Gout

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Polyarthritis in an ill patient

THE CASE

A 72 year old man was admitted as an emergency complaining of a one week history of severe polyarticular joint pain. He had a prior 10 year history of osteoarthritis of his knees. A year earlier he had been seen by the haematologists with a blood film and bone marrow examination suggestive of myelodysplasia. There was a history of a possible gastrointestinal bleed two months before this admission, possibly relating to a non-steroidal anti-inflammatory drug (NSAID) he had been taking for his osteoarthritis; this had subsequently been discontinued. He had mild chronic obstructive pulmonary disease and his medication on admission was: ranitidine 150 mg twice daily; ferrous sulphate 200 mg three times a day; quinine sulphate 300 mg at night; and salbutamol and becotide inhalers. He had been started recently on unknown antibiotics by his general practitioner for a possible lower respiratory tract infection. There was no family history of note. He admitted to drinking 30 units of alcohol per week. There were no known previous episodes of acute synovitis.

On examination he was afebrile but dehydrated and in extreme discomfort; even minor movements of his limbs caused severe pain. There was a suspected tophus on the left third toe and the left wrist. Both elbows, both knees and both ankles were hot and erythematous.

Initial investigations demonstrated: haemoglobin 9.6 g/dl; total white cell count 13.3 × 10⁹/l; neutrophil count 6 × 10⁹/l; platelet count 107 × 10⁹/l; C reactive protein >300 mg/l (normal range (NR) < 10 mg/l); serum sodium 126 mmol/l; serum potassium 4.9 mmol/l; serum urea 36 mmol/l; serum creatinine 224 µmol/l; and serum urate 700 µmol/l (NR 150–400 µmol/l). The knees and both olecranon bursae were aspirated. No organisms were seen on Gram stain but multiple negatively birefringent crystals morphologically typical of monosodium urate monohydrate (MSUM) were identified under compensated polarising light microscopy.

His dehydration was corrected with intravenous fluids and his renal impairment improved over the next 10 days. His severe pain required modified release morphine sulphate 60 mg twice daily to control it. After specimens of synovial fluid, blood, sputum and urine were obtained for microbiological investigation, intravenous benzyl-penicillin and flucloxacillin were given because of the possibility of joint sepsis. These specimens yielded no growth although this was in the presence of prior antibiotics from his general practitioner. The benzyl-penicillin was changed to cefotaxime on microbiological advice and after the failure to isolate an organism and with a presumptive diagnosis of acute polyarticular gout his antibiotics were discontinued on day seven. On day six he was given prednisolone at a dose of 30 mg per day. Colchicine was not used because of concern about his myelodysplasia and a wish not to induce diarrhoea given the patient's immobility and severe pain on movement. His renal impairment was also a consideration but not an absolute contraindication. NSAIDs were not used because of his recent history of possible peptic ulceration, his myelodysplasia and his renal impairment.

His arthralgia and swelling responded over the next five days and after day 16 the prednisolone dose was progressively reduced. In view of the presence of some non-correctable risk factors for gout and the impression that the clinical situation could not be worsened, on day 11 he was given allopurinol 100 mg daily. This was increased five days later to 200 mg and then to 300 mg daily on day 19.

He had a prolonged stay in hospital complicated by Clostridium difficile diarrhoea, heel and sacral pressure sores and urinary retention requiring temporary transurethral catheterisation. By discharge his serum uric acid was 176 µmol/l taking allopurinol 300 mg daily.

Subsequently he remained well, walking with two elbow crutches and had no further attacks of acute gout. Seven months later, however, the patient was readmitted with septicaemia secondary to a urinary tract infection, which possibly related to a urethral stricture. His myelodysplasia had progressed with spontaneous bleeding, particularly from the eyelids and gums and he had also developed congestive cardiac failure. Despite treatment the patient rapidly succumbed to his illnesses.

Discussion

This case raises the following questions for discussion:

- The diagnosis and differential diagnosis of acute gout
- The best treatment of acute gout in patients with multiple medical problems
- The choice and introduction of hypouricaemic agents.
Diagnosis of gout

Gout usually presents as acute synovitis affecting one or more joints but may also present as asymptomatic tophi or less commonly as renal stones and/or renal impairment. Hyperuricaemia is more common than gout; arthralgia plus hyperuricaemia is not synonymous with gout. Epidemiological surveys have used the definition of recurrent acute episodes of arthritis in the presence of hyperuricaemia as being gout and this can make their interpretation problematic. Synovial fluid is rarely obtained in large population studies and criteria for the classification of gout in the absence of crystal identification have been proposed. In clinical practice however crystal identification remains the gold standard. In the case described above the diagnosis of gout was secured by the demonstration of morphologically typical, negatively birefringent crystals in affected joints and olecranon bursae.

