Crystal arthropathies

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Abstract

Crystal arthropathies are a diverse group of disorders characterized by the deposition of various minerals in joints and soft tissues, leading to inflammation. Clinical presentations of the different types of crystal arthritis are often characteristic enough to differentiate them from each other and other inflammatory arthropathies; however, mistakes can be made, leading to delayed or incorrect management. Gout, the most common crystal arthropathy, is caused by monosodium urate crystal precipitation and appears to be increasing in clinical complexity and prevalence. Two other main crystal types are also associated with inflammatory symptoms resulting from crystal deposition in and around joints: calcium pyrophosphate dihydrate, causing pseudogout, and basic calcium phosphate (hydroxyapatite). The common forms of crystal-associated arthritis are most accurately diagnosed by identifying the specific crystals in synovial fluid. Crystal arthritis causes exquisite pain, and management is directed towards control of acute flares, followed by prevention of recurrent episodes, where possible. Traditionally, gout prophylaxis has depended predominantly on the use of allopurinol, but newer drugs such as febuxostat are proving to be useful for individuals who cannot tolerate allopurinol. Better understanding of the pathophysiology of the disorder has led to the development of biological treatments, which are showing promise for resistant cases.

Keywords Allopurinol; crystal arthritis; febuxostat; gout; MRCP; pseudogout

Key points

- When diagnosing gout, joint infection *must* be considered as an alternative or concurrent diagnosis. Joint aspiration is the investigation of choice, particularly as serum urate concentration can be normal during acute episodes
- Acute attacks of gout should be managed with non-steroidal anti-inflammatory drugs (NSAIDs), colchicine or glucocorticoids, alone or in combination, taking into account co-morbidities and response to initial treatment
- Anti-interleukin-1 therapy can be considered in treatment-resistant episodes of acute gout. Other new treatments include the uricosuric agent, lesinurad, which is approved by the US Food and Drug Administration in combination with allopurinol as urate-lowering therapy
- A new presentation of gout should prompt an assessment of associated co-morbidities and modifiable lifestyle risk factors
- Urate-lowering therapy should be considered early, but not commenced during the acute phase. Allopurinol remains the first-line agent, and a serum urate of 300–360 micromol/litre should be targeted. NSAID/colchicine or even corticosteroid prophylaxis is generally needed to cover the initiation of urate-lowering therapy and prevent the development of an acute flare

Gout

Gout is an ancient medical disorder famously described by Hippocrates. The term 'gout' covers a spectrum of clinical presentations, ranging from acute joint inflammation to chronic erosive arthritis; it also includes tenosynovitis, bursitis, tophi (soft tissue urate deposits), nephrolithiasis and urolithiasis.

Epidemiology of gout

Acute gouty arthritis is five times more common in men and seldom occurs in premenopausal women. The prevalence of gout in the UK is about 2.5% and was noted to have increased by 64% between 1997 and 2012[1]; this is largely because of factors such as an ageing population, hypertension, diabetes mellitus and hyperlipidaemia. Gout most commonly affects men >75 years of age.

Pathogenesis

Gout is a disorder of purine metabolism characterized by acute, recurrent attacks of arthritis. The precise mechanisms by which monosodium urate (MSU) crystals enter the leucocyte, and the subsequent leucocyte response, are unclear. Phagocytosis of crystals in the joint initially occurs in synovial lining cells, stimulating a brisk, neutrophil-mediated inflammatory response. MSU crystals activate caspase-1, stimulating monocytes and macrophages to produce interleukin (IL)-1β and set in motion an inflammatory cascade that involves a variety of other proinflammatory molecules.

Recent studies have identified up to 18 significant genetic variations associated with uric acid homeostasis, including *SLC2A9*; these are potential therapeutic targets.

Clinical presentation and progression of gout

The diagnosis of gout is usually based on the clinical presentation, with sudden onset of intense pain, redness and swelling in a joint. The erythema can be diffuse and can be confused with cellulitis (Table 1). If inflammation is severe, desquamation of overlying skin can ensue.

Gout is usually monoarticular. The first metatarsophalangeal joint is classically affected in about 75% of cases, causing pain on

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Differential diagnosis of crystal arthritis

- Gout/pseudogout
- Septic arthritis
- Cellulitis
- Trauma/haemarthrosis
- Palindromic rheumatism
- Reactive arthritis
- Psoriatic/rheumatoid arthritis
- Capsulitis

Table 1

weight-bearing and impaired mobility. Other typical sites include the ankle, knee, elbow and small joints of the hands and feet. Fever can accompany the attacks. Elderly individuals can present with non-specific symptoms including confusion. Acute attacks last from a few days to weeks. It is important to recognize that gout can coexist with septic arthritis, highlighting the need for joint aspiration when the diagnosis is unclear.

The three clinical stages of gout are acute gouty arthritis, intercritical gout and chronic tophaceous gout (Figure 1). The latter can be confused with nodular rheumatoid arthritis and nodal osteoarthritis.

