CHAPTER **40**

GOUT: Diagnosis and Management

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ETIOLOGY

Gout is a disease that results from the deposition of monosodium urate crystals in synovial fluid and other tissues, as well as formation of uric acid stones in the kidney. Gout can cause renal disease. When gout affects joints, it can involve the subchondral bone and lead to destructive and painful changes. Primary gout is a metabolic disease, having its basis in an inborn error of metabolism in purine metabolism. Hyperuricemia can occur with decreased renal function and in genetic disorders that increase the production or limit the excretion of uric acid. Several medications can increase serum uric acid concentration by modifying the filtered load of uric acid or its tubular transport process. Aspirin, ingested above 2 grams per day is uricosuric. Aspirin, at a dose of 81 mg per day, thought to be cardioprotective, does not interfere with renal filtration of uric acid. Other doses of aspirin do cause underexcretion of uric acid. There are many etiologies of gout, and the secondary causes are numerous (Table 1).

Serum uric acid concentrations are elevated when there is rapid cell proliferation and turnover; where there is an excess of nucleoproteins. Conditions that result in elevated serum uric acid concentrations include psoriasis (severe), Paget's disease, rhabdomyloysis, exercise, alcohol intake, obesity, a purine-rich diet, Down's Syndrome, starvation ketosis, sarcoidosis, berylliosis, lead intoxication, hyperparathyroidism, hypothyroidism, pregnancy toxemia, Bartter's Syndrome, nicotinic acid (niacin or nicolar) and cyclosporine (sandimmune). A combined mechanism – specifically glucose-6-phosphate dehydrogenase deficiency, fructose-1-phosphate aldolase deficiency, alcohol and shock can also lead to elevated concentrations.

The disease is often, but not always, associated with increased serum uric acid levels. Elevated levels are above 6 mg/dl in women and 7 mg/dl in men. Gout typically occurs in men over the age of thirty years. When it occurs in women, they are postmenopausal. Uric acid is the end product of purine metabolism and has no physiologic role. Animals posses the enzyme uricase, however man does not, leaving uric acid, if deposited in tissues, to create an inflammatory reaction, a chronic granulomatous synovitis. The disease is a result of either overproduction of uric acid or under-excretion of uric acid. In 90% of patients, gout is caused by under-excretion.

Hyperuricemia is a risk factor for the disease, however acute gouty arthritis can occur in the presence of normal uric acid levels. Conversely, many patients with high uric acid levels may never experience acute gouty attacks.

Table 1

ETIOLOGIES OF GOUT

Overproduction of urate

- Primary idiopathic hyperuricemia
- Hypoxanthine-guanine phosphoribosyl transferase deficiency
- Phosphoribosylpyrophosphate synthetase over-activity
- Hemolytic processes
- Lymphoproliferative disease
- Myeloproliferative disease
- Polycythemia vera

Decreased excretion of uric acid

- Primary idiopathic hyperuricemia
- Renal insufficiency
- Polycystic kidney disease
- Diabetes insipidus
- Hypertension
- Acidosis (lactic, diabetic ketoacidosis)
- Drug ingestion
  - salicylates (less than 2 g per day)
  - diuretics
  - alcohol
  - levodopa-carbidopa (Sinemet)
  - Ethambutol, myambutol
  - Pyrazinamide

Up to 75% of uric acid is excreted by the kidneys. Uric acid is first filtered by the glomeruli and then reabsorbed by the proximal renal tubules. Whatever is not reabsorbed, is excreted. A total of 98% of patients with hyperuricemia have defective renal management of uric acid.

PREVELANCE

Although hyperuricemia is common, most patients never develop gout. With serum uric acid levels above 10 mg/dl, for 5 years, the incidence of gout is 30%. With serum uric acid concentrations of less than 7 mg/dl, the incidence is 0.6 %. Gout affects 6/1000 population for men and 1/1000 population for women. The incidence of gout, worldwide is increasing.

