Case 039: Painful big toe.

Authors: David C Chung MD, FRCPC
         Thomas YK Chan MD, PhD, FRCP
Affiliation: The Chinese University of Hong Kong

A 48-year-old man presented to the Emergency Department because he was woken up with pain in his right big toe. The pain was not relieved by acetaminophen. He was previously healthy, was not on long term medication, and had no other complaints on functional enquiry. This was his first attack.

Clinical examination revealed a somewhat obese individual. His vital signs were: oral temperature 37.5 °C, blood pressure 145/85 mmHg, pulse rate 76/min. His right big toe was red, warm, and swollen over and around the metatarsophalangeal (MTP) joint. The area was exquisitely tender to touch and joint mobility was limited by pain. Other joints of both the lower and upper extremities were spared.

1. What are the differential diagnoses?

This is a painful arthritis of acute onset. Differential diagnoses include: gout, pseudo-gout, other inflammatory arthritides (e.g. rheumatoid arthritis, psoriatic arthritis) and septic arthritis. In an acute situation it is most important to differentiate septic arthritis from the rest because the former can cause rapid
destruction of the joint. The following clinical features of septic arthritis can be helpful in making a diagnosis:

- Septic arthritis tends to affect bigger joints.
- Source of infection is mostly from hematogenous seeding of the synovium; a diligent search for the primary infection (e.g. gonorrhea) site is important.
- Infection may be from direct extension of adjacent osteomyelitis.
- Infection may be the result of trauma (e.g. complication of intra-articular injection or aspiration).

Definitive diagnosis depends on microscopic examination of joint fluid and culture but these can cause unnecessary delay. When in doubt, the patient should be treated for septic arthritis while waiting for results of investigation. In this patient, however, the presentation is most suggestive of acute gout.

2. What is gout?

Gout is an inflammatory arthritis in response to deposition of monosodium urate microcrystals in the joint space. Urate (uric acid) is the product of purine metabolism and is excreted by the kidneys. A combination of excessive urate production and impaired renal clearance contributes to hyperuricemia, defined as serum urate concentration > 420 \( \mu \text{mol/L} \), beyond which urate supersaturation occurs. Hyperuricemia and urate supersaturation favor the formation and deposition of urate microcrystals and these crystals can be observed under a polarized light microscope in fluid aspirated from affected joints. The disease affects more men than women and more women after their menopausal years, probably because estrogens increase the renal clearance of urate. Factors that favor the development of gout include:

- Old age due to a decline in renal urate clearance.
- Weight gain and obesity.
- Rapid weight reduction.
- Diet rich in meat and fish, the breakdown of which yields urate.
- Heavy consumption of beer and spirits (beer has high purine content); wine consumption is less serious.
- Concurrent use of loop or thiazide diuretics and low dose aspirin, which cause hyperuricemia by decreasing renal clearance of urate.
- The metabolic syndrome. This syndrome is associated with hyper-insulinemia. Insulin favors renal tubular reabsorption of urate and urinary excretion of urate is less avid in hyper-insulinemia. ("The Metabolic Syndrome": http://www.medicine-on-line.com/en/detail_revisited.php?id=5)
- Increased purine turnover as in myelo-proliferative and lympho-proliferative diseases.
- Reduced renal excretion in chronic renal impairment.

3. What are the clinical features of gout?

The clinical presentation of gout can be divided into acute, interval (intercritical) and chronic (tophaceous):

**Acute Gout**
- Attack frequently occurs in the middle of the night; onset is abrupt and symptoms progress rapidly within a few hours.
- Mono-articular involvement more common; poly-articular involvement unusual. Affects the first MTP joint in more than 70% of cases; can also involve the mid-foot joints, the ankle, the knee, the fingers, the wrist, and the elbow. The hip, the shoulder, and joints of the spine are usually spared possibly because the higher temperature of these central joints does not favor microcrystal formation.
- The affected joint is red, swollen, and tender; adjacent tissues commonly involved; movement is limited by pain.
- Not uncommon to find serum urate level normal during an acute attack.
- Fever and leukocytosis with left shift is usual.
- Acute inflammation subsides spontaneously in 7 – 10 days if left untreated.
- Skin over affected area often desquamates during recovery.
Interval gout

- In some patients there may be no recurrence after a single attack. In others there is chronic hyperuricemia and acute attack recurs, in the same joint and/or another joint.
- With repeated attacks the asymptomatic interval between attacks shortens, poly-articular involvement becomes more common, resolution of symptoms is slower, and recovery is less complete.

