Crystal arthritis: contemporary approaches to diseases of antiquity

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Microscopic crystals (microcrystals) within articular and periarticular tissues are among the most common causes of acute mono/polyarthritis and, less frequently, chronic arthritis. The two most common types of microcrystal synovitis are those associated with:

- monosodium urate monohydrate (MSUM): gout
- calcium pyrophosphate dihydrate (CPPD): pseudogout.

These arthritides are frequently encountered in medical inpatients in whom intercurrent illness and dehydration may trigger attacks. Other rarer forms of microcrystal arthritis are also recognised (oxalate and hydroxyapatite) but are beyond the scope of this article.

Gout

Introduction and clinical features

Hippocrates described acute gout in the 4th century BC. Dr Thomas Sydenham's classic description in the 17th century illustrates the typical clinical features (Box 1).

Gout, a common condition affecting approximately 1% of men in the UK, is a metabolic disorder characterised by chronic hyperuricaemia (uric acid serum concentrations >0.45 mmol/l). Uric acid is produced endogenously during purine metabolism and also ingested in purine rich food and drink (particularly red meat, seafood and alcohol);[1] it is excreted via the kidneys. Causes of chronic hyperuricaemia are shown in Table 1. Insulin resistance may be an important contributor to the pathogenesis of gout, since elevated insulin decreases renal excretion of uric acid.[2] Chronic elevation of serum uric acid allows the formation of MSUM microcrystals within the synovium, articular cartilage, skin and tendons. These microcrystals can trigger a significant monocyte-driven, neutrophil-mediated acute synovitis or tenosynovitis.[3]

Acute attacks of gout most commonly involve a single joint and affect men more frequently than women (the first attack usually occurring between 40 and 60 years of age). The feet are usually involved in early attacks (the 1st metatarsophalangeal joint is involved first in over 50% of cases), although the olecranon bursa and the hands can also be involved (the upper limb is more frequently affected in women).[4] Hospital inpatients not infrequently present with polyarticular attacks.[5]

Attacks can be precipitated by intercurrent infections or acute changes in serum uric acid concentration (binge drinking, dehydration, uric acid lowering treatments) and present with severe pain, swelling and redness of the affected area (appearing similar to acute cellulitis). A low-grade pyrexia is often found but the patient is usually systemically well (unless an intercurrent infection has triggered the attack). Tophi (caused by MSUM microcrystal deposition in the skin) are occasionally seen overlying the affected area (tophi overyling involved distal interphal aneal joints of the fingers are shown in Fig 1), in the pinna of the ear or over areas such as the olecranon bursa. The affected joint/joints will be warm, markedly tender and erythematous – septic arthritis and crystal arthritides, unlike other inflammatory arthropathies, are associated with overlying erythema.

Initially, attacks are generally short lived and self-limiting (characteristically lasting ca 1 week). There are frequently prolonged, symptom-free intercritical

Box 1. Dr Thomas Sydenham's description of gout ca 1680.

The victim goes to bed and sleeps in good health. About two o'clock in the morning he is awakened by a severe pain in the great toe; more rarely in the heel, ankle or instep. This pain is like that of a dislocation, and yet the parts feel as if cold water were poured over them. Then follow chills and shivers and a little fever. Now it is a violent stretching and tearing of the ligaments – now it is a gnawing pain and now a pressure and tightening … it cannot bear the weight of bedclothes, nor the jar of a person walking in the room. The night is passed in torture, sleeplessness, turning of the part affected, and perpetual change of posture; the tossing about of the body being as incessant as the pain of the tortured joint.

Key Points

Gout

Consider gout in any acute monoarthritis, not just arthritis involving the great toe

Uric acid levels are unreliable during acute attacks

Synovial fluid analysis is the key to diagnosis and enables exclusion of septic arthritis

Colchicine is best used as prophylaxis rather than for acute treatment of gout

Allopurinol is the treatment of choice for recurrent attacks of gout

Pseudogout

Pseudogout is part of a spectrum of arthritides associated with calcium pyrophosphate microcrystal deposition

Consider pseudogout in any elderly patient with acute monoarthritis of the knee, shoulder, elbow or wrist

Radiographs can be helpful in identifying chondrocalcinosis

Synovial fluid analysis is the key to diagnosis and enables exclusion of septic arthritis

Colchicine can be used for prophylaxis in patients with recurrent attacks

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periods. If untreated, the frequency of attacks increases, although the severity of individual attacks may decrease. At this later stage symptoms frequently do not entirely resolve between attacks and tophi may develop.

