Clinical Aspects of Pathology

Joint Diseases

**Systems:** Bone and Skin

**Causes:** Cancer, metabolic, degenerative, infection and Immunity

**Quiz:** IMED4121 – Musculo-skeletal

**Introduction:** Joint conditions are very common and it is stated that 30% of the US population over the age of 50 years will develop some form of clinically significant joint disease.

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### Classification of Joint Disease

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| Degenerative joint disease    | Osteoarthritis |

| Neuropathic joint disease    | Primary neurologic diseases |

| Metabolic bone disease       | Gout, pseudogout (CPPD), haemochromatosis, ochronosis, hyperparathyroidism, Wilson’s Disease |

| Primary synovial disease     | osteochondromatosis, transient synovitis, eosinophilic synovitis |

| Non-neoplastic - miscellaneous | Amyloidosis, haemophilia, relapsing polychondritis, lipoid dermatoaahritis (reticulohistiocytosis) |

| Reactive tumour-like conditions | Ganglion, Baker’s cyst |

| Soft tissue tumours           | Tenosynovial giant cell tumour (pigmented villonodular synovitis), synovial haemangioma, synovial sarcoma, synovial chondrosarcoma |

Wednesday, July 06, 2016
INFECTIOUS ARTHRITIS

Acute infectious arthritis (Septic arthritis)

Definition: is the purulent invasion of a joint by an infectious agent which produces arthritis.

Sites: most common is the knee, then hip, wrist or elbow.

Small joints are more likely affected after a bite or inoculation. IV drug users are more likely to have involvement of the spine, sacro-iliac joints or sterno-clavicular joints.

Polyarticular infection is more likely in rheumatoid arthritis.

Age: all ages

Clinical presentation:

- severe pain that is localized around the joint.
- joint effusion
- muscle spasm
- decreased range of movement
- fever is common but can be absent especially in persons with rheumatoid arthritis, renal or hepatic insufficiency, or taking immunosuppression therapy.
- an extra-articular site of infection such as a boil or pneumonia may be present.

Etiology: Micro-organisms must reach the synovial membrane of a joint. This can happen by:

- dissemination of pathogens via the blood, from abscesses or wound infections, or from an unknown focus
- dissemination from an acute osteomyelitic focus
- dissemination from adjacent soft tissue infection
- entry via penetrating trauma
- entry via iatrogenic means e.g. aspiration of a joint, arthrography or surgery

Organisms: the haematogenous route is most common. In infants group A streptococci, gram negative enteric bacilli and *S.aureus* are the usual pathogens.

In young adults and adolescents *N. gonorrhoeae*.

All ages *S.aureus*. In older adults gram negative bacilli, pneumococci, β – haemolytic streptococci – (especially groups A and B) are involved in 30%, particularly in those with co-morbid illnesses.

Infections following surgical instrumentation are often *S.aureus*.

Anaerobic organisms are found with human bites and when decubitus ulcers or intra-abdominal abscesses spread into adjacent joints.

Traumatic injuries may be complicated with several organisms.

Cat bites or scratches can be associated with *Pasteurella multocida* infection in joints.
Risk factors:

- Rheumatoid arthritis patients have the highest incidence of infective arthritis, usually due to *S.aureus*. This is related to the fact that the joints are chronically inflamed, medication may include glucocorticoids, and there is frequent breakdown of rheumatoid nodules, vasculitic ulcers and skin overlying deformed joints.
- Also the following conditions carry an increased risk of infection with *S.aureus* and gram-negative bacilli:
  - Diabetes mellitus
  - Glucocorticoid therapy
  - Haemodialysis
  - Malignancy
  - Alcoholism, immune deficiency, haemoglobinopathies – prone to pneumococcal infections
  - H.I.V. patients – pneumococci, *Salmonella* and *H.influenzae* cause septic arthritis
  - Primary immunoglobulin deficiency patients are at risk of mycoplasmal arthritis which results in permanent damage if prompt treatment with antibiotics and immunoglobulin replacement is not received
  - I.V. drug users acquire staphylococcal and streptococcal infections from their own flora and acquire pseudomonal and other gram negative infections from drugs and needles/syringes

Imaging: The images below, courtesy of Paul and Juhl. Essentials of Radiologic Imaging, is the knee of an 8 month old child showing in A. soft-tissue swelling, joint distension and obliteration of fascial planes. B is comparison with a normal.

![Images of knee](image)

**Sub-acute suppurative arthritis** will occur if the acute infection is untreated or inadequately treated.

Image A is an AP view of the shoulder demonstrating destruction of the opposing margins of the joint. The humeral head has an irregular surface and there is poor definition of the rim of the glenoid – see white arrow. The joint space is widened. The CT scan – image B – confirms those findings. In addition it shows there is joint distension, and surrounding soft tissue swelling with obliteration of the fascial planes and partial obliteration of the subcutaneous fat. (Courtesy of Paul and Juhl).
**Diagnosis:** Diagnosis is by aspiration (giving a turbid, non-viscous fluid), Gram stain and culture of fluid from the joint, as well as highly elevated neutrophils (approx. 90%), ESR or CRP. The ESR and CRP are almost always raised on admission, CRP being faster in diagnostics.

**Treatment of Acute/ sub-acute septic arthritis:** administer empiracally IV antibiotics, then change determined by sensitivity. Antibiotics may need to be continued for several weeks.

Drainage of pus and necrotic debris may be needed for the best outcome.

**Chronic infectious arthritis**

**Definition:** infectious arthritis which develops slowly over weeks and is usually caused by mycobacteria, fungi, or bacteria with low pathogenicity.

**Frequency:** accounts for 5% of septic arthritis.

**Risk factors:** It can develop in healthy people, but patients at increased risk include those with:

- rheumatoid arthritis
- HIV infection
- immunosuppression (eg, hematologic or other cancers, immunosuppressive drug use)
- prosthetic joints

**Etiology:** *Mycobacterium tuberculosis, M. marinum, M. kansasii, Candida sp, Coccidioides immitis, Histoplasma capsulatum, Cryptococcus neoformans, Blastomyces dermatitidis, Sporothrix schenckii, Aspergillus fumigatus, Actinomyces israelii, and Brucella* sp. Unusual opportunistic organisms are possible in patients with haematologic cancers or HIV infection or who are taking immunosuppressive drugs. A prolonged illness and lack of response to conventional antibiotics suggest a mycobacterial or fungal cause.

**Clinical presentation:** Onset is often indolent, with gradual swelling, mild warmth, minimal or no redness of the joint area, and aching pain that may be mild. Usually a single joint is involved.

**Pathology:**

In chronic infectious arthritis, the synovial membrane can proliferate and can erode articular cartilage and subchondral bone. Patients should have fungal and mycobacterial cultures taken of synovial fluid or synovial tissue, as well as routine studies.

**Imaging:** Plain x-ray findings may differ from those of acute infectious arthritis in that joint space is preserved longer, and marginal erosions and bony sclerosis may occur.

In the image below of a chronic pyogenic infection,, courtesy of Paul and Juhl, on the left, erosion of the bony articular surfaces can be seen medially and there is narrowing of the joint space medially and laterally. In the centre – B – 4 months later, further destruction of bone is seen and the joint space has disappeared indicating destruction of the joint cartilage. In C, 9 months after the onset, the infection has subsided and there is early bony ankylosis. However, periarticular osteoporosis is still present.
**Chronic neonatal infections:** septic arthritis occurs as a complication of neonatal osteomyelitis. This occurs in premature and term infants who have had catheterization of their umbilical vessels. In neonates, the blood supply of the epiphysis is contiguous with that of the metaphysis so extension of infection into a joint can easily occur.

The image below, courtesy of Paul and Juhl, is a 2 week old infant. Image A shows a soft tissue swelling around the shoulder. Image B taken 2 weeks later shows poorly defined destruction in the metaphysis with surrounding periosteal reaction and severe distension of the shoulder joint with pseudodislocation. The arrow shows the inferior displacement of the epiphysis.

**Tuberculosis:** usually involves a single joint. The source of the infection may be by haematogenous spread to the synovial membrane or secondary to a tuberculous abscess in bone nearby. It usually begins as a synovitis with proliferation of inflammatory granulation tissue—pannus—commencing at the perichondrium and extends over the joint surfaces. This causes destruction of the cartilage. However, there is a tendency to preserve the joint cartilage at sites of maximum weight-bearing or close apposition of cartilage. **This is the opposite of pyogenic infections where the joint exudate, containing proteolytic enzymes rapidly destroys the entire cartilagenous joint surface.**

The image below, courtesy of Paul and Juhl, shows tuberculous arthritis in the wrist in an 82 year old. Diffuse osteoporosis is present with narrowing of the radiocarpal and mid-carpal joints and erosion and destruction of their opposing margins. The metacarpo-hamate joint is involved and the distal margin of the ulna, including the ulnar styloid, is eroded.
Lyme disease:

The arthritis of Lyme disease is usually acute but may be chronic and recurrent. In the MRI sagittal image of the knee of a 17 year old boy, with a knee swelling for 7 months, it shows an effusion has displaced the medial meniscus anteriorly – curved white arrow. There are ribbon-like folds of hypertrophied synovium and frond-like extensions of synovium and synovial fluid into the infrapatellar fat pad – black arrows. Image courtesy of Lawson JP and Rahn DW 1992, AJR; 158 (5) 1065-1069.

Treatment: Mycobacterial and fungal joint infections require prolonged treatment. Mycobacterial infections are often treated with multiple antibiotics, guided by sensitivity testing results.

ARTHRITIS of COLLAGEN DISEASE

Rheumatoid Arthritis

Definition: Rheumatoid arthritis is a chronic autoimmune disease that causes a nonsuppurative proliferative arthritis which causes destruction of cartilage and subsequent ankylosis of the joint, especially the peripheral joints and deformity of the joints.

Sites of rheumatoid: joints and systemic problems may occur, including vasculitis, systemic amyloid, the development of rheumatoid nodules in various parts of the body, lung disease, blood disorders, and osteoporosis.

Incidence: In the US alone there are 2 million patients.

Gender: F: M = 3: 1

Age: 80% are diagnosed between 30 and 50 years.

Racial: all races.

Risk factors: The most significant genetic risk factors for rheumatoid arthritis are variations in human leucocyte antigen gene, especially the HLA-DRBI gene. The proteins produced from HLA genes help the immune system distinguish the body’s own proteins from proteins made by foreign invaders (such as viruses and bacteria).

Etiology: unknown.
**Immunology:** patients have circulating autoantibody – the rheumatoid factor – so referred to as seropositive arthritis.

**Clinical presentation:** it can occur gradually but 10% have acute onset. Stiffness, worse in the morning, is noted in one or more joints. There may be swelling in one or 2 joints lasting days or weeks which then goes away only to recur.

