Diagnosis of Gout: Clinical, Laboratory, and Radiologic Findings

Naomi Schlesinger, MD

Abstract

Acute gouty arthritis typically presents with a sudden and severe exquisitely painful joint, most classically in the first metatarsophalangeal joint (toe). Demonstrating the presence of monosodium urate (MSU) crystals in the joint fluid or tophus has been the gold standard for the diagnosis of gout. However, many physicians do not perform synovial fluid analysis. In the absence of demonstrating the presence of MSU crystals in aspirated joint fluid or tophus, clinical, radiologic, and laboratory criteria are helpful. This article presents an overview of the various classification criteria, clinical presentations, and laboratory and radiologic studies needed to make the diagnosis of gout.

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Gout is a common systemic metabolic disease, affecting more than 1% of the population. It is the most common inflammatory arthritis, afflicting 1 or more joints in men older than 40 years of age.[1] The majority of patients have primary gout, meaning that no identifiable underlying disease causing the hyperuricemia can be found. Secondary gout, which is less common, can result from many conditions (**Table 1**).

To understand gout adequately, it is important to define the relationship between uric acid, hyperuricemia, and gout. Humans do not express the enzyme urate oxidase (uricase), because of a mutation during evolution of the uricase gene, which converts urate to the more soluble and easily excreted compound allantoin. Among mammals, only humans and other primate species excrete uric acid as the end product of purine metabolism. Uric acid is a weak organic acid that exists mainly as the urate ion at pH >5.75 and as the un-ionized uric acid form at more acidic (lower) pH levels.

Thus, the urate form predominates in all extracellular fluids, including serum, in which physiological pH is 7.4. In urine, which is usually acidic, the un-ionized uric acid form predominates.

When overproduction or underexcretion of uric acid occurs, the serum urate (SU) concentration may exceed the solubility of urate (a concentration approximately >6.8 mg/dL), and supersaturation of urate in the serum (and other extracellular spaces) results. This state, called hyperuricemia, imparts a risk of crystal deposition of urate in tissues from the supersaturated fluids.

Four clinical stages result from hyperuricemia, including asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout (intervals between acute attacks), and chronic tophaceous gout.[2] Inflammatory arthritis in patients with gout is caused by crystals of monosodium urate (MSU) that form as a result of chronically elevated levels of urate in plasma and extracellular fluids.

Although the first descriptions of gout can be traced to the dawn of recorded medical history, questions remain regarding the diagnosis of gout.[3] The gold standard for establishing a definite diagnosis of gout is the presence of MSU crystals in aspirated joint fluid or tophus.[4] Physicians, however, do not routinely perform synovial fluid (SF) analysis, even in hospitalized patients with acute gout,[5] opting instead to reach a diagnosis based on clinical features and demonstration of hyperuricemia.

There are many limitations to this diagnostic approach. In a study of 9108 consecutive new patients seen in an outpatient rheumatology clinic, 155 (1.7%) were diagnosed with gout. A higher number of patients (164, 1.8%) had been incorrectly diagnosed with gout in the community.[6]

Table 1. Causes of Hyperuricemia

**Increased uric acid production
(5%-10% of patients)**

Genetic enzymatic defects
- Hypoxanthine-guanine phosphoribosyltransferase deficiency, glucose-6-phosphatase deficiency, 5-phosphoribosyl-1-pyrophosphate synthetase overactivity

Acquired causes
- Dietary indiscretions: excessive purine diet/pancreatic extracts
- Obesity
- Increased tissue turnover—tumors, lymphoproliferative disorders
- Vigorous muscle exertion causing increased turnover of ATP
- Alcohol-induced turnover of ATP
- Chemotherapy

**Decreased uric acid excretion
(90%-100% of patients)**

Genetic causes
- Down syndrome
- Polycystic kidney diseases

Acquired causes
- Diminished renal function
- Inhibition of tubular urate secretion: competitive anions (eg, ketoacidosis and lactic acidosis)
- Enhanced tubular urate reabsorption: dehydration, starvation, insulin resistance (metabolic syndrome)
- Medications: low-dose aspirin, thiazide diuretics, ethambutol, niacin
- Lead nephropathy

ATP indicates adenosine triphosphate.

