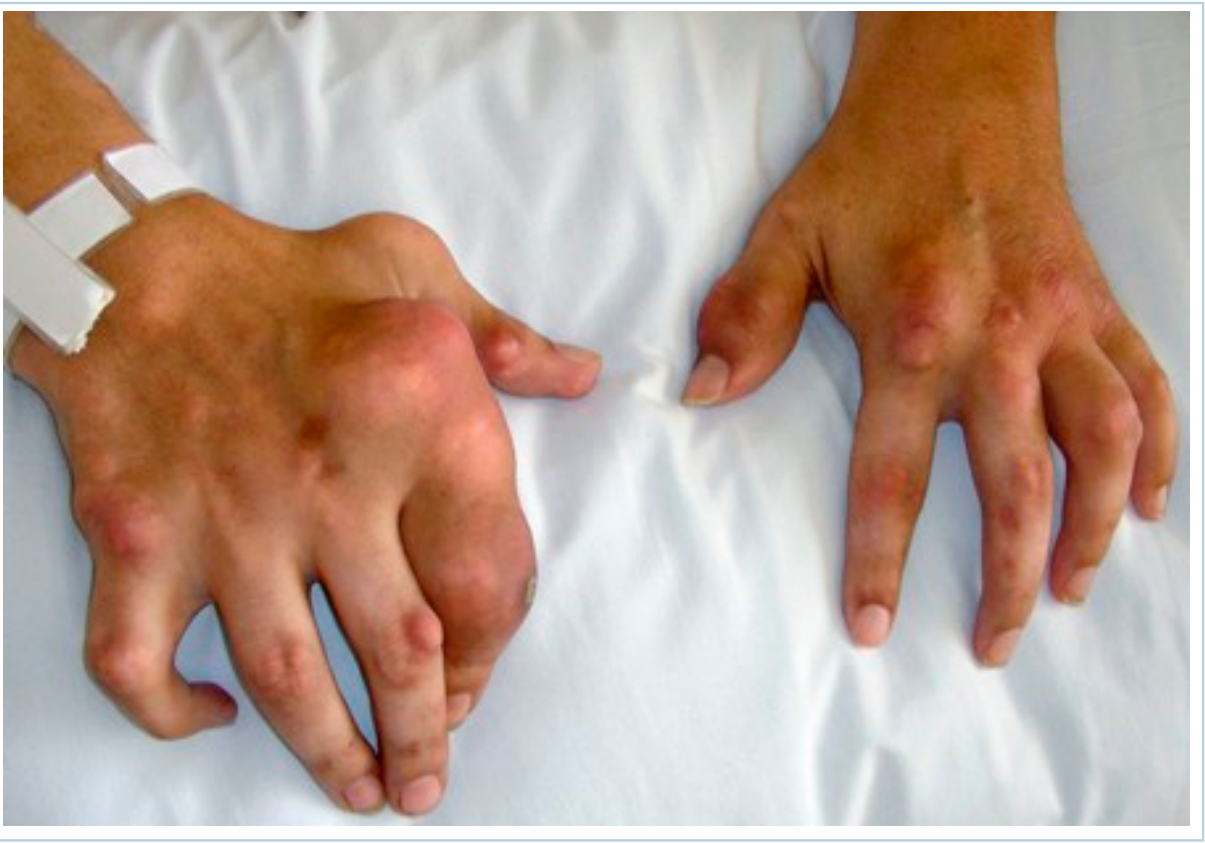
A typical history might include recent bacteremia, skin infection, or joint surgery, and the presence of prosthetic joints. Acute onset of swelling, with severe pain and very limited range of motion in a single joint or, rarely, in a few joints, is accompanied by constitutional features such as fever and malaise. The knee joint is affected in 50% of patients.[43] Identification of bacteria in the synovial fluid by Gram stain, with subsequent recovery of the organism on culture, is the definitive diagnostic test. If synovial fluid cannot be obtained with closed needle aspiration, the joint should be aspirated under computed tomography (CT) or ultrasound guidance.

Other conditions presenting with acute monoarthritis include gonococcal arthritis, acute gout, acute pseudogout, hemarthrosis with or without joint trauma, a monoarticular presentation of reactive arthritis, Lyme arthritis, tenosynovial giant cell tumor (formerly, pigmented villonodular synovitis), synovial osteochondromatosis, and lipoma arborescens.

- Disseminated gonococcal infection (DGI) occurs in 0.5% to 3% of patients infected with *Neisseria gonorrhoeae* . It presents with fever, chills, malaise, and mono- or polyarthralgia, along with tenosynovitis (wrists, fingers, ankles, toes) and sparse (between 2 and 10) pustular or vesiculopustular

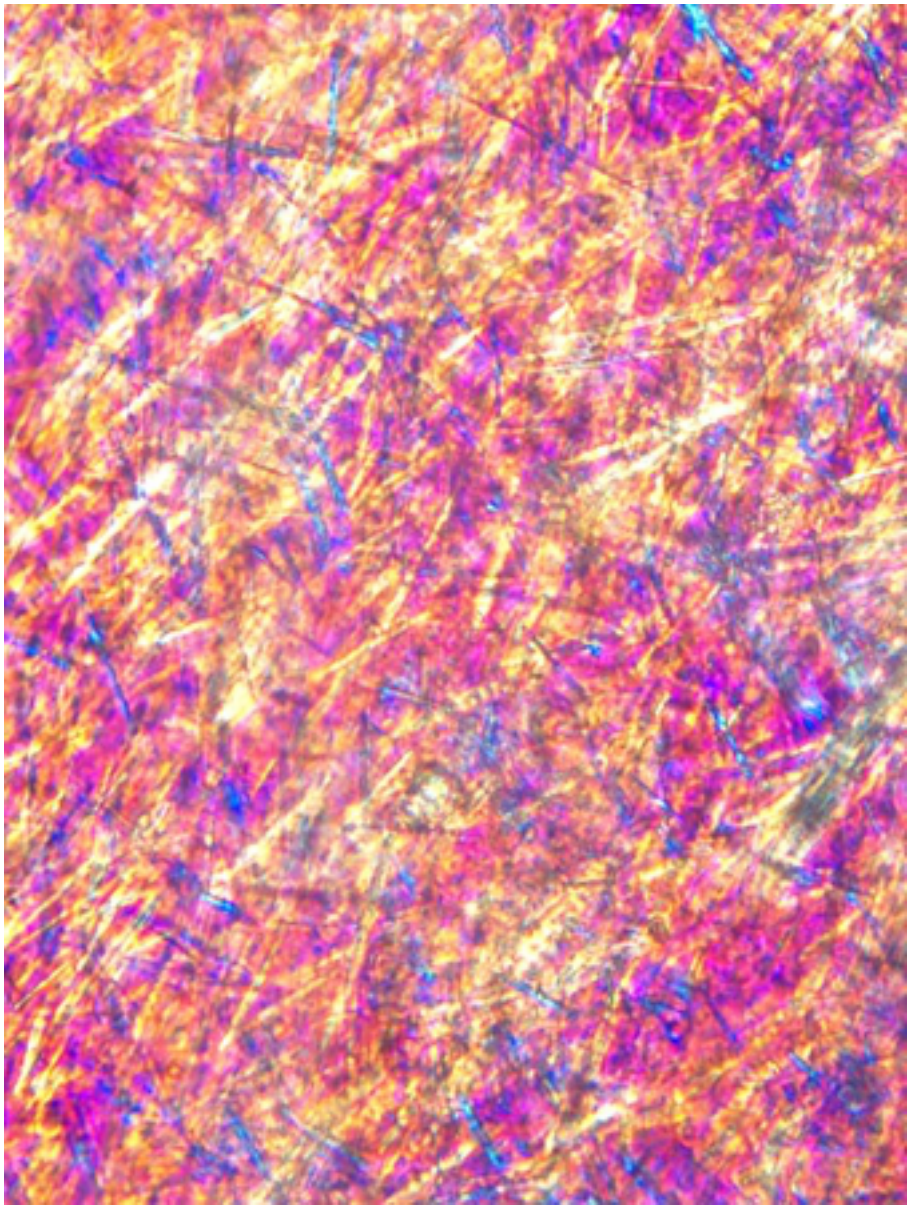
skin lesions.[44] These skin lesions may be subtle and missed unless specifically looked for. Mono- or oligoarthritis resulting from DGI typically affects the knees, wrists, or ankles. Pain along tendon sheaths with active or passive joint movement is a feature of gonococcal tenosynovitis. Blood and synovial fluid culture on Thayer-Martin medium can grow *N gonorrhoeae* .

- Clinical gout comprises a heterogeneous group of disorders characterized by deposition of monosodium urate (MSU) crystals in the joints and tendons.[31] The usual manifestations of acute gout are severe pain, redness, and swelling involving a single joint (approximately 80% of patients), often in the lower extremity, typically at the first metatarsophalangeal joint (podagra). Maximal severity of the attack is usually reached over several hours. Even if untreated, the episode almost always resolves completely within a few days to several weeks. Longstanding gouty arthropathy is often associated with tophaceous deposits. Under polarized light microscopy, MSU crystals (both intra- and extracellular) are visible in the synovial fluid aspirate and in an aspirate from a tophus.[45] [46]



Tophaceous gout

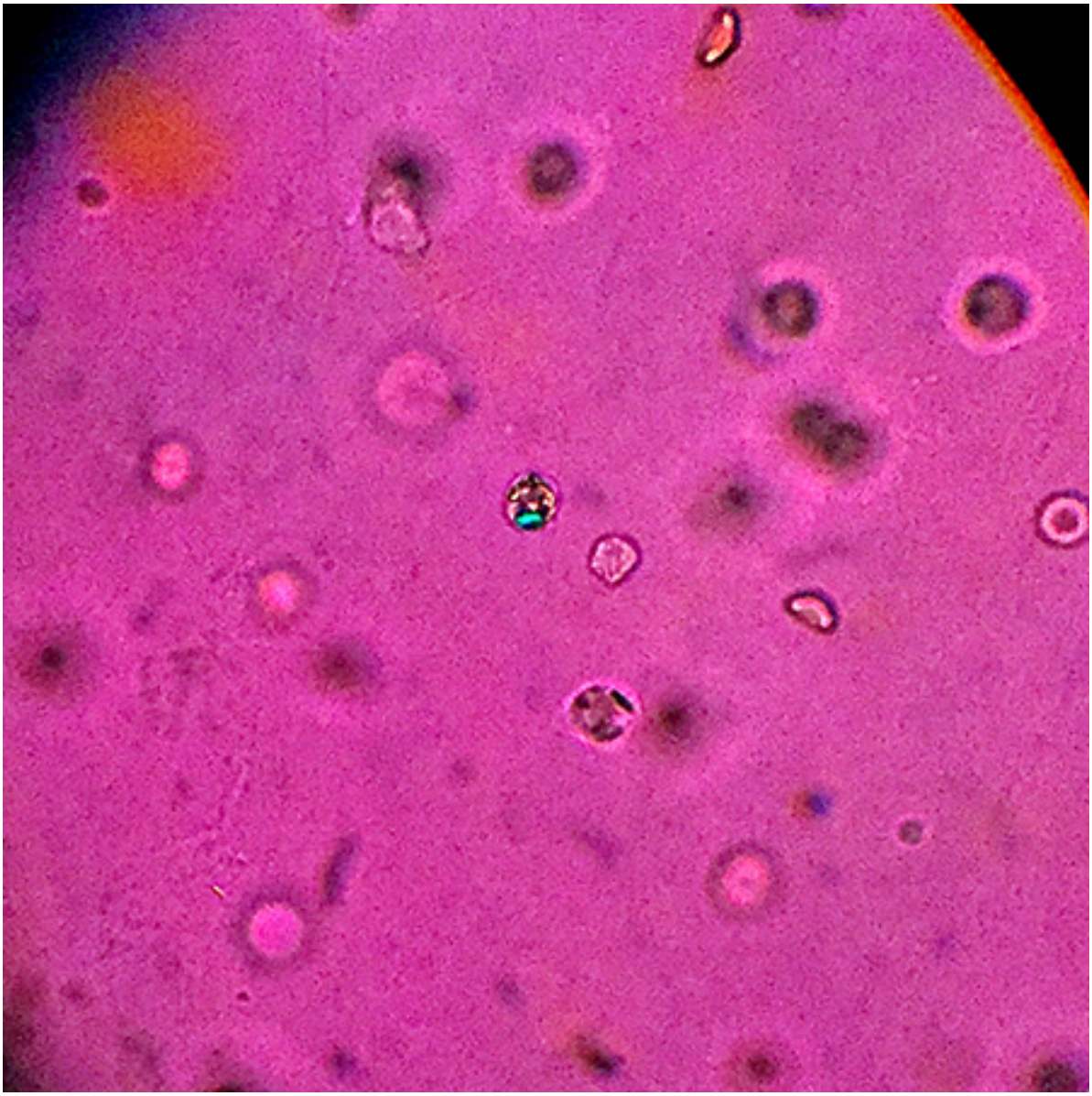
From the collection of Dr Soumya Chatterjee



Monosodium urate crystals from a tophus (polarized light microscopy)

From the collection of Dr Soumya Chatterjee

- Acute pseudogout results from crystal precipitation of calcium pyrophosphate dihydrate (CPPD). CPPD crystal-induced synovitis can clinically resemble gout: self-limited acute or subacute attacks of mono- or oligoarthritis (involving <5 joints).[47] Trauma, surgery, or medical illness can precipitate these attacks. The typical patient is >65 years old with a history of recurrent episodes of arthritis. The knee is affected in >50% of patients, although attacks may also involve the wrists, metacarpophalangeal (MCP) joints, shoulders, and elbows. A symmetric pattern of joint involvement is common, but unilateral involvement may also occur. Chondrocalcinosis (presence of calcification in fibrocartilage and hyaline cartilage that is visible on x-ray) is commonly present in patients with CPPD crystal deposition disease. Disorders associated with CPPD deposition disease include hemochromatosis, hyperparathyroidism, hypomagnesemia, hypophosphatasia, hypothyroidism, and familial hypocalciuric hypercalcemia.[48] Screening for associated diseases should be guided by the clinical presentation and level of suspicion.[49]



Calcium pyrophosphate dihydrate (CPPD) crystals in synovial fluid under compensated polarized light microscopy

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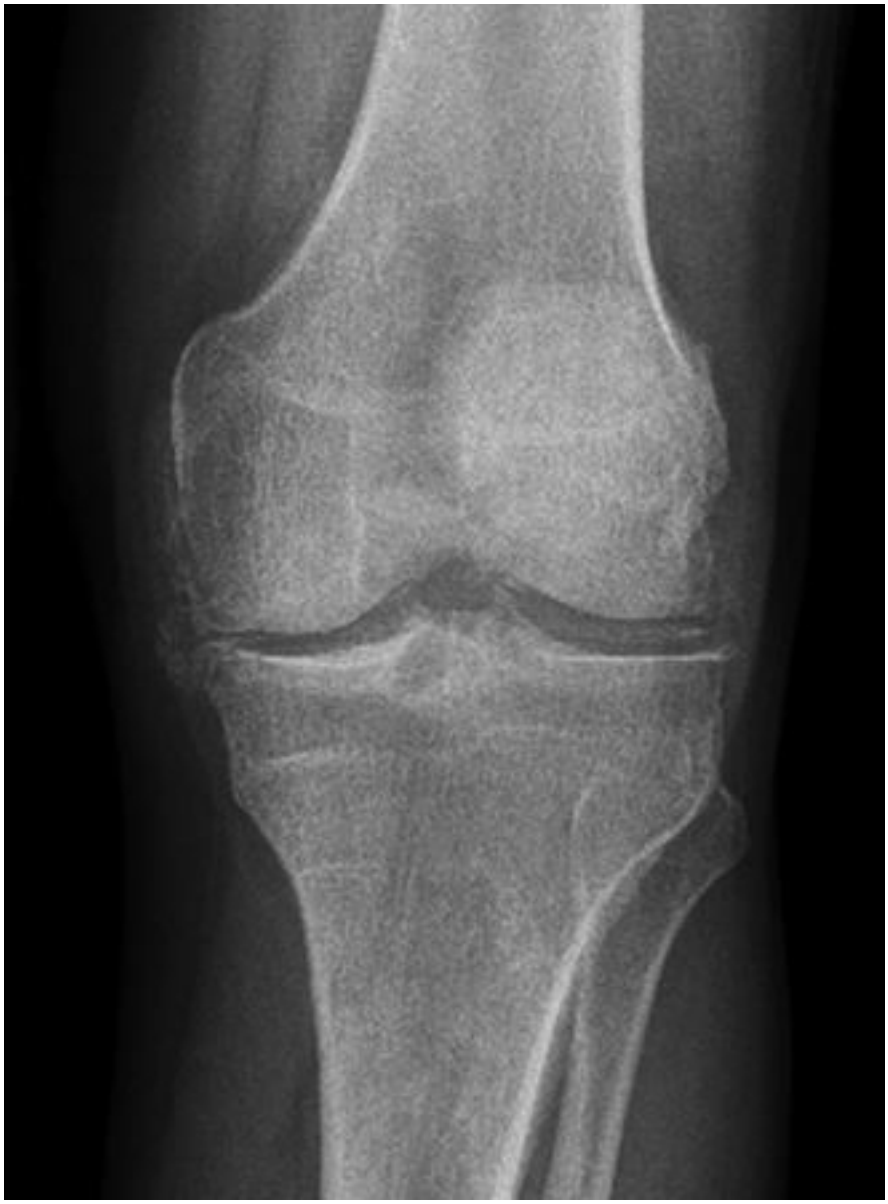