COMORBIDITIES

Hyperuricemia has been associated with hypertriglyceridemia and diabetes mellitus. It may be a risk factor in the development of coronary artery disease (25%) and vascular disease in general. Specifically, the risk with comorbidities is as follows: type II diabetes mellitus (15%), insulin resistance (63%), hyperglycemia, dyslipidemia, hypertriglyceridemia, low HDL level, hypertension (>50%), obesity (>71%), renal insufficiency (creatinine level >1.5, 5%), and kidney stones (14%). Gout has been associated with increased risk of myocardial infarction.

Risk factors for gout include heredity, obesity, dietary excess, and renal insufficiency.

Certain medications decrease uric acid excretion (Table 2). The elderly are therefore at increased risk of acute gouty attacks. Attacks can also be precipitated by dehydration.

CLINICAL PRESENTATION

Initial attacks of gout are often monoarthric. However, polyarthric attacks can occur, especially in the elderly. Fifty percent of attacks affect the great toe. Attacks can occur without cause however, injury, stress, surgery, ingestion of purine rich foods and others can help provoke an attack. Purine rich foods include red meat, salmon, bacon, scallops, turkey, sweetbreads. The affected joint will be erythematous, hot, swollen and painful (Figure 1).

Diagnostic Evaluation

Consideration should be given to CBC with differential, urinalysis, serum creatinine, blood urea nitrogen, and serum uric acid. These tests will allow you to evaluate the cardiovascular and renal systems, which are affected by gout. Radiographs will show soft tissue inflammation or perhaps joint effusion early in the disease. Late, destructive arthropathy shows hallmark signs of sharp, peri-articular punched out erosions with preservation of the joint space, and normal bony calcification (Figure 2). Tophi are a late

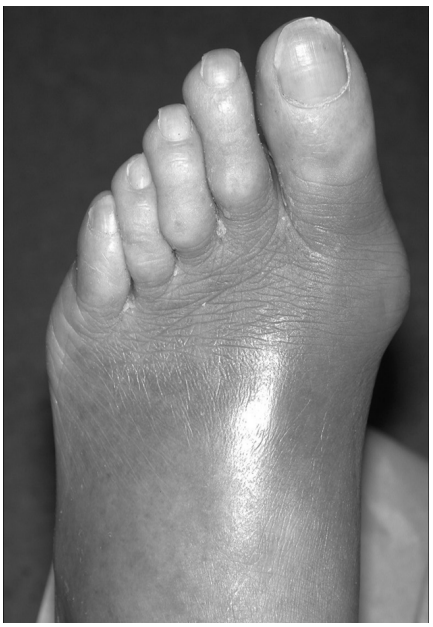

Figure 1. Besides acute gout, tophi can develop in chronic cases as can chronic destructive gouty arthropathy. Interstitial renal disease as well as urolithiasis is common. Uric acid nephrolithiasis occurs in 10-25% of patients. Leukocytosis and low grade fever are common.

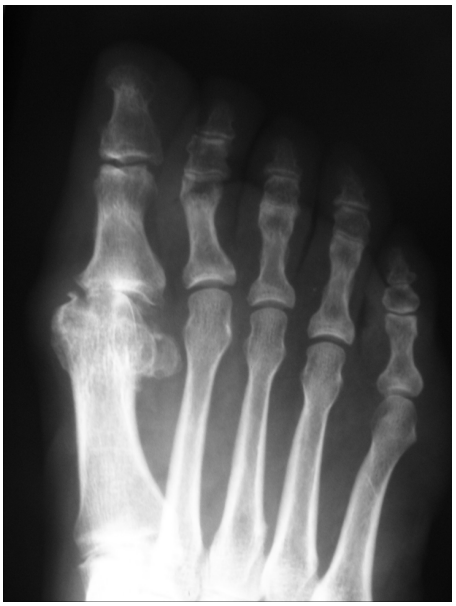

Figure 2. Hallmark signs of gout.