Some have maintained that gout can be diagnosed clinically by the triad of inflammatory arthritis, elevated SU level, and response to colchicine.[6]

In the absence of demonstrating the presence of MSU crystals in aspirated joint fluid or tophus, clinical, radiologic, and laboratory criteria are helpful. It is important to diagnose gout early so that underlying hyperuricemia and the acute attack can be treated appropriately. This article describes current knowledge regarding the diagnosis of gout and provides an overview of the various classification criteria and clinical examination, laboratory, and radiologic findings needed to make the diagnosis of gout.

Classification Criteria

The first criteria for the classification of gout were proposed at the Rome symposium on population studies in the rheumatic diseases.[7] According to the Rome criteria, to be diagnosed with gout, patients must meet 2 of the following 4 criteria: (1) an SU level >7 mg/dL in men or >6 mg/dL in women; (2) the presence of tophi; (3) the presence of MSU crystals in SF or tissues; and (4) a history of painful joint swelling with abrupt onset and remission within 2 weeks.

These criteria were modified in an international symposium held in New York in 1966. The major changes were the addition of a response to colchicine and the removal of SU levels from the list of criteria.[8] The New York criteria are still helpful in routine clinical practice. They include the presence of a clear history of at least 2 attacks of painful joint swelling with complete resolution within 2 weeks, a clear history or observation of podagra, the presence of a tophus, and a rapid response to colchicine within 48 hours of starting treatment. Two of these criteria are required for a clinical diagnosis, but a definitive diagnosis can be made if MSU crystals are seen in SF or in the tissues.

Rigby and Wood[9] compared the New York and Rome criteria in 59 patients with gout and 761 patients with other arthropathies. They found that the best individual criterion was 1 or more attacks of podagra (New York criteria). In contrast, the presence of a tophus was the least valuable criterion. The New York criteria were more sensitive and specific than the Rome criteria. Rigby and Wood also investigated the value of determining the SU level in new patients in a rheumatology outpatient clinic. The gold standard in this study was clinical assessment by rheumatologists. Determining the SU level was a criterion for the diagnosis of gout in the Rome criteria but not in the New York criteria. Rigby and Wood concluded that in a clinical picture resembling gout, with a low SU level independent of the gouty attack, the diagnosis of gout is very unlikely.

In 1977, the American College of Rheumatology published preliminary criteria for the classification of gout for use in either clinical settings or population-based epidemiologic studies.[10] Subjects were classified as having gout when they had MSU crystals in their SF, the presence of a proven tophus, or at least 6 of the remaining 11 criteria (**Table 2**). These criteria were extrapolated from a rheumatic population in which 6 or more of the 11 criteria were present in 87.6% of the 178 patients with acute gout.[10] Tophi were present or suspected in 30% of the 178 patients with acute gout, with a specificity of 99%. Most likely, the specificity was not 100% because there were 1 or more cases of bacterial arthritis in gouty patients with tophi.

No studies have been published on the validity and usefulness of any of these diagnostic criteria. New classification criteria need to be defined and validated.

Clinical Diagnosis

In his classic description of a gouty attack, translated from Latin in 1848, Sir Thomas Sydenham wrote:

The victim goes to bed and sleeps in good health. About two o'clock in the morning he is awakened by a severe pain in the great toe; more rarely in the heel, ankle, or instep. This pain is like that of a dislocation...Then it is a violent stretching and tearing of the ligaments—now it is a gnawing pain and now a pressure and tightening...He cannot bear the weight of bedclothes nor the jar of a person walking in the room. The night is passed in torture, sleeplessness, turning of the part affected, and perpetual change of posture; the tossing about of the body being as incessant as the pain of the tortured joint.[11]