The joints affected are the proximal interphalangeal joints, metacarpal-phalangeal joints and metatarso-phalangeal joints. The distal interphalangeal joints and the spine are often spared, with the exception of the cervical spine, particularly the atlanto-axial joints at C1-C2 in long-standing disease.

Other joints involved are the shoulders, elbows, knees and ankles.

Inflamed joints are warm to touch. Eventually permanent deformity occurs. Persistent tenosynovitis and synovitis leads to synovial cysts and displaced, or ruptured tendons especially the extensor tendons on the dorsum of the hand. Advanced disease shows ulnar deviation of the fingers at the metacarpal joints or hyperflexion or hyperextension at the metacarpal phalangeal joints and proximal interphalangeal joints. Also flexion contractures of the elbows and subluxation of the carpal bones and toes develop.

**Gross pathology:**

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**Morphology:**

- infiltration of the synovium by inflammatory infiltrate
- increased vascularity
- aggregation of organizing fibrin covering synovium – can float in the joint
- Accumulation of neutrophils in the synovial fluid
Osteoclastic activity allows synovium to penetrate bone and cause juxta-articular erosions, subchondral cysts, osteoporosis.

Pannus – fibrocellular mass of synovium erodes underlying cartilage.

This leads to fibrous ankylosis, especially the peripheral joints.

**Pannus** is responsible for the erosions that occur in the ‘bare’ areas between the peripheral edge of the joint cartilage and the insertion of the joint capsule. See figure below, courtesy of Paul and Juhl.

Skin – shows rheumatoid nodules in 25% of patients.

Also find nodules in lungs, spleen, heart, aorta, viscera.

**Laboratory tests:**

No laboratory test will definitively confirm a diagnosis of rheumatoid arthritis. However, the information from the following tests contributes to diagnosis and management.

- complete blood count (CBC) – mild anaemia in 30% patients. White cell count may be elevated secondary to inflammation. Platelets usually normal but thrombocytosis can occur.
- comprehensive metabolic panel (CMP)
- rheumatoid Factor (RF)
- antibodies to citrullinated peptides including anti-CCP
- erythrocyte Sedimentation Rate (ESR)
- C-reactive protein (CRP)

A positive rheumatoid factor is present in 70-80% of patients with Rheumatoid arthritis. A positive Anti-CCP is a more specific marker for Rheumatoid arthritis and is found in similar proportions of patients over the course of disease. High levels of Anti-CCP also appear to be linked to a greater severity of the disease. The erythrocyte sedimentation rate (ESR) is usually elevated in and in some patients is helpful in following the activity of the disease. The C-reactive protein (CRP) is another measure of inflammation that is frequently elevated, and improves with control of disease activity.

Testing for hepatitis B and C and testing for tuberculosis are commonly done as part of an initial evaluation.

Chemistry tests are usually normal in rheumatoid arthritis with the exception of a slight decrease in albumin and increase in total protein reflecting the chronic inflammatory process. Renal and liver
function are important to check before beginning treatment and are followed over time with the use of many medications.

**Imaging:** Baseline X-Rays of the hands, feet, and other affected joints are common at initial evaluation, and sometimes a baseline chest X-Ray is obtained. Image of metacarpophalangeal joints and wrist, courtesy of Paul and Juhl, shows in A, extensive erosion of the heads of the metacarpals and small erosions at the proximal interphalangeal joints. B shows narrowing of the radiocarpal and mid-carpal joints, with erosions of the opposing margins. The ulnar styloid is involved and has associated soft tissue swelling.

![X-Rays of hands and wrists](image)

**Juvenile Rheumatoid (Still’s disease)** Occurs in patients under 16 years. It affects larger joints (knee, ankle or wrist) and has a systemic onset. Seropositive is common. X-ray shows joint effusions, soft-tissue swelling and peri-articular osteoporosis. Joint space narrowing may not be seen for many months. Acceleration of skeletal maturation leads to shortening of the bone due to premature fusion of ossification centres. Involvement of the spine is more common in children than adults. There can be atlanto-axial subluxation and erosion and ankylosis of facet joints.

In the image A below, courtesy of Paul and Juhl, there is erosion of the articular surfaces in most of the joints of the hand and wrist, as well as severe osteoporosis. Image B is an older child with shortening of the digits, deformity of the carpal bones and erosions of the heads of the metacarpals.

![Radiographs of hands](image)

**FLAG:** *Two-thirds of all patients with a positive rheumatoid factor DO NOT have rheumatoid*

Other conditions with rheumatoid factor are:

- systemic lupus erythematos
du
- Sjogren’s syndrome
- chronic liver disease
- sarcoidosis
- interstitial pulmonary fibrosis
- infectious mononucleosis
- hepatitis B
- tuberculosis
- leprosy
- syphilis
- subacute bacterial endocarditis
- visceral leishmaniasis
- schistosomiasis
- malaria
- In normal individuals after vaccination or transfusion
- In relatives of individuals with RA

Extra-articular manifestations of Rheumatoid Arthritis

- Tend to occur in the 2/3 of rheumatoid arthritis patients who have high titres of autoantibodies to the Fc component of immunoglobulin G (rheumatoid factors).

Rheumatoid nodules

- occur in 25% of persons with rheumatoid arthritis.
- found on periarticular structures, extensor surfaces, but also in pleura and meninges.
- common sites are olecranon bursa, proximal ulna, Achilles tendon and the occiput.
- nodules rarely symptomatic but can break down and become ulcerated.
- consist of a central zone of necrotic material, a midzone of macrophages and an outer zone of granulation tissue.

Atrophy of skeletal muscle and weakness are common within a few weeks of the onset of RA and involves muscles around affected joints.

Rheumatoid vasculitis

Can affect any organ in the body.

- can cause polyneuropathy or mononeuritis
- cutaneous ulceration and dermal necrosis, digital gangrene, visceral infarction.
- can cause small brown spots in the nail beds and digital pulp.
- large ischaemic ulcers in the lower extremities
- myocardial infarction
- vasculitis involvement of lungs, bowel, liver, spleen, pancreas, lymph nodes and testes.
  Renal vasculitis is rare.

Pleuropulmonary manifestations

- pleural disease - pleural fluid has low glucose in absence of infection
- interstitial fibrosis – impairs diffusing capacity of the lung
- pleuropulmonary nodules – can be single or clusters. If present in a patient who also has a pneumoconiosis, a diffuse large nodular fibrosis – Caplan’s syndrome develops.
  Nodules can cavitate and cause pneumothorax or bronchopleural fistula.

If sufficient vasculature is obliterated by a vasculitic process, pulmonary hypertension can develop.
- pneumonitis
- arteritis

**Upper airways obstruction**

- due to cricoarytenoid arthritis
- laryngeal nodules

**Heart**

- myocardial disease can develop
- pericarditis in 50% and chronic constrictive pericarditis can develop

**Neurological features:**

1. Atlantoaxial or midcervical spine subluxation causing compression of the spinal cord

2. Nerve entrapment secondary to proliferative synovitis or joint deformities may produce neuropathies of median, ulnar, radial or anterior tibial nerves.

**Ocular involvement:** 1% cases. Get episcleritis and scleritis, with thinning/perforation of the globe.

**Sjogren’s syndrome** occurs in 20% persons with rheumatoid arthritis → keratoconjunctivitis sicca

**Felty’s syndrome:**

- chronic rheumatoid arthritis
- splenomegaly
- neutropenia
- sometimes anaemia and thrombocytopenia
- patients frequently have high titres of rheumatoid factor,
- subcutaneous nodules
- and other manifestations of systemic rheumatoid disease
- can develop after the joint inflammation has regressed
- increased susceptibility to infection

**Osteoporosis:** common and aggravated by steroid therapy, even low doses.

Osteoporosis involves the juxta-articular bone and long bones distant from the involved joints, with an increased risk of fracture.

**Laboratory findings in Felty’s syndrome:**

- raised ESR in nearly all patients
- normochromic, normocytic anaemia is often present
- synovial fluid may confirm the presence of inflammatory arthritis but not specific.

**CLASSIFICATION** of rheumatoid arthritis (2010 American College of Rheumatology)


Patient has to have 6 of the 10 criteria in Categories A - D to be diagnosed as RA.

Categories are: A. Joint involvement

- B. Serology
- C. Acute phase reactants e.g. CRP and ESR
- D. Duration of symptoms

**Rheumatoid variants** – includes ankylosing spondylitis, psoriatic arthritis, Reiter’s syndrome and colitic arthritis.
Usually have a negative rheumatoid factor but many do have the HLA-B27 antigen. More common in males and cause symptoms in the axial skeleton. These differ from Rheumatoid arthritis, in that there is absence of peri-articular osteoporosis, development of periostitis with new bone formation and asymmetrical involvement of the peripheral skeleton.

**Ankylosing spondylitis**

**Gender:** M: F = 15 : 1

**Sites:** commences in the sacro-iliac joints, then involves the spine, starting in the lumbar region and progresses to finally involve the cervical spine.

30% of patients have involvement of the shoulders, knees and hips.

*Those with juvenile onset* have pain in the hips, knees or shoulders with more distal joints affected less frequently. The limb joint changes are seen early in the disease but eventually the changes in the axial skeleton of sacral ileitis and spondylitis occur.

**Clinical features:** persistent low back pain of slow onset.

**Imaging:** All patients with this disease have sacro-iliac involvement. The process is symmetrical with blurring and irregularity of the joint margins on the iliac and sacral side of the joint. The joints may appear irregularly widened. Finally the joint space is lost. Bony irregularity on the margins of the pelvis occurs: the ischial tuberosities, the iliac wings and the greater trochanters and erosions may be present on the margins of the symphysis.

Image shows complete ankylosis of the sacro-iliac joints and calcification and ossification of the interspinous ligaments of the lumbar spine. Courtesy of Paul and Juhl.

**Psoriatic arthritis:**

**Definition:** it is a rheumatoid variant in which the serum is negative for rheumatoid factor.

**Incidence:** occurs in 10% of patients with psoriasis. The severity and extent of the arthritis does not correlate with the degree of skin disease.

Note: less than 10% develop classic rheumatoid arthritis and a few develop a combination of the two.

**Sites:** tends to involve the small joints of the hands and feet and is not symmetrical.

**Age:** most common between 30 and 50 years.

**Pathogenesis:** The joint symptoms may appear before the skin condition. In the left photo below of an elbow (Courtesy of K Wolff, RA Johnson and R.Suurmond, Fitzpatrick’s Colour Atlas and synopsis of Clinical Dermatology, 5th ed), note the well-demarcated, dull-red plaque with a thick whitish scale,
which has arisen from the coalescence of smaller papular lesions. Also view the photo on the right, showing joint swelling of distal interphalangeal joints and metacarpophalangeal joints, with associated severe nail dystrophy. The transverse nail ridges are associated with psoriatic involvement of the nail matrix.