Chronic gout

- Chronic gout is the end result of persistent hyperuricemia. Urate deposits called tophi aggregate in joints, the olecranon bursa, the Achilles tendon, and subcutaneous tissues. These tophi invoke a foreign-body giant-cell inflammatory reaction that destroys cartilage and bone and cause joint deformity. The most commonly affected joints are that of the great toe, the knee, and that of the fingers and wrist.
- Onset and progress of chronic tophaceous gout is insidious. The patient complains of joint stiffness, pain, and swelling over time. Symptoms of nerve compression (e.g. carpal tunnel syndrome) are not uncommon. It takes an average of 10 years for tophi to appear.

Renal complications

- Patients with chronic hyperuricemia may develop nephrolithiasis and acute and chronic gouty nephropathy.
- Nephrolithiasis is not invariable in patients suffering from chronic gout. This is because urine pH, hydration status, and family history of kidney stone are important contributing factors.
  - Urate are more soluble when urine pH becomes more alkaline; patients whose urine is more alkaline (e.g. patients who consume a lot of fruits and vegetables) are less likely to form urate kidney stones.
  - Patients who consume more fluid and have higher urine flow are less likely to form urate kidney stones.
Not all kidney stones are urate stones in patients who have chronic hyperuricemia. Urate can act as a nidus in the formation of calcium oxalate or phosphate stones and family history is a contributing factor in the formation of calcium stones.

- Acute gouty nephropathy is the result of a massive load of urate appearing in the urine following chemotherapy of myeloproliferative or lymphoproliferative disorders. Precipitation of urate crystals in the renal tubules and collecting ducts leads to an acute obstructive nephropathy with oliguria and renal failure.
- Chronic gouty nephropathy is a less dramatic form of renal impairment in which deposition of urate in the renal parenchyma causes proteinuria and inability of the kidney to concentrate urine.

4. What are the principles of treatment?

Treatment is dependent on whether the arthritis is acute or repetitive and chronic.

Acute gout

- Affected area is ultra sensitive to touch, even to bedcover. The affected joint should be elevated if possible and mechanical support may be required to keep bedcover away. On the other hand, an ice pack may be soothing.
- Anti-inflammatory treatment should be instituted immediately and continued until symptoms have subsided. Delay of therapy is associated with less satisfactory response.

- By way of their anti-inflammatory and analgesic effects, non-steroidal anti-inflammatory analgesics (NSAIDs) are the drugs of choice in the absence of contraindications (peptic ulcer disease, bronchospasm, congestive heart failure, renal dysfunction, and concurrent anticoagulant therapy). They should be started immediately and continued until pain is completely resolved. NSAIDs like indomethacin, ibuprofen, and naproxen are non-selective inhibitors of both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes and have the propensity to cause gastritis and upper gastrointestinal hemorrhage. Selective COX-2
inhibitors are better tolerated in this respect but are not free of gastrointestinal side effects in high doses. They can also cause adverse cardiovascular events in long term use.

- The action of colchicine, an anti-mitotic agent, in gout is not clear. Anti-inflammatory effect may be dependent on its ability to inhibit the migration of neutrophils into joints and to prevent the production of inflammatory glycoprotein by neutrophils that have phagocytosed urate crystals. Oral colchicine is an alternative to NSAID drugs if the latter are contraindicated but it can also cause gastrointestinal upset (nausea, vomiting, and diarrhea). The dose should be lowered in patients with renal dysfunction. Intravenous administration of colchicine cannot be justified on account of toxicity.
- Glucocorticoids, either given intramuscularly or orally, should be considered if NSAIDs and colchicine are not tolerated or contraindicated. Systemic steroid is particularly suitable for patients with multiple-joint involvement. Intra-articular injection of a "depo" preparation requires expertise and is an alternative in mono-articular involvement.

