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123 Gout

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Gout encompasses a spectrum of diseases caused by precipitation of uric acid crystals in tissue. The gouty disorders include (1) acute monarticular arthritis caused by uric acid crystals in joints; (2) nephrolithiasis; (3) soft tissue deposits of urate crystals known as tophi; and (4) uric acid renal disease. Gout is about six times more common in men than in women,[1] although there is evidence that the relative prevalence of gout in women has increased.[2] The prevalence of gout increases with age, and it is more common in persons of African or Polynesian ancestry.

Hyperuricemia

Hyperuricemia is caused by either increased production of uric acid or decreased ability to excrete it; some of the more common disorders characterized by hyperuricemia are listed in Table 123.1. Hyperuricemia is defined as the presence of a serum uric acid over 7.0 mg/dl (420 μmol/L), as uric acid is less likely to form crystals at concentrations below this level; the risk of having all the gouty disorders increases proportionately to the serum uric acid level. Prophylactic treatment to lower the uric acid level incurs no benefit to patients with asymptomatic hyperuricemia and is more risky and expensive than no treatment, although the discovery that a patient has hyperuricemia should lead to an attempt to determine its etiology and significance.

Acute Gout

Acute gout is characterized by severe pain in a single joint that develops over a period of a few hours.[3] Uric acid is more likely to crystalize at lower temperatures, so the metatarsophalangeal joint of the great toe, the coolest part of the body, is the most common site of gouty attacks, but other joints, typically a knee, shoulder, hand or another part of the foot or ankle, is the site of presentation in 30% to 50% of cases.[4] Gout can present in any joint, and the inflammation can be extremely subtle in some cases; hence a search for crystals should be undertaken for all arthritis of unknown etiology.[5] More than half of the women with gout have polyarticular disease,[6] a presentation that is also common in the elderly. Chronic gout is uncommon but does occur, most often in postmenopausal women.[2] Attacks of acute gout commonly follow trauma or surgery, especially in patients with hyperuricemia.

With acute oligoarticular gout the skin over the affected joint is usually red and warm; peeling of the skin is common, and pain is typically so severe the patient does not allow anything to touch the affected joint. Low grade fever, elevated peripheral white blood cell (WBC) count, and elevated erythrocyte sedimentation rate (ESR) are commonly seen in patients with acute gout. Because of these characteristics the appearance of acute oligoarticular gout is distinctive, and the most important item in the differential diagnosis is joint infection. The serum uric acid level is not helpful for excluding or confirming a diagnosis of gout. Acute gout can be diagnosed on clinical grounds, especially in a patient with a history of gout; examination of synovial fluid under polarized light provides the only definitive diagnosis. Acute synovitis due to deposition of pyrophosphate crystals (pseudogout) becomes more common after age 65, so joint aspiration is particularly important for this age group.[2]

Synovial fluid can easily be obtained by passing an 18-gauge or smaller needle into the joint and aspirating it. Many clinicians prefer to numb the surrounding soft tissue with lidocaine before attempting joint entry. Joint fluid is then sent for crystal examination, cell count, Gram stain, and culture. The cell count is over 20,000/cu ml in

Table 123.1. **Some Possible Causes of Hyperuricemia**

Endogenous causes
Family history
Overproduction or underexcretion of urate
Large body build
Rapid cell turnover (malignancy)
Renal failure
Hypertension
Exogenous causes
Dietary purine: organ meats, kale, spinach, shellfish, beans
Alcohol, especially beer
Medications: especially diuretics and antimetabolites (e.g., cyclosporine)
Poisons: lead, others

those with gout or infection, and counts as high as 100,000/cu ml may be seen with either; the presence of crystals is the only reliable indicator that gout rather than infection is present. The needle-shaped crystals of gout have a unique appearance under polarized light; they are about the size of a neutrophil and are commonly seen inside them. In patients with acute gout the joint radiographs may be normal, but the erosions seen with chronic gout are fairly specific and can be helpful in making that diagnosis. Radiographs can help identify unsuspected fractures or osteomyelitis in patients with acute arthritis.[7]

Treatment of Gout and Hyperuricemia

Treatment of gout specifically addresses one of three clinical entities: (1) acute gout; (2) the intercritical period that occurs for 2 to 3 months after an acute attack; or (3) long-term management of chronic hyperuricemia.

Attacks of acute gout are most commonly managed by nonsteroidal antiinflammatory agents (NSAIDs) (see Chapter 112). High doses are needed. Although all NSAIDs are probably effective for acute gout, indomethacin (Indocin) is commonly used. One regimen involves giving indomethacin 50 mg four times a day for the first 2 days, then 50 mg three times a day for a week, then 50 mg twice a day for a week, then 25 mg two or three times a day for 2 to 3 weeks (or more). Acute gout can also be treated with colchicine in a dose of 0.6 mg/hr by mouth up to a total of 5 or 6 mg until relief or severe gastrointestinal side effects occur. At one time it was thought that colchicine was effective only for acute gouty arthritis, and so its use had utility in the differential diagnosis; it is now known that colchicine is at times successful for any form of acute arthritis.[7] Colchicine can be given intravenously, a method that reduces side effects; but the drug is potentially toxic in this form, and it is recommended that physicians considering the use of intravenous colchicine carefully review the instructions for its use. For patients who are unlikely to tolerate treatment with NSAIDs or colchicine (e.g., those with gastrointestinal disease or renal failure) intraarticular or even systemic steroids can be used. Another option is the use of a single dose of 60 mg of depotriamcinolone (Kenalog) intramuscularly.[8] ACTH is also effective in a dose of 0.4 mg (40 units) IM, which may have to be repeated every 12 hours for 2 to 3 days.[9]

Patients who have had resolution of an acute gouty attack are susceptible to a recurrence in the same joint for the next 2 to 3 months, a period known as the intercritical period. Hence preventive therapy is indicated for several months after an acute attack. Oral colchicine at 0.6 mg one or two times a day is effective for this purpose and is unlikely to have any side effects. Low-dose colchicine can be started along with NSAIDs at the time of an acute attack. Another alternative is low-dose NSAID therapy, such as indomethacin 25 mg twice a day, though this alternative is more likely to cause side effects.