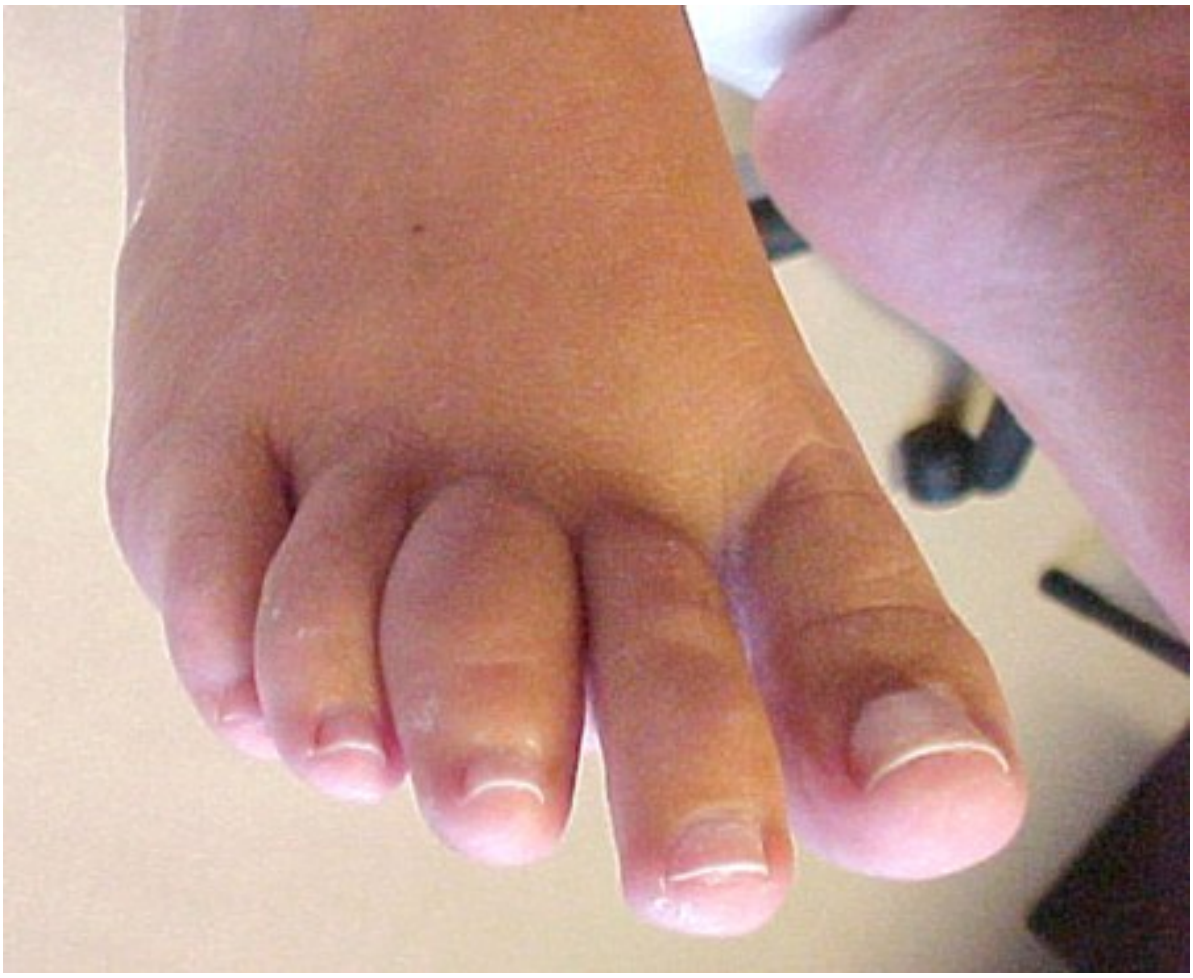
Chondrocalcinosis (lateral meniscus of left knee)

From the collection of Dr Soumya Chatterjee

A familial form of CPPD disease has been associated with ANKH gene mutation.[50] [51]

- Bleeding into a joint (hemarthrosis) is an important cause of monoarticular joint pain and swelling. Factors that may influence hemarthrosis include trauma, bleeding disorders (hemophilia), neurologic deficits (Charcot joint), intra-articular neoplasms (e.g., tenosynovial giant cell tumor), or a vascular abnormality (hemangioma, arteriovenous malformation, aneurysm, and synovial vascular structural anomalies). The joint is swollen and warm, and has a very painful and restricted range of motion. Superficial bruising and ecchymoses can be seen. Lipohemarthrosis due to leakage of marrow fat into the synovial fluid strongly suggests an intra-articular fracture. Bloody effusion in hemarthrosis usually fails to clot due to chronic fibrinolysis, while blood from a traumatic aspiration generally clots. X-ray of the affected joint may identify an intracapsular fracture, whereas a magnetic resonance imaging (MRI) scan is necessary to demonstrate injury to the cartilage, intra-articular ligament rupture, or tenosynovial giant cell tumor.

- Traumatic synovial effusion is suggested by history and should prompt immobilization and appropriate imaging studies to rule out any anatomic derangement.
- Reactive arthritis develops soon after an infection elsewhere in the body, but the microorganisms cannot be recovered from the joint. The classic pathogens in reactive arthritis are *Chlamydia trachomatis* , *Chlamydia pneumoniae, Yersinia* , *Salmonella* , *Shigella* , *Campylobacter* , *Clostridium difficile* , and bacillus Calmette-Guérin (BCG, following intravesical instillation in the treatment of bladder cancer). The lag period between the preceding symptomatic infection and onset of arthritis ranges from several days to several weeks. The typical presentation is an asymmetric mono- or oligoarthritis (involving <5 joints), which predominantly affects the lower extremities. However, about 50% of patients also have arthritis in the upper extremities, and some have small joint polyarthritis. Dactylitis, enthesitis, and tenosynovitis may be present. Extra-articular manifestations include conjunctivitis and anterior uveitis, oral ulcers, urethritis, keratoderma blennorrhagicum (psoriasiform skin changes on the soles of the feet), nail changes similar to psoriasis, and circinate balanitis. Urethritis can cause dysuria and pelvic pain. Infections by *Yersinia* , *Salmonella* , *Campylobacter* , and *C pneumoniae* cause strong antibody responses. IgM and rising IgG titers (paired sera) may be useful in diagnosis of recent *Yersinia* and *Campylobacter* infections, even in communities where seroprevalence is high. HLA-B27 testing is not useful for the diagnosis of reactive arthritis irrespective of prior probability. However, it is useful prognostically in that HLA-B27-positive patients have more severe and prolonged duration of arthritis and are more likely to develop chronic spondyloarthritis. Reactive arthritis can behave more aggressively in patients with coexistent HIV disease.



Dactylitis of right third toe (reactive arthritis)

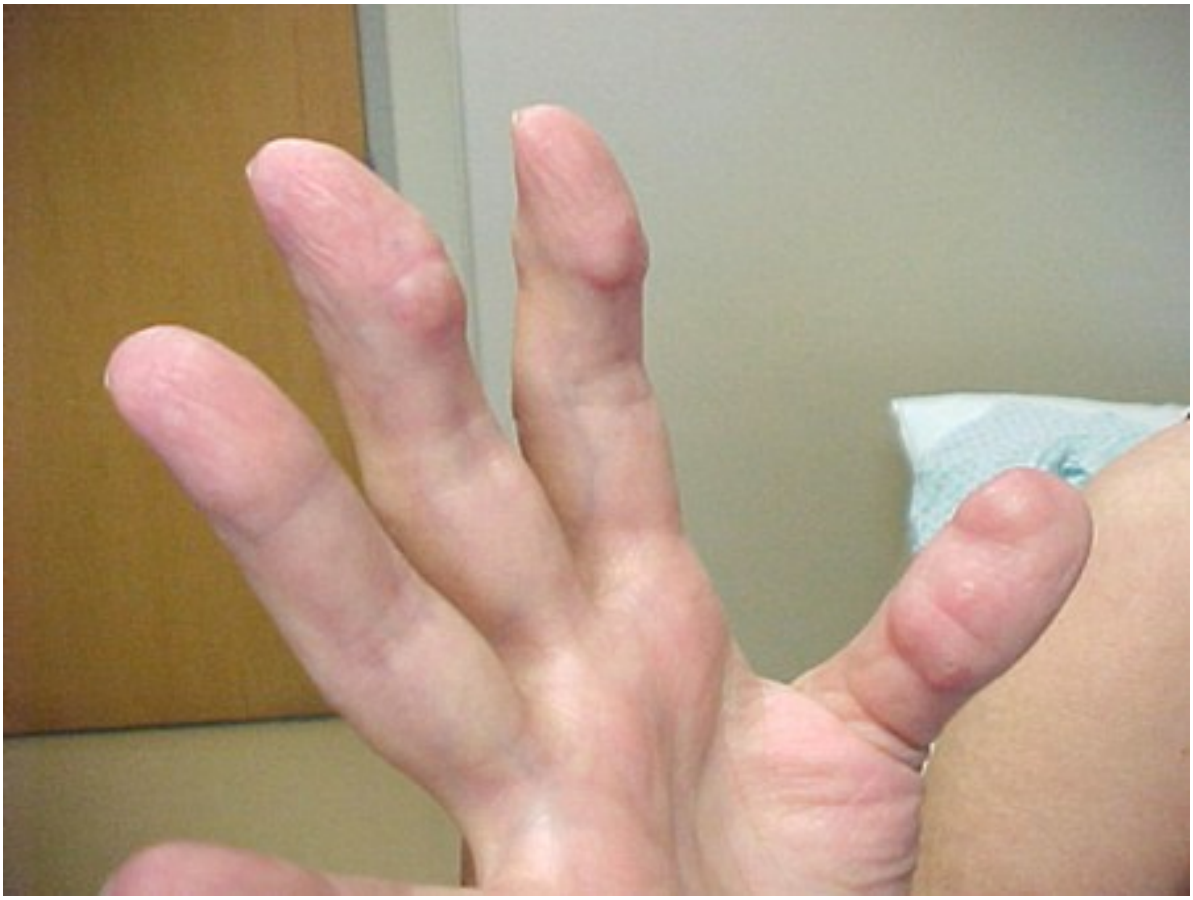
From the collection of Dr Soumya Chatterjee

- Lyme disease, caused by an infected tick bite (*Ixodes* species), is now the most common vector-borne illness the northern hemisphere.[52] Joint manifestations usually arise late in the course of the disease and are characterized by recurrent attacks of asymmetric swelling and pain in a few large joints. A detailed travel and activity history, with inquiries about prior residences and prior clinical findings that might be consistent with Lyme disease, is important.[53] Intermittent mono- or oligoarthritis (involving <5 joints) occurs in about 60% of untreated patients with late disseminated disease; about 10% of untreated patients develop persistent monoarthritis. An antecedent bull's eye rash (erythema migrans) develops at the site of the tick bite in up to 85% of patients. The most commonly involved joints are the knee, shoulder, ankle, elbow, temporomandibular joint, and wrist.
- Tenosynovial giant cell tumor occurs predominantly in young and middle-aged adults. This benign disorder is characterized by synovial hypertrophy, most commonly in the knee joint, with diffuse intra-articular hemosiderin deposition.
- In synovial chondromatosis, loose cartilaginous bodies develop that may ossify in 70% to 95% of patients (osteochondromatosis). It mostly affects men and also commonly affects the knee joint.
- Lipoma arborescens is characterized by benign lipomatous proliferation of the synovium, most often of the knee joint. This idiopathic condition is more common in men in the fourth and fifth decades.

Acute polyarthropathy

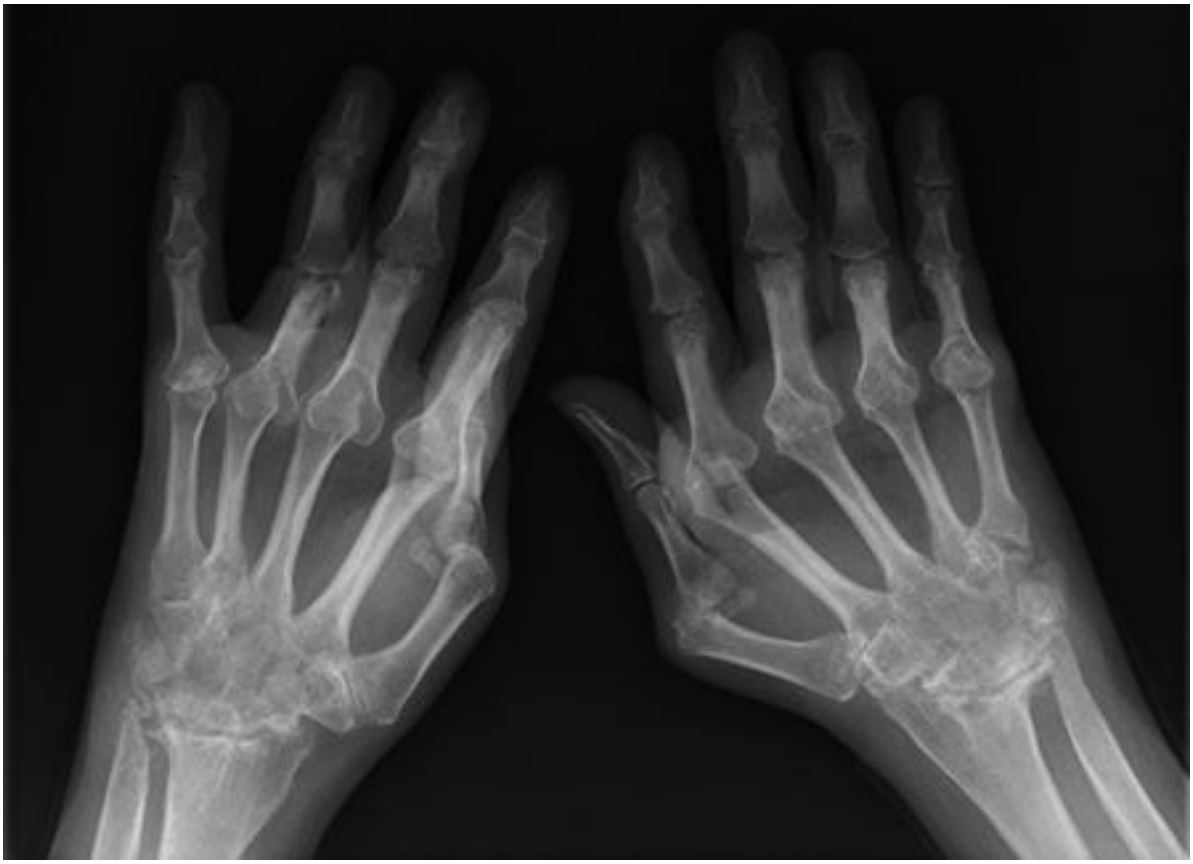
Causes of acute polyarthritis include RA, systemic lupus erythematosus (SLE), psoriatic arthritis, enteropathic arthritides (e.g., ulcerative colitis, Crohn disease, celiac disease, Whipple disease), reactive arthritis (note that this condition is also a cause of acute monoarthritis), Lyme disease (also a cause of acute monoarthritis), SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis), adult-onset Still disease (AOSD), ankylosing spondylitis (AS), acute rheumatic fever (ARF), sarcoidosis, parvovirus B19 syndrome, paraneoplastic articular syndromes, arbovirus infections (such as chikungunya), remitting seronegative symmetrical synovitis with pitting edema (RS3PE), and drug-induced acute polyarthritis.

- RA is characterized by pain, swelling, and stiffness of the MCP and proximal interphalangeal (PIP) joints of both hands, as well as peripheral polyarthritis involving the wrists, elbows, shoulders, knees, ankles, and metatarsophalangeal joints. Morning stiffness for at least 30 to 60 minutes is typical. Rheumatoid nodules tend to occur later in the course of the disease. Serum rheumatoid factor (RF) and antibodies to cyclic citrullinated peptides (CCP) are positive. The sensitivity of RF for the disease is 26%, with a specificity of 60%.[54] Anti-CCP antibodies have a higher sensitivity and specificity for RA, at 99.4% and 66%, respectively.[55] [56] Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) indicate active joint inflammation. Characteristic marginal erosions of cartilage and bone around the MCP and PIP joints can be seen on x-ray of the hands, with severe subluxations and joint damage in advanced cases. Classification criteria for rheumatoid arthritis developed by the American College of Rheumatology/European League Against Rheumatism focus attention on earlier diagnosis and treatment.[57] [58] [59]