As described so vividly by Sydenham, acute gouty arthritis is characterized by rapid onset and buildup of pain. The speed of the onset of pain and swelling is relevant to making the diagnosis; symptoms that take days or weeks rather than hours to develop probably indicate a disorder other than gout. The pain is described as the worst pain that the person has ever endured. The exquisite pain in acute gout is

Table 2. Preliminary Criteria for Diagnosis of Acute Gout

- Monosodium urate monohydrate microcrystals in joint fluid during attack
- More than 1 attack of acute arthritis
- Maximum inflammation developing within 1 day
- Monoarthritis attack
- Redness observed over joints
- First metatarsophalangeal joint painful or swollen
- Unilateral first metatarsophalangeal joint attack
- Unilateral tarsal joint attack
- Tophus (proven or suspected)
- Hyperuricemia
- Asymptomatic swelling within a joint on x-ray
- Subcortical cysts without erosions on x-ray
- Joint fluid culture negative for organisms during attacks

The combination of crystals, tophi, and/or 6 or more criteria is highly suggestive of gout.

Source: Reference 10.

associated with warmth, redness, and swelling of the affected joint.

In men, the initial episode is usually monoarticular (1 joint). The typical patient tends to experience gout initially in the lower extremities. The first metatarsophalangeal joint (misnamed podagra) is initially involved in approximately half of all men with gout. Other joints involved (in decreasing order of frequency) include insteps, knees, wrists, fingers, and olecranon bursae.[12] Systemic symptoms and signs of fatigue, fever, and chills may accompany the acute arthritis. The first episode of gouty arthritis often begins at night. This may be because there is a stable level of urate in the joint fluid and during rest, water is absorbed more rapidly than urate, increasing the concentration of urate or MSU crystals in the joint and precipitating attacks. The natural course of untreated gouty arthritis varies from episodes that last several hours to several weeks.

With uncontrolled hyperuricemia, the body urate pool expands and joint involvement becomes additive and ascending. Later attacks may be polyarticular. Polyarticular attacks tend to be less abrupt

in onset, less severely painful, and more likely to be associated with constitutional upset than monoarticular attacks.[13] It is important to note that the acute inflammatory events of gout are not limited to joints. Patients who present with symptoms in bursae and tendons should be evaluated for gout, which can occur in these locations. Minor trauma, alcohol abuse, surgery, dietary excess, hypouricemic or diuretic therapy, and severe medical illness can precipitate attacks.[14]

Gout in women follows a different pattern from that in men. Only a small number of women start with acute podagra (first metatarsophalangeal joint arthritis). The most common presentation is acute polyarticular gout, especially of the hands, tarsal joints, knees, and ankles.[15] Women tend to develop tophaceous deposits on Heberden's and Buchard's nodes (hard bony enlargements of the small joints of the fingers seen in osteoarthritis), sometimes with minimal inflammation.[16] This atypical joint involvement can cause diagnostic confusion with rheumatoid arthritis. Gouty arthritis, however, tends to be less symmetric than typical rheumatoid arthritis.

Gouty arthritis is often less severe in the elderly than in younger patients,[17] and is often mistaken for osteoarthritis. This is further complicated by the coexistence of gout and osteoarthritis in the same joints, especially Heberden's nodes.[18]

Chronic tophaceous gout usually develops after 10 or more years of acute intermittent gout, although in rare cases, tophi may be the initial manifestation of the disease.[19] Tophi appear as firm swellings. If they are inflamed, there is erythema of the overlying skin. Whitish chalky material may be seen in ulcerated tophi. Tophi may appear at any site, but the most common sites are the digits of the hands and feet and the olecranon bursa. Tophi of the helix or antihelix of the ear are classic but less common. Tophi have also been reported in the eye,[20] carpal tunnel,[21] and heart valves.[22] In these situations, diagnosis is often unsuspected until surgery. Tophi may be associated with destructive deforming arthritis and may ulcerate, in which case secondary infection may be a problem. Of note, tophi sometimes tend to

be confused with rheumatoid nodules, and, therefore, when in doubt, needle aspiration should be done to detect MSU crystals.