Clinical symptoms: fatigue, a rash, swollen, painful and warm joints in fingers and toes and foot pain. The latter occurs where tendons and ligaments are attached to bone such as the tendon Achilles at the back of the heel and in the sole of the foot as plantar fasciitis. Low back pain occurs due to sacro-ileitis. A small percentage of patients with psoriatic arthritis develop arthritis mutilans which is very painful and disabling. The small bones in the hands, especially in the fingers, are destroyed leading to permanent deformity and disability.

Laboratory tests: psoriatic arthritis usually does not have the rheumatoid factor in the serum, which distinguishes it from rheumatoid arthritis. However, 10% do have it.

Aspiration of fluid from a swollen joint may be done as finding uric acid crystals will make the diagnosis gout, not psoriatic arthropathy.

Imaging: in the x-ray of a foot below, courtesy of Paul and Juhl, there is a mutilating destruction of the metatarsal-phalangeal joints and ankylosis of the proximal interphalangeal joints. This last feature is rarely seen in rheumatoid arthritis or other rheumatoid variants. Another characteristic of psoriatic arthritis is the destruction of the interphalangeal joints resulting in widening of the joint space, with sharply demarcated bony margins.

In the images below, the left one of fingers shows erosions and fine periosteal new-bone formation at the margins of several joints. There is involvement of the distal interphalangeal joints of the index and middle fingers and bony ankyloses of the distal interphalangeal joint of the index finger. Also there is widening of the distal interphalangeal joint of the middle finger.

The image on the right, of the foot shows mutilating destruction of the metatarsal-phalangeal joints and ankylosis of the proximal interphalangeal joints.
Treatment: there is no cure, so controlling the symptoms to prevent joint pain and disability is the goal.

- nonsteroidal anti-inflammatory drugs can relieve pain and reduce inflammation
- disease-modifying anti-rheumatic drugs can slow the progression of the arthritis and save the joints from permanent damage
- immunosuppressants e.g. azathioprine and cyclosporine
- TNF-alpha inhibitors – reduce the pain, morning stiffness and tender, swollen joints e.g. Infliximab inhibits the production of the inflammatory substance called tumor necrosis factor-alpha.
- steroid injections into one joint.
- joint replacement surgery with artificial prostheses.

Prognosis: Most people with psoriatic arthritis will have ongoing problems with arthritis throughout the rest of their life. Remissions are uncommon; occurring in less than 20% of patients with less than 10% of patients having a complete remission off all medication with no signs of joint damage on X-rays.

Reiter’s syndrome (RS)

Definition: it is a chronic inflammatory disease which is rheumatoid factor negative and occurs mainly in young men, and shows spontaneous remissions and recurrences.

Sites: this consists of urethritis, conjunctivitis, mucocutaneous lesions in the oropharynx and tongue, glans penis, skin, heart and arthritis. Arthritis occurs in 50% of sufferers.

Age: 22 years in the post-venerale type.

Gender: RS primarily affects sexually active males between ages 20-40, particularly males who are HIV positive. Most women and children who develop RS acquire the disease in its intestinal form.

Incidence: may be increased in HIV-infected individuals.

Genetic: since 1998, scientists think the disease results from a combination of genetic vulnerability and various disease agents. Over 80% of Caucasian patients and only 8% of healthy Caucasians as well as 50-60% of African Americans test positive for HLA-B27, which suggests that the disease has a genetic component. Patients who are HLA-B27 negative have a milder course, with less sacral ileitis, uveitis and carditis.

Pathogenesis: In sexually active males, most cases of RS follow 1 – 4 weeks after infection with Chlamydia trachomatis or Ureaplasma urealyticum.
Other patients develop the symptoms following gastrointestinal infection with *Shigella*, *Salmonella*, *Yersinia*, or *Campylobacter* bacteria.

**Clinical features:** The initial symptoms of RS are inflammation either of the urethra with a discharge from the penis, or the intestines, followed by acute arthritis four to 28 days later. The arthritis usually affects the fingers, toes, and weight-bearing joints in the legs. Have pain over the ischial tuberosities, iliac crest, long bones, ribs, as well as heel pain at the site of attachment of plantar aponeurosis and/or Achilles tendon, and back pain.

Other symptoms include:- keratoderma blennorrhagica, - patches of scaly skin on the palms, soles, trunk, or scalp of RS patients. In the photo, courtesy of Fitzpatrick’s Colour Atlas and Synopsis of Clinical Dermatology note red-to-brown papules, vesicles, and pustules with central erosion and characteristic crusting and peripheral scaling on the dorso-lateral and plantar aspect of the foot.

**Diagnosis:** No specific test but culture the urethral discharge to rule out gonorrhoea (*Neisseria gonorrhoeae*). It may be positive for *Chlamidia* or *Ureaplasma*. Culture of the stool may find *Shigella*, and *Yersinia*.

Haematology: anaemia, leucocytosis, thrombocytosis, raised ESR

Serology: rheumatoid factor negative. Rule out HIV infection.

Genetic marker: HLA-B27 usually positive.

**Imaging:** findings are similar to psoriatic arthritis except that the axial skeleton is not so frequently involved and changes in the upper limbs are rare. The major involvement is in the lower limbs, especially the feet. Sacro-iliac joint involvement tends to be symmetrical.

A particular feature is periostitis with fluffy or whisker-like appearance, at the site of tendon insertions, most frequent at the attachment of plantar fascia, forming a poorly defined spur on the plantar surface of the calcaneum. Image courtesy of Paul and Juhl – see arrow.

The destructive process may involve the interphalangeal, metatarsal phalangeal and tarsal joints of the foot. Ankle and knee involvement is less common. In the image below, courtesy of Paul and Juhl, note the periarticular osteoporosis and erosions of several of the metatarsophalangeal and interphalangeal joints. Fine periosteal new bone is seen on the distal margins of the 3rd and 4th metatarsals – see arrows.
Treatment: No specific treatment except antibiotics for a proven prior infection. Joint inflammation may be eased by non-steroidal antiflammatory drugs and skin eruptions with corticosteroids. Testing of sexual partners is done. Highly active anti-viral therapy may lessen the symptoms in HIV cases.

Prognosis: Only 30% develop the complete triad of arthritis, conjunctivitis and urethritis. 40% may have only one of the three. The disease has a self-limited course in the majority, with resolution in 3 – 12 months. However, in 50% the disease may relapse over many years. Chronic deforming arthritis is evident in 10-20%. Some patients develop complications that include inflammation of the heart muscle, stiffening and inflammation of the vertebrae, glaucoma and eventual blindness.

In males, Reiter’s syndrome can be prevented by the use of condoms.

Colitic arthritis

Definition: is arthritis that occurs in patients with chronic inflammatory bowel disease, especially Crohn’s disease and ulcerative colitis.

Site: sacro-ileitis is most common and similar to but not as extensive as ankylosing spondylitis and usually symmetrical.

Joint effusions and soft-tissue swelling are occasionally in proximal major joints but deforming arthritis is rare.

The axial skeletal disease is unrelated to the severity of the bowel disease but peripheral joint disease does so.

Clinical: rarely symptomatic and diagnosed as an incidental finding on an abdominal xray for some other purpose.

Imaging: in the image below, from a patient with Crohn’s Disease, courtesy of Paul and Juhl, note the marginal erosions and sclerosis of the sacro-iliac joints.
Connective tissue diseases associated with arthritis

Viz: Systemic lupus, dermatomyositis, scleroderma, Jaccoud’s arthropathy

Systemic Lupus Erythematosis arthritis

**Definition:** Systemic lupus erythematosus (SLE) is an autoimmune disease in which the body’s immune system attacks healthy tissue. The arthritis is non-erosive involving two or more peripheral joints which are tender, swollen and may contain an effusion.

**Sites:** It can affect the skin, joints, kidneys, brain, and other organs.

**Gender:** SLE is much more common in women than men.

**Age:** It may occur at any age, but appears most often in people between the ages of 10 and 50.

**Race:** African Americans and Asians are affected more often than people from other races.

**Etiology:** SLE may also be caused by certain drugs and symptoms appear after taking the drug for 3 – 6 months.

- The most common medicines known to cause drug-induced lupus erythematosus are: Isoniazid, hydralazine, procainamide
- Other less common drugs may also cause the condition. These may include:- anti-seizure medication, Capoten, Chlorpromazine, TNF – alpha inhibitors, methyldopa, minocycline, penacillamine, quinidine, sulphasalazine

**Clinical symptoms:** may include: blurred vision, fever, general ill feeling (malaise), joint pain and swelling, loss of appetite, pleuritic chest pain. Also a skin rash that gets worse with sunlight – the so called butterfly rash or malar rash across the bridge of the nose and cheeks. See the photo below, courtesy of Fitzpatrick’s Colour Atlas and Synopsis of Clinical Dermatology, of a young woman with bright red, sharply defined erythema with slight oedema and slight scaling.
**Extra-cutaneous involvement:** arthritis (80%), renal disease and lymphadenopathy (50%), hepatomegaly and myopathy (30%), pneumonia, pericarditis and splenomegaly (20%), peripheral neuropathy (14%), CNS disease – 10%, with seizures and organic brain disease – 14%.

**Laboratory findings:** more than 95% have the antinuclear antibody ANA

**Haematology:** normocytic, normochromic anaemia, leucopaenia, lymphopenia, thrombocytopenia, elevated ESR.

**Urine analysis** – persistent proteinuria and casts.

**Imaging:** x-ray changes in only 30%. See soft-tissue atrophy and osteoporosis. Main feature is an abnormality of joint alignment without articular erosions. There is extension of the proximal interphalangeal joints and flexion of the distal interphalangeal joints – the “swan neck” deformity.

Involvement of the metacarpal phalangeal joints and interphalangeal joint of the thumb causes ulnar deviation of the digit. Jaccoud’s arthritis has a similar deformity. See x-ray, courtesy of Dr Matt A Morgan. Radiopaedia.org, rID37569.

Avascular necrosis of bone is common but it is unclear whether this is due to the SLE itself or the steroid treatment received.

**Treatment:**

There is no cure for SLE. The goal of treatment is to control symptoms.

Mild forms of the disease may be treated with:
- NSAIDs for joint symptoms and pleurisy
- low doses of corticosteroids such as prednisone
- corticosteroid creams for skin rashes
- hydroxychloroquine

Treatments for more severe SLE may include:
- High-dose corticosteroids
- Immunosuppressive drugs - include methotrexate, azathioprine, cyclosporine, mycophenolate and cyclophosphamide
Prognosis: The outcome for people with SLE has improved in recent years, depending upon whether the patient has mild symptoms. The disease tends to be more active during the first years after diagnosis and in people under age 40 years. Many women with SLE can get pregnant and deliver a healthy baby. A good outcome is more likely for women who receive proper treatment and do not have serious heart or kidney problems. However, the presence of SLE antibodies raises the risk of miscarriage.

Scleroderma

Definition: it is a multisystem disorder characterized by inflammatory, vascular and sclerotic changes of the skin and various internal organs especially lungs, heart and gastro-intestinal tract.

Incidence: 20 cases per million population.