Diagnosis

The diagnosis can usually be made from the history and examination if there is 1st metatarsophalangeal joint involvement, but exclusion of septic arthritis is paramount in the context of an acute monoarthritis. Identification of MSUM microcrystals in a joint aspirate should be attempted whenever there is diagnostic doubt. Aspirated synovial fluid (usually cloudy in appearance) should be sent for crystal analysis as well as for microbiology. MSUM microcrystals are negatively birefringent and needle shaped (Fig 2) when viewed under compensated polarised light, the gold standard for the diagnosis of gout.

Other investigations can be unhelpful in differentiating acute gout from septic arthritis. Neutrophil leucocytosis and elevated C-reactive protein (CRP)/erythrocyte sedimentation rate (ESR) are found in both septic and crystal arthritis and radiographs are usually normal. Uric acid levels are unreliable in acute attacks – a drop in uric acid levels frequently accompanies an attack.[6]

Treatment

Guidelines for the general management of the acute hot joint have been published by the British Society for Rheumatology.[7] The specific management of gout is threefold:

- treatment of the acute attack
- prophylaxis against future attacks
- reduction of serum uric acid levels.

The acute attack. Acute attacks can generally be managed with early non-steroidal anti-inflammatory drugs (NSAIDs) until the symptoms resolve (there is little to choose between different NSAIDs). If NSAIDs are contraindicated or the patient fails to respond, intra-articular steroid injections, a short course of oral prednisolone (0.5 mg/kg/day for 5 days) or intramuscular depot steroid (eg methylprednisolone acetate 120 mg) can be given. Colchicine at escalating doses is effective, but the gastrointestinal (GI) side effects are significant and the experience frequently puts patients off taking colchicine as prophylaxis (see below). The author's practice is to use alternative options in the acute setting.

Table 1. Causes of chronic hyperuricaemia.

Increased uric acid synthesis	
Purine rich foods*	Alcoholic beverages (particularly beer) Seafood (anchovies, sardines, herring) Yeast Offal (liver, kidneys) Legumes (dried beans, peas) Meat extracts (consommé, gravy) Vegetables (mushrooms, spinach, asparagus, cauliflower)
Genetic predisposition	Lesch-Nyhan syndrome
Increased cellular turnover	Malignancy (particularly haematological) Psoriasis Lymphoproliferative disorders
Decreased renal uric acid excretion	
Renal disease	
Insulin resistance/type 2 diabetes	
Drugs	Thiazide diuretics (bendroflumethazide) Loop diuretics (furosemide) Ciclosporin Low-dose aspirin

* based on the American Medical Association guidelines.

Prophylaxis against future attacks. Colchicine (600 µg bd), a drug that inhibits neutrophil microtubule formation, reduces both the frequency and severity of attacks of gout.[8] If a patient is experiencing recurrent attacks or treatment with uric acid lowering therapy is anticipated, colchicine prophylaxis is appropriate. It is generally well tolerated

Fig 1. Tophaceous gout. Typical gouty tophi, overlying the distal interphalangeal joints, due to monosodium urate monohydrate microcrystal deposition within the skin. Tophi have a chalky appearance but are radiolucent. The chalky coloured aspirate is from the wrist joint of this patient. Image courtesy of Mr M Moughton, Medical Photographer, Hinchingbrooke Hospital, Huntingdon.