Laboratory Diagnosis

SF Analysis. Even when the clinical appearance strongly suggests gout, the diagnosis must be confirmed by needle aspiration of the acutely inflamed joint or suspected tophus.[18] During the 1960s, McCarty and Hollander described this method.[4] A drop of SF should be examined promptly under routine light and polarizing light microscopy. SF is best examined while fresh. If MSU crystals cannot be identified on the wet preparation after 5 to 10 minutes, the remaining SF should be centrifuged and the pellet examined. This technique can increase yield if only a few crystals are present. Gouty tophi should be examined by smearing a small amount of tophaceous material onto a slide. A smear from gouty tophi will show a mass of brilliantly birefringent, needle-shaped crystals.
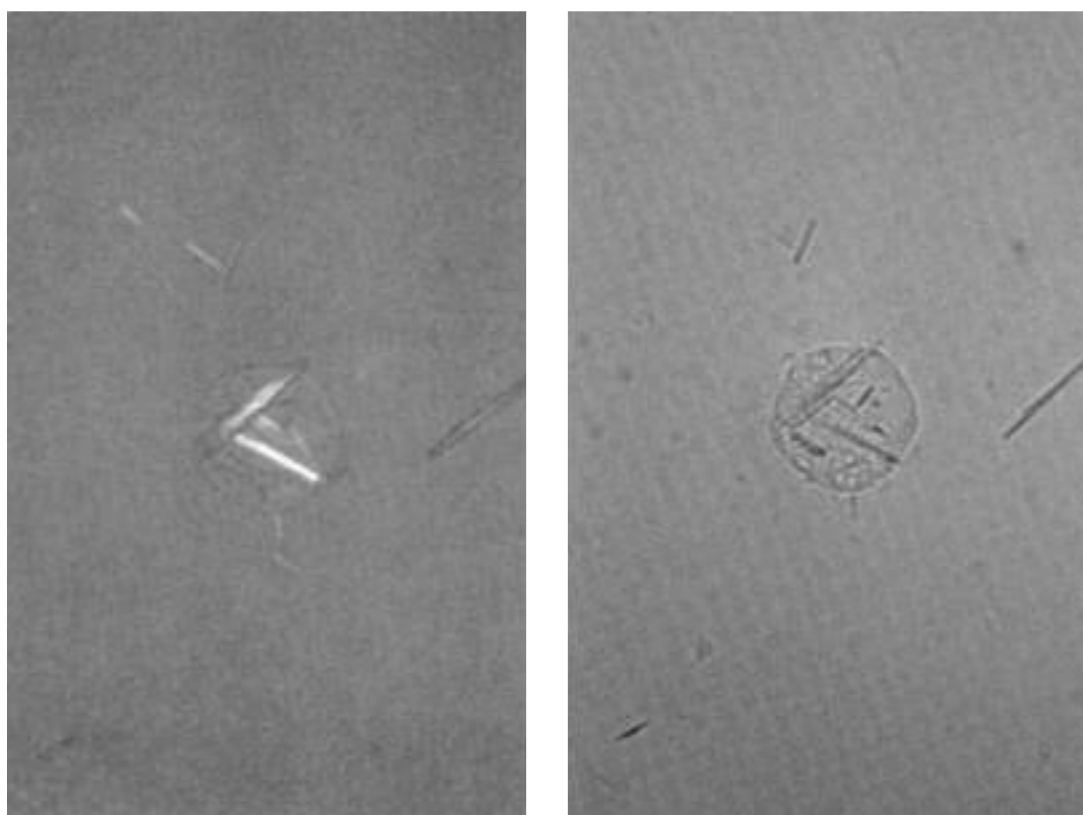
MSU crystals are needle-shaped and approximately 2 to 20 mm long. They exhibit strong negative birefringence under polarized light. They appear yellow when they are parallel to the axis of the slow vibration of the compensator and blue when lying perpendicular to the same axis.[22] MSU crystals can be observed in more than 95% of patients with acute gouty arthritis.[13] In some asymptomatic patients, MSU crystals are also detected in joints in which there is no inflammation,[23,24] and this is thought to confirm the diagnosis. MSU crystals are largely intracellular during acute gouty attacks and the intercritical period, whereas they are mostly extracellular and free in the SF in chronic gout (**Figure**). SF leukocyte counts are elevated from 2000 to 100 000/mL in patients with acute gout.

