Crystal arthropathies

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Abstract

Crystal arthropathies are a diverse group of disorders characterized by 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, but 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. In addition to gout, two other main crystal types are associated with inflammatory symptoms resulting from their deposition in and around joints. These are calcium pyrophosphate dihydrate, causing pseudogout, and basic calcium phosphate (BCP/hydroxyapatite). The most accurate way of diagnosing the common forms of crystal-associated arthritis is through the identification of specific crystals in synovial fluid. Crystal arthritis causes exquisite pain, and management is directed towards the control of acute flares, followed by prevention of recurrent episodes. Traditionally, the prophylaxis of gout has depended largely on the use of allopurinol, but newer drugs such as febuxostat are proving to be useful for those who cannot tolerate allopurinol. Better understanding of the pathophysiology of the disorder has led to the development of biologic treatments, which are showing promise as potential treatment strategies in resistant cases.

Keywords Allopurinol; crystal arthritis; febuxostat; gout; pseudogout

What's new?

- Febuxostat is now approved by NICE for the treatment of chronic gout where allopurinol is contraindicated or not tolerated
- Uricase converts urate to a more soluble form and has potential value in refractory gout; however, current infusion preparations have clinical limitations
- Targeting the inflammatory cascade, for example, by blockade of interleukin-1, may have a role in complex cases with active recalcitrant gout

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, and also includes tenosynovitis, bursitis, tophi (subcutaneous urate deposits), nephrolithiasis and urolithiasis.

Epidemiology of gout

The prevalence of gout in the UK is about 1–2%,[1,2] peaking to greater than 7% in men aged over 75 years. Acute gouty arthritis is five times more common in males than females and seldom occurs in premenopausal females. The prevalence of gout has risen threefold in the UK over 20 years of follow-up, largely as the result of factors such as an ageing population, hypertension, diabetes mellitus and hyperlipidaemia.[3,4] Obesity, chronic kidney disease and diuretic use are also associated with hyperuricaemia and gout.[5]

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 IL-1β and setting in motion an inflammatory cascade that involves a variety of other pro-inflammatory molecules. Recent studies have identified up to 18 significant genetic variations associated with uric acid homeostasis, including SLC2A9, which 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 is often confused with cellulitis (Table 1); if inflammation is severe, desquamation of overlying skin may ensue.

Gout is usually monoarticular. The first metatarsophalangeal joint is classically affected in about 75% of cases, causing pain on weight bearing and impaired mobility. Other typical sites involved include the ankle, knee, elbow and small joints of the hands and feet. Fever can accompany the attacks. The elderly

Differential diagnosis of crystal arthritis

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

Table 1

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may present with non-specific symptoms including confusion. The duration of acute attacks ranges from a few days to weeks.

It is important to recognize that gout can co-exist 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 or nodal osteoarthritis.

The majority of untreated patients will experience further acute attacks within 2 years but 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 may be evident.

Synovial aspiration:

- A definitive diagnosis may depend on identifying MSU crystals in fluid aspirated from an acutely affected joint.
- MSU crystals are needle-shaped and negatively birefringent when examined under polarized light microscopy (Figure 2).

Microbiology:

- Even when crystals are present in joint fluid, cultures of joint aspirate and blood are indicated if any sign of systemic toxicity is present.

Radiology:

- Radiographs during early attacks can be normal or reveal only soft-tissue swelling. Chronic gout can lead to erosions, typically described as 'punched out' lesions (Figure 3).

Management

The main objectives of gout treatment are the immediate relief of the attack and prophylaxis to prevent recurrence. Lifelong prophylactic treatment is recommended in patients who have tophi, renal stones or more than two attacks per year, aiming to reduce serum urate either by promoting renal excretion or by decreasing synthesis. Antihyperuricaemic therapy should be commenced only once the acute inflammatory attack has fully resolved. Co-morbidities such as hypertension should be treated aggressively.

Asymptomatic hyperuricaemia generally does not require treatment, but co-morbidities and associations (e.g. diuretics and diet) should certainly be addressed.