Peak age: 30 – 50 years but can occur at any age.

Gender: it is 4 – 9 times more common in women.

Genetic: is not inherited but a genetic predisposition plays an important role in its development.

Race: occurs worldwide.

Pathophysiology: Consists of - 1. severe fibroproliferative vascular lesions of small arteries and arterioles, 2) excessive and often progressive deposition of collagen and other extracellular matrix (ECM) macromolecules in skin and various internal organs, 3) alterations of humoral and cellular immunity. The endothelial cell abnormalities result in either increased production and release of potent mediators including cytokines, chemokines, polypeptide growth factors, and various other substances such as prostaglandins, reactive oxygen species (ROS), or in the reduction of important compounds such as prostacyclin and nitric oxide. The endothelial cell dysfunction allows the chemokine- and cytokine-mediated attraction of inflammatory cells and fibroblast precursors (fibrocytes) from the bloodstream and bone marrow and their transmigration into the surrounding tissues, resulting in the establishment of a chronic inflammatory process with participation of macrophages and T and B lymphocytes, with further production and secretion of cytokines and growth factors from these cells.

The immunological alterations include innate immunity abnormalities, tissue infiltration with macrophages and T and B lymphocytes; production of numerous disease-specific autoantibodies; and dysregulation of cytokine, chemokine, and growth factor production. The released cytokines and growth factors induce the activation and phenotypic conversion of various cellular types, including resident fibroblasts, epithelial cells, endothelial cells, and pericytes into activated myofibroblasts, which initiate and establish the fibrotic process.

This sequence of events results in the development of a severe, progressive fibroproliferative vasculopathy, and exaggerated and widespread accumulation of fibrotic tissue, the hallmark of the fibrotic process characteristic of the disease.
Vascular dysfunction is one of the earliest alterations of scleroderma. Severe alterations in small blood vessels of skin and internal organs, including endothelial dysfunction, subendothelial fibrosis, and perivascular cellular infiltration with activated T cells and macrophages, are almost always present in scleroderma affected tissues.

The activation of endothelial cells induces the expression of chemokines and cell adhesion molecules, causes the attraction, transendothelial migration, and perivascular accumulation of immunologic-inflammatory cells, including T- and B-lymphocytes and macrophages. The inflammatory cells produce and secrete a variety of cytokines and/or growth factors including transforming growth factor beta (TGF-β) and other profibrotic mediators such as endothelin-1, which induce increased proliferation of smooth muscle cells, marked accumulation of subendothelial fibrotic tissue, and initiation of platelet aggregation and intravascular thrombosis, eventually causing microvascular occlusion.

The fibrotic process is characterized by the excessive production and deposition of types I, III, and VI collagens and other ECM and connective tissue macromolecules including COMP, tenascin glycosaminoglycans, and fibronectin. This crucial component results from the accumulation in skin and other affected tissues of myofibroblasts, cells possessing unique biological functions, including increased production of fibrillar type I and type III collagens, expression of α-smooth muscle actin, and reduction in the expression of genes encoding ECM–degradative enzymes. Thus, the accumulation of myofibroblasts in affected tissues and the uncontrolled persistence of their elevated biosynthetic functions are crucial determinants of the extent and rate of progression of the fibrotic process in scleroderma.

The immunologic alterations include the production of numerous autoantibodies, some with very high specificity for the disease, as well as abnormalities in the innate and acquired cellular immune responses. The exaggerated connective tissue production by scleroderma fibroblasts is induced by cytokines and growth factors released from the tissue-infiltrating inflammatory cells.

One of the growth factors in the fibrosis that accompanies scleroderma is TGF-β. Is stimulation of ECM synthesis by stimulating the production of various collagens and other ECM proteins. TGF-β also induces the generation of myofibroblasts and decreases the production of collagen-degrading metalloproteinases as well as stimulating the production of protease inhibitors, which prevent ECM breakdown.

**Clinical presentation:**  Photo (courtesy of Fitzpatrick’s Color Atlas and Synopsis of Clinical Dermatology) shows in the *left photo* oedematous fingers and hands, with erythema. Skin is shiny and bound down and the distal fingers are tapered. Note the shortened index finger associated with bony resorption. Nails are dystrophic. The *photo on the right* is an advanced case (courtesy of Robbins and Cotran. Pathologic Basis of Disease. 8th ed) showing extensive sub-cutaneous fibrosis which has immobilized the fingers into a claw-like flexion deformity.
Inflammation of the synovium associated with hypertrophy and hyperplasia of the synovial soft tissues is common early and fibrosis occurs later. Joint destruction as such is not common.

**Imaging:** scleroderma is commonly associated with characteristic changes in the hands. There is atrophy in the tips of the fingers resulting in a tapered appearance, resorption of bone in the terminal tufts giving a pointed appearance to the phalanx (acro-osteoysis) and small punctate calcified deposits in the soft tissue of the tips of the fingers. See xray below, courtesy of Paul and Juhl.

![X-ray Image](image_url)

Joint space narrowing occurs in the intercarpal and radiocarpal joints and there is rarely intra-articular calcification.

**Diagnosis:** scleroderma is also called Systemic sclerosis. ACR is American College of Rheumatology and EULAR is European League Against Rheumatism.

### Table 1: ACR/EULAR Revised Systemic Sclerosis Classification Criteria

<table>
<thead>
<tr>
<th>Item</th>
<th>Sub-item(s)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin thickening of the fingers of both hands extending proximally to the metacarpophalangeal joints (presence of this criterion is sufficient criterion for SSc classification)</td>
<td>None</td>
<td>9</td>
</tr>
<tr>
<td>Skin thickening of the fingers (count the higher score only)</td>
<td>Puffy fingers</td>
<td>2</td>
</tr>
<tr>
<td>Fingertip lesions (count the higher score only)</td>
<td>Digital ulcers</td>
<td>2</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>None</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal nailfold capillaries</td>
<td>None</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension and/or interstitial lung disease (maximum score is 2)</td>
<td>Pulmonary arterial hypertension</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Interstitial lung disease</td>
<td>2</td>
</tr>
<tr>
<td>Raynaud phenomenon</td>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td>Systemic sclerosis–related autoantibodies (maximum score is 3)</td>
<td>Anticentromere</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Anti-topoisomerase I</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Anti-RNA polymerase III</td>
<td>3</td>
</tr>
</tbody>
</table>

*The total score is determined by adding the maximum score in each category. Patients with a total score equal to or greater than 6 are classified as having definite systemic sclerosis (modified from van den Hoogen F, Khanna D, Fransen J. et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum.* Nov 2013;65 (11)2737-47.[50]*)
Treatment: Because of the heterogeneity of scleroderma and potential treatment toxicity, therapy must be customized to each patient’s clinical presentation and needs. No disease-modifying agent has been proven to prevent or reverse fibrosis, although retrospective studies and case series show that d-penicillamine (Cuprimine), mycophenolate mofetil (Cellcept), and cyclophosphamide (Cytoxan) may be effective in some patients. There has been significant improvement in treatments for organ-specific complications, especially Raynaud phenomenon, scleroderma renal crisis, and gastrointestinal and pulmonary complications.

Prognosis: the 5-year survival is estimated to be about 80%. Five-year survival in patients with limited cutaneous disease is approximately 90%.

Factors associated with a more severe prognosis:

- younger age
- African descent
- rapid progression of skin symptoms
- greater extent of skin involvement
- anemia
- elevated erythrocyte sedimentation rate (ESR)
- pulmonary, renal, and cardiac involvement

Complications:

- digital infarctions
- pulmonary hypertension
- myositis
- renal failure
- wound infections

Jaccoud’s Arthropathy

Definition: it is a migratory polyarthritis with painless onset of a reducible joint deformity after resolution of the active polyarthritis of originally only acute rheumatic fever (Chronic Post-rheumatic fever arthritis). Patients have rheumatic valvular heart disease.

Occurs also in SLE (5%), Sjögren syndrome, scleroderma, dermatomyositis, psoriatic arthritis, vasculitis, ankylosing spondylitis, mixed connective tissue disease, and pyrophosphate deposition disease. It is distinct from bone erosion which is commonly associated with rheumatic arthritis, and also distinct from mild deforming arthropathy which is associated with SLE. There have also been cases of non-rheumatic Jaccoud’s arthropathy associated with Lyme disease, HIV-infection.

Sites: Hand - joint deformities consist of ulnar deviation, flexion deformity or subluxation of the metacarpophalangeal joints. Joints can be reduced early but later become fixed. The proximal interphalangeal joints are hyperextended.

Toes – hallux valgus may be involved with subluxation of the big toe.

Treatment: focuses toward alleviating pain and in maintaining functionality of the affected joints through use of nonsteroidal anti-inflammatory drugs, corticosteroids, antimalarial drugs and physiotherapy.
Surgery is also a possibility, with osteotomy or stabilization with Kirschner intramedullary wire. Tendon relocation, however, has been shown to only work in 30% of cases.

Dermatomyositis

Definition: it is one of the inflammatory myopathies with symmetrical proximal muscle weakness, flat-topped papules over the knuckles, increased serum levels of muscle-derived enzymes and non-suppurative inflammation of skeletal muscle.

Incidence: 6 cases per million population.

Gender: more common in females.

Age: can affect children and adults.

Clinical: slow onset over weeks or months of proximal muscle weakness. Dysphagia and difficulty holding up the head show involvement of pharyngeal and neck flexor muscles. Unlike the other myopathies dermatomyositis patients have a characteristic rash on the upper eyelids, face, trunk and papules on the knuckles.

It may occur alone or in combination with scleroderma, mixed connective tissue disease and other autoimmune conditions. In a middle-aged male it has an increased risk of epithelial cancer especially lung cancer, and in females ovarian cancer, whereas polymyositis and inclusion body myositis do not.

In the photos below, courtesy of Fitzpatrick’s Color Atlas & Synopsis of Clinical Dermatology, see in A, the violaceous erythema on the face, neck and chest and the oedematous swelling of the entire face. In B, there is violaceous erythema and papules on the dorsum of the hands and fingers, especially over the metacarpophalangeal and interphalangeal joints.
X-ray: the most characteristic finding is soft-tissue calcification in the subcutaneous tissues and fascial planes. Bone and joint changes are rare. Severe flexion contractures occur in the late stages and osteoporosis secondary to disuse and steroid therapy is common. See xray courtesy of Radiopaedia.org, rID: 11355. The knee below is courtesy of Radiopaedia.org, rID: 11354 and shows sheets of calcification in muscle.
MRI shows focal lesions in muscle.

**Laboratory examinations:** serum creatine phosphokinase is elevated in 65% patients in the acute phase and elevated aldolase in 40%. Lactate dehydrogenase and glutamic oxaloacetic transaminase are also elevated.

**Autoantibodies** to 155kDa and/or Se in 80% and to Jo-1 in 20%. Both have a high specificity for dermatomyositis. Also antibodies to low specificity antinuclear antibodies in 40%.