Table 2

THE EFFECT OF MEDICATIONS ON URIC ACID EXCRETION

Medications that reduce uric acid excretion	Medication that increase uric acid excretion (Uricosuric)
• Thiazide diuretics	• High dose aspirin
• Loop diuretics	
• Low-dose aspirin	
• Cyclosporine	
• Niacin	
• Ethambutol	
• Pyrasinamide	
• Didanosine	

development of the disease and often affect the elbows, knees, wrists, hands, great toe, Achilles tendon, and pina of the ear (Figure 3). Tophi can invade the subcondral bone and cause painful destruction. Classically gout was diagnosed by a clinical triad of inflammation, elevated serum uric acid, and clinical response to colchicine. Gout responds to colchicine quite predictably.

Differential Diagnosis

Differential diagnosis includes cellulitis, septic arthritis, tumor, fracture, and pseudogout (Figure 4).

Limitations in Diagnosis

Serum uric adic levels are normal in 40% of acute gouty attacks. Chronic polyarticular gout occurs with increasing age. Psuedogout (calcium pyrophosphate crystal deposition disease [CCPD]) can mimic gout. CPPD does respond to colchicine as well. Chondrocalcinosis may be seen on radiographs, which can help in confirming the diagnosis. Joint aspiration, looking for negatively birefringent sharp needle-shaped crystals is necessary for appropriate diagnosis of the disease (Figure 5). The aspirate should be kept in a simple syringe and sent for microscopic review. Proper observer accuracy is often a problem. If infection is in the differential diagnosis, then gram stain as well as culture and sensitivity are needed.

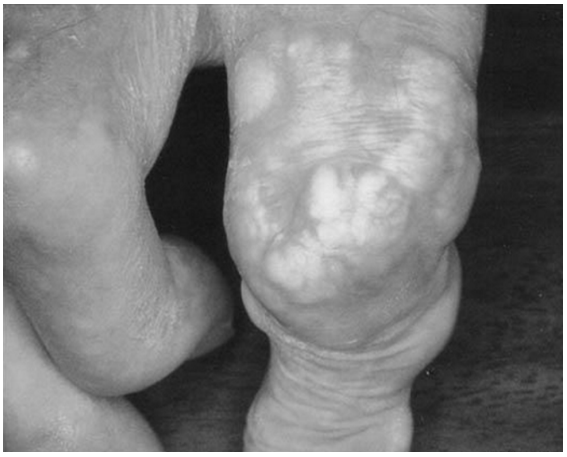

Figure 3. It takes approximately 11 years for gouty tophi to develop.

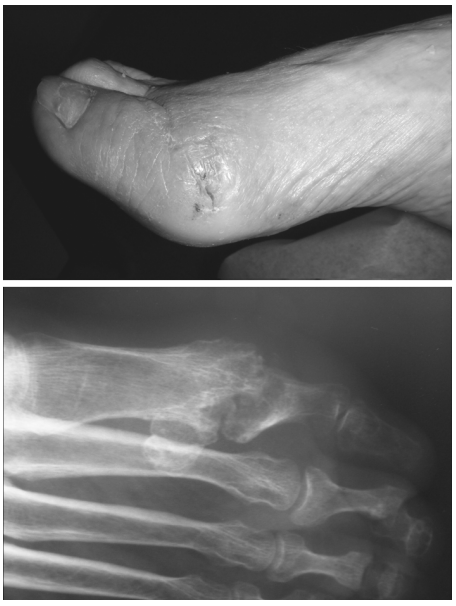

Figure 4. Osteomyelitis masquerading as gout.