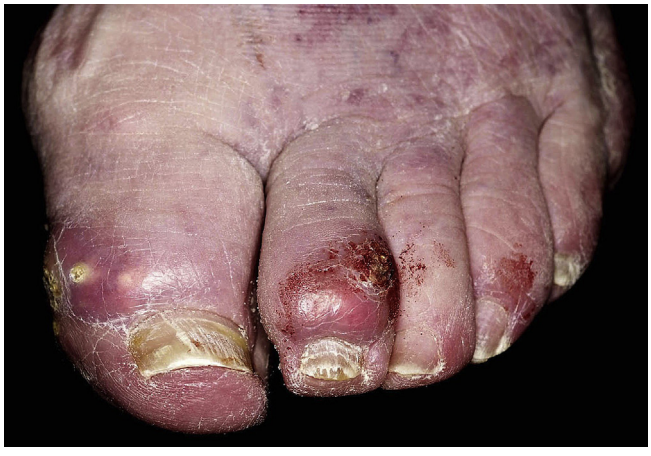

Figure 1 A patient with tophi.

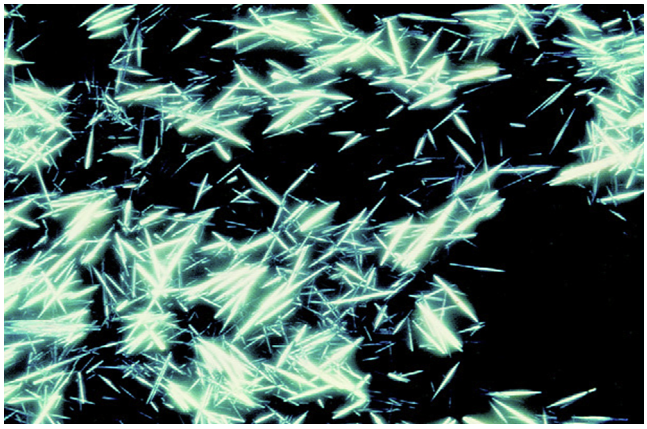

Figure 2 Polarized light microscopy (400×) of synovial fluid demonstrating negatively birefringent crystals. From: van der Klooster JM, Peters R, Burgmans JPJ, Grootendorst AF. Chronic tophaceous gout in the elderly, *The Netherlands Journal of Medicine* 1998; **3**: 69–75. Reproduced by permission of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

How should we treat acute gout?

- Non-steroidal anti-inflammatory drugs (NSAIDs) at the maximum recommended dose should be commenced immediately and continued for 1–2 weeks, if there are no contraindications. Etoricoxib, naproxen, diclofenac and indometacin (now rarely used due to its adverse effects profile) are all effective agents. Dosage should be reduced after 48 hours where possible. Gastro-protective cover is

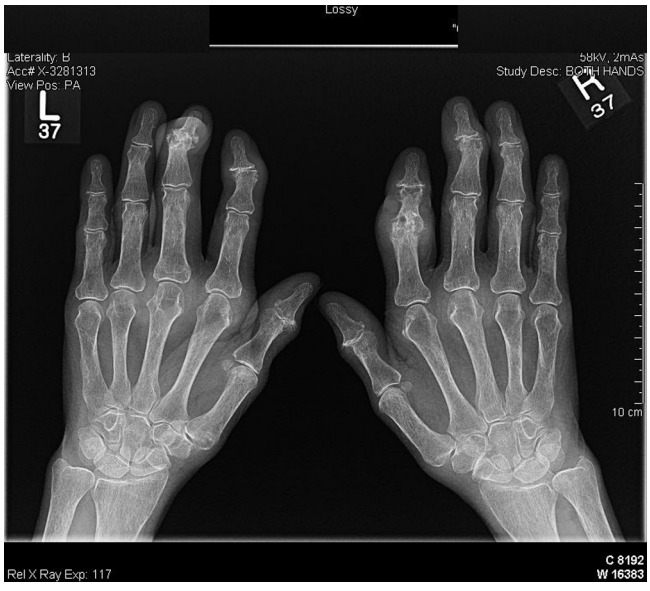

Figure 3 Radiology of erosive tophaceous gout.