SF should ideally be examined within 6 hours of arthrocentesis to reduce the rate of artifactual results. If microscopic examination is delayed, SF should be refrigerated.[25] Postaspiration changes particularly affect cell counts. Changes in MSU crystals are less of a problem, and the crystals can usually still be identified, but become smaller, less numerous, and less birefringent with time.

Although demonstrating the presence of MSU crystals by aspiration of SF is the gold standard for the diagnosis of gout, there is great variability between examiners. Several studies have looked at the quality of SF identification. Of the 25 laboratories studied by Von Essen and Holtta, for instance, 19 identified all MSU crystals correctly.[26] In a study by Hasselbacher, crystals were correctly detected in 39 of 50 samples.[27] Petrocelli and associates found equally good results for MSU identification with gram-stained and wet preparations of SF.[28] Studies of the reproducibility of SF analyses, however, have shown that some laboratories perform very poorly.[29,30] Crystal concentration is important in making the diagnosis.[31] The higher the crystal load in the SF, the more likely it is that observers will obtain accurate results.

It is sometimes difficult to differentiate whether a patient with acute arthritis has gout or pseudogout. Pseudogout is one main form of calcium pyrophosphate dihydrate (CPPD) deposition disease, chronic arthritis being the other. Pseudogout gets its name because the clinical presentation of an acute attack is similar to that of gout (**Table 3**). Almost half of acute attacks of CPPD crystal deposition disease affect the knees, but the wrists, metacarpophalangeal joints, elbows, and shoulders may also be involved. Furthermore, some CPPD crystals may be difficult to distinguish from MSU crystals with a regular microscope. Under compensated polarized light, however, the difference between the 2 types of crystals is evident, and the correct diagnosis can be made. The CPPD crystals are rhomboid-shaped and have weakly positive birefrin-

Figure. Intracellular and Extracellular MSU Crystals Under Polarized Light x400 (left) and Under Light Microscopy x4000 (right)

MSU indicates monosodium urate.
Source: Schumacher HR, Reginato AJ. *Atlas of Synovial Fluid Analysis and Crystal Identification.* 1st ed. Philadelphia, Pa: Lea and Febiger; 1991.

gence, whereas MSU crystals are needle-shaped with strong negative birefringence.

SU Level. The diagnostic value of an SU level is limited. A normal SU level clearly does not exclude acute gout. Despite the fact that SU levels <8 mg/dL are considered normal in many hospitals, levels >6.8 mg/dL are above saturation level and may allow deposition of gouty crystals. SU levels can clearly either rise or fall with attacks and may even be below saturation levels for urate. As many as 42% of patients may have normal SU levels during bouts of acute gouty arthritis.[32,33]

Despite these limitations, SU levels will be elevated at some point in a patient with gout, and it is important to follow the SU level during the course of treatment. An elevated SU level alone, however, does not serve as the sole criterion for gout. Although sustained hyperuricemia is a risk factor for acute gouty arthritis, tophaceous gout, and uric acid nephrolithiasis, most patients with hyperuricemia will never have an attack of gout. No treatment is required for asymptomatic patients, but it is prudent to determine the cause of hyperuricemia and correct it if possible.