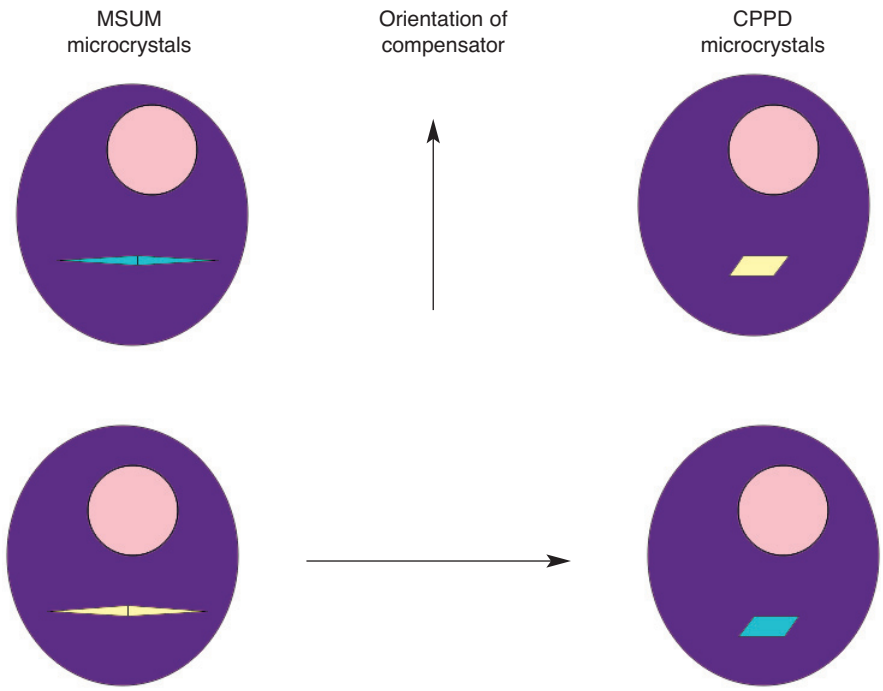

Fig 2. Diagram of microcrystal characteristics under compensated polarised light. An average white cell (pink circle) 10–15 μm in diameter is shown relative to the size of an average crystal. Compensated polarised light gives a purplish background to the field of vision since the first-order red compensator (540–575 nm) inserted between the polariser and the slide eliminates green light. Monosodium urate monohydrate (MSUM) microcrystals (needle shaped) are negatively birefringent (yellow when parallel to the orientation of the compensator, green/blue when perpendicular). Calcium pyrophosphate dihydrate (CPPD) microcrystals (rhomboid shaped) are positively birefringent (green/blue when parallel to the orientation of the compensator, yellow when perpendicular).

but a dose reduction can be helpful if there is GI upset. (The published trial[8] used colchicine 600 μg bd; only 500 μg tablets are available in the UK, so 500 μg bd or tds should be prescribed.)

Reduction of serum uric acid levels. Dietary modification with reduced intake of purine rich foods and alcohol (Table l) should usually be tried before long-term drug therapy. If insulin resistance is a possibility, reduction in total calorie intake should also be advised.[9]

Allopurinol, a xanthine oxidase inhibitor that reduces endogenous uric acid production, is generally the first-line pharmacological treatment to reduce serum uric acid levels. It is usually prescribed when more than two attacks occur in any six-month period (with hyperuricaemia) or in patients with tophi or chronic arthritis. Acute changes in uric acid concentrations during treatment initiation can prolong an acute attack or precipitate a flare. This can be reduced by delaying treatment until an acute attack has settled, then starting allopurinol at 100 mg/day with colchicine or NSAID prophylaxis. Allopurinol should then be increased by 100 mg/month (maximum 900 mg, but adjusted according to the creatinine clearance) until the uric acid level is below 0.35 mmol/l (Table 2).[10,11] Prophylaxis can be discontinued then or after six months' treatment.

If allopurinol is not tolerated, probenecid or sulphinpyrazone (uricosuric agents) are alternatives, but are generally used second-line and require caution in their use particularly in those with renal impairment.

Table 2. Recommended maximum daily allopurinol doses in renal impairment (based on the guidelines assessed in Ref 11).

