Gout—an ancient disease reviewed

Gout is a very common disease, particularly in older men. It manifests as swollen painful joints resulting from intra-articular deposition of monosodium urate crystals. Initial treatment is with high doses of non-steroidal anti-inflammatory drugs, and if patients are unresponsive, colchicine or corticosteroids can be used. Managing modifiable risk factors such as diet and exercise is useful after the acute phase has passed. Patients with chronic gout may need lifelong uric-acid lowering therapy.

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The stereotypical presentation of gout is a fifty-year-old man who develops an acute, painful, erythematous, hot, and swollen big toe. The individual may describe an intolerance to touch at the affected site, having woken up with pain and swelling to the extent that the pressure of bed-clothes on the affected site is painful. Often the patient cannot identify preceding trauma or obvious precipitating factors such as infections.

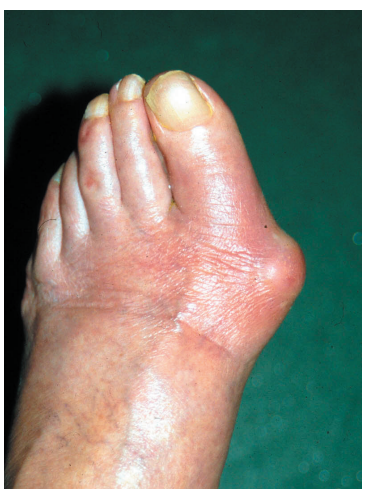

Figure 1: Podagra of gout affecting the first metatarsophalangeal joint

Examination may reveal classical podagra—synovitis of the first metatarsophalangeal joint described in Roman times—a red, hot, swollen toe that is painful and tender to light touch. Tracking cellulitis is often absent, but generally the patient will be overweight.

Several other diagnoses may need to be considered including septic arthritis, reactive arthritis, other crystal arthropathies such as pseudogout, and synovitis as a manifestation of multisystem diseases.[1–4] Gout is one of the oldest recorded arthropathies dating back to Hippocrates. It is characterised by acute self-limiting attacks of arthritis secondary to intra-articular precipitation of monosodium urate crystals. In 90% of acute gout, the first metatarsophalangeal joint (figure 1) is involved, although gout may occur in other joints (eg, the knees—gonagra; the hands—cheiragra; and the shoulders—omagra). Proximal joints are rarely affected.[5]

Gout is common; historically it was a disease of affluent men who indulged in port and cheese. The overall prevalence of gout is estimated as 1·4%, but approaches 7% in men older than 65 years.[6] There is a male

Box 1: The 1977 ACR Criteria for the classification of acute arthritis of primary gout[9]

A patient has gout if they have at least 6 of the listed signs or symptoms.

1. More than one attack of acute arthritis
2. Maximum inflammation develops within one day
3. Oligoarthritis attack
4. Redness observed over the joint
5. First metatarsophalangeal joint is painful or swollen
6. Unilateral first metatarsophalangeal attack
7. Unilateral tarsal joint attack
8. Tophus (proven or suspected)
9. Hyperuricaemia
10. Asymmetrical swelling within a joint on radiology
11. Subcortical cysts without erosion
12. Monosodium urate monohydrate microcrystals in joint fluids during attacks
13. Joint fluid culture negative for organisms during attack

preponderance with a male-to-female ratio of 5:1. The incidence of gout peaks in men aged 40–60 years and in women after the menopause.

Common risk factors for gout include hypertension, hyperlipidaemia, excessive dietary purine and alcohol intake, and renal impairment. It can also develop secondary to therapeutic drugs that reduce uric acid excretion such as thiazide diuretics and low-dose aspirin, or increase uric acid production, for example, chemotherapy.[7]

Diagnosis

Both the American College of Rheumatology (ACR) and the and European League against Rheumatism (EULAR) have made recommendations on diagnosing gout (boxes 1 and 2).[8,9] Gout may be diagnosed from clinical history and examination. The presentation previously described is consistent with acute gout. Gout is traditionally associated with a high plasma uric acid concentration (hyperuricaemia). Hyperuricaemia may result from either overproduction such as in metabolic syndrome or abnormal purine enzyme activity, or as is more commonly the case, undersecretion of urate (box 3 and figure 2).[10,11] Acute gout may occur with normal serum urate concentration and hyperuricaemia is not a prerequisite.[12]

The gold standard for diagnosis of gout is examination of synovial aspirate from the affected joint for the presence of negatively birefringent needle-shaped monosodium urate crystals under polarised light microscopy (figure 2). This contrasts with the rhomboid-shaped positively birefringent crystals of calcium pyrophosphate seen with pseudogout.