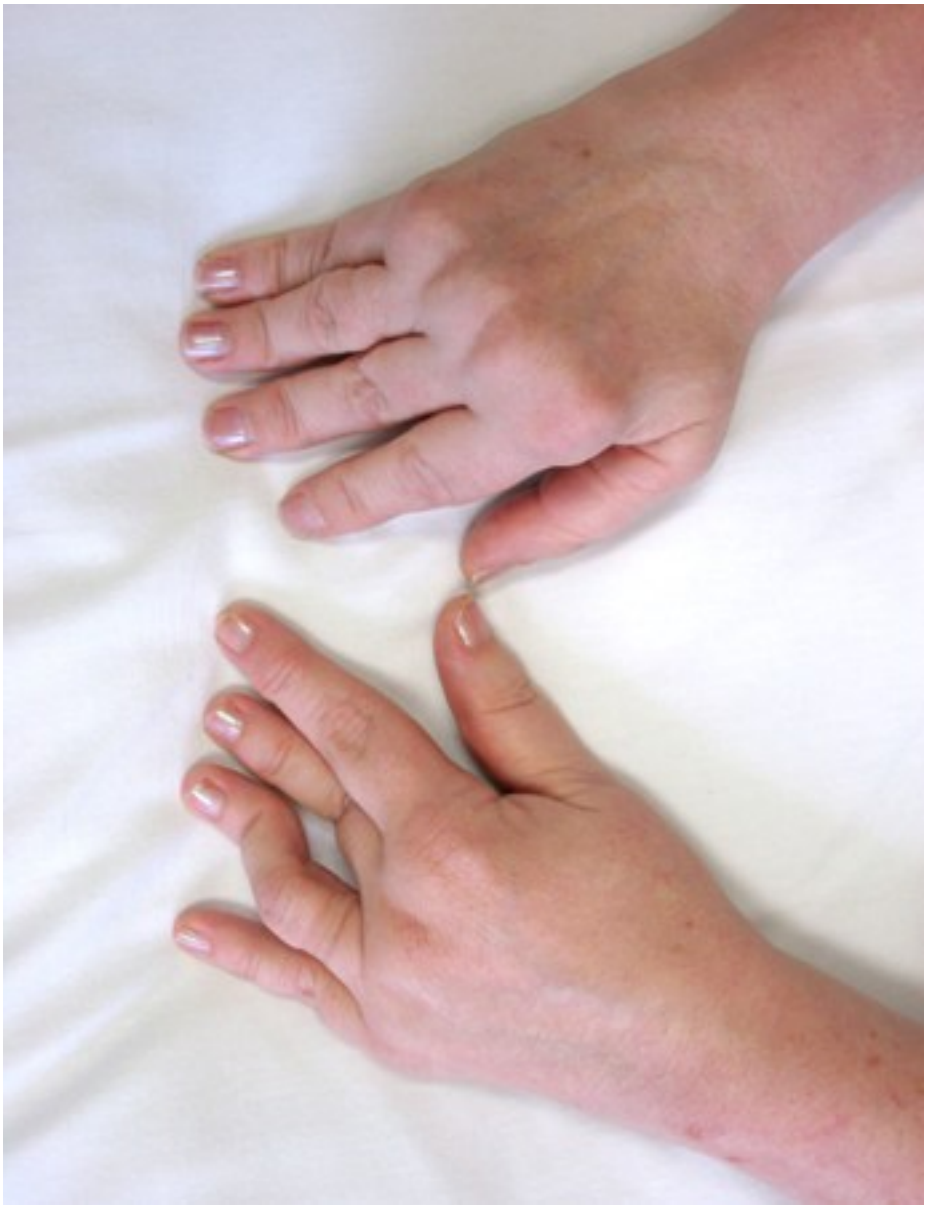
Rheumatoid nodules

From the collection of Dr Soumya Chatterjee



Rheumatoid hand x-ray

From the collection of Dr Soumya Chatterjee

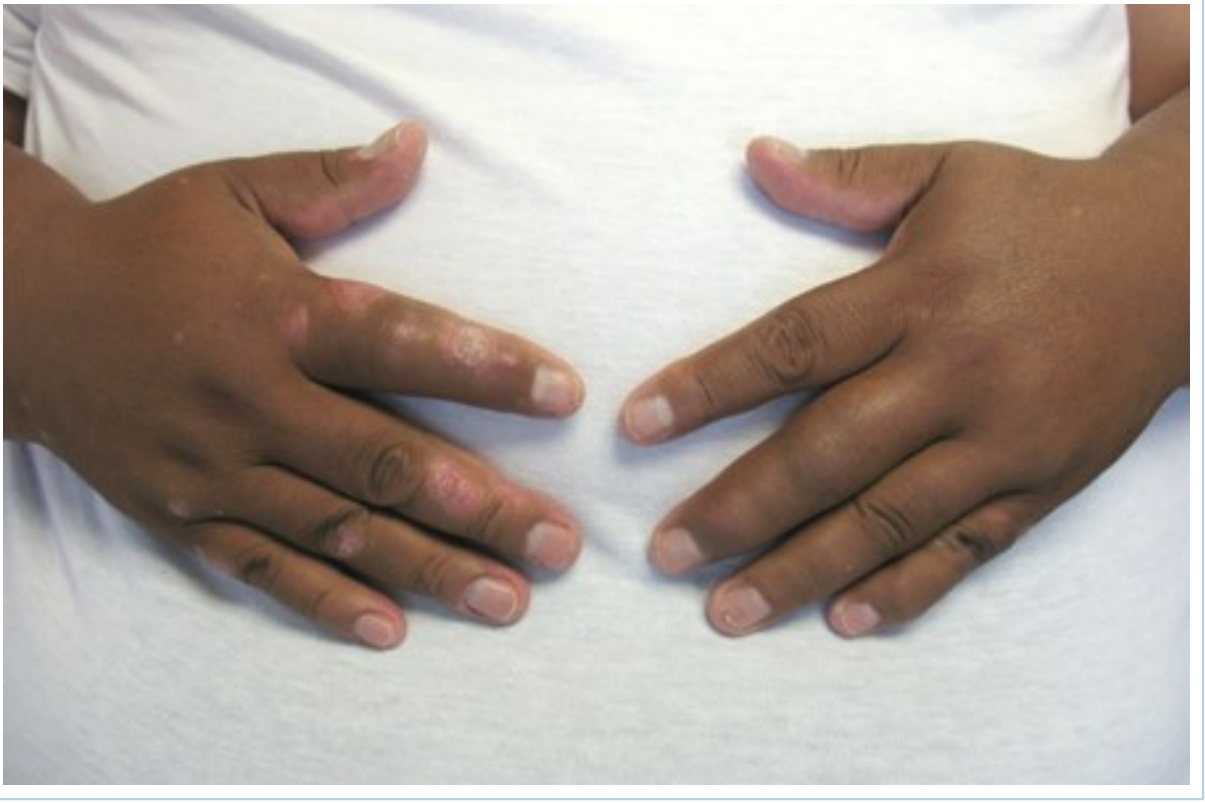


Rheumatoid arthritis (chronic hand deformities)

From the collection of Dr Soumya Chatterjee

- SLE is a chronic autoimmune inflammatory disease that can affect the skin, joints, kidneys, lungs, nervous system, and serous membranes.[60] Young women (20-30 years) are most frequently affected. Joint symptoms occur in over 90% of patients at some point and are often the earliest manifestation. Arthritis tends to be migratory and asymmetric. Rarely, a progressively deforming, but reducible arthropathy (consisting mainly of ulnar deviation of the fingers at the MCP joints, called Jaccoud arthropathy) can develop. Antinuclear antibody (ANA) is positive in a significant titer (usually ≥1:160) in nearly all patients with SLE. This is the best diagnostic test, with high sensitivity, and should be performed whenever SLE is suspected.[61] A positive ANA (at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test at least once) is a required (entry) criterion for the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) Classification Criteria for SLE.[62] Antibodies to double-stranded DNA and anti-Smith (Sm) antibodies are highly specific for SLE.[63] [64]

- Patients with psoriatic arthritis present with pain, swelling, and stiffness in the affected joints, with morning stiffness lasting >30 minutes in 50% of patients. The most frequent presentation is oligoarthritis (involving <5 joints). Dactylitis (sausage digit), enthesitis (inflammation of the entheses, the location where a bone has an insertion of a tendon or a ligament), and tenosynovitis are not uncommon.[16] The distal interphalangeal (DIP) joints and spine are affected in 40% to 50% of patients. Cutaneous psoriasis is present in 90% of cases.[65] Nail psoriasis can also be seen. DIP joint arthritis and arthritis mutilans (an extremely severe form of chronic destructive arthritis, characterized by resorption of bones and the consequent collapse of soft tissue leading to pencil-in-cup deformity and telescoping digits) can be seen in psoriatic arthritis. Psoriatic arthritis can behave more aggressively in patients with coexistent HIV disease. The Classification Criteria for Psoriatic Arthritis (CASPAR) study group has developed a validated set of classification criteria for psoriatic arthritis with a sensitivity of 91.4% and a specificity of 98.7%.[66] [67]



Psoriatic arthritis with dactylitis (left middle and right index finger); skin and nail changes (left ring finger)

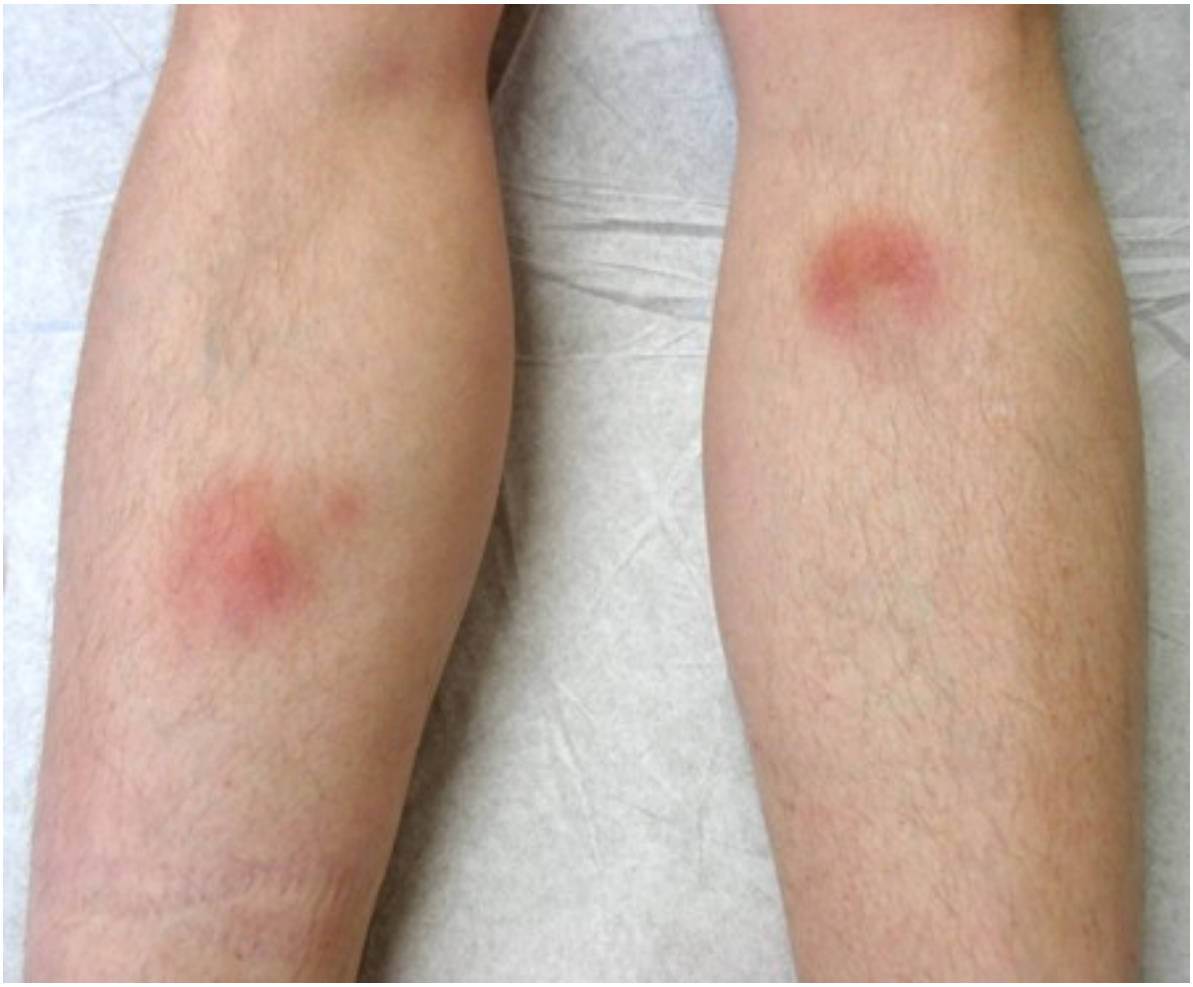
From the collection of Dr Soumya Chatterjee

- Enteropathic arthritides: these conditions lead to an inflammatory arthritis secondary to an immune-mediated process affecting the gastrointestinal tract. Examples include:
  - Inflammatory arthritis associated with inflammatory bowel disease (i.e., ulcerative colitis and Crohn disease)
  - Reactive arthritis following infection with enteric pathogens such as *Salmonella* , *Shigella* , *Campylobacter* , *Yersinia* , *Chlamydia* , and *Clostridium difficile* (described above under "reactive arthritis")
  - Inflammatory arthritis associated with intestinal bypass procedures (also known as bowel-associated dermatosis arthritis syndrome)
  - Celiac disease
  - Whipple disease (caused by a Gram-positive bacterium, *Tropheryma whipplei*).

- Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome has some clinical manifestations that resemble psoriatic arthritis. Sternoclavicular joint arthritis is a characteristic feature. Osteitis is the most prominent skeletal lesion, but lytic, sclerotic, and hyperostotic bone lesions also develop. Palmoplantar pustulosis and acne are the main skin lesions.[68]
- Inflammatory arthritis similar to reactive arthritis has been described in association with acne conglobata, hidradenitis suppurativa, and dissecting cellulitis of the scalp (follicular occlusion triad).
- Monoarthritis of the knee is the most common rheumatologic manifestation of late disseminated Lyme disease, but an asymmetric large joint oligoarthritis (<5 joints) can also develop.
- AOSD presents with polyarthralgia or a severe polyarthritis. This may be accompanied by severe muscle pain. In addition, there is a febrile rash that is nonpruritic, macular or maculopapular, salmon colored, and usually found over the trunk or extremities. A severe, nonsuppurative pharyngitis is also common in AOSD and may presage disease relapses. Pericarditis, pleural effusions, and transient pulmonary infiltrates occur in 30% to 40% of patients.[69] [70] Fusion of the wrist joints is characteristic of AOSD, although it occurs in only a minority of patients.[71] Serum ferritin concentration >3000 nanograms/mL is common in AOSD, with some patients having values >10,000 nanograms/mL.[72] The elevation of ferritin correlates with disease activity. Bone marrow examination demonstrates pathognomonic evidence of macrophage activation syndrome (hemophagocytosis) in 12% of patients, with numerous, well-differentiated macrophages (histiocytes) that are involved in the phagocytosis of hematopoietic elements.[72]
- AS is a chronic inflammatory disease of the axial skeleton, presenting with low back pain (sacroiliitis) and progressive stiffness of the spine. It characteristically affects young adults, with a peak age of onset between 20 and 30 years.[73] In 75% of patients, the first symptom is low back pain for >3 months: a constant dull ache in the low back, gluteal regions, and posterior thighs that typically improves with exercise but not with rest (as opposed to mechanical back pain), may awaken the patient from sleep, and is associated with morning stiffness of >30 minutes' duration. Groin pain (indicating hip arthritis), shoulder pain, and shoulder stiffness are common. Less commonly, other peripheral joints are affected. Costochondral, manubriosternal, sternoclavicular, and costovertebral joints can also be affected. Another possible sign is enthesitis, which can manifest as Achilles tendinitis or plantar fasciitis. Limited range of motion and pain on movement of the hips and shoulders is common. AS can coexist with psoriasis and inflammatory bowel disease. Extra-articular manifestations include acute unilateral anterior uveitis, aortic valve disease, cardiac conduction abnormalities, and apical pulmonary fibrosis. Among white people, HLA-B27 is present in 95% of AS patients, compared with 8% of the general population.[74] HLA-B27 is more useful than radiography for diagnosis in patients who have chronic low back pain, where a positive result for HLA-B27 is associated with a 30% to 60% chance of having AS.[74] Even after 10 years of AS, only 40% of patients have radiographic evidence of sacroiliitis on plain films.[75] MRI is the most sensitive and specific test in detecting the changes of sacroiliitis. It is indicated when plain radiographs are normal but suspicion of AS is high (known as "nonradiographic axial spondyloarthritis"). For these early cases, MRI has a sensitivity of 60%.[76] Based on its performance in evaluating patients presenting with peripheral arthritis, enthesitis, and/or dactylitis, classification criteria for peripheral spondyloarthritis have been developed by the Assessment of SpondyloArthritis international Society (ASAS).[77]
- Acute rheumatic fever (ARF) is a delayed, nonsuppurative sequela of group A *Streptococcus* tonsillopharyngitis. There is usually a latent period of 2 to 3 weeks following pharyngitis before the first manifestations of ARF appear.[78] An acute migratory arthritis may develop, affecting the knees, ankles, elbows, and wrists. The lower extremity joints are typically involved first. Streptococcal antibodies are most useful in diagnosis, as they reach a peak titer at about the time of onset of ARF,

and indicate true infection rather than carriage. Other manifestations may include endocarditis, chorea, subcutaneous nodules, and erythema marginatum (Jones criteria).[79]

- Sarcoidosis is a multisystem disorder of unknown etiology. It typically affects young adults 20 to 40 years old, and may present with bilateral hilar and right paratracheal lymphadenopathy, pulmonary infiltrates, and skin or eye lesions (anterior and/or posterior uveitis). About 25% of patients develop sarcoid arthropathy.[80] Diagnosis may be difficult when a patient presents solely with joint pain. Löfgren syndrome is characterized by the triad of bilateral hilar adenopathy, acute polyarthritis, and erythema nodosum. Although it is usually self-limited, about one third of patients have a more persistent course. Chronic sarcoid arthropathy is frequently associated with interstitial lung disease and elevated angiotensin-converting enzyme levels.[81] In the presence of typical pulmonary or other extrapulmonary features of sarcoidosis, synovial histology revealing multiple noncaseating granulomata supports the diagnosis.



Erythema nodosum

From the collection of Dr Soumya Chatterjee

- Symptoms are usually symmetric and in multiple joints after parvovirus infection, and may mimic RA. The diagnosis is suggested by a viral prodrome with flu-like symptoms, and a rash (in some patients), shortly prior to joint inflammation.[82]
- Paraneoplastic articular syndromes include hypertrophic osteoarthropathy, palmar fasciitis with polyarthritis syndrome, and paraneoplastic arthritis.[33] [34]
- In patients with inflammatory polyarthritis who have a history of travel to endemic areas, arbovirus infections such as chikungunya should be suspected. Patients may develop fever, a rash, myalgias, headache, and arthralgias 2 to 10 days after a mosquito bite (typically *Aedes albopictus*) and arthritis

involves small joints of hands and feet, wrists, and ankles in the majority of those affected. About half of the patients continue to have arthritis 6 months after the onset of the disease. Diagnosis is made by viral culture or reverse transcriptase polymerase chain reaction (PCR) from an acute-phase specimen of serum.

- Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome presents with acute-onset polyarthritis, with significant pitting edema of the dorsal surfaces of the hands and feet. It is more commonly seen in males, in older patients (≥50 years), and is usually nonerosive. As the name implies, rheumatoid factor is negative.[21]
- A detailed drug history is important in patients with an immune-mediated inflammatory arthropathy. Use of certain drugs, such as procainamide, hydralazine, minocycline, isoniazid, propylthiouracil, and tumor necrosis factor inhibitors can be associated with drug-induced lupus. Serum sickness-like reaction can be seen with various oral and parenteral pharmacologic agents, including plasma-derived products and biologic response modifiers (e.g., infliximab and rituximab). In addition, arthralgia, inflammatory arthritis, and tendinitis have also been associated with the use of aromatase inhibitors (e.g., anastrozole and letrozole), clopidogrel, quinolone antibiotics (e.g., levofloxacin and ciprofloxacin), statins, and dipeptidyl peptidase (DPP)-4 inhibitors (e.g., sitagliptin and saxagliptin).[25] Immune-related adverse events, including inflammatory arthritis, have been reported secondary to immune checkpoint inhibitor therapy for cancer.[26] [27] [28] [29] In one case series of 13 patients treated with ipilimumab (anti-CTLA-4) and/or nivolumab (anti-PD-1) for solid tumors, 9 patients developed inflammatory arthritis (primarily polyarticular arthritis involving small and large joints similar to rheumatoid arthritis), and 4 had sicca symptoms.[83]

Laboratory investigations

The choice of laboratory investigations required varies according to the suspected differential diagnosis.

Septic arthritis

Definitive diagnosis of a septic joint requires joint aspiration and synovial fluid analysis (including Gram stain and culture).

Culture for gonococci on Thayer-Martin medium should be requested in suspected DGI. All patients with DGI should undergo evaluation for concomitant *Chlamydia* , syphilis, and HIV infections. If urethritis is simultaneously present, a Gram stain of the urethral exudate should be obtained.

