GOUT

A. GOALS

1. Understand pathogenesis of gouty arthritis
2. Learn pharmacologic treatment for gout

B. CASE

- 55-year-old man with history of episodic pain and swelling in the 1st MTP joints
- Started allopurinol one week earlier
- Physical examination showed rock-hard lump on right pina and hot, tender purplish-blue swelling in the knee and the left midfoot.
- Serum uric acid concentration 7.8 mg/dl
- Synovial fluid aspirate contained intracellular needle-shaped crystals with strong negative birefringence

THE FOUR PHASES OF GOUT

1. Asymptomatic hyperuricemia

Serum urate is typically raised (>7 mg/dl for men and >6 mg/dl for women) for 20 years before the first attack of gouty arthritis or urolithiasis

2. Acute gouty arthritis

The first attach usually occurs between the 4th and 6th decades. Onset before the age of 30 years raises the question of an unusual form of gout, perhaps related to an enzymatic defect that causes purine overproduction.

Precipitating factors are antihyperuricemic therapy (probenecid, allopurinol), diuretics, IV heparin, cyclosporine, trauma, surgery, alcohol (beer), chronic lead poisoning, dietary excess, hemorrhage, foreign protein therapy, and infections.

Medical conditions associated with gout are obesity, diabetes mellitus, hypertriglyceridemia, hypertension, atherosclerosis, syndrome X (resistance to insulin-stimulated glucose uptake, hyperinsulinemia, hypertension, and dyslipoproteinemia with high levels of plasma triglycerides and high-density lipoprotein cholesterol).

Usually a single joint is affected, and the first metatarsophalangeal joint is the most commonly affected site. The attack begins suddenly and is common at night. Involvement is usually in the lower extremities. The involved joint becomes dusky, red, and swollen. Pain is intense and “the night is passed in torture”.

The pathogenesis of acute gouty arthritis is centered about the monosodium urate crystal, which is always present. Of interest, hyperuricemia is often present but is not necessary for the reaction to occur. Urate crystals, which were likely deposited in synovium, are thought to "flake off" and initiate an intense inflammatory response. The crystals become heavily coated with IgG and iron, both of which increase their inflammatory potential. Leukocytes are necessary for the reaction; almost all of the crystals in an affected joint have been ingested at the height of the reaction. The release of lysosomal mediators and the release of superoxide anion contribute to the local inflammation. Many serum factors mediate the inflammatory response, including complement, fibronectin, IgG, and a number of cytokines among which is transforming growth factor-beta.

Leukocytosis, fever, and high erythrocyte sedimentation rate may accompany the acute attack. Radiographs are normal in the acute phase.

3. Intercritical gout.

Most patients will have a second attack 6 – 24 months after the first attack. The period between attacks is known as the intercritical period. Joints appear normal during this time.

4. Chronic tophaceous gout.

Eventually, patients may enter a phase of chronic polyarticular gout without pain-free periods. This may occur 3-42 years after the first attack; the average period is about 12 years. Tophi are a manifestation of the inability to eliminate urate as rapidly as it is produced. Urate deposits appear in the cartilage, synovium, tendons, and soft tissues. A favored location is extensor surfaces and pressure points, and the lesions may resemble rheumatoid nodules. In untreated disease, massive destruction of joints may occur. Tophi have been reported to resolve over periods of years in patients who receive probenecid or allopurinol.

E. PRINCIPLES OF THERAPY

1. Asymptomatic hyperuricemia

First, consider the multiple causes of secondary hyperuricemia: consider drugs, renal insufficiency, myeloproliferative and lymphoproliferative diseases, hemolytic anemia, anemias associate with ineffective erythropoiesis, psoriasis, Paget's disease of bone, and enzyme defects (see below).

Treatment is not recommended for asymptomatic hyperuricemia. Exceptions to this rule are enzyme defects that lead to lifelong hyperuricemia. Exceptions to this rule are enzyme defects that lead to

lifelong hyperuricemia (examples: deficiency of hypoxanthine-guanine phosphoribosyltransferase in the Lesch-Nyhan syndrome, partial deficiency of HGPRT, superactivity of 5-phosphoribosyl – 1-pyrophosphate) and the hyperuricemia associated with tumor chemotherapy.

2. Acute gouty arthritis

Principles of treating acute gout include use of nonsteroidal anti-inflammatory drugs, colchicines, and corticosteroids. Do not attempt to reduce plasma urate concentrations in the patient who is experiencing an acute attack.

1. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Treatment of acute gouty arthritis is based upon the judicious use of nonsteroidal anti-inflammatory drugs (NSAIDS). Many of these agents are effective. Maximum-dose NSAID treatment is started at the first sign of an attack and the dose is lowed within a day or two and continued until the arthritis has resolved. NSAIDS are also effective in the well-established attack. Indocin (starting dose 50 mg po TID or QID) is often employed; the dose is tapered to 0 after about 1 week.

Renal insufficiency is a contraindication to this therapy so is active peptic ulcer disease. Consider a history of bleeding from the upper gastrointestinal tract when deciding upon therapy for acute gout.

Undesirable side effects of traditional NSAIDS: Gastric/esophageal irritation, exacerbations of peptic ulcers, anti-platelet effects, reversible hepatocellular toxicity, decreased creatinine clearance, skin rashes, aspirin-like reactions in the presence of the rhinitis, nasal polyposis, and asthma syndrome, and headaches and confusion in the elderly.

Aspirin increases renal retention of uric acid in low doses, whereas high doses (3.5-5.0 gm/day) are uricosuric. It is avoided as an agent to treat an acute attack of gout.