Infection may coexist with gout, and the aspirate should be sent for culture and sensitivity analysis, especially in the presence of systemic sepsis signs.[13] Appropriate antibiotics should be started empirically whilst waiting for results.

Other modalities used to diagnose gout include imaging with magnetic resonance, X-ray, and ultrasound. Late changes such as punched-out lesions, periarticular erosions, and microtophi can be detected by X-ray or magnetic resonance, but are not specific to gout. Ultrasound may reveal a hyperechoic, irregular band over the superficial margin of the articular cartilage, a double contour sign highly specific in acute gout.[14] Effusions, early erosions, synovial hypertrophy, and hypervascularity may be assessed at the same time.

Box 2: EULAR evidence-based recommendations for diagnosis of gout[8]

1. In acute attacks the rapid development of severe pain, swelling, and tenderness that reaches maximum within 6–12 hours, especially with overlying erythema, is highly suggestive of crystal inflammation but is not specific for gout
2. For typical presentations of gout (such as recurrent podagra with hyperuricaemia) a clinical diagnosis alone is reasonably accurate but is not definitive without crystal confirmation
3. Demonstration of monosodium urate crystals in synovial fluid or tophus aspirates permits a definitive diagnosis of gout
4. A routine search for monosodium urate crystals is recommended in all synovial fluid samples obtained from undiagnosed inflamed joints
5. Identification of monosodium urate crystals from asymptomatic joints may allow definite diagnosis in intercritical periods
6. Gout and sepsis may coexist, so when septic arthritis is suspected Gram staining and culture of synovial fluid should still be performed, even if monosodium urate crystals are identified
7. Although they are the most important risk factor for gout, serum uric acid levels do not confirm or exclude gout, as many people with hyperuricaemia do not develop gout, and during acute attacks serum levels may be normal
8. Renal uric acid excretion should be determined in selected gout patients, especially those with a family history of young-onset gout, onset of gout under age 25 years, or with renal calculi
9. Although radiographs may be useful for differential diagnosis and may show typical features in chronic gout, they are not useful in confirming the diagnosis of early or acute gout
10. Risk factors for gout and associated comorbidity should be assessed, including features of the metabolic syndrome (obesity, hyperglycaemia, hyperlipidaemia, hypertension)

Management of acute gout

In 2007, the British Society for Rheumatology published guidelines for the management of gout.[16] High-dose non-steroidal anti-inflammatory drugs (NSAIDs) are the first line of treatment but if contraindicated, colchicine may be used.[15–17] Colchicine is a mitotic inhibitor and has dose-related side-effects including nausea, abdominal cramps, and diarrhoea at high doses. The recommendation is therefore to start low-dose colchicine at 500 µg twice to four times daily to decrease the risk of side-effects. Corticosteroids in oral, intramuscular, or intra-articular

forms are effective in patients who are refractory to treatment with NSAIDs and colchicine. Elevation, rest, and ice compression of affected joints are useful adjuncts.

On resolution of an acute episode of gout, modifiable risk factors should be addressed. Information leaflets and lifestyle advice should be given. Examples include a balanced diet, weight control with regular exercise, keeping well hydrated, decreasing alcohol consumption, and emphasis on the importance of being screened for cardiovascular disease, insulin resistance, and hyperlipidaemia.[18,19]

A complex cause and effect relationship between renal dysfunction, obesity, alcohol, hyperlipidaemia, and hyperuricaemia as part of the metabolic syndrome has been described.[20,21]

Natural history

Many patients are asymptomatic after their first acute attack of gout. Others have further monoarthritic or polyarthritic attacks after a period of quiescence, which is known as intercritical gout. Persistent hyperuricaemia and recurrent acute attacks of gout may result in chronic tophaceous gout. Tophus is derived from the Latin word tophos, meaning a porous volcanic rock. Tophi are solid masses of monosodium urate crystals that develop in fingers, toes, tendons, and the pinna. Complications of chronic gout include joint destruction, renal calculi, and urate nephropathy.[5]