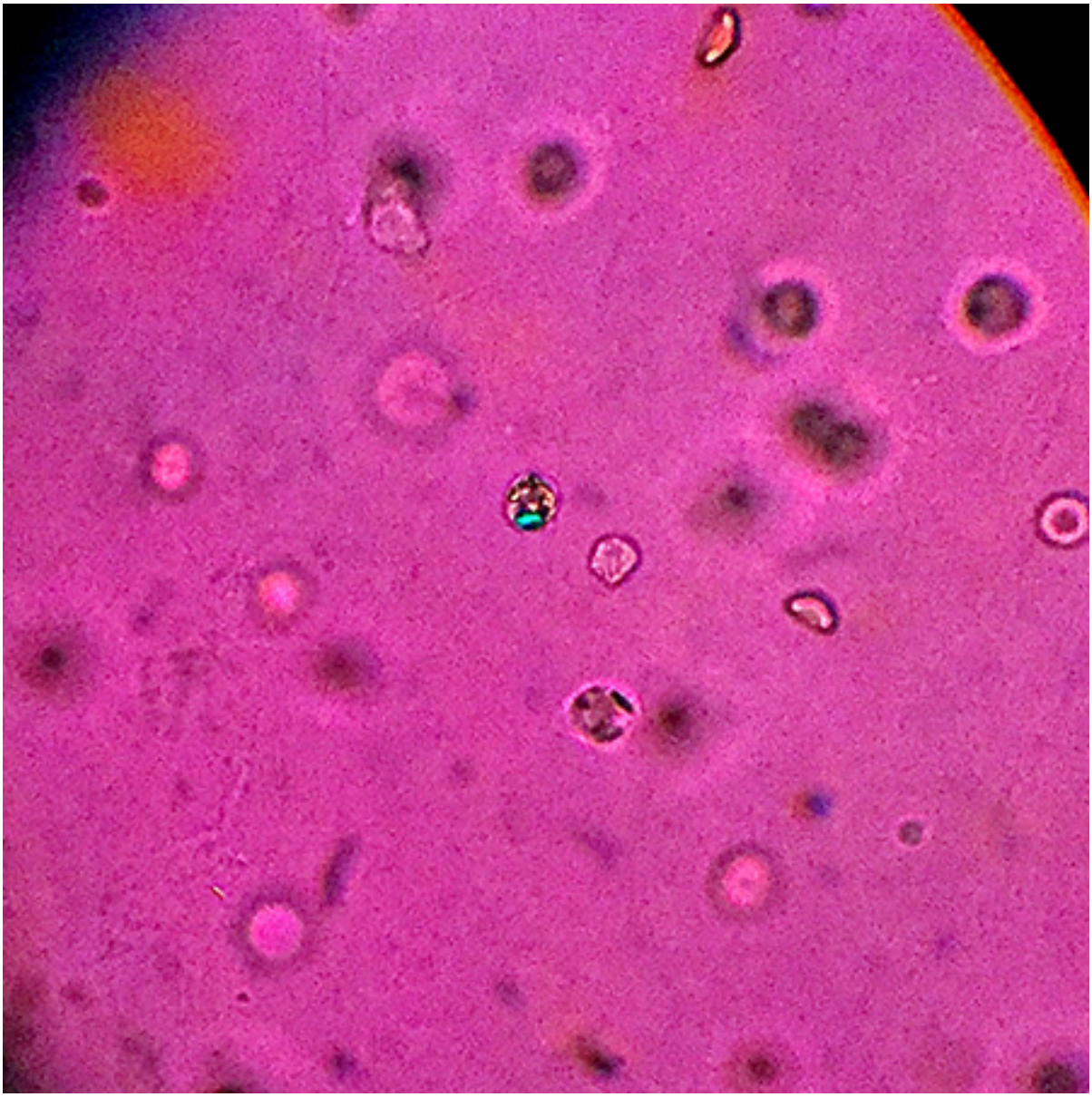
Gout and pseudogout

US guidelines recommend synovial fluid analysis when diagnostic testing is necessary in patients with possible acute gout.[45] Monosodium urate (MSU) crystals are visible in the joint aspirate from a gouty joint on polarized light microscopy.[45]

UK guidance states that a serum urate level of 360 micromol/L (6 mg/dL) or more confirms the diagnosis in those with signs and symptoms of gout.[31] If the serum urate level is below 360 micromol/L (6 mg/dL) during a flare and gout is strongly suspected, serum urate measurement should be repeated at least 2 weeks after the flare has settled.[31] Consideration should be given to joint aspiration and microscopy of synovial fluid if a diagnosis of gout remains uncertain or unconfirmed.[31]

The presence of calcium pyrophosphate dihydrate crystals in the joint aspirate (on polarized light microscopy) is the hallmark of pseudogout. Pseudogout can be accompanied by a number of comorbid

findings (e.g., hemochromatosis, hyperparathyroidism, hypomagnesemia, hypophosphatasia, hypothyroidism, and familial hypocalciuric hypercalcemia).[48]



Calcium pyrophosphate dihydrate (CPPD) crystals in synovial fluid under compensated polarized light microscopy

From the collection of Dr Soumya Chatterjee

Reactive arthritis

Urine screening for *C trachomatis* is indicated in suspected cases of reactive arthritis with recent sexual activity and urethritis. Stool culture or serology for specific organisms should be guided by the clinical presentation and degree of suspicion. Note, however, that by the time arthritis develops, stool cultures are usually negative. Infections with *Yersinia* , *Salmonella* , *Campylobacter* , and *Chlamydia* cause strong antibody responses.

Lyme disease

Serologic diagnosis for Lyme disease includes IgM and IgG antibodies via a 2-tier approach:[84] [85] [86] The first step should include a sensitive enzyme immunoassay (EIA) or immunofluorescence assay (IFA), and if positive or equivocal, this should be confirmed with a standardized Western blot assay. In the US, some EIAs have been approved by the Food and Drug Administration for serologic diagnosis of Lyme disease and can be used in place of Western blot assays for the second step.[84] For early Lyme disease (first 4 weeks), both IgM and IgG antibodies should be tested for in the second confirmatory step. No further testing is needed if specimens are negative by a sensitive EIA or IFA.

Indolent infections

Routine blood cultures and routine synovial fluid analysis, including cultures, are not useful in the diagnosis of indolent infections such as tuberculosis, brucellosis, or fungal infections. Specific synovial fluid studies (acid-fast bacilli, brucella, and fungal stains and special cultures) are required.

Anti-CCP antibodies are superior to RF in making the diagnosis of RA.[56]

Juvenile idiopathic arthritis

Children with systemic juvenile idiopathic arthritis (JIA) often have anemia, thrombocytosis, and leukocytosis. ESR and CRP are elevated in different subtypes of the disease.

ANA is positive in oligoarticular JIA, and to a lesser extent in polyarticular JIA.

Systemic lupus erythematosus

The presence of ANA should be sought in cases suggestive of SLE, as it is positive in significant titer (usually ≥1:160) in nearly all patients with SLE. In addition to ANA, serology supporting a diagnosis of SLE includes positive anti-double stranded DNA and anti-Smith (Sm) antibodies.

Ankylosing spondylitis

HLA-B27 is present in 90-95% of white patients with AS.[87]

Enteropathic arthritides

For enteropathic arthritides, the following laboratory tests are helpful:

- Fecal calprotectin: elevated levels are suggestive of inflammatory bowel disease. Confirmation of diagnosis requires colonic biopsy or small bowel biopsy.
- Anti-transglutaminase, anti-endomysial, and anti-gliadin antibodies: celiac disease is suggested by presence of these antibodies. Confirmation of diagnosis requires small bowel (duodenal) biopsy showing subtotal villous atrophy, and its reversibility with a gluten-free diet.
- *Tropheryma whipplei* PCR on blood: suggestive of Whipple disease, although the clinical use of this test has not yet been defined. Confirmation of diagnosis requires upper endoscopy with duodenal biopsy, and analysis of the specimen for periodic acid-Schiff (PAS) staining and PCR plus/minus immunohistochemistry staining for *T whipplei* . Fluid and/or tissue from synovium, cerebrospinal fluid, or affected lymph nodes may be used for the same tests.

Adult-onset Still disease

Serum ferritin is markedly elevated in adult-onset Still disease (AOSD); the degree of elevation correlates with disease activity. The appearance of macrophage activation, in which the cells phagocytose hematopoietic elements, on bone marrow biopsy can sometimes be seen (12% of patients).[72]

Acute rheumatic fever

There is no diagnostic laboratory test specific for ARF, and diagnosis is mostly based on high index of clinical suspicion. Throat cultures are negative in the majority of patients by the time ARF develops. If the antistreptolysin O (ASO) titer is negative, testing for other antistreptococcal antibodies, such as anti-DNAse B, antistreptokinase, and antihyaluronidase, should be performed.

Sarcoidosis

Very high serum ACE levels indicate the extent of granulomatous inflammation and may help differentiate sarcoid from other causes of seronegative polyarthritis.

Parvovirus

Detectable levels of parvovirus B19-specific IgM can be found within 7 to 10 days of parvovirus exposure and remain measurable for several months.[88]

Arbovirus

The diagnosis of arbovirus infections (e.g., chikungunya) can be confirmed by viral culture, reverse transcription (RT)-PCR to detect viral RNA, or antibody tests including ELISA, immunofluorescence assays, and plaque-reduction neutralization test.[89]

Imaging

X-rays of affected joints can provide useful clues regarding the nature of the joint problem.

X-ray following joint injury may reveal a fracture, a finding specifically sought whenever lipoid elements are present in the joint aspirate on microscopic examination.

In addition, typical changes can be seen in erosive arthritis, and characteristic features (periarticular osteopenia, joint-space narrowing, new bone formation, bony ankylosis, calcinosis, chondrocalcinosis, or acro-osteolysis) can differentiate between RA, psoriatic arthritis, gout, pseudogout, hemochromatosis, hyperparathyroidism, scleroderma, osteoarthritis, erosive osteoarthritis, reflex sympathetic dystrophy, and multicentric reticulohistiocytosis.

DIP joint arthritis and arthritis mutilans (gross destruction of isolated joints; pencil-in-cup appearance) are typical radiographic findings for psoriatic arthritis. Other findings include acro-osteolysis, fluffy periostitis, and new bone formation at the site of enthesitis, joint lysis, and ankylosis.

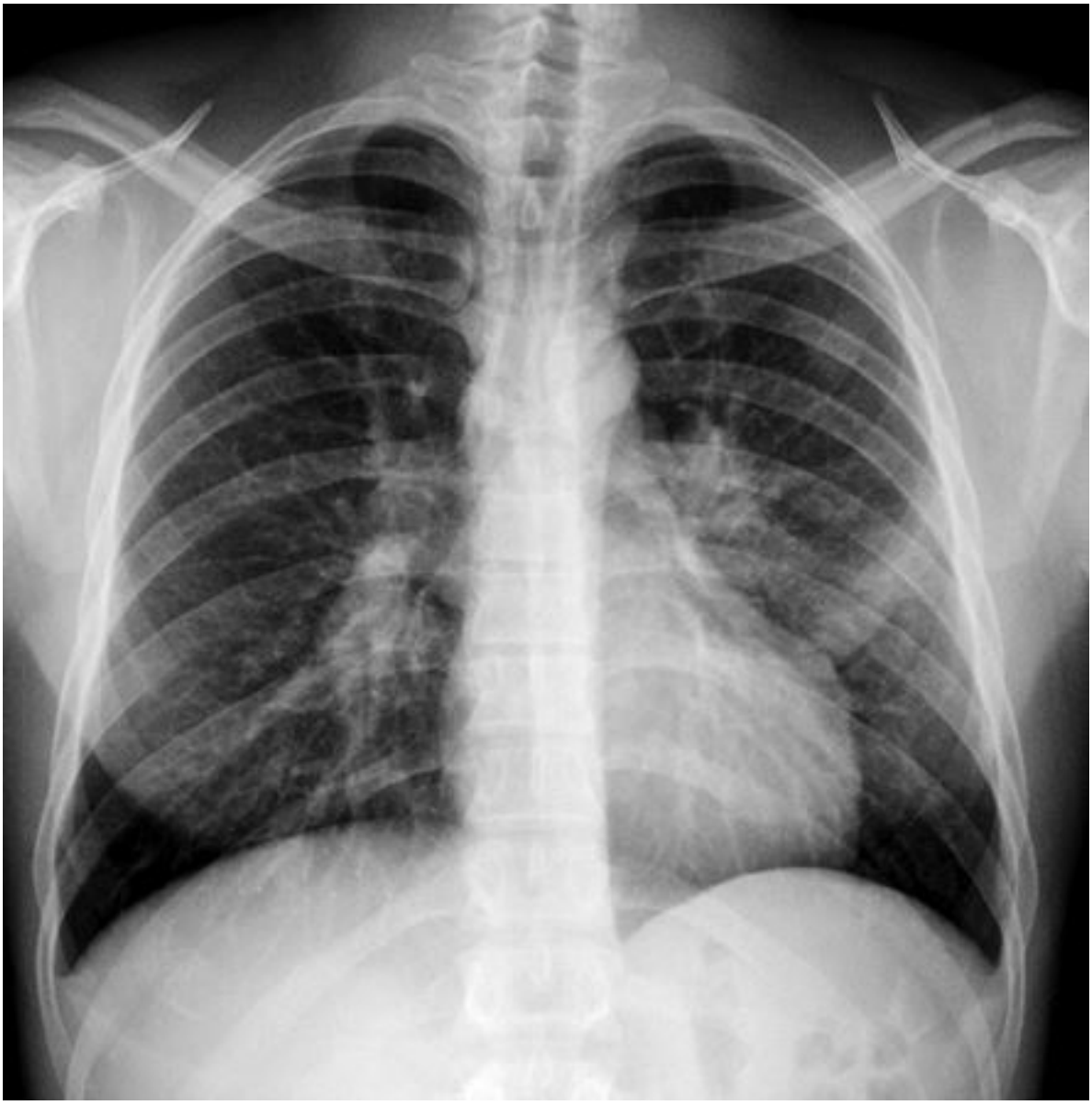
In SAPHO syndrome, radiographs, isotope bone scans, and MRI scans may reveal evidence of sternoclavicular joint arthritis, osteitis, and lytic, sclerotic, and hyperostotic bone lesions.

Cartilage loss in JIA presents as joint-space narrowing on joint x-ray, and, in longstanding disease, erosions are noted.

In RA, characteristic marginal erosions around MCP and PIP joints are often seen on x-ray or MRI scan. Subluxations and more severe joint damage are seen in advanced cases, but these findings are not specific.

Joint radiographs from patients with osteoarthritis show loss of joint space, subchondral sclerosis, cystic changes, and osteophytes. Typical central erosions, “gull-wing” and “saw-tooth” deformities, and ankylosis are seen in erosive osteoarthritis of fingers.

Half of patients with sarcoidosis present on chest x-ray with characteristic bilateral hilar lymphadenopathy, right paratracheal adenopathy, and pulmonary reticular opacities usually in the upper zones. A PET scan may be helpful to identify the extent and distribution of occult sarcoid lesions.[90]



Pulmonary sarcoidosis: right paratracheal, bilateral perihilar, and subcarinal adenopathy

From the collection of Dr Soumya Chatterjee

Musculoskeletal ultrasound is a very useful imaging modality that is noninvasive and radiation-free, and can be used at the bedside. It can be used both for diagnostic and therapeutic purposes (e.g., ultrasound-guided arthrocentesis, joint and soft-tissue injections). Musculoskeletal ultrasound has significantly improved diagnostic accuracy for a variety of rheumatologic conditions. The American College of Rheumatology has published a report on reasonable use of musculoskeletal ultrasonography in rheumatology,[91] which

discusses its use in the diagnosis of synovitis, synovial proliferation, bone erosions, joint effusion, tendinitis, tenosynovitis, enthesopathies, and crystal arthropathies (gout and calcium pyrophosphate arthropathy). Presence of large erosions in the second and fifth MCP, and the fifth MTP joints and distal ulna, are highly specific for and predictive of RA.[92] It has been shown that color Doppler ultrasound is quite useful in distinguishing OA from inflammatory arthritis of the knee.[93] The recommendations of the European Society of Musculoskeletal Radiology also reinforce the use of this imaging modality.[94] On musculoskeletal ultrasound, the characteristic double contour sign helps establish a diagnosis of chronic gout.[95]

Dual-energy CT (DECT) scan has become an excellent noninvasive imaging modality for establishing a diagnosis of chronic gout, even during the intercritical periods.[95]

Biopsy

Synovial biopsy and culture may be necessary in the evaluation and diagnosis of tuberculosis, and in nontuberculous mycobacterial and fungal infections. Biopsy and cytology may also be helpful in providing histologic evidence of primary or metastatic intra-articular malignancy, synovial sarcoma, lipoma arborescens, and pigmented villonodular synovitis. Sarcoid arthropathy may rarely require synovial biopsy for diagnosis. Confirmation of diagnosis of celiac disease requires small bowel (duodenal) biopsy showing subtotal villous atrophy, and its reversibility with a gluten-free diet. Confirmation of diagnosis of Whipple disease requires upper endoscopy with duodenal biopsy, and analysis of the specimen for PAS staining and PCR and/or immunohistochemistry staining for *T whipplei* . Fluid and/or tissue from synovium, cerebrospinal fluid, or affected lymph nodes may be used for the same tests.

Differentials overview

Common

- Septic nongonococcal arthritis
- Gonococcal arthritis
- Rheumatoid arthritis
- Gout
- Pseudogout
- Psoriatic arthritis

Uncommon

- Indolent infections
- Parvoviral syndrome
- Lyme disease
- Juvenile idiopathic arthritis (oligo-articular type)
- Acute rheumatic fever (ARF)
- Sarcoidosis
- Spondyloarthropathy
- Systemic lupus erythematosus (SLE)
- Adult-onset Still disease (AOSD)
- Reactive arthritis
- Ankylosing spondylitis (AS)
- Osteoarthritis
- Trauma
- Nontraumatic hemarthrosis

Uncommon
Hypertrophic osteoarthropathy
Intra-articular metastatic cancer
Synovial sarcoma
Arbovirus infections (e.g., chikungunya)
Inflammatory bowel disease (ulcerative colitis and Crohn disease)
Celiac disease
Whipple disease
Bowel-associated dermatosis arthritis syndrome
Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome
Drug-induced
Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome
Ebola virus
Diffuse tenosynovial giant cell tumor (formerly, diffuse pigmented villonodular synovitis)
Localized tenosynovial giant cell tumor (formerly, localized pigmented villonodular synovitis)
Synovial osteochondromatosis
Amyloid arthropathy
Fibroblastic rheumatism
Multicentric reticulohistiocytosis (MRH)

Differentials

Common

Septic nongonococcal arthritis

History	Exam	1st Test	Other tests
acute onset, severe pain, fever, malaise; patients at risk include intravenous drug users, those with recent bacteremia, immunocompromised patients (e.g., those with HIV disease, on immunosuppressive agents, or with other immunocompromised states), patients with sickle cell disease or other hemoglobinopathies, patients with rheumatoid arthritis or those with prosthetic joints, those who have had recent arthroscopy or arthrocentesis	joint is warm and swollen, with severely limited range of motion	»**needle joint aspiration:** identification and recovery of pyogenic bacteria on microscopic examination (Gram stain) of synovial fluid and culture; WBC count in synovial fluid is often >100,000/mm³ (polymorphonuclear leukocytes >75%) The most common organism is *Staphylococcus aureus* , followed by *Streptococci* , *Haemophilus influenzae* , *Escherichia coli* (older adults), *Pseudomonas aeruginosa* (immunocompromised), mycobacteria, and fungi. 10-20% are culture negative.[43] [96] [97] [98]	»**blood cultures:** growth of causative organism - positive in 50% of cases[99] »**ultrasound-guided joint aspiration:** WBC count in synovial fluid is often >100,000/mm³ (polymorphonuclear leukocytes >75%) »**CT-guided joint aspiration:** WBC count in synovial fluid is often >100,000/mm³ (polymorphonuclear leukocytes >75%)

Gonococcal arthritis

History	Exam	1st Test	Other tests
fever, chills, malaise, involvement of predominantly lower-extremity joints (knees, ankles), urethritis	mono- or oligoarthritis, tenosynovitis (wrists, fingers, ankles, toes), pustular or vesiculopustular skin lesions	»**needle joint aspiration:** identification and recovery of *Neisseria gonorrhoeae* from synovial fluid (extremely uncommon); microscopic	