2. COLCHICINE

Colchicine can be used to treat acute gout, but should be limited to low oral doses or cautious intravenous use (the latter for the hospitalized patient only). Colchicine should be used in reduced doses or avoided altogether in the patient with renal insufficiency.

Some clinicians will give a brief course of oral colchicines, 2-3 tablets a week, in geriatric patients or patients with renal insufficiency.

No patient should receive the traditional high-dose treatment in which numerous tablets of colchicines are given by mouth. This therapy can cause very servere diarrhea and dehydration.

Intravenous administration should be given according to strict guidelines: (1) Single IV doses should not exceed 1 to 2 mg and the total cumulative dose should not be > 4mg, (2) No additional colchicines should be prescribed for 7 days, (3) the dose of IV colchicines should be halved in those with creatinine clearance < 50 ml/min and in those > 65 years of age in whom the creatinine clearance is not known.

Patients with renal insufficiency, especially those who are on dialysis, are at risk of developing colchicine neuromyopathy. This complication is characterized by elevated CPK and muscle weakness. Discontinuation of colchicine leads to improvement in the myopathy over several w3eeks. Associated neuropathy resolves more slowly.

3. CORTICOSTEROIDS

Intraarticular corticosteroids are very useful in breaking attacks of acute gout and have special value when other treatments cannot be utilized. In some instances, ACTH injections or oral corticosteroids are required.

F. LONGTERM PROPHYLACTIC TREATMENT

a. PROPHLAXIS

Prophylaxis of the acute attack can be achieved by administering daily low doses of colchicine (0.5 or 0.6 mg tablet by mouth, 1 or 2 times daily; or in the presence of renal insufficiency, one tablet 3 times per week). An alternate prophylactic drug is Indocin, 25 mg by mouth twice a day. **ALWAYS USE PROPHYLAXIS WHEN STARTING DRUGS TO LOWER THE SERUM URIC ACID LEVEL.**

b. URICOSURIG THERAPY

Uricosuric agents facilitate urate excretion by the kidney and increase urate clearance and the fractional excretion of filtered urate. Probenecid is the most commonly used drug in this class. It is started at a dose of 0.5 gm/.day, and the dose is increased gradually to 1 – 3 gm/day, given in 2-3 divided doses. Renal insufficiency and a history of nephrolithiasis are contraindications to uricosuric treatment.

c. XANTHINE OXIDASE INHIBITION

The xanthine oxidase inhibitor, **allopurinol**, is used long-term to lower serum uric acid. It is indicated in overproduction of urate (examples: 24 hour urine uric acid >0.8 gm while on a normal diet; enzyme defect that leads to lifelong overproduction such as deficiency of hypoxanthine-guanine phosphoribosyl-transferase), Tophi, renal insufficiency, nephrolithiasis, or intolerance to uricosuric agents.

Allopurinol can paradoxically initiate acute polyarticular gout. For this reason, it should never be used in the patient who is experiencing acute gouty arthritis. Remember to start prophylactic treatment and to continue it for at least 6 weeks when allopurinol is started.

The dose of allopurinol should be adjusted according to the patient's renal function. The nomogram for maintenance allopurinol, adapted from Am J Med 76:43, 1984, is:

CCr 0, 100 mg every 3 days; CCr 10, 100 mg every 2 days;
CCR 20, 100 mg/day; CCR 40, 150 mg/day; CCr 60, 200 mg/day
CCr 80, 250 mg/day; CCr 100, 300 mg/day; CCr 120, 350 mg/day
CCr 140, 400 mg/day

The risk in using allopurinol in renal insufficiency is the allopurinol hypersensitivity syndrome. Use of diuretics is also a risk factor. The syndrome develops within 2 – 4 weeks of starting allopurinol and mortality is 20%. It is characterized by skin rash, fever hepatocellular injury, Leukocytosis, eosinophilia, and worsening renal function.

Also, be aware that allopurinol causes potentiation of azathioprine, which as a purine analogue is metabolized by xanthine oxidase. The use of allopurinol requires a 50 to 75% reduction in the azathioprine dose. Careful monitoring of the leukocyte count is required; the margin between leucopenia and inadequate immunosuppression is narrow.

II. PSEUDEOGOUT

Pseudogout refers to articular disease associated with calcium pyrophosphate dehydrate crystals in synovial fluid or synovium. It is often associated with *chondrocalcinosis*, a radiographic finding in which calcium-containing crystals are visualized in fibrocartilage or articular cartilage. It is discussed here because some clinical features resemble gout. Differentiation from grout is important; the Pseudogout patient should not receive allopurinol.

Pseudogout can occur as a hereditary disease, as a sporadic disease, or as a condition that is associated with metabolic diseases or trauma. The hereditary disease usually shows an autosomal dominant pattern of inheritance. Pseudogout is clearly associated with **OLD AGE,** and associations with hyperparathyroidism, hemochromatosis, hypothyroidism, amyloidosis, hypomagnesemia, and hypophosphatasia have been reported.

The manifestations of Pseudogout are:

1. Acute inflammation in one or more joints lasting for several days to 2 weeks. Joints commonly involved are: knees (50%), wrists, and shoulders. As with gout, the attacks can occur spontaneously or be provoked by trauma, surgery or severe illness.

2. About one half of these patients have progressive degeneration of numerous joints, and acute flares of arthritis may be superimposed on the degenerative problem.

3. About 50% of patients have pseudo-rheumatoid presentation with multiple joint involvement. Rheumatoid factor is present in 10% of these patients, leading to confusion with rheumatoid arthritis.