**Urine:** elevated 24 hour creatinine excretion > 200 mg / 24 hours.

**EMG** – increased irritability on insertion of electrodes, spontaneous fibrillations, pseudomyotonic discharges, positive sharp waves. The test excludes neuromyopathy. If there is evidence of denervation, suspect a co-existent tumour.

**Microscopic: Muscle biopsy** - There is cell mediated injury targeted at striated muscle with resultant atrophy, oedema, coagulation necrosis, fibrosis and calcification. See segmental necrosis within muscle fibres with loss of cross-striations, inflammatory cells, histiocytes, macrophages and lymphocytes, plasma cells. Vasculitis is seen in juvenile dermatomyositis. The image below (courtesy of Rubin’s Pathology, 6th ed) shows there is perifascicular atrophy demonstrating the flattening and shrinkage of fibres at the periphery of the fascicle – see arrow.
**Treatment**: Prednisone combined with azathioprine. Alternatives used are methotrexate, cyclophosphamide. High dose IV immunoglobulins at monthly intervals spares glucocorticoid doses to achieve or maintain remissions. Unfortunately steroid myopathy may occur after 4 – 6 weeks of therapy.

**Prognosis**: is relatively good except for those with associated malignancy or pulmonary involvement. With aggressive immunosuppressive treatment the 8 year survival rate is 70-80%. If there has been successful treatment of an associated neoplasm, there can be improvement or even resolution of dermatomyositis.

**DEGENERATIVE JOINT DISEASE**

**Osteoarthritis**

**Definition**: it is slowly progressive destruction of articular cartilage that affects weight-bearing joints and fingers of older persons or the joints of younger joints subjected to trauma (c.f. Rubin’s Pathology).

**Incidence**: it is the most common form of joint disease.

**Age**: 85% of those 75-79 years are affected. Before age 45 years, the disease mainly affects men. After the age of 55 years, women predominate.

**Types**: Primary osteoarthritis – this is due to progressive degradation of the articular cartilage leading to joint narrowing and subchondral bone thickening and finally a non-functioning painful joint. There are secondary effects on muscles due to disuse on account of pain with movement.

Secondary osteoarthritis – has a known underlying cause which may be congenital or acquired mal-alignment of joints, trauma, crystal deposits, infection, metabolic diseases, endocrinopathies, inflammatory diseases, osteonecrosis and haemarthrosis.

**Etiology**: increased unit load, decreased resilience of the articular cartilage and increase in the stiffness of coarse cancellous bone.

**Molecular pathogenesis**: biochemical abnormalities mainly involve proteoglycans. Collagen fibres are thicker than normal and the water content of osteoarthritic cartilage increases due to proteoglycan content being reduced. Means the damaged cartilage swells more than normal.

When chondrocytes die within hyaline cartilage this leads to cracking of the articular cartilage which permits the synovial fluid to enter. That influx causes additional loss and degeneration of cartilage which is then worn away. New vessels grow in from the epiphysis below the tidemark and new fibrocartilage is deposited in the crack. This material is not strong so can be eroded so the subchondral bone plate becomes thickened. Even a tiny crack in this area will permit synovial fluid to leak into the marrow producing a subchondral bone cyst. Any localized reformation of the articular surface will produce osteophytes usually at the lateral aspect of the joint. When this occurs in the fingers at the distal interphalangeal joints, it is called Heberden’s nodes.

**Clinical features**: symptoms vary depending upon which joint is involved. However, deep pain after exercise and relieved by rest is characteristic of osteoarthritis. The pain fibres are in the periarticular structures, as articular cartilage itself has no nerve supply.
Restriction of joint movement indicates severe joint disease which may be due to contractures of the joint or adjacent muscles, loose bodies in the joint, the presence of large osteophytes and loss of alignment of the joint surfaces.

**Macro:** courtesy of University of Tasmania, Discipline of Pathology

The articular surface over half of the femoral head is denuded of cartilage with exposure of underlying smooth bone (eburnation). The remaining cartilage shows fissuring and flaking. The margins of the articular surface are extremely irregular. This irregularity is due to the formation of multiple small osteophytes, most of which are covered by cartilage.

**Micro:** articular cartilage has loss of proteoglycans, so the surface of the articular cartilage which should be smooth shows *fissuring, pitting and flaking*. In some areas the articular cartilage has disappeared altogether, exposing subchondral bone. This leads to increased vascularity and thickening of the bony trabeculae in a number of areas. In other areas death of osteocytes or increased osteoclastic activity has led to thinning of the bony trabeculae with microcyst formation. As a result of all these changes, deformation of the articular ends of the bone may occur.
**X-ray:** main features for all joints are asymmetrical joint space narrowing, subchondral sclerosis of bone, marginal osteophytes and subchondral cysts.

**Case 1**

In the xray of the hand – *image A*, courtesy of Paul and Juhl, note the characteristic changes of the distal interphalangeal joints with asymmetrical narrowing, subchondral sclerosis and marginal spurs but minimal subluxation. The proximal interphalangeal joints are almost spared.

*Image B* displays subluxation, subchondral sclerosis and spur formation of the first carpo-metacarpal joint of the thumb.

**Case 2.** Xray of shoulder osteoarthritis has superior migration of the humeral head so that it is in contact with the undersurface of the acromion and the glenohumeral joint is asymmetrically narrowed. This picture is associated with a tear of the rotator cuff. Note the marginal spur formation on the inferior aspect of the humeral head – see arrow. Courtesy Paul and Juhl.

**Case 3.** *Image A.* Osteoarthritis of the hip with characteristic joint changes: asymmetrical joint space narrowing, spurs, subchondral sclerosis and cyst formation.

*Image B,* a CT scan shows better the subchondral cyst formation – block arrow and the spurs on the anterior and posterior rims of the acetabulum – straight arrows. Courtesy Paul and Juhl.
Case 4. Osteoarthritis of the knee – courtesy of Paul and Juhl.

Image A – shows a narrowed medial compartment with marginal spurs and there is a ‘bow leg deformity’.

Image B – a lateral view shows spur formation of the patellofemoral joint and of the posterior margin of the femoral condyles.

Case 5. Severe osteoarthritis of the knee with subluxation.

Treatment: Medical - exercise, weight loss, and administration of glucosamine, chondroitin capsules.

Surgical: Joint replacement may be necessary.

Prognosis: untreated the arthritis becomes progressively worse.

Joint replacements have varying lives from 5 years to 20 years.

Unfortunately one of the complications of surgery is always infection and loosening of the prosthetic devices can occur requiring re-operation. In the image below, courtesy of Paul and Juhl, shows in image A the strip of radiolucency following the stem of the prosthesis – white arrows. Wire sutures are in the greater trochanter. In image B, from a hip arthrogram where contrast was injected into the joint space, shows contrast – black arrows – has been able to track down along the space around the stem of the prosthesis showing the prosthesis is loosening.
NEUROPATHIC JOINT DISEASE

**Definition**: a consequence of Primary neurologic disease - syringomyelia, tabes dorsalis, leprosy, transection of the spinal cord, peripheral nerve injury, diabetes.

**Site**: Tabes dorsalis affects the weight-bearing joints of the lower limbs most frequently followed by involvement of the lumbar spine.

Syringomyelia is more likely to involve the upper limbs.

Diabetes – neuropathy affects the feet and ankles.

**Pathogenesis**: Due to impaired sensation, repeated minor trauma results in fragmentation of the articular cartilage and the apposing margins of bone, with severe disorganization of the joint. Haemorrhage occurs into the joint and adjacent soft tissues.

**x-ray**: The principal features are soft-tissue swelling, bone fragmentation and sclerosis of bone at the margins of the joint. In the early stages the findings are confined to soft tissue swelling due to the presence of effusions. The apposing margins of the bone become fragmented. Later there is a general breakdown of the joint. Progress can be rapid, within one to six weeks after looking a normal joint.

Multiple small ossific fragments are found in and around the joint and sometimes these are quickly absorbed. The debris can extend out of the joint capsule, dissecting along fascial planes. Subluxation is frequent and can occur early.

In the spine, vertebral bodies increase in density and undergo some degree of compression and fragmentation as well as change in alignment. The intervertebral disc becomes thin and may disappear altogether.

In the image below, courtesy of Paul and Juhl, the x-ray of the shoulder of a patient with syringomyelia shows in A, small fragments of bone within both the joint and the soft tissue lateral to the head of the humerus – see arrows. The humeral head is flattened and there is inferior subluxation. In image B, one week later, there is complete disintegration of the humeral head with multiple fragments of bone in and around the joint which are more widely dispersed than one week earlier.
**Diabetes** arthropathy is confined almost exclusively to the ankle and foot, rarely involving the hands, femur and tibia. Main features are fractures and dislocations, fragmentation, sclerosis, osteolysis and periosteal reaction. Calcification of the small arteries of the foot is frequent. Destructive changes are extensive, progressing to absorption of the distal ends of the metatarsals with pencil-point narrowing and arthritis mutilans. Fractures and fracture-dislocations of the tarsals or metatarsals are common.

In the images above, courtesy of Paul and Juhl, image A shows there has already been amputation of the fifth toe and metatarsal. There is a radiolucent area – white solid arrow – at the site of an ulcer. Periosteal new bone formation is present along the distal lateral margin of the 4th metatarsal – open arrow. In image B the ankle joint is completely destroyed and there is calcification in the posterior tibial artery.

**METABOLIC JOINT DISEASE**

**Gout**

**Definition:** is a metabolic abnormality of purine metabolism characterized by intermittent acute attacks of arthritis, an increase in serum uric acid and deposition of sodium urate in joints, bones and periarticular tissues.

**Sites:** any joint but especially the first metatarso-phalangeal joint of the great toe. Feet, ankle, knees, wrists and hands can be affected.

**Incidence:** affects 1 – 2% of the Western population.
Gender: more common in males but women become more susceptible after menopause.

Age: in men between 30 and 50 years. Women develop signs and symptoms usually after the menopause.

Etiology: attacks occur when urate crystals accumulate within joints

Clinical presentation: sudden acute attacks of pain, often at night and lasting for several hours. The pain can last several days or weeks. The joint is swollen, hot and red. Decreased joint mobility occurs with progression of the disease.

The patient may have irregular, superficial soft tissue masses of varying size in the periarticular region – called tophi. These are accumulations of monosodium urate monohydrate crystals. The photo below, courtesy of Wikipedia, shows the redness over the swollen joint – see arrow.

Complications: gout may be a single attack but if recurrent can result in erosion and destruction of a joint. Untreated gout may cause deposits of urate crystals to form under the skin as nodules called tophi. Tophi can develop in fingers, hands, feet, elbows, Achilles tendon. These are not tender but can become swollen and tender during gout attacks.

Kidney stones formed of urate crystals can collect in the renal tract.

Risk factors: diet high in uric acid, obesity, hypertension, use of thiazide diuretics, a family history of gout.