Common

Gonococcal arthritis

History	Exam	1st Test	Other tests
		examination and culture of synovial fluid in Thayer-Martin medium Diagnosis can also be established by DNA probe of fluid from the affected joint. »**blood cultures:** recovery of *N gonorrhoeae* Blood culture on Thayer-Martin medium. Positive in 50% of cases.[99] »**culture of skin lesion aspirate; urethral, cervical, rectal, or oropharyngeal cultures:** recovery of *N gonorrhoeae* »**urethral discharge Gram stain:** gram-negative diplococci	

◊ Rheumatoid arthritis

History	Exam	1st Test	Other tests
pain, swelling, and morning stiffness for at least 30-60 minutes	swelling and tenderness of metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints; symmetric polyarthritis of small and large joints; rheumatoid nodules; later characteristic deformities include subluxations at wrist and MCP joints, ulnar deviation of fingers, swan-neck and boutonniere deformities	»**serum rheumatoid factor (RF):** positive The sensitivity of RF is 26%, with a specificity of 60%.[54] »**serum antibodies to cyclic citrullinated peptides (CCP):** positive Anti-CCP antibodies have a higher sensitivity and specificity for RA than	»**ultrasound scan:** synovial proliferation; joint effusion; joint erosion; increased power Doppler signal (increased vascularity in synovitis)[92] [102] »**hand MRI scan:** bone edema; synovial enhancement; bone erosion »**multibiomarker disease activity (MBDA) score:** predicts radiographic

Common

◊ Rheumatoid arthritis

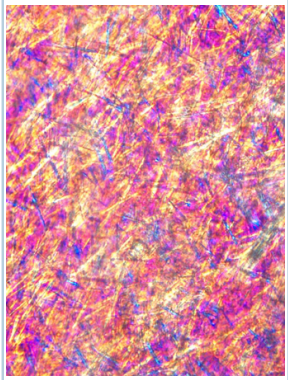
History	Exam	1st Test	Other tests
	of fingers, Z-deformities of thumbs	rheumatoid factor, at 99.4% and 66%, respectively.[55] »**ESR:** elevated in untreated cases »**serum CRP:** elevated in untreated cases »**hand x-ray:** soft tissue swelling, periarticular osteopenia, joint space narrowing, erosions of cartilage and bone around metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints Often seen in more advanced disease, but are not specific for RA.	joint damage at baseline and during disease course; low disease activity (<30), moderate disease activity (30-44), and high disease activity (>44)[103] [104]

◊ Gout

History	Exam	1st Test	Other tests
typically an obese, hypertensive man age between 30 and 50 years, may have history of frequent alcohol consumption	redness, warmth, swelling, and exquisite tenderness of the affected joint(s)	»**compensated polarized light microscopy of synovial fluid:** negatively birefringent, needle-shaped intra- and extracellular monosodium urate (MSU) crystals US guidelines recommend synovial fluid analysis when diagnostic testing is necessary in patients with possible acute gout.[45] MSU crystals can also be seen on polarized light	»**ultrasound scan:** synovial proliferation; joint effusion; joint erosion; increased power Doppler signal (increased vascularity in synovitis); characteristic "double contour" sign, indicating chronic urate frosting on the surface of articular cartilage; intra-articular and extra-articular (tendons, ligaments, and soft tissues) tophi ("wet sugar clumps" or "snow storm" appearance)[108] [109] [110]

Common

◊ Gout

History	Exam	1st Test	Other tests
		microscopy of material obtained from tophus aspirate.  *Monosodium urate crystals from a tophus (polarized light microscopy)* *From the collection of Dr Soumya Chatterjee* UK guidance recommends consideration of joint aspiration and microscopy of synovial fluid if a diagnosis of gout remains uncertain or unconfirmed following measurement of serum urate level in those with signs and symptoms of gout.[31] »**serum urate:** >360 micromol/L (6 mg/dL) UK guidance states that a serum urate level of 360 micromol/L (6 mg/dL) or more confirms the diagnosis in those with signs	»**dual energy CT (DECT) scan:** distinct attenuation of MSU deposits color-coded in green[108] [111]

Common

◊ Gout

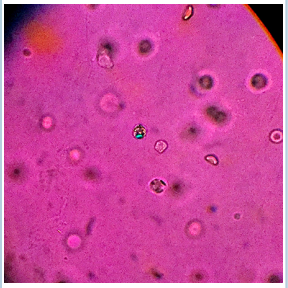
History	Exam	1st Test	Other tests
		and symptoms of gout.[31] If the serum urate level is below 360 micromol/L (6 mg/dL) during a flare and gout is strongly suspected, serum urate measurement should be repeated at least 2 weeks after the flare has settled.[31] Consideration should be given to joint aspiration and microscopy of synovial fluid if a diagnosis of gout remains uncertain or unconfirmed.[31] »**x-ray of hand, foot:** bone erosions may be subtle; characteristic overhanging edges	

◊ Pseudogout

History	Exam	1st Test	Other tests
acute onset; mono- or oligoarthralgia; may be preceded by trauma, surgery, intercurrent illness	knee most often affected; also wrists, metacarpophalangeal joints, shoulders, elbows; joints are warm, swollen, often with effusions	»**needle joint aspiration:** WBC 15,000-30,000/mm^3, 90% neutrophils »**compensated polarized light microscopy of synovial fluid:** weakly positively birefringent crystals of calcium pyrophosphate dihydrate (CPPD), crystals phagocytosed within polymorphonuclear leukocytes	»**ultrasound scan:** synovial proliferation; joint effusion; joint erosion; increased power Doppler signal (increased vascularity in synovitis); characteristic "pseudo double contour" sign, indicating chronic calcium pyrophosphate deposition within the substance of the articular cartilage; hyperechoic sparkling spots within articular fibrocartilage or mobile intra-articular

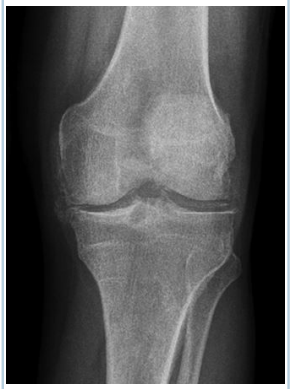
Common

◊ Pseudogout

History	Exam	1st Test	Other tests
		The presence of CPPD crystals in joint fluid does not exclude concomitant infection.  *Calcium pyrophosphate dihydrate (CPPD) crystals in synovial fluid under compensated polarized light microscopy* *From the collection of Dr Soumya Chatterjee* »**x-ray of joint:** chondrocalcinosis (calcification in fibrocartilage and hyaline cartilage)	hyperechoic deposits also suggest calcium pyrophosphate dihydrate crystal deposition disease[112]

Common

◊ Pseudogout

History	Exam	1st Test	Other tests
		 *Chondrocalcinosis (lateral meniscus of left knee)* *From the collection of Dr Soumya Chatterjee*	

◊ Psoriatic arthritis

History	Exam	1st Test	Other tests
joint pain and swelling, morning stiffness lasting >30 minutes	asymmetric small and/or large joint oligo- or polyarthritis (clinical synovitis), nail pitting, and hyperkeratosis, onycholysis	»**x-ray of hand, foot:** acro-osteolysis, fluffy periostitis, and new bone formation at the site of entheses; gross destruction of isolated joints, pencil-in-cup appearance (arthritis mutilans), both joint lysis and ankylosis[113]	»**ultrasound scan:** proliferative synovitis shows as joint space widening with clusters of soft echoes (bushy and villous appearance) and/or homogeneous synovial thickening; bone erosion shows as intra-articular discontinuity of the bone surface visible in two perpendicular planes[113] [114] [115] »**MRI:** subchondral bone edema is characteristically observed[113] Abnormal findings can occur in asymptomatic patients or those with

DIAGNOSIS

Common

◊ Psoriatic arthritis

History	Exam	1st Test	Other tests
			early pre-radiographic sacroiliitis.

Uncommon

Indolent infections

History	Exam	1st Test	Other tests
chronic infection, joint pain and swelling	joint swelling and tenderness, usually monoarthropathy	»**joint aspiration:** may show acid-fast bacillus with special preparation and stains, fungal elements Ziehl-Neelsen stain of the synovial fluid to detect acid-fast bacilli (AFB) may be helpful. Cultures for AFB on conventional Lowenstein-Jensen or Middlebrook 7H10 media may take 6-8 weeks before becoming positive. Preferred media: MGIT (Mycobacteria Growth Indicator Tube) »**blood culture:** growth of causative organism	»**synovial biopsy:** identification of organism (on special stains and culture); caseating or noncaseating granulomas may be seen

◊ Parvoviral syndrome

History	Exam	1st Test	Other tests
acute onset, pain in multiple joints, flu-like prodrome, rash	arthralgia in symmetric rheumatoid arthritis-like distribution, erythematous macular rash	»**serum IgM and IgG antibodies:** positive Detectable levels of B19-specific IgM can be found within 7-10	»**qualitative polymerase chain reaction testing:** Additional testing may include detection of viral nucleic acid

Uncommon

◊ Parvoviral syndrome

History	Exam	1st Test	Other tests
		days of parvovirus exposure and remain measurable for several months.[88]	(parvovirus B19 DNA) in blood by qualitative polymerase chain reaction (PCR) testing[100] This test is critical in immunocompromised patients because they may not test positive for IgM and IgG antibodies.

◊ Lyme disease

History	Exam	1st Test	Other tests
intermittent knee pain and swelling, antecedent tick bite, rash	bull's-eye rash (erythema migrans), central clearing, vesicles; monoarthritis involving knee, shoulder, ankle, elbow, temporomandibular joint, wrist	»**sensitive enzyme immunoassay or immunofluorescence assay:** positive for Borrelia antibodies. A positive result should be confirmed by a Western blot immunoassay or a second sensitive enzyme immunoassay[84]	»**Western blot testing for Borrelia burgdorferi:** positive (confirmatory) The CDC criteria for a positive Western blot are as follows. For IgM, 2 of the following 3 bands: OspC (22-25), 39, and 41. For IgG, 5 of the following 10 bands: 18, OspC (22-25), 28, 30, 39, 41, 45, 58, 66, and 93.[101]

◊ Juvenile idiopathic arthritis (oligo-articular type)

History	Exam	1st Test	Other tests
more likely to be female, joint pain >6 weeks' duration, seen in childhood	≤4 joints, rash, enthesitis, uveitis	»**CBC:** normal or reduced hemoglobin and elevated platelets »**ESR:** normal or elevated »**CRP:** normal or elevated	»**x-ray of affected joint:** soft-tissue swelling; joint-space narrowing or erosions

Uncommon

◊ Juvenile idiopathic arthritis (oligo-articular type)

History	Exam	1st Test	Other tests
		»**serum antinuclear antibodies (ANA):** positive or negative	

◊ Acute rheumatic fever (ARF)

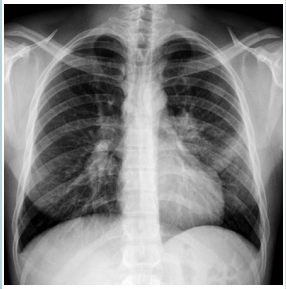
History	Exam	1st Test	Other tests
latent period following sore throat; adult or child; joints affected serially in quick succession	joint pain and swelling; knees and ankles are usually involved first; subcutaneous nodules, rash (erythema marginatum)	»**throat culture for group A beta-hemolytic streptococci or rapid streptococcal antigen test:** positive for group A beta-hemolytic *Streptococcus* »**serum antistreptolysin O (ASO):** elevated or rising titer If the ASO titer is negative, testing for other antistreptococcal antibodies, such as anti-DNAse B, antistreptokinase, and antihyaluronidase, should be performed. »**x-ray of chest:** cardiomegaly	»**ECG:** heart block, prolonged PR interval »**echocardiography:** cardiomegaly[78] »**serum anti-DNAse B, antistreptokinase, and antihyaluronidase:** positive

◊ Sarcoidosis

History	Exam	1st Test	Other tests
joint pain in knees or ankles	warm, swollen, and tender joints; tendinitis, enthesopathy (inflammation of the entheses, the location where a bone has an insertion to a tendon or a ligament), dactylitis	»**serum ACE:** level elevated »**x-ray of chest:** bilateral hilar adenopathy, right paratracheal adenopathy, pulmonary reticular opacities	»**PET scan:** may reveal occult sarcoid lesions »**synovial biopsy:** may be nonspecific, or show typical sarcoid granulomata

Uncommon

◊ Sarcoidosis

History	Exam	1st Test	Other tests
	(sausage digit); erythema nodosum	 *Pulmonary sarcoidosis: right paratracheal, bilateral perihilar, and subcarinal adenopathy* *From the collection of Dr Soumya Chatterjee*	

◊ Spondyloarthropathy

History	Exam	1st Test	Other tests
back pain, associated enteropathy, more common in males, onset is typically in late teens to early 20s	asymmetric joint tenderness and swelling in lower extremities; uveitis	»**x-ray of pelvis:** sacroiliac joint irregularity (especially lower part), widening, erosions, and ankylosis at a later stage	»**MRI scan of pelvis:** evidence of sacroiliitis (bone edema, erosions)[105]

◊ Systemic lupus erythematosus (SLE)

History	Exam	1st Test	Other tests
commonly females (typical onset at age 20-30 years); polyarthralgia, with minimal swelling	moderate tenderness and stiffness with joint manipulation, malar rash, discoid rash, alopecia, oral ulcers	»**antinuclear antibodies (ANA):** ≥1:160 dilution ANA is positive in significant titer in nearly all patients with SLE.[106]	»**x-ray of hand:** ulnar deviation of the MCP joints, swan neck deformities, but no erosions (Jaccoud arthropathy) »**urinalysis:** presence of blood and protein (in lupus nephritis)

DIAGNOSIS

Uncommon

◊ Systemic lupus erythematosus (SLE)

History	Exam	1st Test	Other tests
		»**antibodies to double-stranded DNA:** positive Highly specific for SLE.[63] [64] »**anti-Smith (Sm) antibodies:** positive Highly specific for SLE.[63] [64]	»**urine microscopy:** RBC or mixed casts, dysmorphic RBCs (in lupus nephritis)

◊ Adult-onset Still disease (AOSD)

History	Exam	1st Test	Other tests
daily fever ≥102°F (≥39°C); sore throat, joint pain and swelling	nonpruritic, macular or maculopapular truncal rash of salmon pink color with Koebner phenomenon; pericardial rub	»**CBC with differential:** WBC ≥10,000/mm³, with at least 80% neutrophils; thrombocytosis, anemia »**serum albumin:** hypoalbuminemia »**serum hepatic enzymes:** often there is elevation in aspartate and alanine aminotransferase and lactate dehydrogenase »**serum ferritin:** >3000 nanograms/mL (normal 40-200 nanograms/mL) Elevation of ferritin correlates with disease activity. »**x-ray of wrist:** nonerosive narrowing of carpometacarpal and intercarpal joint spaces of wrist Fusion of the wrist joints is characteristic of AOSD, although it occurs in only a minority of patients.[71]	»**bone marrow biopsy:** numerous, well-differentiated macrophages (histiocytes) that are involved in phagocytosis of hematopoietic elements Bone marrow examination demonstrates pathognomonic macrophage activation in 12% of patients.[72]

Uncommon

◊ Adult-onset Still disease (AOSD)

History	Exam	1st Test	Other tests
		»**x-ray of chest:** pleural effusion and/or transient pulmonary infiltrate Occur in 30% to 40% of patients.[69] [70]	

◊ Reactive arthritis

History	Exam	1st Test	Other tests
lag period between infection and onset of arthralgia; dysuria, pelvic pain	asymmetric mono- or oligoarthritis, most commonly in lower extremities; dactylitis, conjunctivitis, anterior uveitis, oral ulcers, keratoderma blennorrhagica, circinate balanitis	»**urine screen for Chlamydia:** may be positive Rapid, noninvasive, and specific. »**stool cultures for enteric microbes:** may grow causative organism By the time arthritis develops, stool cultures are usually negative. »**serology for etiologic organism:** *Yersinia* , *Salmonella* , *Campylobacter* , and *Chlamydia* cause strong antibody responses	»**HLA-B27 testing:** positive HLA-B27 testing is useful prognostically as HLA-B27-positive patients have more severe and prolonged duration of arthritis and are more likely to develop chronic spondyloarthritis. Prevalence in patients with reactive arthritis is <50%.[107]

◊ Ankylosing spondylitis (AS)

History	Exam	1st Test	Other tests
low back pain for >3 months, stiffness, improves with exercise but not with rest	groin pain (indicating hip arthritis), shoulder pain and shoulder stiffness, sacroiliac (SI) tenderness with limited range of motion and pain on movement; SI joint pain with flexion, abduction, and external rotation of the	»**HLA-B27 testing:** positive Among white people, HLA-B27 is present in 95% of AS patients. HLA-B27 is more useful for diagnosis in patients who have chronic low back pain, where a	»**MRI of sacroiliac (SI) joint:** increased T2-weighted signal from bone and bone marrow adjacent to SI joint (bone marrow edema) The most sensitive and specific test in detecting the changes

Uncommon

◊ Ankylosing spondylitis (AS)

History	Exam	1st Test	Other tests
	corresponding hip joint (Patrick test)	positive result for HLA-B27 is associated with a 30% to 60% chance of having AS.[74] »**x-ray of sacroiliac (SI) joint:** SI joint irregularity, widening, erosions, sclerosis; ankylosis in advanced disease, with complete obliteration of SI joint space »**x-ray of lumbar, thoracic, and cervical spine:** squaring of vertebral bodies, bridging syndesmophytes, ankylosis of facet joints and calcification of anterior longitudinal ligament, anterior atlantoaxial (C1-C2) subluxation	of sacroiliitis. Indicated when plain radiographs are normal but suspicion of AS is high. For these early cases, MRI has a sensitivity of 60%.[76]

◊ Osteoarthritis

History	Exam	1st Test	Other tests
joint pain, age commonly >50 years, obesity, minimal morning stiffness (gelling phenomenon)	PIP, DIP, first CMC joint, hip, and knee tenderness; limited range of motion, misalignment of joints	»**CRP:** normal »**ESR:** normal »**x-ray of affected joint:** joint-space narrowing, new bone formation (osteophytes), subchondral sclerosis, cysts; in erosive osteoarthritis: erosions, gull-wing deformity; saw-tooth deformity; ankylosis	

Uncommon

Trauma

History	Exam	1st Test	Other tests
prior trauma, joint pain and swelling	joint swelling, ecchymosis, tenderness with manipulation of extremity, restricted and painful range of motion	»**x-ray of affected joint:** fracture through joint line, subluxation, soft-tissue swelling »**needle aspiration of joint:** hemorrhagic effusion (red, pink, or brown) »**MRI of affected joint:** may demonstrate cartilage injury, ligament rupture	»**aspiration of joint:** lipohemarthrosis (presence of lipid globules and blood) »**CT of affected joint:** may show bony and/or soft-tissue injury »**MRI of affected joint:** may show bony and/or soft-tissue injury; better visualization of soft tissues than CT

Nontraumatic hemarthrosis

History	Exam	1st Test	Other tests
joint pain; may be history of underlying bleeding disorder, sickle cell anemia, pigmented villonodular synovitis, synovioma, ruptured aneurysm, AV fistula, hemangioma, Charcot joint, anticoagulant therapy, scurvy	swollen, warm, very painful joint; restricted and painful range of motion	»**needle aspiration of joint:** hemorrhagic effusion (red, pink, or brown)	»**arthroscopy and synovial biopsy:** intra-articular abnormality Pathologic diagnosis on biopsy.