Creatinine clearance (ml/min)	Maximum recommended daily allopurinol dose
Normal (>100)	≤900 mg (normal maintenance dose 300–400 mg/day)
80–100	250 mg
60–80	200 mg
40–60	150 mg
20–40	100 mg
10–20	100 mg every other day
<10	100 mg every 3 days

Calcium pyrophosphate dihydrate arthropathy and pseudogout

Introduction and clinical features

CPPD microcrystals are radio-opaque so, unlike MSUM microcrystals, can be seen deposited in the articular cartilage as chondrocalcinosis on plain radiographs (Fig 3). Predisposing conditions for CPPD microcrystal formation are shown in Table 3 and should be investigated in younger patients. CPPD microcrystals can cause a spectrum of arthropathies:

1 Chondrocalcinosis without active synovitis can be considered as a variant of nodal osteoarthritis[12] and managed identically to conventional osteoarthritis.[13]
2 CPPD microcrystals can trigger an acute, neutrophil-mediated inflammatory synovitis (pseudogout). Like gout, pseudogout presents with an acute monoarthritis (occasionally polyarthritis in inpatients[5]) with pain, erythema and swelling, frequently accompanied by low-grade pyrexia and commonly

precipitated by intercurrent illness and dehydration. The pattern of joint involvement is different from gout, tending to affect the wrists, knees, shoulders and elbows and attacks are generally more prolonged (2–3 weeks). Pseudogout tends to affect more elderly patients, usually on a background of nodal osteoarthritis. It is not uncommon for an elderly patient to develop acute pseudogout one or two days following treatment for an intercurrent infection.

3 CPPD microcrystals are also associated with chronic inflammatory synovitis, again most commonly affecting wrists, knees, shoulders and elbows,[14] presenting with similar symptoms to other inflammatory arthropathies (ie pain, swelling and prolonged early morning stiffness). This may mimic rheumatoid arthritis (RA).

4 A rarer presentation is the crowned dens syndrome where CPPD microcrystal deposition around the odontoid peg (Fig 4) causes intermittent severe neck pain, fever and elevated inflammatory markers which may be mistaken for giant cell arteritis, meningitis or malignancy.[15]

Diagnosis

Diagnosis of pseudogout generally requires exclusion of septic arthritis. The synovial fluid is frequently cloudy and blood stained and aspiration often relieves symptoms. Identification of positively birefringent, rhomboid shaped microcystals (Fig 2) with compensated polarised light microscopy is the gold standard for diagnosis of all CPPD arthropathy, although CPPD microcrystals are more difficult to identify than MSUM crystals.[16]

Mild neutrophil leucocytosis and elevated CRP/ESR are usually found in acute pseudogout, whilst chronic CPPD arthritis is characterised by an elevated CRP/ESR with a negative rheumatoid factor. Radiographs may show chondrocalcinosis of the articular cartilage of the knee (Fig 3) or triangular fibrocartilage of the wrist and can be helpful in diagnosis.

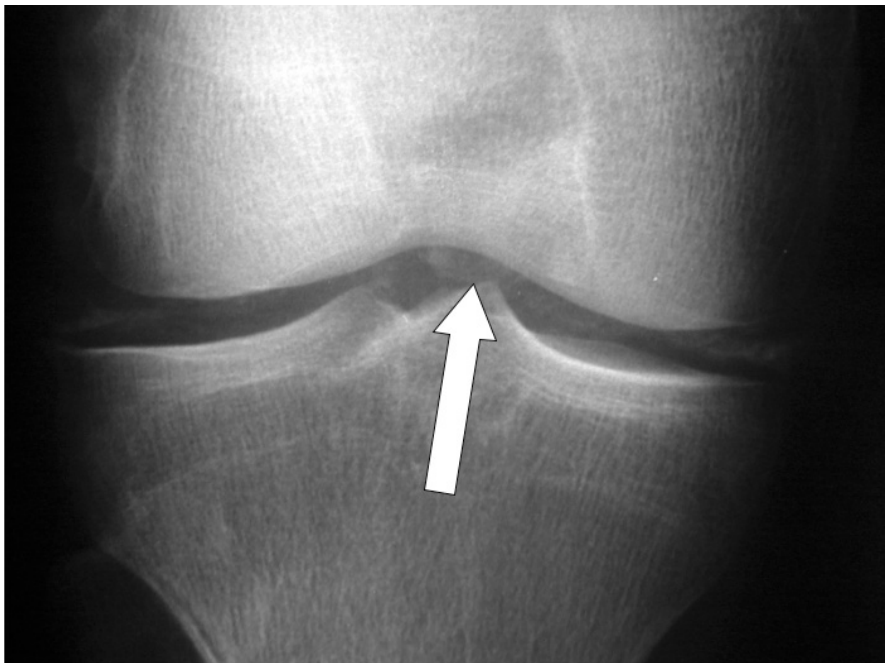

Fig 3. Chondrocalcinosis. A plain radiograph showing chondrocalcinosis of the knee (arrowed). Image courtesy of Dr P Bearcroft, Consultant Radiologist, Addenbrooke's Hospital, Cambridge.