Acute gout typically presents with a hot, red, swollen, tender joint and thus there is an important differential diagnosis including sepsis. The first metatarsophalangeal joint is commonly involved at presentation but other commonly affected joints are the ankle, knee and tarsal area. Any joint including the spine may be affected. Among 106 patients with gouty arthritis, 42 had involvement of two or more joints and patients with polyarticular gout (defined as involvement of four or more joints) tended to have a more smouldering onset of attack; an asymmetric distribution and an ascending pattern of joint involvement.

Gouty tophi are aggregates of MSUM crystals usually, but not exclusively, found in connective tissue. Patients may rarely present with tophi but no history of acute gout.

Hyperuricaemia is more common than gout. Among 2046 initially healthy men followed up for 14.9 years (30 147 person-years of prospective observation), urate concentrations of 416 to 534 µmol/l were associated with an annual incidence of “gouty arthritis” of only 0.5%. Urate concentrations of more than 535 µmol/l were associated with an increased annual incidence of 4.9%. “Gout” was diagnosed on the basis of history and chart review but the demonstration of urate crystals was not required.

Prophylactic treatment of gout is usually lifelong and the diagnosis should be secured by the demonstration of MSUM crystals. Many patients are still given potentially long-term treatment without this. Among 9108 consecutive new patients seen in an outpatient clinic 164 had been misdiagnosed in primary care as having gout. Of these, 76% had received allopurinol, 9.8% probenecid and 6.1% probenecid with colchicine. A study using pharmacy records to identify patients receiving allopurinol treatment identified 286 such patients, most of whom (95.7%) had not had a joint aspiration.

Diagnosis of the acute episode

In the case described the diagnosis of gout was made via crystal identification but other coexistent joint problems may have been present, contributing to the clinical picture. With a recent chest infection, the possibility of joint sepsis was raised. Prior antibiotics may have rendered microbiological investigation problematic. Among gout patients and renal impairment can coexist and the priority is not to miss treatable infection because septic arthritis has a significant mortality of 9–23%. Patients may be feverish, tachycardic and confused with gout, septic arthritis and cellulitis. An acute phase response may be observed including substantial increase in the C reactive protein and the peripheral blood white cell count may also be raised; neither, therefore, helps in differentiation from sepsis. Relevant microbiological specimens must be obtained if there is any diagnostic doubt. A useful algorithm for the assessment of hot, swollen joints is available.

Identification rates for crystals on polarised microscopy vary but specificity for MSUM crystals may be better than for calcium pyrophosphate dihydrate crystals. Mixed crystal deposition disease also occurs. In the absence of polarised light microscopy, ordinary light microscopy can be used but is not as specific. Synovial fluid should ideally be examined within six hours of arthrocentesis to reduce the rate of artefactual results and if microscopic examination is delayed the fluid should be refrigerated. Post-aspiration changes particularly affect cell counts. Changes in MSUM crystals are less of a problem and the crystals can usually still be identified but become smaller, less numerous, and less birefringent with time.

The measurement of the serum uric acid concentration in acute gout is problematic. In one study the serum uric acid was found to fall during an acute episode. Others have found that the serum uric concentration level may be lower or higher as compared with the intercritical period.

Diagnosis in the intercritical period

Aspiration of joints in the intercritical period can help make the diagnosis of gout. In nine men with gout, previously diagnosed by MSUM crystal identification in synovial fluid from clinically affected knees, aspiration of clinically uninvolved first metatarsophalangeal joints revealed urate crystals in six. Interestingly MSUM crystals were not identified in the first metatarsophalangeal joints in two patients who had aspiration during an episode of gout at other joint sites. Thirteen of 14 patients who were currently asymptomatic but gave a history of podagra had MSUM crystals identified in an aspirate of the first metatarsophalangeal joint.

Among 23 patients with a clinical diagnosis of gout, aspiration of the first metatarsophalangeal joint demonstrated MSUM crystal in 9 of 11 patients with a history of gouty involvement at that site compared with 8 of 12 with no history of clinical involvement of the joint. Most of these patients were taking allopurinol or colchicine and interestingly 14 of 20 patients taking allopurinol had positive aspirations. No correlation was found between the degree of control of hyperuricaemia and the presence of crystals, but numbers were small. In the same study 1 of 19 patients with asymptomatic
hyperuricaemia and 2 of 9 patients with renal failure and hyperuricaemia had positive aspirations. Among 50 patients with crystal positive, non-tophaceous gout, successful aspiration of 69 of 71 currently asymptomatic knees yielded MSUM crystals in 37 knee fluids from 29 patients. In a study of gout patients who had never had hypouricaemic treatment, 36 of 37 currently asymptomatic but previously involved knees contained uric acid crystals; uric acid crystals may persist if the serum uric acid is not lowered by treatment. The finding of MSUM crystals in patients with asymptomatic hyperuricaemia and renal impairment in the absence of a history of synovitis suggests that a false positive diagnosis of gout may occur.