Hypertrophic osteoarthropathy

History	Exam	1st Test	Other tests
painful and swollen joints (wrists, ankles, knees), distal long bone pain	clubbing, roughening of skin, swollen joints, pachydermoperiostosis	»**CBC:** may show anemia »**x-ray of affected joint:** periosteal reaction; hypervascularization of digits	»**isotope bone scan:** increased uptake in areas of periosteal reaction

Uncommon

Intra-articular metastatic cancer

History	Exam	1st Test	Other tests
joint pain and swelling >6 weeks, known malignancy	joint swelling, warmth, and tenderness; typically monoarthritis	»**joint fluid cytology:** positive	»**synovial biopsy:** pathology of underlying malignancy

Synovial sarcoma

History	Exam	1st Test	Other tests
age 30-40 years, joint pain and swelling	joint swelling in lower extremities	»**joint fluid cytology:** positive	»**synovial biopsy:** synovial sarcoma

◊ Arbovirus infections (e.g., chikungunya)

History	Exam	1st Test	Other tests
history of travel to endemic areas; fever, rash, myalgias, headache, and arthralgias 2-10 days after mosquito bite (typically *Aedes albopictus*)	fever and rash at early stage; arthritis resembling rheumatoid arthritis involving small joints of hands, feet, wrists, and ankles	»**viral culture:** positive Performed on an acute-phase specimen of serum. »**reverse transcriptase (RT)-PCR to detect viral RNA:** positive Performed on an acute-phase specimen of serum.	»**antibody tests:** positive Antibody tests of serum including ELISA; immunofluorescence assays; plaque-reduction neutralization test. Chikungunya is a biosafety level 3 agent that requires special laboratory containment because of risk of laboratory-acquired infections.

◊ Inflammatory bowel disease (ulcerative colitis and Crohn disease)

History	Exam	1st Test	Other tests
abdominal pain, bloody diarrhea, tenesmus, mucus in stool, peripheral large joint oligoarthritis, inflammatory back pain (sacroiliitis) may be	pallor, abdominal tenderness and distension, perianal and abdominal wall fistulas; peripheral large joint clinical synovitis (knees, ankles); clinical evidence of sacroiliitis	»**colonic biopsy and/or small bowel biopsy:** continuous distal disease, mucin depletion, basal plasmacytosis, diffuse mucosal atrophy, absence of	»**ESR:** elevated »**CRP:** elevated »**CBC:** reduced hemoglobin and elevated platelets »**stool studies:** fecal RBCs and

Uncommon

◊ Inflammatory bowel disease (ulcerative colitis and Crohn disease)

History	Exam	1st Test	Other tests
present, enthesitis, dactylitis	joint pain, enthesitis, dactylitis	granulomata, and anal sparing (ulcerative colitis); mucosal bowel biopsies demonstrate transmural involvement with noncaseating granulomas (Crohn disease)	leukocytes; elevated fecal calprotectin

◊ Celiac disease

History	Exam	1st Test	Other tests
weight loss, fatigue, bloating, failure to thrive, diarrhea, fatty stools, blistering itchy rash	low BMI, pallor, abdominal distension; blistering rash over elbows, knees, sacral area, and buttocks (dermatitis herpetiformis)	»**serum anti-transglutaminase, anti-endomysial, and anti-gliadin antibodies:** positive	»**small bowel (duodenal) biopsy:** subtotal villous atrophy, reversible with gluten-free diet Confirms the diagnosis.

◊ Whipple disease

History	Exam	1st Test	Other tests
arthralgias, oligo- or polyarthritis, hyperpigmentation, weight loss, abdominal pain, fatigue, bloating, failure to thrive, diarrhea, neurologic manifestations	low BMI, pallor, abdominal distension, hyperpigmentation, lymphadenopathy, joint tenderness with or without frank clinical synovitis in multiple joints	»**upper endoscopy with duodenal biopsy:** duodenal mucosa may appear macroscopically pale yellow with clumsy and dilated villi and ectatic lymph vessels Should include analysis of the specimen for periodic acid-Schiff staining and PCR +/- immunohistochemistry staining for *T whipplei* . Fluid and/or tissue from synovium, cerebrospinal fluid, or	»**Tropheryma whipplei PCR on blood:** positive

DIAGNOSIS

Uncommon

◊ Whipple disease

History	Exam	1st Test	Other tests
		affected lymph nodes may also be used.	

◊ Bowel-associated dermatosis arthritis syndrome

History	Exam	1st Test	Other tests
prior history of a gastric or intestinal bypass procedure (e.g., roux-en-Y gastric bypass, jejuno-ileal bypass, bilio-pancreatic diversion, or Billroth II gastrectomy); polyarthralgia/joint swelling, fever[116] [117]	clinical synovitis of small and large joints (symmetric or asymmetric); tenosynovitis may also occur; skin lesions may develop (ulcerating lesions and pustules on the trunk and extremities)[116] [117]	»**ESR and CRP:** elevated »**rheumatoid factor (RF) and antinuclear antibodies (ANA):** usually negative	»**x-rays:** may rarely show erosive arthritis »**skin biopsy:** evidence of neutrophilic dermatosis »**synovial fluid analysis:** mild to moderate inflammation (with lymphocyte or neutrophil predominance)

◊ Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome

History	Exam	1st Test	Other tests
presents with joint pain and swelling; back pain; palmoplantar pustulosis; acne	sternoclavicular joint swelling, redness, tenderness; palmoplantar pustulosis; acne	»**radiography:** suggestive Radiographs may reveal evidence of sternoclavicular joint arthritis, and lytic, sclerotic, and hyperostotic bone lesions.	»**isotope bone scan:** positive Positive isotope bone scan indicates increased uptake. »**MRI:** positive MRI scans may be necessary for more subtle lesions of inflammation.

◊ Drug-induced

History	Exam	1st Test	Other tests
history of exposure to relevant drugs: procainamide, hydralazine,	rash, fever, urticaria (serum sickness); other features of lupus (if drug-induced	»**ANA:** positive in drug-induced lupus	

Uncommon

◊ Drug-induced

History	Exam	1st Test	Other tests
minocycline, isoniazid, tumor necrosis factor inhibitors, etc. (drug-induced lupus); various oral and parenteral pharmacologic agents, including plasma-derived products and biologics (serum sickness-like reaction); aromatase inhibitors, clopidogrel, quinolone antibiotics, statins, and dipeptidyl peptidase (DPP)-4 inhibitors (arthralgia, inflammatory arthritis, and tendinitis); immune checkpoint inhibitors (inflammatory arthritis and tenosynovitis)	lupus); tendinitis and tendon rupture (quinolone antibiotics); inflammatory arthritis and tenosynovitis (immune checkpoint inhibitors)	»**antihistone antibodies:** positive in drug-induced lupus »**double-stranded DNA:** negative Positive ANA and antihistone antibodies, but usually negative double-stranded DNA antibodies (drug-induced lupus).	

◊ Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome

History	Exam	1st Test	Other tests
acute-onset polyarthritis; males ≥50 years of age	clinical synovitis; significant pitting edema of the dorsal surface of hands and feet	»**ESR:** elevated »**CRP:** elevated »**serum rheumatoid factor (RF):** negative	»**x-ray of affected joint:** usually no erosions

◊ Ebola virus

History	Exam	1st Test	Other tests
history of residence in or travel to an Ebola-endemic area in the 21 days before onset of illness; secondary exposure (human-to-human or primate-to-human exposure)	fever, pharyngitis, myalgia, severe headache, abdominal pain, vomiting, diarrhea, or unexplained bleeding or bruising; maculopapular rash on trunk (may be present around day 5 of infection); bilateral conjunctival	»**reverse transcriptase (RT)-PCR to detect viral DNA:** positive	»**antigen-capture enzyme-linked immunosorbent assay (ELISA):** positive for Ebola virus RNA Can be used to confirm the diagnosis along with a positive RT-PCR result.

Uncommon

◊ Ebola virus

History	Exam	1st Test	Other tests
	infection; bleeding from intravenous puncture sites and mucous membranes		»**CBC:** thrombocytopenia; marked lymphopenia; decreased hemoglobin (if bleeding manifestations) »**IgM and IgG antibodies:** positive

◊ Diffuse tenosynovial giant cell tumor (formerly, diffuse pigmented villonodular synovitis)

History	Exam	1st Test	Other tests
twice as common in males; age 20-50 years; sudden onset; entire synovium affected; typically occurs in large joints such as the knee (80% of cases) or hip	unexplained joint swelling (effusion), pain, warmth, and tenderness; decreased motion; increased pain and locking of the joint occur with disease progression	»**MRI scan:** nodular intra-articular masses that demonstrate low signal intensity on T1-, T2-, and proton-density sequences	»**plain x-ray:** detects calcifications »**CT:** hyperdense soft-tissue mass in the joint or tendon sheath »**histopathology:** nodules and/or villi with abundant (pigmented) hemosiderin-laden macrophages

◊ Localized tenosynovial giant cell tumor (formerly, localized pigmented villonodular synovitis)

History	Exam	1st Test	Other tests
predominantly occurs in females; age 20-50 years; sudden onset; typically occurs in small joints such as the hands and feet	slow-growing mass; painless, becoming symptomatic	»**MRI scan:** nodular intra-articular masses that demonstrate low signal intensity on T1-, T2-, and proton-density sequences	»**plain x-ray:** detects calcifications »**CT:** hyperdense soft-tissue mass in the joint or tendon sheath »**histopathology:** nodules and/or villi with abundant (pigmented) hemosiderin-laden macrophages

Uncommon

◊ Synovial osteochondromatosis

History	Exam	1st Test	Other tests
chronic, progressive pain; swelling of the affected joint exacerbated by physical activity; locking of the affected joint can occur	joint effusion; tenderness; limited range of motion; clicking, grating, or locking (due to intra-articular bodies within the affected joint); grinding and popping; osteochondral nodules (close to the skin) in knee, ankle, or elbow	»**CT scan with radiography:** multiple, smooth, oval-shaped calcified masses within the joint space or bursa	»**histopathology:** cartilaginous bodies or osteocartilaginous bodies with central ossification, typically spherical

◊ Amyloid arthropathy

History	Exam	1st Test	Other tests
commonly presents as shoulder pain or carpal tunnel syndrome	juxta-articular soft-tissue swelling; osteolytic bone lesions (amyloidomas); symptoms commonly bilateral	»**synovial biopsy and synovial fluid analysis:** positive on Congo red staining	»**x-ray:** demonstrates erosive and destructive arthropathy; osteolytic bone lesions (amyloidomas) »**MRI:** extensive deposition of an abnormal soft tissue that has low or intermediate signal intensity on T1- and T2-weighted images

◊ Fibroblastic rheumatism

History	Exam	1st Test	Other tests
relatively acute onset; appearance of cutaneous nodules, flexion contractures, and polyarthritis[118] [119]	multiple erythematous cutaneous nodules; multiple joint swelling, tenderness, and flexion contractures	»**skin and synovial biopsy:** fibroblastic proliferation associated with a collagenous stroma	»**x-ray of small joints of hands and feet:** demonstrates an erosive arthropathy

◊ Multicentric reticulohistiocytosis (MRH)

History	Exam	1st Test	Other tests
progressive painful and deforming arthropathy of hands and feet	tender and swollen MCP, PIP, and DIP joints; multiple firm		»**skin and synovial biopsy:** biopsy of cutaneous nodules

Uncommon

◊ Multicentric reticulohistiocytosis (MRH)

History	Exam	1st Test	Other tests
and more proximal joints; multiple skin nodules[118]	reddish-brown papules and nodules over the dorsum of the hands and in the fingers, with the classical “coral beads” appearance around the nailbeds		shows mononuclear histiocytes and multinucleated giant cells 50–100 mm in diameter, with eosinophilic, periodic acid-Schiff (PAS) positive cytoplasm, that has a fine granular appearance »**x-ray of small joints of hands and feet:** demonstrates a severe erosive arthropathy affecting wrists, MCP, PIP, and DIP joints

Key articles

- Hazlewood GA, Aletaha D, Carmona L, et al. Algorithm for identification of undifferentiated peripheral inflammatory arthritis: a multinational collaboration through the 3e initiative. J Rheumatol Suppl. 2011 Mar;87:54-8. Abstract
- Qaseem A, McLean RM, Starkey M, et al. Diagnosis of acute gout: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2017 Jan 3;166(1):52-7. Full text (http://annals.org/aim/fullarticle/2578527/diagnosis-acute-gout-clinical-practice-guideline-from-american-college-physicians) Abstract
- Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010 Sep;62(9):2569-81. Full text (https://onlinelibrary.wiley.com/doi/full/10.1002/art.27584) Abstract
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Images

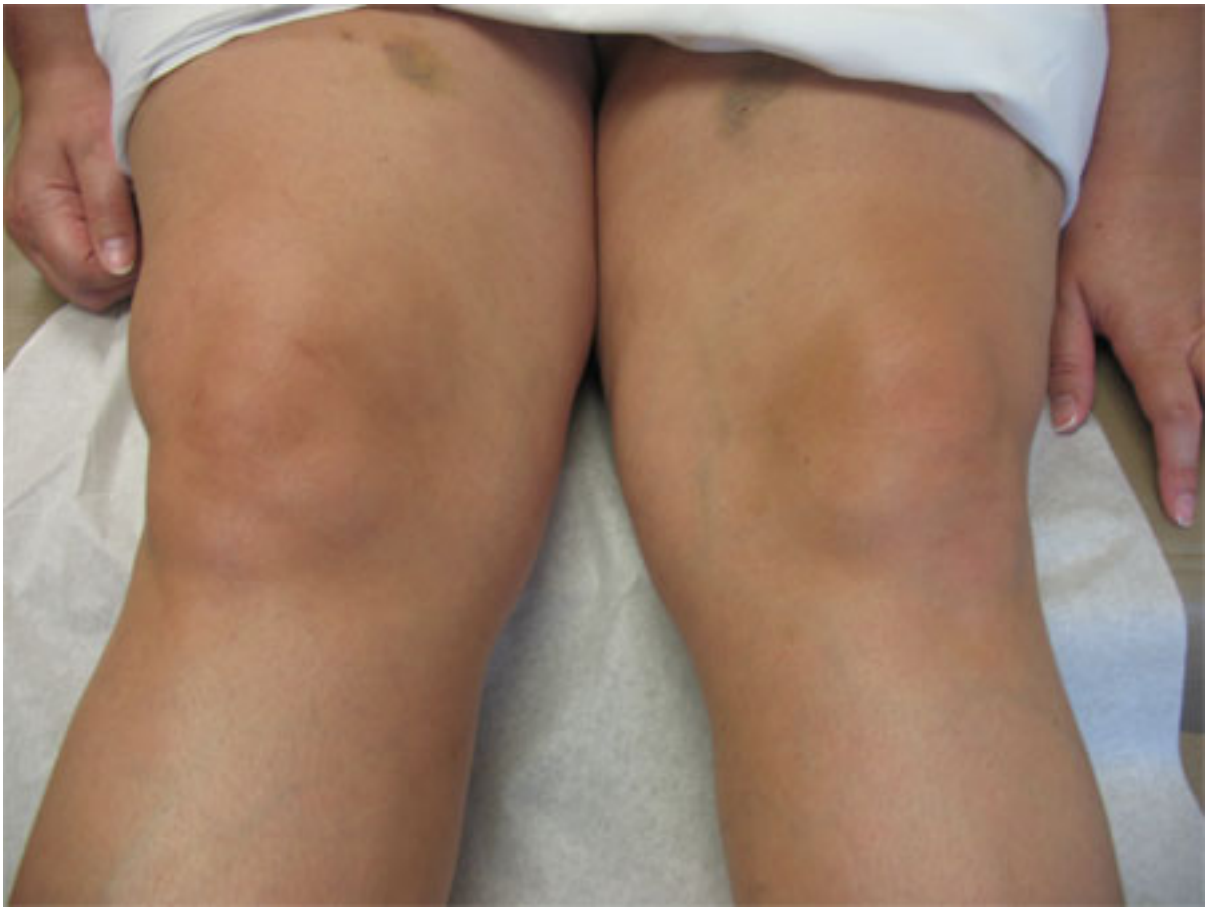

Figure 1: Acute monoarthritis of the right knee

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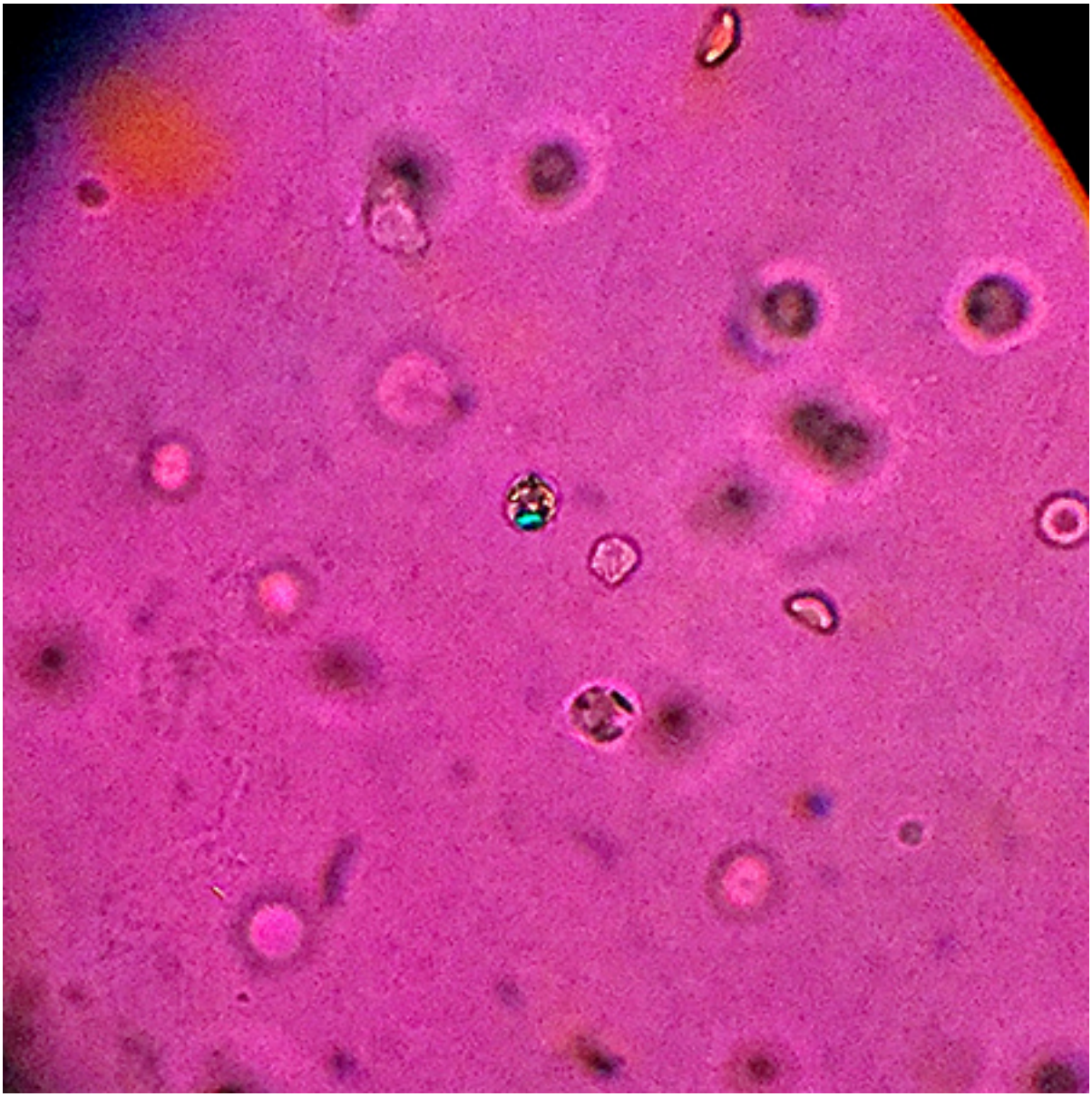