Reducing uric acid in chronic gout

Not everyone with gout requires uric-acid lowering drug therapy. A thorough history should be taken to determine the cause of hyperuricaemia. Renal uric-acid excretion should be determined in selected patients, particularly for individuals with a family history or onset of gout under age 25 years, or with renal calculi.[8]

Guidelines from EULAR and the British Society for Rheumatology recommend uric-acid lowering drug therapy in patients with more than one acute attack per year, with renal impairment, or in chronic tophaceous gout including radiological microtophi.[15,16]

Allopurinol, a xanthine oxidase inhibitor, is the first-line preventive treatment. Caution should be taken in patients with renal impairment because reduced renal excretion can lead to severe skin rashes. Allopurinol should be commenced at a low dose such as 50–100 mg and titrated to renal function and response until a therapeutic target of serum uric acid of less than 360 µmol/l is achieved. Allopurinol should not be started during an acute attack because it can exacerbate and prolong the episode. However if a patient is already on allopurinol it should be continued. During initiation, an NSAID or colchicine should be coprescribed because the mobilisation of tophaceous material increases initially.

In patients who are either intolerant of or resistant to allopurinol, or in underexcretors, the second-line uricosuric agents sulfinpyrazone, benzbromarone and probenecid may be used.[15,22] The latter two drugs are available only on a named-patient basis. Uricosuric agents increase renal tubular excretion of uric acid. Good hydration is required, and in some cases urine alkalinisation with sodium bicarbonate is necessary to prevent uric acid crystalluria. In patients with normal renal function, the drug of choice is sulfinpyrazone at 100–800 mg/day, or benzbromarone at 950–2000 mg in those with mild-to-moderate renal impairment.

Box 3: Causes of hyperuricaemia[11]

Urate undersecretion (more common)

Primary

- Low urate clearance by kidneys

Secondary

- Renal impairment
- Hypertension
- Hypothyroidism
- Drugs (low dose aspirin, diuretics, cyclosporin, ethanol)
- Poison (lead nephropathy)

Urate overproduction

Primary

- Hypoxanthine phosphoribosyl transferase deficiency (Lesh-Nyhan syndrome)

Secondary

- Excessive dietary purine intake
- Malignant or lymphoproliferative disease (tumour lysis)
- Drugs (cytotoxics, ethanol)

More recently febuxostat, a novel oral non-purine xanthine oxidase inhibitor was evaluated by NICE,[22–24] and recommended as an alternative treatment for patients who are intolerant of allopurinol or for whom allopurinol is contraindicated. Uric acid-lowering therapy should be life-long therefore it is imperative that patients are made aware of the risk-benefit considerations and the reasons why they require treatment.

Future pharmacological treatment

Human beings have low levels of uricase to maintain blood pressure under low-salt dietary conditions, and uric acid is a natural antioxidant.

Uricase breaks down existing urate and has a potential role in treatment of tophaceous gout. Rasburicase, a recombinant uricase is licensed for prophylaxis and treatment for hyperuricaemia secondary to chemotherapy for haematological malignancies.[25] Pegloticase, which is a modified recombinant mammalian uricase given by intravenous infusion, shows promise for resolving gouty tophi.[26]

Summary

Gout is a common condition that has existed since ancient times. Optimum management of gout includes both pharmacological and non-pharmacological modalities and should be tailored according to:[15,16]

- specific risk factors—hyperuricaemia, previous attacks, radiographical signs
- clinical phase—acute or recurrent gout, intercritical gout, and chronic tophaceous gout
- general risk factors—age, sex, obesity, alcohol consumption, urate-elevating drugs, drug interaction, polypharmacy, or side-effects, such as with low-dose aspirin and diuretics, and comorbidity

The main aim is to decrease the frequency and severity of acute flares and to achieve target reduction in plasma urate levels in chronic tophaceous gout. Education about gout is important for patients' empowerment in the management of their condition to ensure compliance with lifelong urate lowering therapy.

We have no conflict of interest.

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