Intra-articular MSUM crystals occur in the absence of synovitis. Why crystals can be found in asymptomatic joints is interesting and may relate to the crystals remaining extracellular rather than being phagocytosed and thus invoking an inflammatory response. Should only intracellular MSUM crystals be taken as definitive evidence for gout? In 13 patients with tophaceous gout, 11 had MSUM crystals in clinically quiescent knees, two of whom had not had previous knee involvement. Intracellular crystals were seen in some of these knees and suggests that intracellular crystals may not always produce clinical inflammation. In another series, 19 of 20 synovial fluid samples from asymptomatic knees contained intracellular urate crystals. Thus, factors other than cellular uptake are probably important in producing clinically observable synovitis.

Hyperuricaemia may result from overproduction but is more usually the result of underexcretion of urate. Should all patients with gout be investigated to determine urate overproduction or under-excretion? It has been suggested that this is desirable. Most patients in the United Kingdom with gout do not undergo metabolic investigation unless presenting in childhood or before the female menopause. This may reflect a tendency to use allopurinol, which treats both over-production and under-excretion and thus metabolic investigation is probably not cost effective.

**Treatment**

**TREATMENT OF ACUTE GOUT**

Treatment of acute gout is described in most general medical texts and is usually presented as being straightforward. In our experience some patients, such as the one described above, have multiple medical problems and require a more thoughtful and less standardised approach. For example, in this patient significant problems included renal impairment, myelodysplasia, recent chest infection, previous peptic ulceration, and the possibility of coexistent joint sepsis.

Although simple joint aspiration and analgesics can ease pain, NSAIDs or colchicine are the usual first line treatment for acute gout. There is, however, wide geographical variation in their use. Among 750 French rheumatologists, the United Kingdom with gout do not use colchicine three times per day have a better therapeutic for patients taking warfarin because of concerns regarding major suppression and the wish to avoid diarrhoea.

Intra-articular aspiration and injection of corticosteroids is effective, but in the setting of thrombocytopenia and polyarticular involvement is problematic. Systemic corticosteroid treatment orally or intravenously can be used as can intramuscular injection. Intramuscular injection was contraindicated in our patient but oral corticosteroids did prove effective. Adrenocorticotropic hormone has also been evaluated but it is not commonly used and would seem to offer no advantage over corticosteroids.

**INDICATIONS FOR LONG TERM TREATMENT OF HYPERURICAEMIA**

Although prevention of acute attacks can be achieved by regular NSAIDs or colchicine this does not tackle the underlying hyperuricaemia. Hypouricaemic therapy is generally life long and the introduction of such treatment requires careful consideration. Indications for long term hypouricaemic treatment have been proposed (table 1). Recurrent episodes affect-
ing the patients lifestyle may be an appropriate indication. The patient should be involved in the decision process and the need for long term compliance in the absence of symptoms is an issue that should be considered.

Despite these considerations, hypouricaemic treatment is often started after the first episode of gout. In Canada, up to 27% of family physicians and 11% of rheumatologists state that they would start hypouricaemic treatment after only one episode of gout. This is, in our opinion, inappropriate.

**TREATMENT TO REDUCE HYPOURICAEMIA**

Two complementary approaches are adopted: lifestyle modification and use of hypouricaemic drugs. Lifestyle modification if achievable, would be ideal but is problematic for many patients. All patients should however be encouraged to reduce obesity, alcohol intake and high purine content food. Drugs such as thiazides, loop diuretics and low dose aspirin may reduce urate excretion and should be reviewed although in practice it is often not possible to withdraw them.

Hypouricaemic agents essentially comprise of xanthine oxidase inhibitors (for example, allopurinol) and uricosuric agents (for example, probenecid, sulphinpyrazone, benzbromarone or azapropazone). A combination of allopurinol and a uricosuric may occasionally be used. Differentiation of urate overproducers from underexcretors might be used to determine whether allopurinol or a uricosuric should be used, as the latter tend to have less severe adverse effects. This distinction is not, however, often made in clinical practice. Treatment aims to reduce the serum uric acid concentration into the lower half of the normal range, thus aiming to dissolve existing monosodium urate monohydrate crystals.