Interval gout

Acute gouty arthritis may not recur in some patients despite continued hyperuricemia. Therefore prophylaxis against recurrence is not necessary after a single acute attack. However, secondary prevention is indicated in patients who have 2 or more acute attacks per year (interval gout) and those who have tophi, erosive changes on x-ray, or urate calculi (chronic gout).

- General measures
  - Dietary restriction of purine-rich food (internal organs, meats, fish and other seafood, yeast, legumes, oatmeal, spinach, mushrooms, asparagus, cauliflower) has been advocated as an effective measure of lowering serum urate level. However, only high consumption of meat and fish has definite association with acute gout. Restriction of other food items is not necessary unless there is a convincing relationship between consumption
and acute attacks. Low fat dairy products, on the other hand, are protective against gouty arthritis—probably due to the uricosuric effect of casein and lactalbumin.

- There is ample evidence excessive alcohol consumption is linked to acute attacks. Moderation is advised.
- Obesity is another factor linked to acute gout. While weight reduction is advised, a starvation diet can precipitate an attack and should be avoided.
- Avoiding drugs that can cause hyperuricemia by lowering renal clearance of urate (diuretics and low dose aspirin) should be part of this strategy.

**Pharmacological interventions**

This approach involves the use of drugs to reduce serum urate level. However, by mobilizing tissue urate, these drugs can increase local urate concentration and trigger acute attacks in the first 3 – 6 months of treatment. Therefore, urate-lowering drugs should be started at low dose and increased to full dose gradually. By the same mechanism, they can delay recovery and should be withheld for 3 – 4 weeks after an acute attack.

- **Allopurinol** blocks xanthine oxidase, the enzyme responsible for converting xanthine and hypoxanthine to uric acid—thus inhibiting the production of urate. It is acceptable to start allopurinol empirically at a low dose and increase it at 1 – 2 week intervals until the full therapeutic dose is reached. This dose should be revised downward in the face of renal dysfunction. Side effects include a hypersensitive reaction characterized by a mild rash that is inconsequential or an intense desquamative rash together with fever, eosinophilia, hepatocellular injury and renal failure. The more serious reaction is uncommon and occurs mostly in patients with concurrent renal impairment or on diurectic use. Patient’s blood counts and liver and renal function tests should be followed in the first several months of therapy. Febuxostat is another xanthine oxidase inhibitor that holds promise in clinical trials.

- **Probenecid, sulfinpyrazone, and benzbromarone** are uricosuric agents. They act by lowering tubular reabsorption of uric acid by the kidneys. Probenecid and sulfinpyrazone are ineffective in renal impairment when
creatinine clearance falls below 50 ml/min but benzbromarone may still be effective when creatinine clearance is as low as 25 ml/min. A 24-hour urinary urate excretion test should be performed before their prescription because they are more suited for patients who under excrete urate and not indicated in hyper-excreters. Precipitation of nephrolithiasis is a complication because urate excretion reaches extraordinary levels during the initial stage of therapy. Generous fluid intake and alkalinization of the urine to increase the solubility of urate are advised. (Urine can be alkalinized by a prescription of oral sodium bicarbonate.) Probenecid can prolong the action of penicillins and rifampin and cause gastrointestinal upset, skin rash, and autoimmune hemolytic anemia. Sulfipyrazone has a small risk of causing bone marrow depression and benzbromarone can rarely cause hepatic failure.

- As was pointed out before, urate-lowering drugs can trigger acute gout attacks in the initial 3 – 6 months of therapy. It is recommended that colchicine or an NSAID in low dose be prescribed concurrently with urate-lowering drugs to prevent these attacks, for at least 3 – 6 months or until all visible urate deposits have been reabsorbed. Both colchicine and NSAID have undesirable side effects in long term use. Potential risks should be weighed carefully against expected benefits.

- Losartan, an angiotensin II receptor antagonist used in the treatment of hypertension and heart failure, has therapeutically useful uricosuric activity. Using it to treat hyperuricemia alone is expensive but is the ideal medication for the hypertensive patient who has gout.

- Uricase (urate oxidase) is the enzyme responsible for the degradation of uric acid. A recombinant preparation is under investigation for the treatment of hyperuricemia refractory to conventional therapy.

Chronic gout

The principles of treatment for chronic and interval gout are similar.
Further reading


Underwood M. Diagnosis and management of gout. *British Medical Journal* 2006;332:1315.