Gout frequently occurs in combination with other medical problems. Metabolic syndrome, a combination of abdominal obesity, hypertension, insulin resistance and abnormal lipid levels, occurs in nearly 75% of cases. Other conditions commonly complicated by gout include: polycythemia, lead poisoning, kidney failure, hemolytic anemia, psoriasis and solid organ transplants. A body mass index greater than or equal to 35 increases male risk of gout threefold. Chronic lead exposure and lead-contaminated alcohol are risk factors for gout due to the harmful effect of lead on kidney function.

Vitamin C intake of 1,500 mg per day decreases the risk of gout by 45%.

X-ray: changes are not seen on xray until the disease has been present 6 – 8 years. Plain films can be diagnostic but CT may provide more detail of the crystals. As tophi, which may or may not show calcification, enlarge these cause localized punched-out defects at the margins of the joints and in the ends of the bone.

Xray features also show preservation of the joint space until very late in the disease and no evidence of osteoporosis.

Tophi may also form in bursae, especially the olecranon bursa and then cause erosion of the underlying olecranon.
The bony erosions are often defined by a sclerotic margin and when at the periphery of a joint, seen with an overhanging hook of bone due to a minimal periosteal reaction to the urate deposit.

In the xray below (courtesy of Paul and Juhl), note in A – the great toe, note the asymmetrical soft tissue masses containing calcification, around the 1st metatarso-phalangeal joint and the interphalangeal joint. There are also erosions at the margins of the joints The arrow points to the hook-like overhang at the base of the proximal phalanx. In B there is a very large soft tissue mass around the proximal interphalangeal joint with erosions at the margins of the joint – note the hook-like overhang - but with preservation of the joint space.

**Micro:** urate crystals are shaped like needles with pointed ends – image courtesy of BM Rothschild. Medscape Jan 31, 2016.

**Biochemistry:** serum uric acid and creatinine abnormal.

**Diagnosis:** Aspiration of the joint fluid may find urate crystals. However, the use of ultrasound can find urate crystals in a joint or tophus, avoiding instrumentation.

**Treatment:** is medical. Non steroidal anti-inflammatory drugs and colchicine can relieve pain. Corticosteroids may only be given if the patient cannot have the first two drugs.

As maintenance drugs - xanthine oxidase inhibitors; for example allopurinol.

Probenicid improves the ability of the kidneys to remove uric acid which will decrease the serum level of uric acid.

**Prognosis:** Without treatment, an acute attack of gout usually resolves in five to seven days; however, 60% of people have a second attack within one year.

Without treatment, episodes of acute gout may develop into chronic gout with destruction of joint surfaces, joint deformity and painless tophi. These tophi occur in 30% of those who are untreated for five years, often in the helix of the ear, over the olecranon processes, or on the Achilles tendons. With aggressive treatment, they may dissolve. Kidney stones also frequently complicate gout,
affecting between 10 and 40% of patients and occur due to low urine pH promoting the precipitation of uric acid.

**Pseudogout – also called Calcium pyrophosphate disease (CPPD)**

**Definition:** deposition of calcium pyrophosphate dihydrate crystals in the joint cartilage and periarticular tissues.

**Sites:** most common in knee, radio-carpal joint, the metacarpophalangeal joints of the hand, the shoulder and the hip.

**Age:** elderly persons.

**Clinical presentation:** varies.

- there can be intermittent acute attacks of arthritic pain associated with a joint effusion resulting in acute synovitis caused by the presence of crystals in the joint.
- continuous acute attacks of arthritic pain
- progressive chronic arthritic pain, interrupted by acute attacks.
- progressive chronic arthritis without acute episodes.

**Gender:** acute type is more common in men and the chronic form more common in women.

**Diagnosis:** identification of the calcium pyrophosphate crystals in synovial fluid.

**Sites:** Chondrocalcinosis usually appears in the triangular ligament of the wrist, the menisci of the knee, the symphysis pubis, and the hyaline cartilage of the hip and shoulder. Linear calcifications may be seen in the capsules of the small joints of the hand.

**x-ray:** chondrocalcinosis, calcifications in the fibrocartilage and hyaline cartilage pf the knees and wrists. See the xrays below, courtesy of Paul and Juhl showing the knee with calcification in the menisci, wrist with calcification in the triangular cartilage (see arrow) and in the fibrocartilage of the symphysis pubis.

**Haemochromatosis**

**Definition:** the disease is frequently associated with an arthropathy due to iron accumulation in joint tissues and which may appear before other signs of the disease (diabetes, cirrhosis and brown skin pigmentation).
X-ray: the changes are almost identical to those of CPPD.

It is associated with characteristic radiologic findings; squared-off bone ends and hook-like osteophytes in the metacarpophalangeal (MCP) joints, - see arrows on xray below- particularly in the second and third MCP joints. Symptoms usually do not respond to iron removal.

Bones are very osteopaenic.

Hyperparathyroidism

Discussion: this condition characteristically causes resorption of the radial aspects of the phalanges and erosive changes in the ungual tufts (acro-osteolysis). However, arthritis is sometimes seen as well. Also chondrocalcinosis and capsular calcifications similar to CPPD, subchondral erosion of bone in the sacro-iliac, sterno-clavicular and acromio-clavicular joints, the symphysis pubis and the metacarpo-phalangeal joints of the hand.

Spontaneous ruptures of tendons can occur - usually the quadriceps and infrapatellar tendons.

X-ray: courtesy of Dr Andrew Dixon, Radiopaedia.org, rID 9738. Arrows indicate the acro-osteolysis in the terminal portion of the distal phalanx.
**Ochronosis – alkaptonuria**

**Definition:** is a rare inherited genetic disorder of phenylalanine and tyrosine metabolism.

**Incidence:** 1 in 10,000 newborns. Or 1: 250,000 population.

**Age:** onset is noticed in the 4th or 5th decade.

**Genetic:** autosomal recessive condition caused by a defect in the enzyme homogentisate 1,2-dioxygenase which is involved in the degradation of tyrosine. This means that homogentisic acid and its oxide accumulate in blood and are excreted in large amounts in the urine. The polymer of homogentisic acid – alkapton – impregnates slow-growing tissues.

1993 Pollak found the defect was localized to chromosome 3q21-3. The defect has been associated with 40 mutations of the gene.

**Gender:** M: F = 2 : 1

**Clinical:** the patient notices the urine is very dark or becomes black after standing. Ear wax is dark. There is pigmentation of the conjunctiva and cornea in 70% patients. Colour changes in the pinna of the ear occur by age 15 years and bluish-black lumps develop in the soft tissue. Deposition of homogentisic acid results in degeneration of articular cartilages and arthropathy.

The first subjective difficulties appear at the end of the third decade of life. Objective findings include flattening of thoracic kyphosis and lumbar lordosis, mild rigidity with a tendency to deterioration. Later, in an advanced stage, the contours of the spine worsen with irregular spinous processes and complete ankylosis of the entire lumbar and thoracic spine. The spine is rigid, irregular and the contours do not change when bending forward. As a result of degenerative changes to the plates in the narrowing of the intervertebral space, body height decreases up to 8 cm in 20 years.

In the shoulder joints in the early stages of ochronosis, there are painful episodes of the type of humeroscapular peri-arthropathy that are probably related to the deposition of pigment and calcium deposits tendons in the rotator cuff tendons. Gradually, the mobility gets limited due to the retraction of the joint capsule, destruction of the cartilage and the adjacent bone structures.

**Sites:** While the spine is affected in all patients with ochronotic arthropathy, peripheral joints are also often affected. Small joints are spared and large joints are affected in the following order: knee (64%), shoulders (42%) and hips (34%).

**x-ray:** there is extensive calcification of the intervertebral discs, especially in the thoraco-lumbar region. The disc degenerates and the disc space thins often associated with a vacuum phenomenon. There is subchondral sclerosis in the vertebral end-plates with minimal spur formation. There is severe osteoporosis due to immobility.

Joint findings are similar to osteoarthritis but characteristically have free calcified pea-sized bodies of varying shape. The symphysis pubis may show calcification, subchondral destruction and fusion.

In the images below of the thoraco-lumbar spine, courtesy of Dr Mohammed Taghi Niknejad, Radiopaedia.org, rID: 21293, note the densely calcified discs and syndesmophytes.
Treatment: In children with alkaptonuria, mild restriction of daily intake of proteins rich in phenylalanine and tyrosine, as well as the application of ascorbic acid supplemented with vitamins E, A and selenium is recommended. In addition, the recommendations include a daily regimen saving the sites predilected to be affected – large joints and the spine with corresponding selection and implementation of a profession and care with sports.

Wilson’s disease - hepato-lenticular degeneration

See detailed account of the non-joint aspects in the module Liver and Gallbladder.

Definition: This is an autosomal recessive genetic disorder in which copper accumulates in the tissues causing especially liver disease and neurological or psychiatric symptoms such as tremor and abrupt personality change. Osteoporosis occurs in 50% of patients. The arthropathy of Wilson’s disease is a degenerative process that resembles premature osteoarthritis.

Age: Symptomatic joint disease usually arises late in the course of the disease, frequently after age 20 years

Features of joint involvement: subarticular cysts, and fragmentation of subchondral bones particularly in the hands, feet, wrists and ankles. The fragments are small and look like accessory ossicles.

Also find osteochondritis dissecans, irregularity of the vertebral end-plates, squaring of the vertebral bodies and vertebral body wedging.

Periarticular calcification occurs at the insertions of tendons and ligaments.

Earliest changes are seen in the metacarlo-phalangeal joints, especially the 2nd and 3rd, where there is joint space narrowing, small subchondral cysts and broad based osteophytes. This is very similar to chondrocalcinosis or CPPD.

Cyst formation, erosions and osteophytes may also occur in the carpal joint.

There is a generalized osteoporosis.
PRIMARY SYNOVIAL DISEASE

**Osteochondromatosis**

**Definition:** is a rare disorder of the joint, tendon sheath or bursa characterized by proliferation of synovial villi and cartilage formed by chondrometaplasia of the subsynovial connective tissue. The masses may become detached and lie free within the joint, forming loose bodies. In larger joints these can be 1 cm in diameter.

**Sites:** most frequent in the knee and elbow and occasionally in the shoulder and small peripheral joints.

**Gender:** Male: Female = 2 : 1

**Age:** usually in the 40’s but can occur in the teens or 20’s.

**Pathology:** Calcification and ossification of the masses is common, with a lamellated appearance. Often there is an associated joint effusion and degenerative arthritis can occur.

**Xray:** Loose bodies may cause pressure erosions at the margins of the joint. In 30% there is no calcification. See image of shoulder below, courtesy of Paul and Juhl.

![Image of shoulder](image-url)

**Diagnosis:** arthrography or MRI which demonstrates the hypertrophied villi as irregular masses within the joint. CT shows the loose bodies.