TREATMENT GOALS

Termination of acute attacks, prevention of recurrent attacks and prevention of complications associated with urate deposition in tissues are all treatment concerns. The general medical health of the patient cannot be overlooked. Dietary and lifestyle changes such as weight

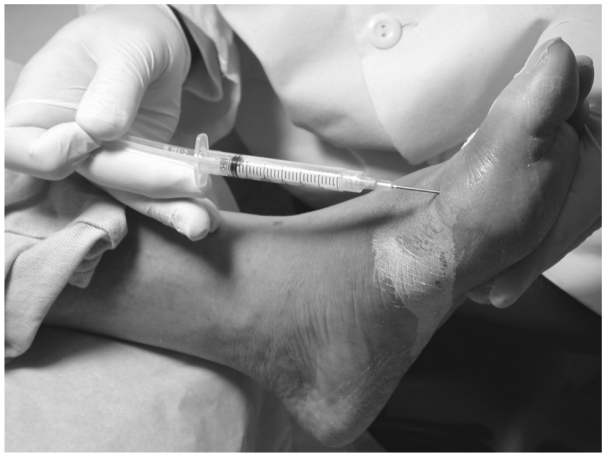

Figure 5. Showing joint aspiration of gouty material.

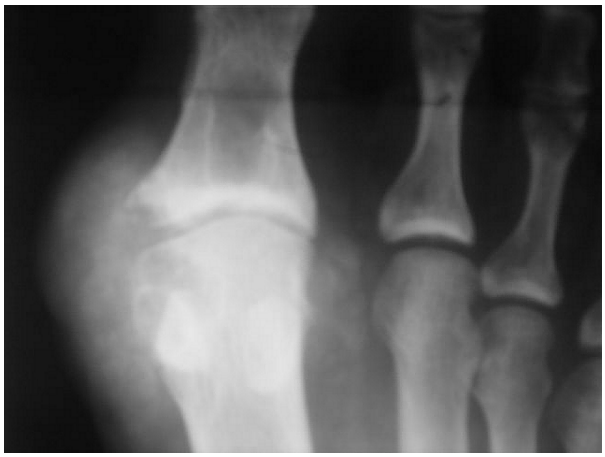

Figure 6. Destructive arthropathy of the great toe metatarsophalangeal joint.

Table 3

EFFECTS OF NSAIDS

- Worsen renal function
- Fluid retention
- Gastropathy
- Hepatotoxicity
- Impaired cognitive function
  - Monitor renal function*
  - Note pre-existing renal* impairment*

*Especially in the elderly

Table 4

Preferred in Renal Impaired	Careful in diabetics
Oral	20-40 mg of prednisone or equivalent tapered over 8 days
IM	40 mg methylprednisolone acetate or equivalent
Intra-articular	long or short acting corticosteroid
Corticotropin	40 units IM q 8 h times

reduction, descreased alcohol intact, a low purine diet, control of hyperlipidemia and hypertension are absolutely needed however, symptomatic hyperuricemia usually requires medication.

Changes

Treatment of acute gout consists of rest, ice, nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular injections of steroids, and perhaps colchicine. NSAIDs can have deleterious effects especially in the elderly and must be used with caution (Table 3). While indomethacin was considered the drug of choice for gout, all NSAIDs are of equal value and help with the treatment of the acute phase inflammation. In those patients who can not tolerate NSAIDs, then oral corticosteroids or corticotropin can be used (Table 4).

In chronic, frequent, or tophaceous gout, treatment is aimed not only at treating the acute phase of the disease, but by reducing serum uric acid levels. Some clinicians feel that gout should be treated from the initial attack so that morbidity does not occur. A general approach is needed as multiple comorbidies have been identified. There is value in 24 hour urinary uric acid quantification. Here, one will identify the young male over-producer or the under-excretor. The acute attack should end prior to treatment of chronic gout. When treating chronic gout, protection is needed to prevent acute gouty attacks which can occur as a result of mobilizing uric acid stores. Low-dose NSAIDs or colchicine are appropriate. Uricosuric drugs have a place in treatment as long as the patient has normal renal function and is an under-excretor (Table 5).