Table 3. Comparison of Gout and Pseudogout

	Gout	Pseudogout
Ratio of men to women	7:1	1:1.5
Age group affected	Men >40 years old Postmenopausal women	Elderly
Serum urate	Elevated	Normal
Joints involved	First metatarsophalangeal joint, insteps, knees, wrists, fingers, olecranon bursae	Knees, wrists, ankles
Involvement of first MTP	Common	Rare
Tophi	Present	Rare tophi-like deposits
Radiographic findings	Erosions with overhanging edges	Chondrocalcinosis
Crystals	Needle-shaped, strong negative birefringence	Rhomboid-shaped, weakly positive birefringence

MTP indicates metatarsophalangeal.

Radiology

X-ray Film. Radiographic abnormalities are not sufficiently sensitive and specific for the diagnosis of gout.[34] Only 45% of patients with gout manifest radiographic bone changes, and then only 6 to 8 years after the initial attack.[34] Typical well-defined, "punched out," periarticular erosions with overhanging edges are not seen radiographically until 6 to 12 years after the initial acute attack.[35,36] The radiographic changes indicate the chronicity of the disease process. The radiographic hallmarks of gout are normal mineralization, joint space preservation, sharply marginated erosions with sclerotic borders, overhanging edges, and asymmetric polyarticular distribution.

Computed Tomography (CT) Scans. CT techniques reveal MSU deposits in vitro as well as within the knee joint, whereas such deposits are not visible on plain radiographs.[37] Increased attenuation of the x-ray beam of the CT scanner could be due to a high concentration of sodium nuclei in the MSU crystals. It is well known that CT scanning can readily diagnose stones of the urinary tract not visible on conventional radiographs.[38] It can be assumed that such calculi are composed mainly of urate.

Magnetic Resonance Imaging (MRI). MRI is a useful method of determining the extent of disease in tophaceous gout and may provide information regarding the patterns of deposition and spread of MSU crystals. Tophi usually have low signal intensity on both TI- and T2-weighted images and a variable enhancement pattern on MRI.[39]

In a study comparing soft tissue and bony changes observed by clinical examination and plain radiographs with those observed by MRI, both plain radiographs and clinical examination were found to markedly underestimate the size and extent of soft tissue and osseous involvement by tophi compared with MRI findings.[40]

MRI also detects early subclinical tophaceous deposits and indicates that urate deposits appear to spread along compartmental and fascial planes as opposed to the traditional view of strict radial growth.

Ultrasound. Plain radiography, MRI, and scintigraphic findings on bone scan provide helpful diagnostic clues but are not useful in

making a definite diagnosis of gout. Ultrasonography is a more reliable, noninvasive method for diagnosing gout.[41] Ultrasonographic investigation can detect deposition of MSU crystals on cartilaginous surfaces, as well as tophaceous material and typical erosions. Future large prospective, randomized, controlled trials of patients with crystal-proved gout are needed to further evaluate the use of ultrasonography in diagnosing gouty arthritis.

Response to Treatment

Response to colchicine treatment is not an accurate tool to diagnose gout because patients with other inflammatory diseases such as psoriatic arthritis, pseudogout, and Bechet's arthritis, as well as those with gout, often respond favorably to colchicine.[42-44]

Heat and cold are adjuvant treatments for arthritis. In gouty arthritis, cold applications, in addition to being a useful adjuvant treatment, are helpful for discriminating patients with gout from other forms of inflammatory arthritis. Topical ice has been shown to help relieve joint pain in patients with gouty arthritis but not in patients with rheumatoid arthritis or other inflammatory arthridities.[45,46]

Conclusion

The presence of MSU crystals in SF or tophus remains the gold standard for the diagnosis of gout. Supportive data to make a diagnosis of gout include a typical clinical history of a sudden and severe exquisitely painful joint, most classically the first metatarsophalangeal joint; a history of underlying renal disease or use of medications that cause hyperuricemia; an elevated SU level; radiologic evidence suggestive of gouty arthritis; and a favorable response to colchicine treatment and topical cold applications.

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