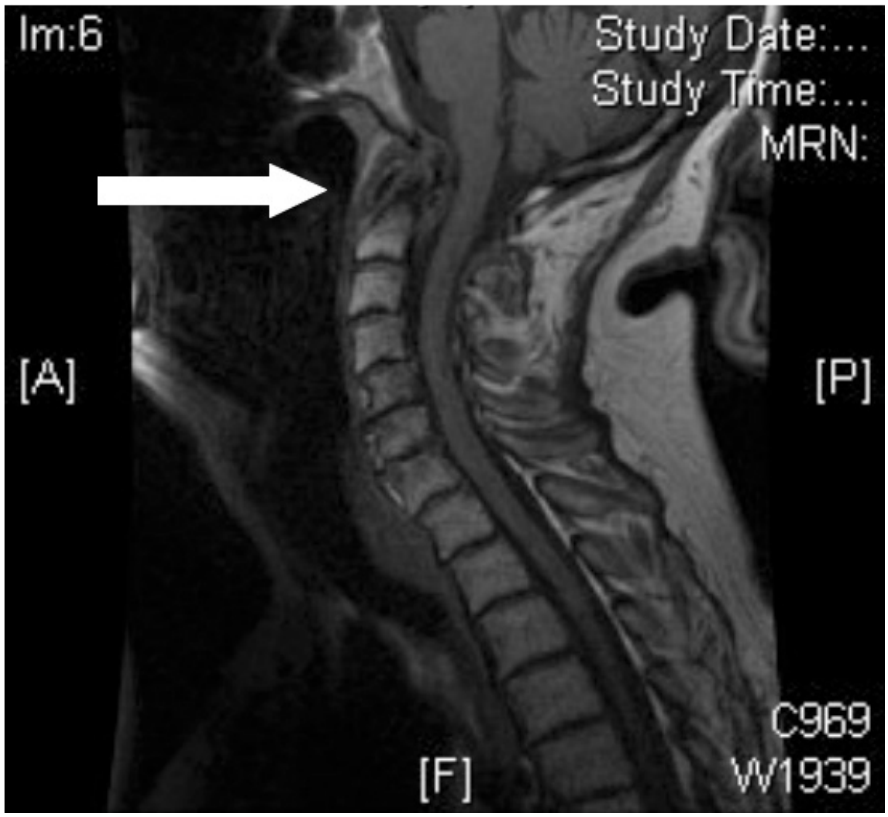

Fig 4. Crowned dens syndrome. A T2-weighted magnetic resonance image scan of the neck in a patient presenting with occipital headaches and an elevated inflammatory response. A longitudinal section shows a soft tissue mass around the odontoid peg (the dens) (arrowed) due to calcium pyrophosphate dihydrate microcrystal deposition.

Table 3. Conditions predisposing to calcium pyrophosphate dihydrate microcrystal deposition.

- Haemochromatosis
- Hypothyroidism
- Hyperparathyroidism
- Wilson's disease
- Hypophosphatasia
- Hypomagnesaemia

Treatment

If there is a predisposing cause for CPPD arthropathy (Table 3) this should be appropriately treated.

Acute pseudogout should be managed with NSAIDs or oral, intramuscular or intra-articular steroids in the same way as for gout.

Empiric treatment with low-dose oral steroids or regular colchicine (see gout prophylaxis above) is frequently considered for recurrent pseudogout or chronic CPPD arthropathy, although these therapies are not supported by any evidence base.

Unlike gout, there are no specific dietary interventions or drug therapies to facilitate resorption of the CPPD microcrystals.

Conflict of interest

None.

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