**Treatment:** Treatment is frequently by means of removal of the loose bodies and of a partial or full Synovectomy.

Full synovectomy involves completely exposing the joint and removing the affected tissue. Partial synovectomy is normally done arthroscopically. Synovectomies are normally carried out by shaving the lining of the knee but there are other ways of achieving this by either freezing the synovium or by the use of radiation treatment.

**Prognosis:**

The need for further procedures is greater than 25% although normally the frequency of the required removal of loose bodies is reduced by the previous synovectomy. There have been documented cases of malignant transformation but this is rare.

**Transient synovitis of the hip**

This characteristically occurs in children under the age of 10 years.

**Clinical:** pain and limping with the thigh held in flexion and a joint effusion may be present.

**Prognosis:** the disease is self-limiting and leaves no sequelae.
Eosinophilic synovitis

Eosinophilia of synovial fluid is an uncommon condition. The majority of the reported cases are associated with diseases such as rheumatoid arthritis, parasitic disease etc. The cases of eosinophilic synovitis with unknown cause – idiopathic -have oligoarthritis (arthritis affecting one to four joints during the first six months of disease), massive eosinophilia, and Charcot-Leyden crystals in synovial fluid (a marker for an allergic condition - see below).

NON-NEOPLASTIC CONDITIONS – MISCELLANEOUS

Amyloidosis

Definition: a rare disease where amyloid is deposited in an extra-cellular location, in many organs, including bones and joints.

Sites: commonly shoulders and hips and less often wrists and elbows and tends to be bilateral.

Age: occurs in the elderly.

Clinical: patients have painful joints and gross enlargement of the periarticular soft tissues.

If it affects the wrist there is frequently bilateral carpal tunnel syndrome.

Amyloid arthropathy results from the deposition of β₂-microglobulin, particularly in renal failure patients undergoing long-term haemodialysis. This abnormal material covers the synovial membrane, fills subchondral defects, and extends to periarticular soft tissue

Pathogenesis probably relates to the duration of renal failure, patient’s age, age at commencing haemodialysis and duration of haemodialysis.

Xray:

- juxta-articular osteoporosis
- soft-tissue swelling
- subchondral cysts which can be large
- pressure erosions from synovial hypertrophy
- joint spaces are preserved until late in the disease
- pathological fractures can occur through subchondral cysts in the femoral neck.
In the shoulder case below, courtesy of Radiopaedia.org, rID: 11182, see these features on CT scan.

Haemophiliac Arthropathy

**Definition:** degeneration of the articular cartilage and erosion of bony surfaces due to repeated haemorrhages causing a synovitis from the irritating effect of the blood.

**Sites:** any joint but especially the knee, ankle and elbow.

**x-ray:**
- first feature is a joint effusion
- after several haemorrhages the soft tissues become thickened
- in chronic cases the soft tissue may have an increase in density due to the deposition of iron pigment
- subchondral cysts form due to haemorrhage into the ends of bones
- joint margins are eroded and irregular
- the intercondylar notch in the femur widens if the knee is involved
- MRI shows synovial hypertrophy as areas of low signal on T1 and T2 sequences
- acceleration of epiphyseal growth from chronic irritation develops into enlargement of the ends of bones
- If haemorrhage occurs into bone distant from a joint, a cyst-like cavity forms which can expand and is called *pseudotumour of haemophilia*. The ilium and calcaneum are frequently sites for this lesion.

In the images below of knees, courtesy of Paul and Juhl, note in the left image of a child there is a dense joint effusion. The right image of a 25 year old shows irregular joint surfaces, marginal osteophytes and subchondral cysts and a widened intercondylar notch in the distal femur – arrow.
The image of the calcaneum shows a haemophiliac pseudotumour – see arrow.

**Relapsing polychondritis**

This is a rare condition with an auto-immune pathogenesis.

**Incidence:** 3 per million

**Age:** 4th or 5th decade

**Gender:** slight female preponderance

**Clinical:** Musculoskeletal - Polyarthritis or monoarthritis, myalgias, back pain, rib pain, sternal pain, calf pain or claudication, and migratory or generalized arthralgias.

Also involves the cartilage of the nose, the ear, the tracheo- bronchial tree (50% cases) and laryngeal structures.

**Xray:** - CT chest findings may add weight to the diagnosis of the arthropathy.

**Diagnosis:** there is no specific test. The ESR and C-reactive protein are elevated in the acute phases of the disease. If tissue cartilage is biopsied, the involved cartilage will demonstrate nonspecific signs of inflammation.

**Other diseases that can be associated with relapsing polychondritis:** Vasculitis, Wegener's granulomatosis, systemic lupus erythematosus, ankylosing spondylitis, Reiter's disease, psoriatic arthritis, rheumatoid arthritis, Behcet's disease, Churg-Strauss syndrome, polyarteritis nodosa and myelodysplasia.

**Treatment:** main drug is systemic corticosteroids. Other medications reported to control symptoms and, perhaps, progression of the disease, include dapsone, azathioprine, methotrexate, cyclophosphamide, and cyclosporin.

**Prognosis:** depends upon which tissues are involved.
Lipoid dermatoarthritis (reticulohistiocytosis)

**Definition:** This is a rare systemic disease of unknown etiology characterized by a nodular eruption of the skin, mucosa and synovia, resulting in destructive arthritis and disfigurement of the facies.

**Imaging:**

It can have similar plain film findings as gout and rheumatoid arthritis (RA), although unlike these two other conditions, it is associated with *joint space widening*.

Features are bilateral and symmetric and include:

- sharply demarcated marginal erosions: can have a strikingly bilateral symmetrical distribution and often sharply circumscribed and rapidly progressive
- nodular soft tissue swelling: may be appreciated as prominent, uncalcified nodules of skin, subcutaneous tissue and tendon sheaths
- predisposition for *interphalangeal joints*
- there can be a tendency toward early and severe atlanto-axial involvement
- no or mild periarticular osteoporosis (unlike rheumatoid arthritis)
- often a disproportion between severity of joint destruction and mildness of symptoms regardless of therapy.
- absent or minimal periosteal reaction

See image of the hand, courtesy of Dr Amir Rezaee, Radiopaedia.org, rID: 21155.

**Diagnosis:** Biopsy of a nodule, whether from skin or synovia, discloses a cellular infiltrate consisting of histiocytes and multinucleated giant cells with lipid inclusions.

**Micro:** electron-dense granules found in the large mononucleated or multinucleated giant cells are characteristic of this entity.

**Treatment:** No effective treatment is known.
REACTIVE TUMOUR-LIKE CONDITIONS

Overview: reactive tumour-like lesions such as ganglions and synovial cysts commonly involve joints and tendon sheaths. They are usually the result of trauma or degenerative processes and are more common than neoplasms.

Ganglion

Definition: a ganglion is a small cyst, usually 1.0 – 1.5 cm diameter usually located near a joint capsule or tendon sheath.

Site: common location is around the joints of the wrist

Pathology: it is a firm, fluctuant pea-sized nodule and is the result of cystic or myxoid degeneration of connective tissue so does not have a true cell lining. It can be multi-locular and can increase in size by coalescence of adjacent areas of myxoid change. The cyst does not communicate with the joint space, unlike the synovial cyst.

Synovial Cyst

This is the result of herniation through a joint capsule or massive enlargement of a bursa. Most common example is the synovial cyst in the popliteal fossa – Baker’s cyst – in patients with rheumatoid arthritis and osteoarthritis. The synovial lining may be hyperplastic and contain inflammatory cells and fibrin.

Site: a Baker’s cyst or popliteal cyst, has a constant location between the tendons of the medial head of gastrocnemius and semi-membranosis muscles. These cysts contain loose bodies or pannus.

In the MRI image T1 weighted below, a patient with osteoarthritis, courtesy of Paul and Juhl, the ovoid area of low signal – block arrow, is overlying the medial head of gastrocnemius muscle – white asterisk. The cyst contains loose bodies which have a higher signal but fine rim of black – black asterisk. Degenerative arthritis is present with narrowing of the articular cartilage and marginal spurs. There is also a tear in the posterior horn of the medial meniscus.
The next case is also a MRI but T2 weighted sequence and shows a posterior protrusion of a popliteal cyst – see black asterisk and situated between the medial head of gastrocnemius – arrowhead and semimembranos tendon - arrow. This cyst is contiguous with the joint space overlying the medial femoral condyle – C.

![MRI Image](image)

**TUMOURS**

**Tenosynovial giant-cell tumour (Pigmented villonodular synovitis)**

**Definition:** It is a disease of unknown etiology occurring in young adults and characterized by villous and nodular hyperplasia of the synovium either in joints or in tendon sheaths. The term is applied to several related benign neoplasms that form in the synovial lining of joints, tendon sheaths and bursae.

There is a localized form affecting the smaller joints (giant cell tumour of tendon sheath) and a diffuse form affecting the larger joints (tenosynovial giant-cell tumour - TSGCT).

**Site of diffuse form:** It is usually monoarticular involving the knee in 80% of cases. The other 20% of cases in descending order of frequency are hip, ankle, small joints of the hands and feet, shoulder and elbow.

**Gender:** More common in men than in women.

**Incidence:** 2 cases per million for the diffuse form and 9 cases per million for the localized form.

**Age:** Any age but commonest between 20 and 50 years.

**Clinical:** Complaint is pain and swelling of the joint.

**Diagnosis:** Joint aspirates are sero-sanguinous. The disorder is difficult to identify and is often not diagnosed for four years or more after presentation due to nonspecific symptoms.

**x-ray:** Most common finding is soft tissue swelling and in the knee this shows by distension of the suprapatellar bursa.

Osteoporosis is not a feature and the joint space is maintained.

Sharply margined cortical and subchondral erosions occur in the majority of cases in joints with tight capsules such as the hip but occur in only 25% of cases when it is the knee affected.
CT demonstrates erosions and nodular soft-tissue masses within the joint.

In the images below, courtesy of Paul and Juhl, the AP film of the right hip shows erosions with a fine sclerotic rim, of the acetabulum, the femoral neck and head. The CT scan confirms those findings and there is distension of the joint with lateral displacement of the femoral head due to an effusion.

Tenosynovial giant cell tumour can be radiologically diagnosed by magnetic resonance imaging. MRI of the same patient shows on the T1-weighted image (upper) there are variable areas of low signal filling the joint space — see arrow. The coronal view of the T2-weighted sequence (lower) shows low signal of the masses filling the joint space — see arrow. The low signal of the masses on both T1 and T2 is due to haemosiderin deposition in the hypertrophied synovial villi which is characteristic of this condition. Another synovial condition that does the same is synovial osteochondromatosis but this can be excluded by the presence of calcification of loose bodies on plain x-rays which is not seen in tenosynovial giant cell tumour. Other synovial conditions show high signal on T2.