Figure 2: Calcium pyrophosphate dihydrate (CPPD) crystals in synovial fluid under compensated polarized light microscopy

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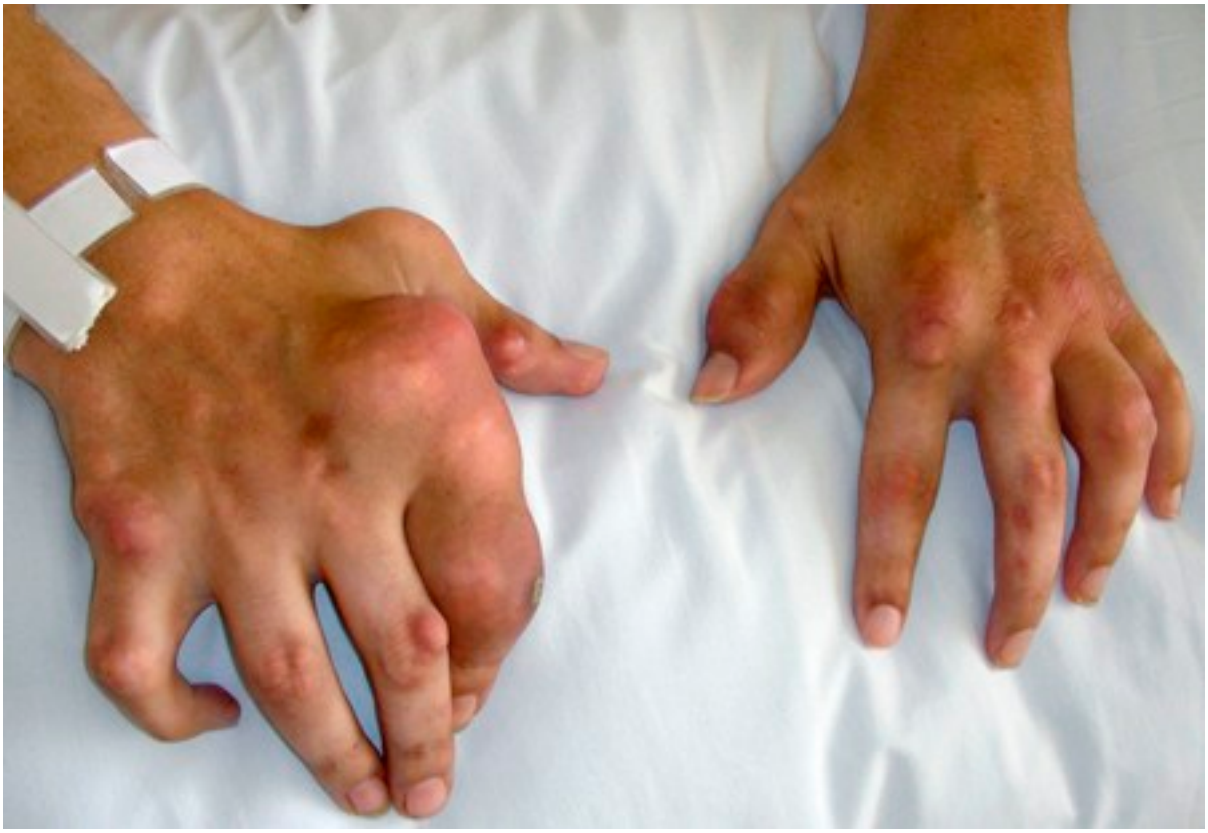

Figure 3: Tophaceous gout

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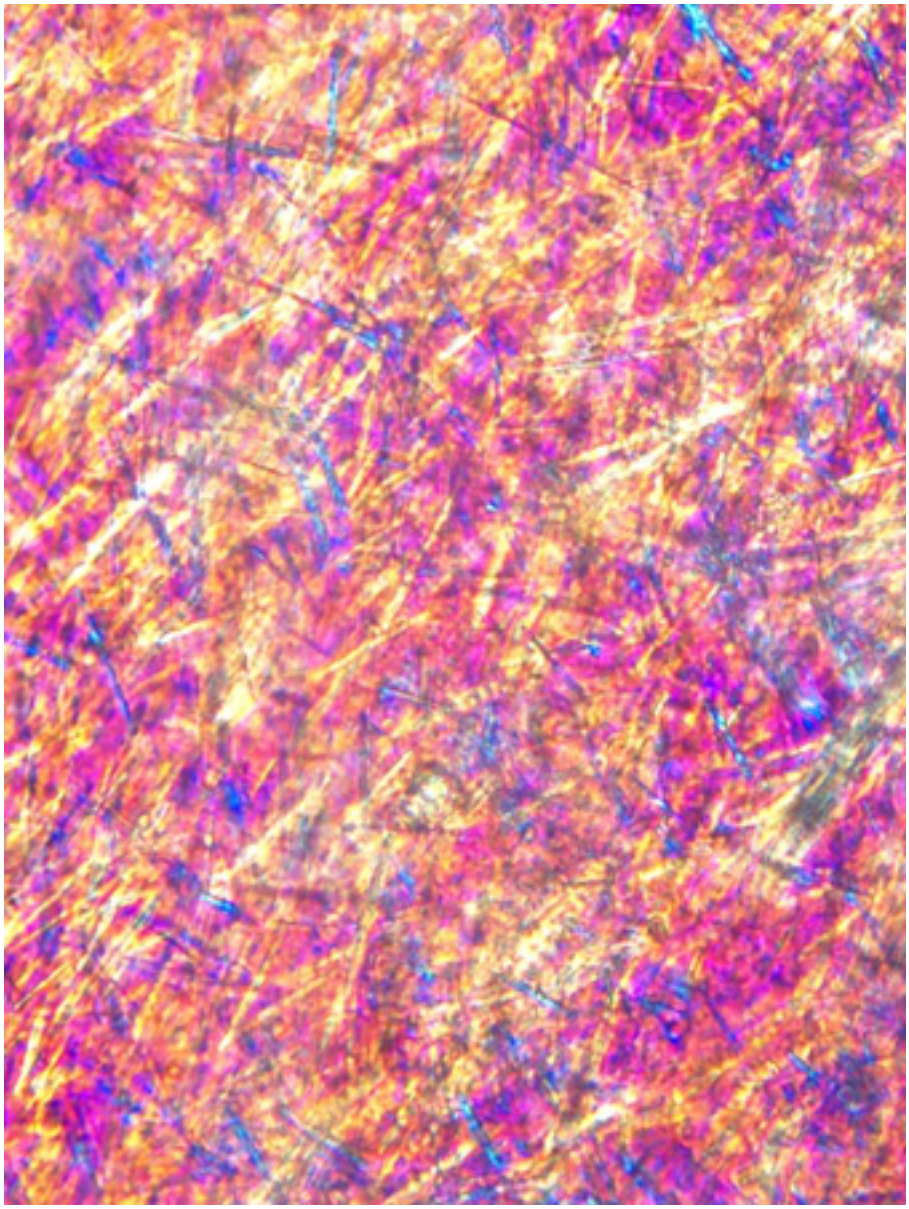

Figure 4: Monosodium urate crystals from a tophus (polarized light microscopy)

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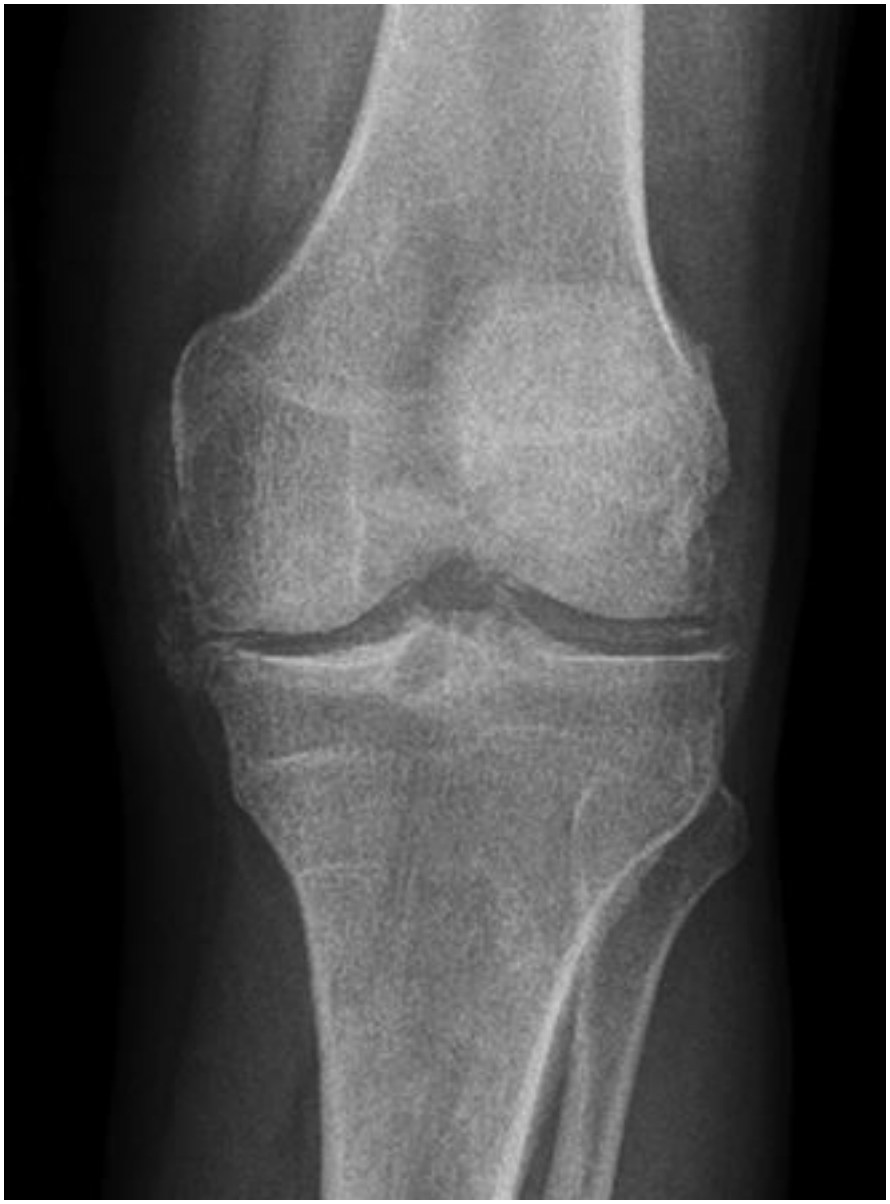

Figure 5: Chondrocalcinosis (lateral meniscus of left knee)

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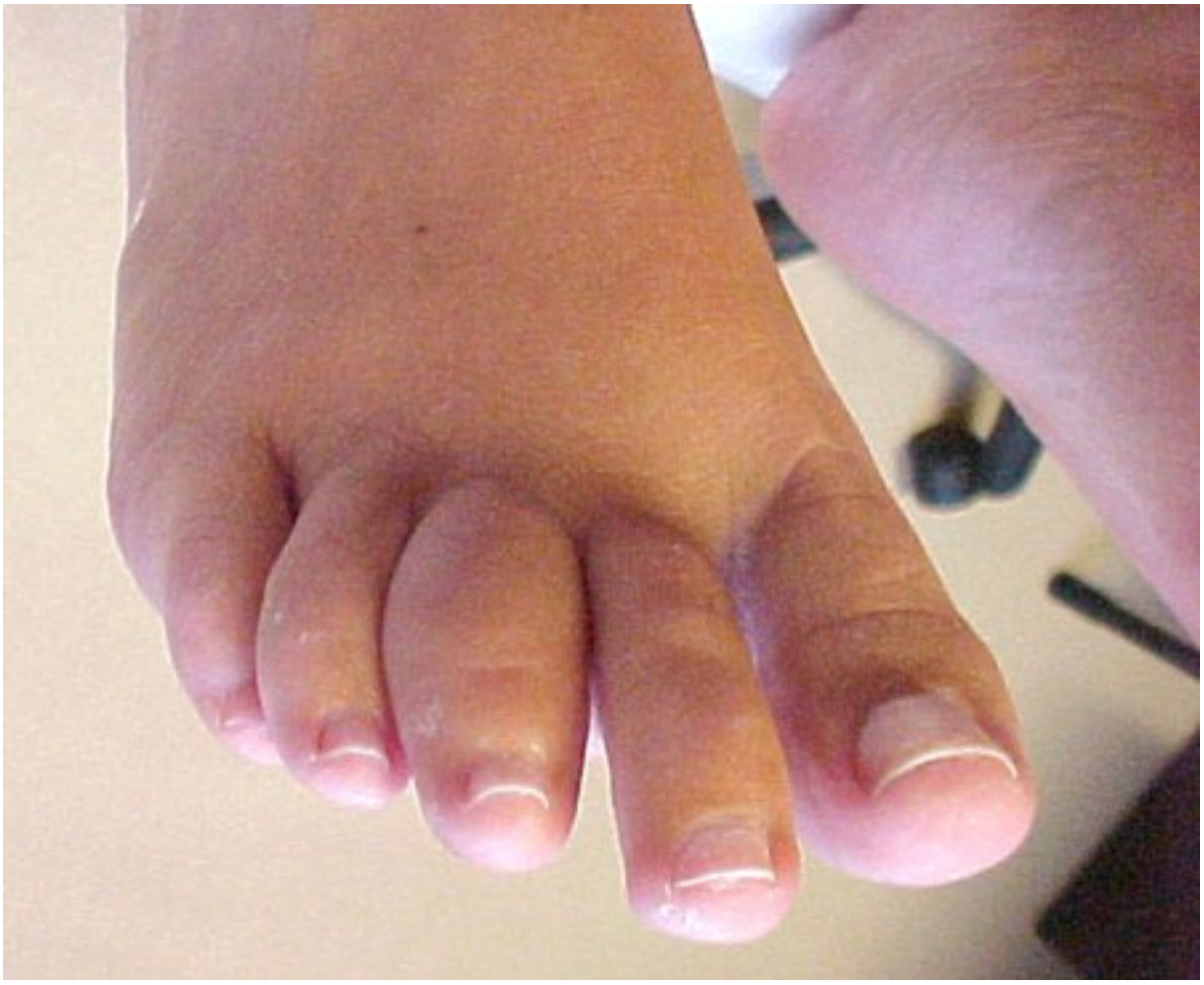

Figure 6: Dactylitis of right third toe (reactive arthritis)

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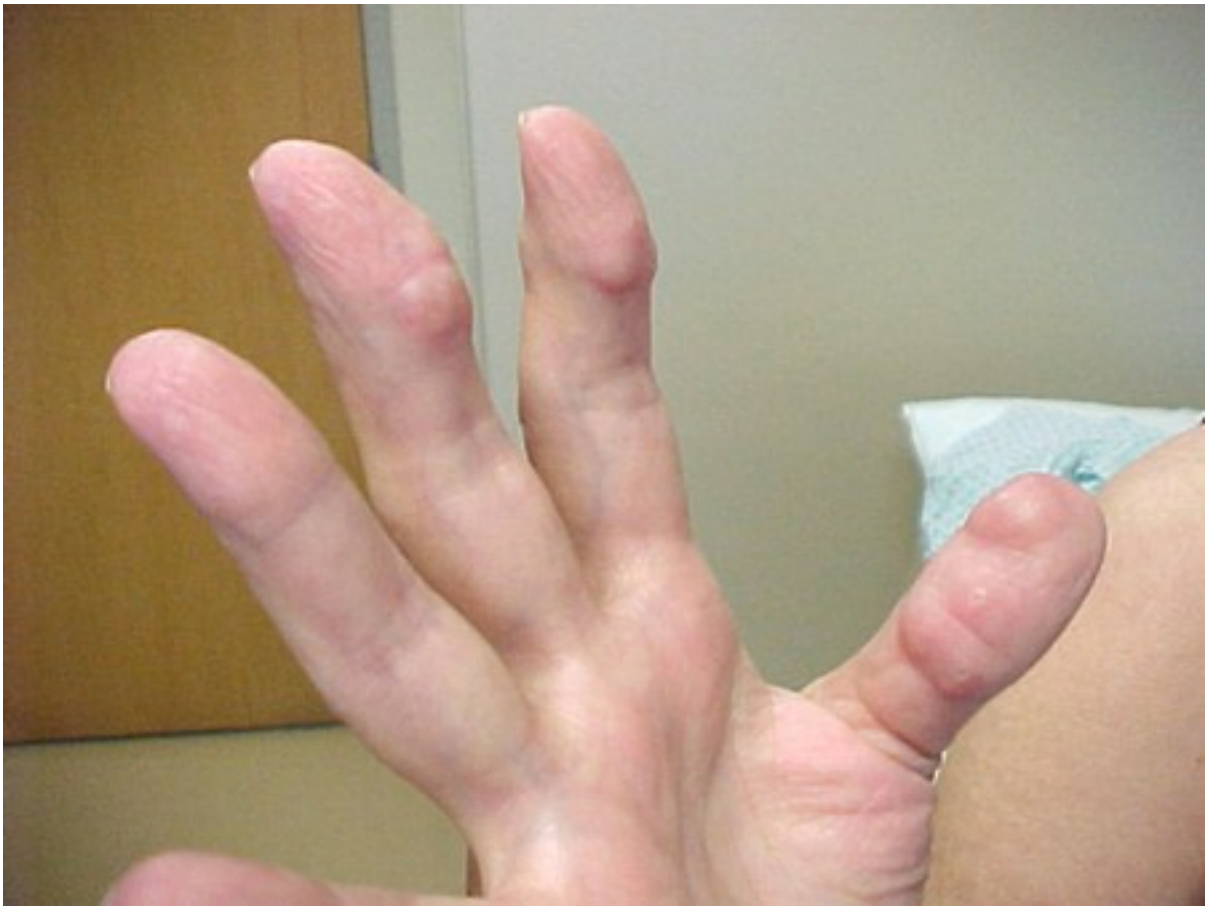