Colchicine is still used today as it was since its inception. It does require dose adjustments in renal insufficiency or liver disease (Table 6). Allopurino (Zyloprim) is a xanthine oxide inhibitor and is a drug of choice for patients with severe tophaceous deposits and urate nephropathy. Dose modifications are necessary in the renal impaired patient (Table 7). Most drugs used today are the same as the drugs of yesterday. Better understanding of gout treatment as well as improved patient dosing can improve treatment failures. Improved patient compliance is also of paramount importance.

Table 5

URICOSURIC DRUG THERAPIES

Probenecid (Benemid)	Sulfinpyrazone (Anturane)	Losartin	Fenofibrate
Limited use in elderly	related to phenylbutazone		
Probenecid 1-2 gm/day	Antiplatelet drug		
Satisfactory control 60-85%	Caution in those anticoagulated or with bleeding problems		
Increases plasma concentrations of penicillins, cephalosporins, sulfonamides and indomethacin.	Can cause GI problems Caution with PUD		

Emerging Therapies

Rasburicase and PEG-uricase, are urate oxidase drugs. Rasburicase is used in pediatric patients to prevent tumor lysis syndrome, during chemotherapy. It has been used off label in cases of treatment failure gout. PEG-uricase is presently an IV medication, now in phase II trials. It is a recombinant porcine urate oxidase. Fuboxostat is a xanthine oxide inhibitor presently in phase III trials. Oxipurinol, another xanthine oxide inhibitor is no longer available in the US.

Surgical Management

There are indications for surgery especially when medical treatments do not alleviate the condition. Surgery is aimed at excision/resection of the soft tissue tophus or joint destructive procedures such as arthroplasty and arthrodesis. Consideration can be given for intra-operative colchicine to prevent gouty flares (Table 8).

SUMMARY

Gout is a chronic disease. Symptoms are often intermittent, acute or even absent. Chronic inflammation is a hallmark of this disease. Patient compliance with treatment is poor as they have to take medications for life, and the physician role in treatment has been less than optimum. Without treatment, severe soft tissue , renal and osseous sequelae develop. (Figure 6). Hyperuricemia may have an impact on vascular disease.

Table 6

COLCHICINE TREATMENT

- Oldest treatment
- Can prevent rebound flare-up
- Dose-dependent toxicity
  - Diarrhea, bone marrow suppressive in high doses
  - Can't be dialyzed
  - Myopathy
- 0.5 or 0.6 mg once or twice daily
  - Inhibits microtubule polymerization
  - Disrupts chemotaxis and phagocytosis
- 0.5 or 0.6 mg two initially; one each hour until relief
  - do not exceed 7 mg.
- 1 mg IV up to 4 mg per day
- adjust dose renal insufficiency or liver disease

Table 7

ALLOPURINAL TREATMENT

Reduces serum uric acid
Adjust dose in renal compromised patients:
- 300 mg qd dose
- 200 mg qd with creatinine clearance 60 ml/min.
- 100 mg qd for creatine clearance of 30 ml/min.

Serum uric acid of 6 mg/dl is target
Hypersensitivity reaction: rash, fever
• *Allopurinal is drug of choice for patients with severe tophaceous deposits and urate nephropathy*

Table 8

SURGICAL MANAGEMENT OF GOUT

- Painful soft tissue lesions
- Questionable lesions requiring biopsy
- Tendon involvement / rupture
- Compression of nerves and vessels
- Destructive arthropathy
  - Arthroplasty
  - Arthrodesis
- Role of peri-operative colchicine
- Complete excision tophus with its capsule
- Resect tophus from tendon
- Curette remaining uric acid deposition
- Excise or curette draining sinus
- Resect bony deformity or grossly diseased bone
  - Keller, May, McKeever arthrodesis
- Resect or arthrodese midfoot involvement
- Surgical intervention adjunctive to medical management.