Hypouricemic agents (e.g., allopurinol or probenecid) worsen an acute gouty attack and are never used during one. After 2 to 3 months of intercritical treatment the possibility of using drugs to lower the serum uric acid level can be considered. In patients who have only an occasional gouty attack and have no complication of gout such as tophi or gouty renal disease (see section below), treatment of hyperuricemia is optional; some patients prefer the risk of an occasional attack to taking medicine on a long-term basis.[4] Patients who believe their attacks are frequent enough to justify treatment or in whom treatment is indicated because of tophi or gouty renal disease should undergo treatment directed at hyperuricemia. Most experts believe that dietary therapy is of marginal benefit.[6] Hydration is important. Avoidance of medicines that elevate the serum uric acid level is also helpful. Low-dose aspirin and diuretics are the most common of these agents, and cyclosporine is another offender.

Medical treatment of hyperuricemia involves use of either uricosuric agents or allopurinol (Zyloprim), an agent that interferes with uric acid metabolism. The choice of agent depends on patient characteristics. Allopurinol is indicated in patients with nephrolithiasis, tophi, or renal disease. It is also indicated in patients with congenital overproduction of uric acid. These patients can be identified by collecting a 24-hour urine specimen for uric acid assay; the uric acid content is more than 1 g in overproducers (some clinicians use 600 or 800 mg as the cutoff). Patients with hyperuricemia who excrete less than 1 g/24 hr are considered to be underexcretors and can be treated with a uricosuric agent instead of allopurinol unless they have nephrolithiasis, tophi, or renal failure. Probenecid (Benemid), the most commonly used uricosuric agent, is started at 250 mg twice a day for a few days, then increased to 500 mg twice a day, and gradually increased up to a total of 3 g/day if needed. The goal of therapy is to get the serum uric acid below 6.0 mg/dl (360 μmol/L), although a level of 5 mg/dl (300 μmol/L) or less more effectively dissolves uric acid crystals. Gastric intolerance

to probenecid is fairly common. The cost of probenecid is also slightly higher than that of allopurinol, and some clinicians prefer to use allopurinol even in underexcretors.[10] It is effective against any form of hyperuricemia.

Allopurinol should be started at a dose of 100 mg/day and increased gradually up to 300 mg/day if needed to keep the serum uric acid under 6.0 mg/dl (360 μmol/L). If the serum uric acid remains elevated in a patient on allopurinol 300 mg/day, noncompliance should be suspected,[10] although doses up to 800 mg/day are occasionally needed.[7] The most common side effect of allopurinol is a rash; a vasculitic syndrome affecting the skin and kidneys accompanied by fever, leukocytosis, eosinophilia and hepatitis may be seen.[6,7] This syndrome is more common among the elderly and in patients with renal failure or on diuretic therapy; in these patients use of the lowest possible dose of allopurinol and a goal of 7 mg/dl (420 μmol/L) rather than 6 mg/dl (360 μmol/L) can be considered. When this syndrome occurs, it is treated with high-dose steroids.

Acute attacks of gout are common when either uricosuric agents or allopurinol are started, even if several months have elapsed since the patient's last attack. It is important to warn patients of this possibility. Continuing prophylactic therapy with colchicine at 0.6 mg once or twice a day for the first year of hypouricemic therapy is advised. Starting with low doses of hypouricemic agents, as noted above, is also helpful.

Uric Acid Nephropathy

Uric acid nephropathy is caused by precipitation of uric acid crystals in the renal tubules (see Chapter 97). It is usually due to a sudden overproduction of uric acid in a dehydrated patient (e.g., following vigorous exercise). Uric acid nephropathy can also be seen in patients with aggressive leukemia or during chemotherapy leading to rapid cell turnover. Uric acid nephropathy can be treated with vigorous hydration, diuretics, and alkalinization of urine; prevention is often possible if patients at risk are kept well hydrated.

Tophi

Tophi are aggregates of uric acid crystals surrounded by a giant cell foreign-body reaction. They gradually enlarge with time and eventually become first radiopaque and then obvious on physical examination. They appear around joints and in the subcutaneous tissues. Their presence is an indication for allopurinol therapy, which gradually leads to their dissolution. Tophi are much less common now than previously, probably because hyperuricemia is treated more aggressively.

Pseudogout

Arthritis due to deposition of calcium pyrophosphate dihydrate, or calcium pyrophosphate deposition disease (CPPD), is often called pseudogout. The knee is the most commonly affected joint; the disease is much more common in the elderly. Radiographs show chondrocalcinosis. The diagnosis is made by synovial fluid analysis; the joint fluid is similar to that seen in gout except that the crystals are characteristic. Treatment of an acute attack is the same as that for acute gout, and colchicine prophylaxis can prevent recurrences.[6]

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