Figure 7: Rheumatoid nodules

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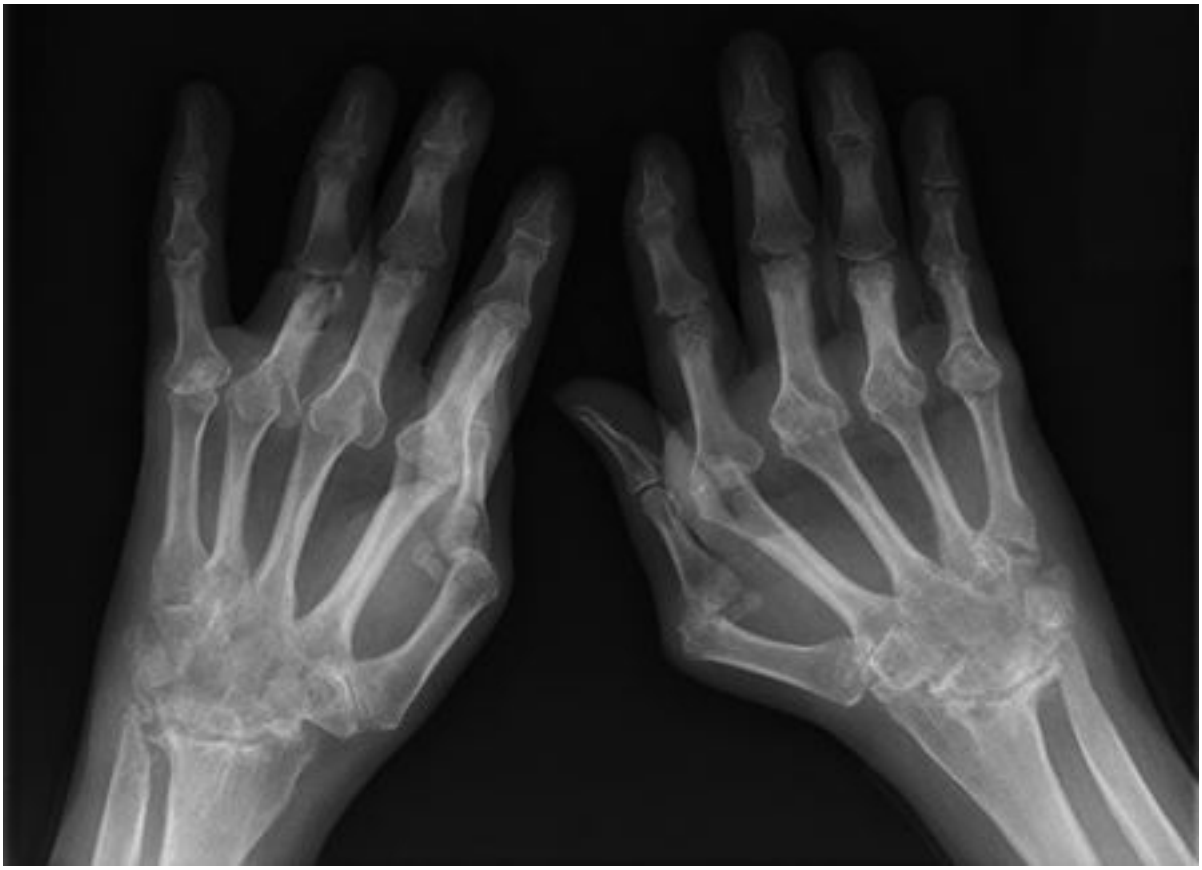

Figure 8: Rheumatoid hand x-ray

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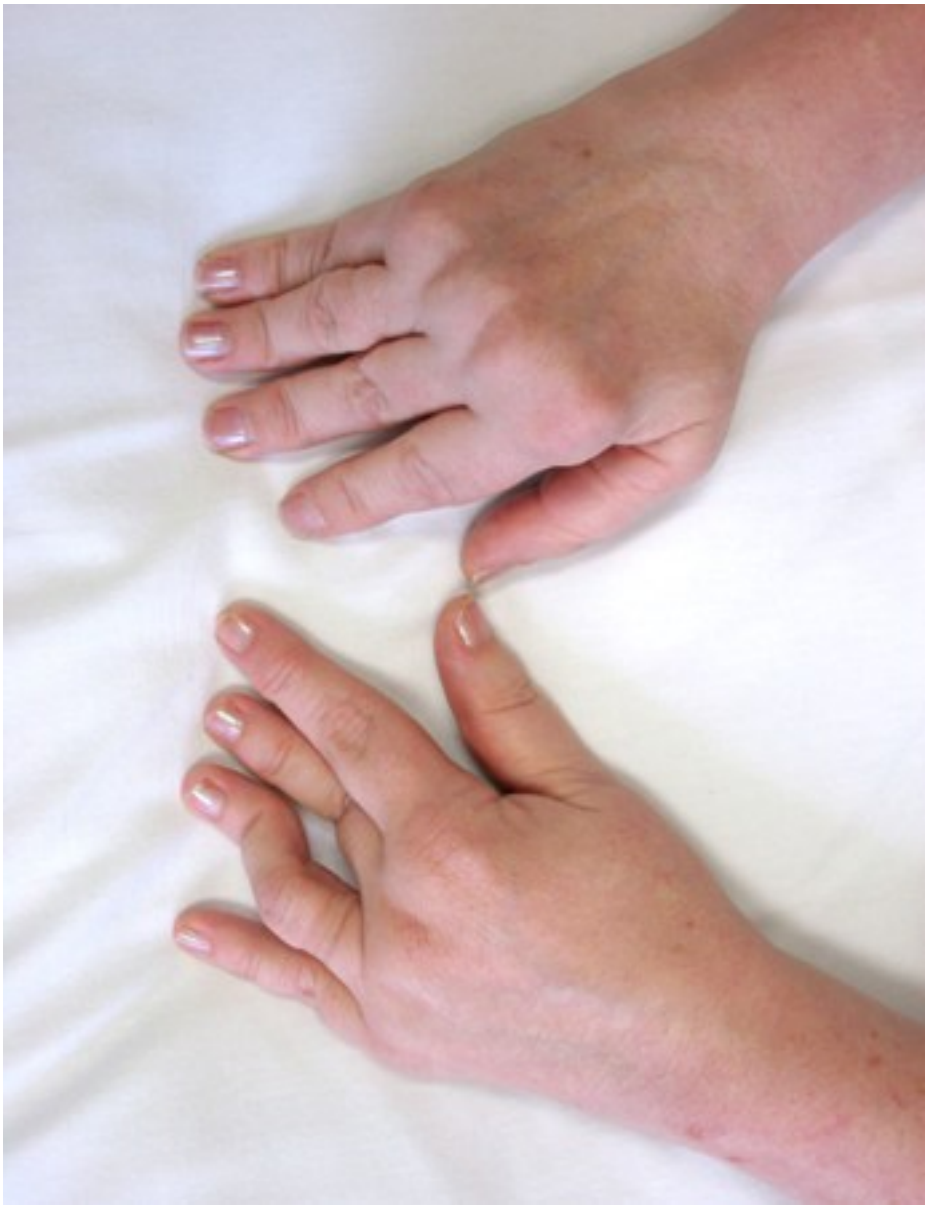

Figure 9: Rheumatoid arthritis (chronic hand deformities)

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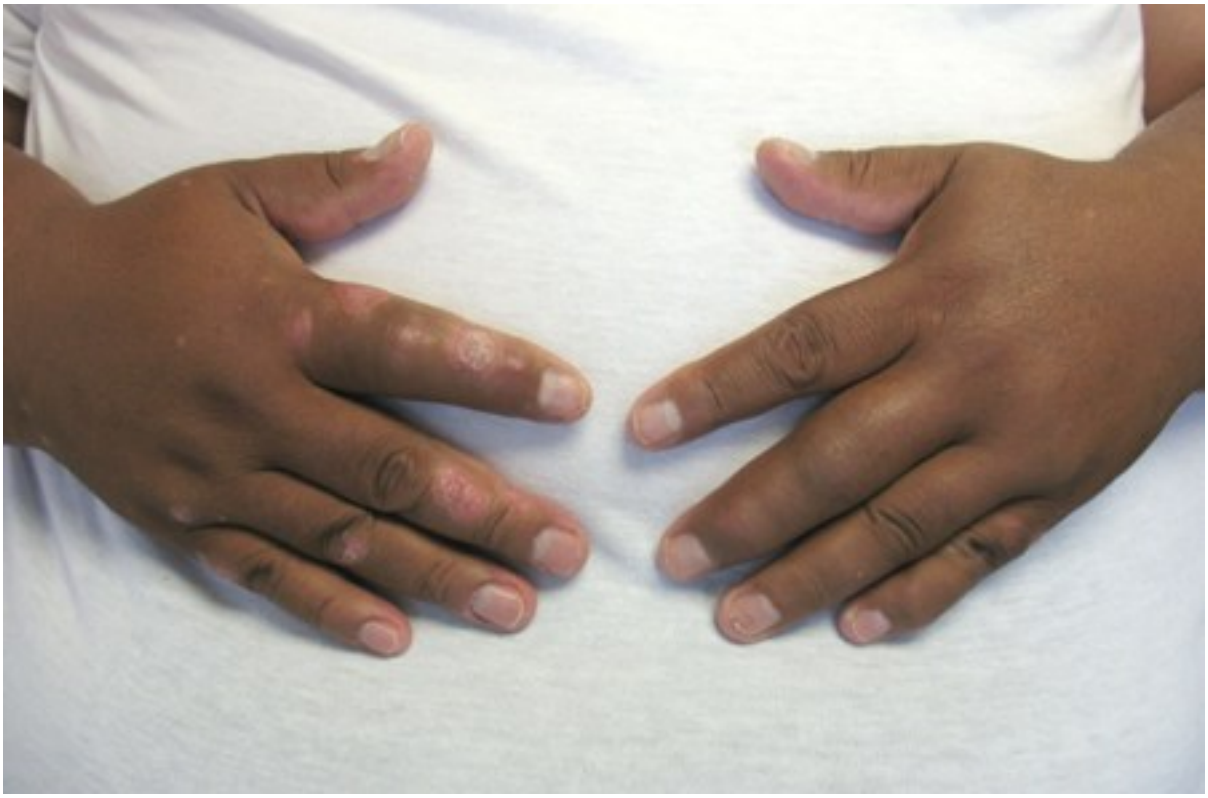

Figure 10: Psoriatic arthritis with dactylitis (left middle and right index finger); skin and nail changes (left ring finger)

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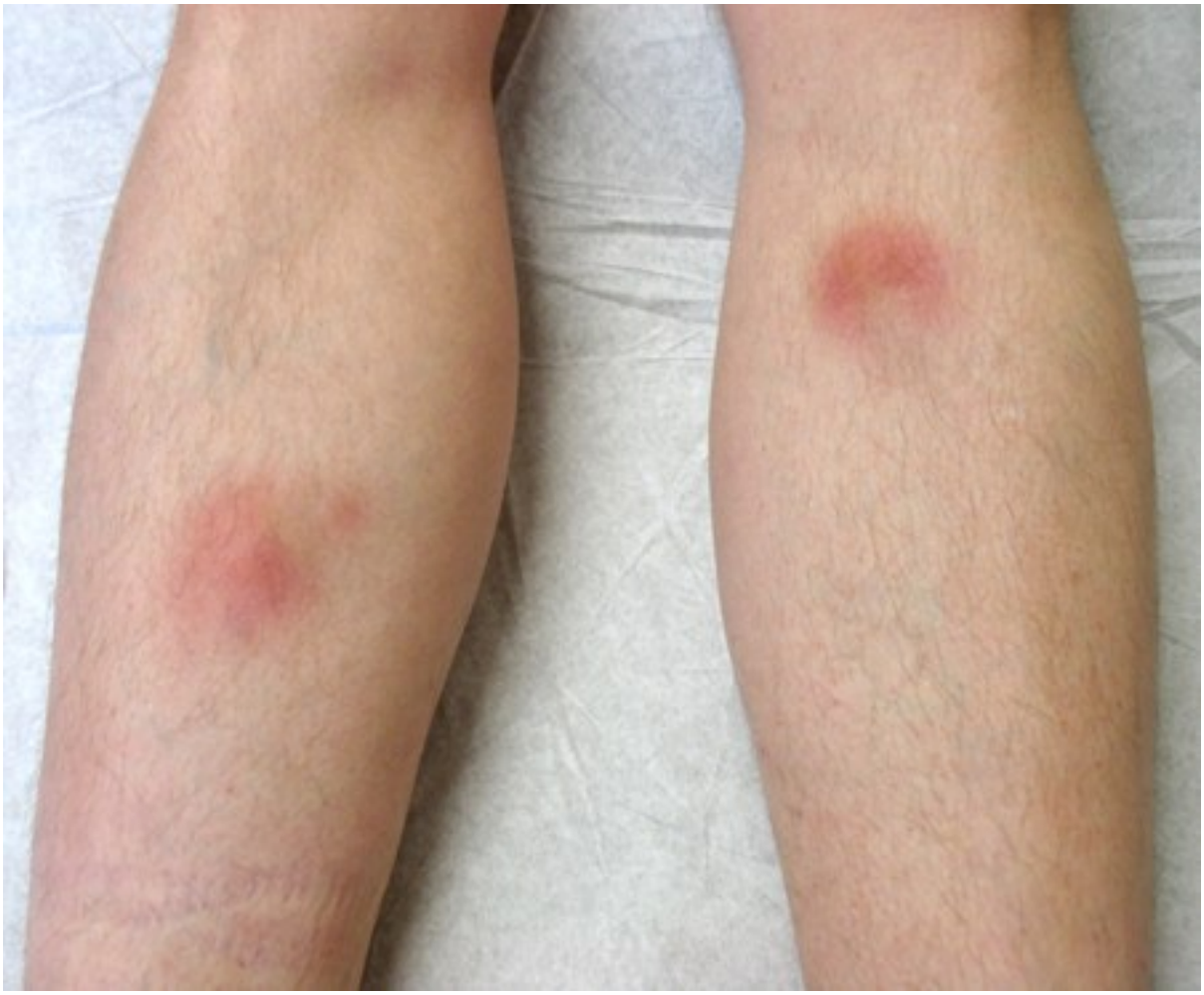

Figure 11: Erythema nodosum

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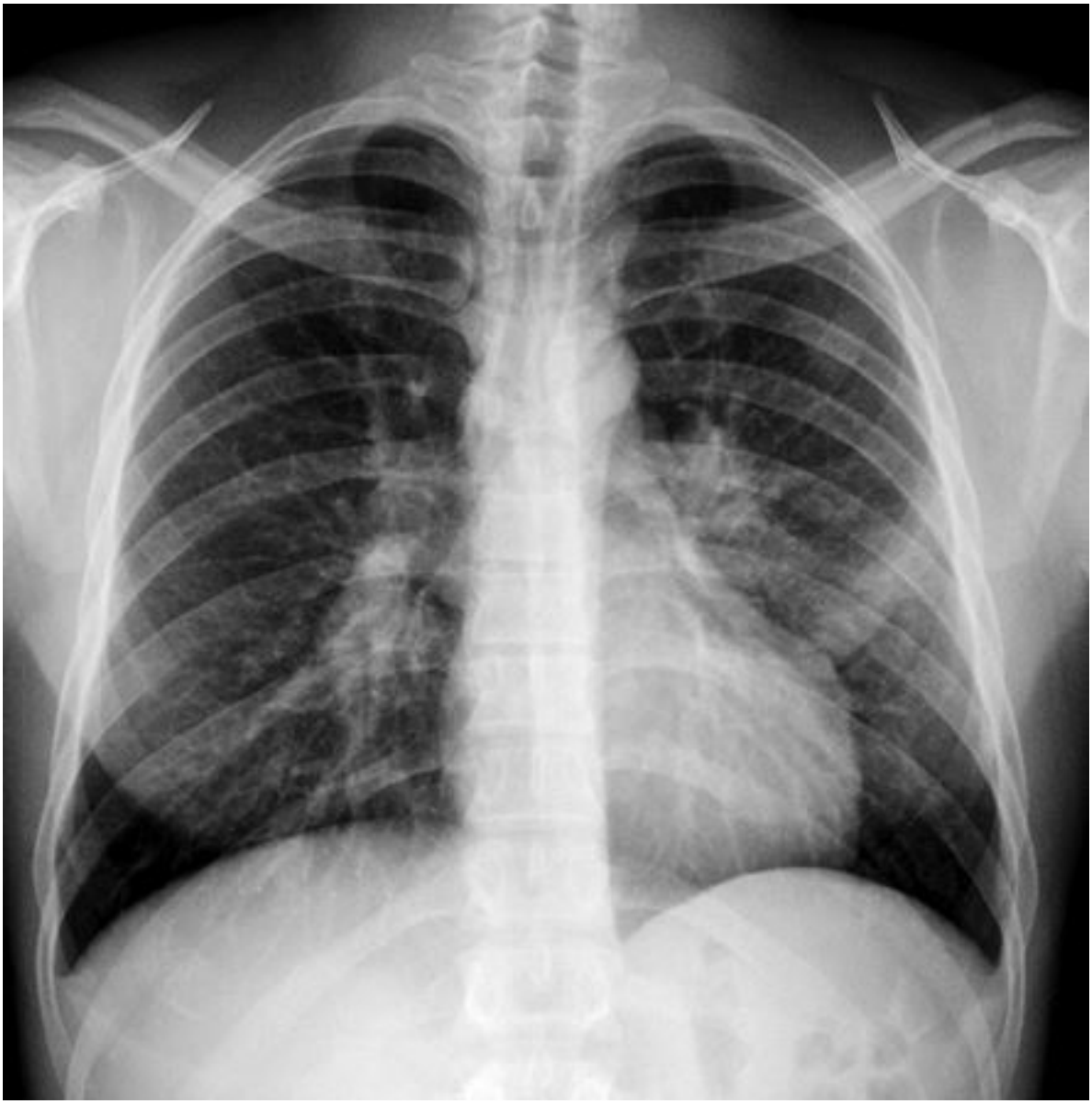

Figure 12: Pulmonary sarcoidosis: right paratracheal, bilateral perihilar, and subcarinal adenopathy

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Figure 1 – BMJ Best Practice Numeral Style

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