**Complications:** Tenosynovial giant-cell tumour is locally aggressive and can spread to surrounding tissues, causing bone erosion and tissue damage. If not treated early, it can spread to areas outside the joint, and potentially cause permanent loss of range of movement, as well as intense pain.
**Microscopic:** Courtesy of Wikipedia - see the haemosiderin-laden macrophages – reddish brown items. It is composed of nodules and/or villi.

**Treatment:** Once the condition is confirmed by biopsy of the synovium of an affected joint, a synovectomy of the affected area is the most common treatment. Bone lesions caused by the disorder are removed and bone grafting is performed. In some cases, a total joint replacement is needed to relieve symptoms when there has been significant joint destruction.

**Prognosis:** Because the diffuse type has a 45% rate of recurrence, radiation therapy may be considered as a treatment option.

**Synovial haemangioma**

**Definition:** rare benign vascular malformations that occur in relation to a joint.

**Site:** most occur around the knee.

**Age:** children and young adults.

**Clinical:** pain, swelling and limited mobility. Patients can have recurrent haemarthroses.

**Xray:** Plain film findings are generally nonspecific and lesion may be seen as a soft tissue mass adjacent to the knee. Accompanying phleboliths may be present.

**MRI:** Typically seen as a lobulated or diffuse intra-articular mass - see image courtesy of Dr Roberto Schubert, Radiopaedia.org, rID: 24712 showing a high intensity background on T2 in the infrapatellar region due to blood lakes, with strands of fibrous tissue running through it.
**Treatment:** Local pedunculated synovial hemangiomas are removed surgically, often through an arthroscope. More diffuse lesions may be treated with intra-articular low-dose radiation therapy, open excision, or both when sufficiently symptomatic.

**Prognosis:**

For the diffuse type those symptomatic enough to indicate treatment are those most likely to be incompletely excised, and thus, to recur. Recurrence rates following surgery range from 18-50%.

Patients with localized synovial hemangiomas tend to have excellent results following surgical excision.

**Synovial sarcoma**

The term is a misnomer because the lesion does not arise from synovium or differentiate towards synovium. Its origin is probably from undifferentiated mesenchymal tissue with variable epithelial differentiation.

**Site:** 60% involve the lower limb, especially around the knee. However, it is the most common malignancy of foot, ankle and lower limb in the age group 6 – 35 years.

Only 10% are intra-articular.

**Age:** 15 – 35 years

**Frequency:** it is the 4th most common primary malignancy of soft tissues neoplasm.

**Clinical:** patients present with a deep-seated mass which may have been present for years.

Tumour metastasizes to lungs, skeleton and lymph nodes in 80% of patients.

Metastases are present on initial consultation in 25% of patients.

**Macroscopic:** The gross pathologic appearance of synovial sarcoma is non-specific, with a gray to yellow color and fish flesh consistency. These lesions may be well defined, if they are small, or poorly defined. Synovial sarcomas are frequently multi-lobulated, and areas of necrosis, hemorrhage, and cyst formation are common.

**Imaging:** **Radiographs** appear normal in 50% of cases. Synovial sarcomas detected at radiography typically appear as nonspecific, round to oval juxt-articular soft-tissue masses. Calcification is present in 30%. Calcifications are often eccentric or peripheral within the soft-tissue mass and nonspecific in appearance. In rare cases, extensive chondroid or osteoid mineralization has been described. Extensively calcified lesions may also be associated with an improved prognosis.

Involvement of underlying bone is not uncommon, particularly in comparison to the low frequency of osseous extension seen with other soft-tissue sarcomas. Extrinsic erosion of bone or periosteal reaction has been reported in 11%–20% of synovial sarcomas.

The bone erosion often has an indolent nonaggressive appearance on radiographs, which can lead to misinterpretation of the lesion as representing a benign process. Aggressive bone invasion and
destruction of the trabeculae in the marrow canal is less common and may be seen in approximately 5% of cases.

**Angiography** shows the lesion is hypervascular and displaces the native vessels. Arteriovenous shunting is seen in approximately 25% of cases.

**CT** appearance of synovial sarcoma is a heterogeneous deep-seated soft-tissue mass with attenuation similar to or slightly lower than that of muscle. Areas of lower attenuation representing necrosis or hemorrhage are also common. Smaller lesions may be more homogeneous. In a minority of cases, low-attenuation areas may be predominant, an appearance that simulates a haematoma or cystic mass. Synovial sarcoma frequently demonstrates a multi-nodular morphology on CT scans. A well-defined margin is present in 50%. CT scans post intravenous contrast show heterogeneous enhancement in 90%–100% of cases. This feature is quite helpful for distinguishing those synovial sarcomas that initially appear as a cystic lesion or haematoma on pre-contrast images, as the heterogeneous enhancement pattern excludes these diagnoses. Nodular areas of enhancement may also be seen in these lesions.

CT is also useful for detecting calcification and bone involvement in synovial sarcoma, particularly in complex areas of the anatomy such as the pelvis, hip, or shoulder or when the lesions are small and subtle. Calcification has been seen on CT images in 27%–41% of synovial sarcomas. Calcification may also be identified in metastatic deposits, particularly in the lung, on chest CT scans. Bone involvement, either as erosion or marrow invasion, can be seen in nearly 25% of lesions.

MR imaging is the optimal radiologic modality for assessing the extent and intrinsic characteristics of synovial sarcomas for staging and diagnosis. On T1-weighted MR images, synovial sarcoma typically appears as a prominently heterogeneous multi-lobulated soft-tissue mass with signal intensity similar to or slightly higher than muscle.

In the case below, (courtesy of MD Murphey, MS Gibson, BT Jennings, AM Crespo-Rodriguez, J Fanburg-Smith, DA Gajewski. 2006 Radiographics 26 (5) Sept-Oct) the 36 year old woman had had a mass anterior to the elbow enlarging over 15 months.

Plain film lateral – left – show a large calcified soft-tissue mass – see arrows – anterior to the elbow with no effusion in the joint. The middle image is a CT scan also showing the calcified mass – arrow.

The right image, MRI - shows a large heterogenous soft tissue mass - arrowheads – with low to intermediate signal intensity areas corresponding to the calcifications. As there is no joint effusion, this is thought to be juxta-articular, not intra-articular.
**Microscopic:** There are three main histologic subtypes of synovial sarcoma: biphasic, monophasic, and poorly differentiated.

**Biphasic synovial** sarcoma - 20%–30% of lesions have both a mesenchymal spindle cell component and an obvious epithelial component as seen at light microscopy. The epithelial cells usually form glands, but they may also be seen as solid sheets, nests, cords, and papillary structures, and they may show squamous metaplasia. The glandular component may predominate and occasionally obscure the spindle cell elements, an appearance suggestive of adenocarcinoma and that has been referred to as the purely glandular type monophasic synovial sarcoma.

In the image below, the blue spindle-cell component – arrow - and pinker glandular elements – arrowhead.

**Monophasic** synovial sarcoma represents 50%–60% (the most common subtype) of all lesions, and in this subtype the mesenchymal spindle cell component predominates. These relatively bland spindled cells have ovoid pale-staining nuclei with indistinct nucleoli, a fascicular interlacing growth pattern, and mild to moderate mitotic activity. The stroma is often pinkish. Scattered mast cells are more obvious in the monophasic subtype and can aid in diagnosis of this tumor (although mast cells are also observed in nerve sheath tumors, lipomatous tumors, and other neoplasms). The monophasic subtype also generally demonstrates a hemangiopericytoid vascular pattern, often stromal collagen, and occasionally microcalcifications and metaplastic bone (calcifying synovial sarcoma).

The image below shows fascicles and sheets of uniform oval cells but without a glandular component. The inset shows scattered mast cells – arrowheads.
**Poorly differentiated** synovial sarcomas are generally epithelioid in morphology and have high mitotic activity (usually > 15–20/10 high-power field) with geographic necrosis. This subtype represents up to 15%–25% of all synovial sarcomas. There is perivascular tissue sparing, in which rings of tumor form around vessels, with large areas of adjacent geographic necrosis. Poorly differentiated synovial sarcomas can be confused with round cell tumors, such as Ewing sarcoma, although differentiation can be accomplished with immunohistochemical staining and molecular methods. In the image below, there is an epitheloid growth pattern and uniform round cells which differentiates this from other small round blue cell tumours such as Ewing’s sarcoma, difficult without immunohistochemical staining.

![Image of synovial sarcoma](image)

**Genetic:** Cytogenetic studies show the hallmarks for synovial sarcoma are the t(X;18) translocation and SYT-SSX gene fusion products, which can be identified by using FISH (fluorescence in situ hybridization) or RT-PCR (reverse transcription polymerase chain reaction) studies, respectively. This genetic aberration has been identified in greater than 90% of synovial sarcomas and is highly specific, since it has not been identified to date in any other tumors.

**Treatment:** Cross-sectional imaging features are vital for staging extent and for planning surgical resection. Treated with aggressive surgery with limb-sparing and often chemotherapy.

**Prognosis:** 5-year survival varies from 25% to 60% but only 30% are alive at 10 years. Tumour size is the most important factor determining prognosis.

**Synovial chondrosarcoma**

This is a very rare tumour that originates from synovial membrane. It can arise as a primary synovial tumour or it may develop as a malignant transformation of synovial osteochondroma.

**Site:** commonest site is the knee but hip, elbow and ankle are affected.

**Gender:** slight predominance in men.

**Age:** 25 – 70 years.

**Clinical:** pain and swelling that has been present about 12 months.

**Xray:** chondroid calcification within a joint, destruction of the adjacent bones, soft tissue mass
MRI of right hip shows high signal in an adjacent lymph node – white arrow, similar to the mass signal -  courtesy of TR Schlachter and Z Matlynk-Urman, Radiographics, 31(7) :Nov-Dec 2011

Macro:  In the image below, courtesy of TR Schlachter and Z Matlynk-Urman, Radiographics, 31(7) :Nov-Dec 2011, see a cavitary lobule from the right hip, bisected. There is a thick, glistening white capsule – black arrows outer margin and white arrows inner margin, surrounding the central cavity – asterisk.

Microscopic:

- tumour cells arranged in sheets
- myxoid change in the matrix
- hypercellularity with crowding and spindling of nuclei in the periphery
- necrosis
- permeation of bone trabeculae

Same patient as Macro- note tumour tissue permeating cortical bone – arrowhead, and filling marrow spaces – black arrows, between trabecular bone – white arrow.
**Treatment:** Treatment of synovial chondrosarcoma is similar to that of other sarcomas and includes amputation or extraarticular resection with wide surgical margins.

**Summary:** Synovial chondrosarcoma is an extremely rare neoplasm that may arise de novo or secondary to preexistent primary synovial chondromatosis, which is usually the only differential diagnostic consideration. In the presence of either type of lesion, imaging studies show a multilobular intraarticular mass with signal intensity similar to that in cartilage and ring-and-arc calcifications. Recurrence of synovial lesions is suggestive of chondrosarcoma. Additional signs of malignancy include invasion of bone marrow and metastasis to a regional lymph node and the lungs.

**END**