Allopurinol is the most common agent used now; in Canada it accounts for 98% of hypouricaemic agents used by family physicians and 99% by rheumatologists. Its once daily dosing aids compliance compared with the uricosuric agents that have more frequent dosing regimens. Allopurinol is effective in both urate over-production and under-excretion and, unlike uricosurics, can be used in patients with reduced renal function. Treatment should be life long, cessation is associated with recurrence of symptoms and tophi.

Allopurinol is usually well tolerated. Common side effects include rashes and if these occur the allopurinol should be stopped although, if the rash is mild and settles, cautious drug reintroduction may be possible. More severe reactions include fever, eosinophilia and renal impairment. The latter may be associated with lymphadenopathy, exfoliation, vasculitis, hepatitis, interstitial nephritis and rarely epilepsy. Allopurinol can cause haematological problems including thrombocytopenia, haemolytic anaemia, aplastic anaemia and leucopenia. Desensitisation is unwise in patients experiencing a severe reaction and in this situation oxypurinol (the metabolite of allopurinol) may be considered as an alternative although cross reactivity may occur. Transplant patients may develop gout and as azathioprine metabolism is inhibited by allopurinol azathioprine marrow toxicity may be increased. The combination should be avoided, but if essential, dose reduction is necessary.

Uricosuric agents reduce tubular reabsorption of urate and depend on normal renal function. Urate nephrolithiasis may occur although high fluid intake and alkalinisation of urine may help. Probenecid, started at a dose of 250 mg twice daily and increased until serum urate concentration is adequately reduced is the usual agent although sulphinpyrazone is an alternative. The latter can cause fluid retention and marrow suppression. Benzbromarone, available in parts of Europe, but not routinely in the UK, may be effective in the presence of renal impairment and may be useful in combination with allopurinol. Azapropazone is a uricosuric NSAID and as such would seem ideal for both acute and chronic gout. Unfortunately it has a high propensity for peptic ulcer disease and thus its use is restricted.

**TIMING OF INTRODUCTION OF HYPOURICAEMIC TREATMENT**

Standard teaching is that urate lowering drugs should not be introduced during an acute episode as it may worsen or prolong the episode; furthermore initiation of hypouricaemic treatment may precipitate acute gout. Data to support this are limited. Acute episodes of gout after starting allopurinol were reported in 1964. In a different study 11 of 45 patients given allopurinol developed an acute gout. Most of these patients started treatment while on a metabolic ward receiving a low purine diet, oral colchicine 1 mg daily and water (2 litres per day) to induce a brisk diuresis. In another study of 64 patients taking a variety of uricosuric agents under colchicine cover, 15 developed acute gout. In two, this was severe

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Table 1: Indications for hypouricaemic treatment

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<td>Tophaceous gout</td>
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<td>Radiographic erosions because of gout</td>
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<td>Uric acid nephrolithiasis</td>
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<td>Urate nephropathy</td>
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<td>Prophylaxis of chemotherapy induced gout</td>
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<td>Recurrent acute episodes affecting lifestyle in association with patient desire to comply with medication</td>
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enough to stop effective uricosuric treatment. However, 20 patients treated with probenecid and colchicine had on average 2.3 episodes per year compared with six a year in 18 patients treated with probenecid and placebo. In practice it is difficult to achieve full remission of gouty synovitis in many patients particularly if there are non-correctable risk factors. In such patients it is unlikely that a more acute introduction of hypouricaemic agents is inappropriate and indeed this is a practice we adopt.

MANAGEMENT OF ACUTE EPISODES OF GOUT
WHILE RECEIVING HYPOURICAEMIC TREATMENT
Patients receiving hypouricaemic treatment may experience acute gout. This may reflect inadequate treatment or the fact that treatment has not been taken for long enough to reabsorb all MSUM crystals. In this acute situation the hypouricaemic agent should be continued to prevent the patient experiencing recurrent cycles of stopping and starting definitive treatment.

TREATMENT OF RESISTANT CASES
Some patients seem to be resistant to treatment. In such cases there are several considerations:

- Is the diagnosis of both the chronic and the acute problem correct? Is there coexistent sepsis? Have urate crystals ever been demonstrated?
- Is the patient compliant? Check urinary allopurinol metabolites to assess compliance.
- Are other drugs (for example, thiazides) aggravating the situation?
- Have confounding medical problems developed or worsened (for example, renal impairment)?
- Have lifestyle issues such as alcohol consumption and obesity been adequately considered?

It may be reasonable to consider other measures. During an acute episode combination treatment with NSAIDs, colchicine and/or corticosteroids may be necessary to achieve resolution. For reduction of hyperuricaemia the dose of hypouricaemic agents may need to be increased. For example, allopurinol may need to be used at greater than the standard dose of 300 mg daily. Alternatively, if patients are intolerant of high dose allopurinol, combinations of allopurinol and a uricosuric may be necessary.