Most untreated patients experience further acute attacks within 2 years, but the intervals between the attacks are of variable duration.

Investigations

Blood tests:

- A neutrophil leucocytosis is common.
- Inflammatory markers are generally elevated during acute attacks.
- Serum uric acid (SUA) can be normal or elevated during a flare.
- Renal impairment can be evident.

Synovial aspiration:

- A definitive diagnosis may depend on identifying MSU crystals in fluid aspirated from an acutely affected joint.

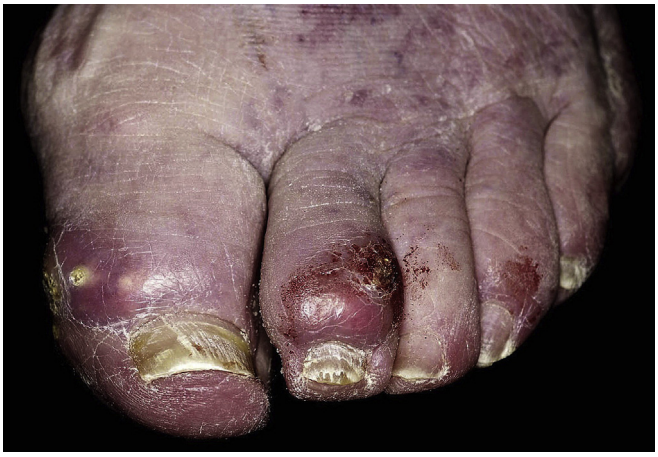

Figure 1 A patient with tophi.

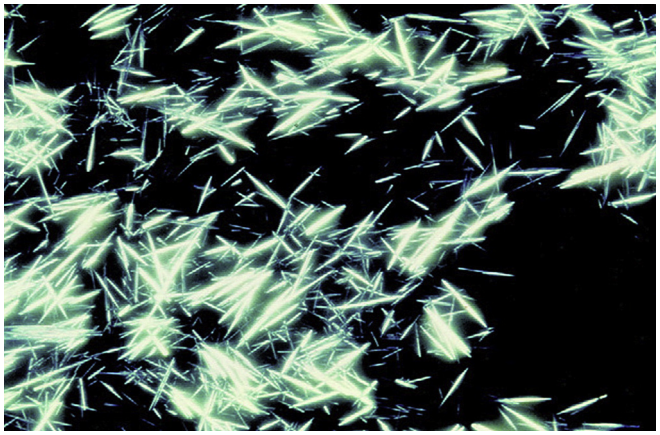

Figure 2 Polarized light microscopy (×400) of synovial fluid demonstrating negatively birefringent crystals. From: van der Klooster JM, Peters R, Burgmans JPJ, Grootendorst AF. Chronic tophaceous gout in the elderly. *Netherlands Journal of Medicine* 1998; 3: 69–75. Reproduced by permission of Elsevier B.V.

- MSU crystals are needle-shaped and negatively birefringent when examined under polarized light microscopy (Figure 2).
- Samples should always be sent for Gram staining and culture to exclude infection as an alternative or concurrent diagnosis.

Radiology:

- **Radiographs** during early attacks may be normal or reveal only soft tissue swelling. Chronic gout can lead to erosions, typically described as 'punched-out' lesions (Figure 3).
- **Ultrasound** is a popular imaging modality for assessing arthritis, with high accessibility, low cost and lack of ionizing radiation. Although ultrasound can demonstrate hyperechoic urate deposits in hyaline cartilage, it is not specific enough to reliable rule out alternative causes of inflammatory arthritis.

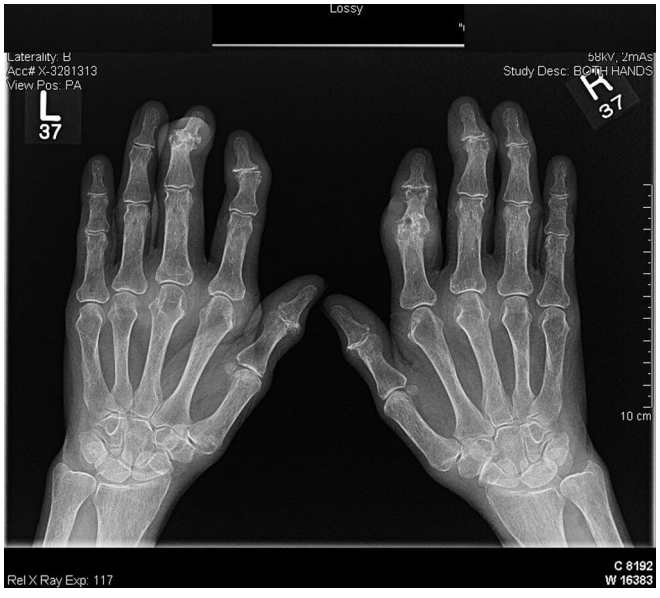

Figure 3 Radiology of erosive tophaceous gout.