Treatment of Hyperuricemia in Patients Without Gout

Allopurinol and rasburicase have been used for prevention and treatment of tumor lysis syndrome associated with hyperuricemia occurring after chemotherapy. Apart from this indication, there is no evidence to support their use for the routine treatment of asymptomatic hyperuricemia.

CALCIUM PYROPHOSPHATE DIHYDRATE DEPOSITION DISEASE

Calcium pyrophosphate dihydrate (CPPD) deposition disease is a clinically heterogeneous disorder that is characterized by the presence of intraarticular CPPD crystals. These crystals are deposited primarily in the cartilage, in the normally unmineralized pericellular matrix of hyaline and fibrocartilage. Calcification of the cartilage is promoted by alterations in the metabolism of inorganic pyrophosphate (PPi) and extracellular matrix leading to extracellular accumulation of PPi, which is necessary to the formation of CPPD crystals. Crystals are phagocytized by resident synovial macrophages, activating the intracellular NALP3 inflammasome complex and leading to recruitment and influx of neutrophils into the joint space.

CPPD deposition disease typically affects the elderly population. Up to 50% of individuals older than 85 years of age have radiographic evidence of CPPD crystal accumulation in cartilage (chondrocalcinosis), but most are asymptomatic. The most commonly involved joints are the knee menisci and the triangular fibrocartilage of the wrist.

The clinical course of CPPD deposition disease may be asymptomatic, acute, subacute, or chronic. The most common clinical manifestation, occurring in more than 50% of patients, is a peculiar type of osteoarthritis called pseudo-osteoarthritis; it is a noninflammatory arthritis involving joints not typically affected by osteoarthritis, such as the wrist, shoulder, ankle, and metacarpophalangeal joints. Asymptomatic disease may be an incidental finding on radiographs showing chondrocalcinosis. Pseudogout is an acute monoarthritis similar in presentation to the acute gouty attack. A chronic symmetric polyarticular arthritis pattern resembling rheumatoid arthritis and a severe destructive arthropathy that mimics neuropathic arthritis on radiographs may be seen.

It is uncommon for CPPD deposition disease to affect patients younger than 50 years of age, unless the disease is familial or related to a metabolic abnormality (e.g., hyperparathyroidism). Acute pseudogout attacks may be precipitated by trauma, surgery (particularly parathyroidectomy for hyperparathyroidism), or severe medical illness. Administration of intraarticular viscosupplementation may also trigger a CPPD flare. Attacks are usually monoarticular or oligoarticular; if left untreated, they may last from a few days to a few months. Involved joints are swollen, with variable erythema and warmth. Fever, elevated erythrocyte sedimentation rate, and leukocytosis can occur.

The diagnosis is confirmed by demonstration in synovial fluid of intracellular rod- or rhomboid-shaped crystals with weak positive birefringence when examined by compensated polarized light microscopy (see Fig. 82-2B). These crystals can be difficult to detect in some patients and are frequently missed in clinical specimens.

The presence of chondrocalcinosis (radiodense deposits on radiographs) is highly suggestive of the diagnosis in the appropriate clinical context. Joint aspiration should always be performed to rule out the possibility of infection. Importantly, joint infection can cause crystal shedding, leading to a concomitant crystal-related inflammation. Synovial fluid is inflammatory (>2000 white blood cells per microliter), with an average of 24,000 cells/μL.

Therapy for CPPD deposition disease is indicated for symptomatic patients. There is no effective treatment to remove CPPD deposits from synovium or cartilage. Treatment options include intraarticular glucocorticoid injection of the affected joint or joints. NSAIDs are effective, but their potential toxicity in elderly patients may limit their utility. Severe polyarticular attacks may require short courses of systemic corticosteroids. In patients with frequent pseudogout attacks, prophylactic daily low-dose colchicine may decrease the frequency.

APATITE-ASSOCIATED ARTHROPATHY

Abnormal accumulation of apatite (basic calcium phosphate, or BCP) may occur in hypercalcemic states and other illnesses. Unlike MSU or CPPD crystals, individual BCP crystals are not identifiable by polarized microscopy and can be seen only by electron microscopy. The most common apatite-associated condition is calcific periarthritis, which typically occurs in the shoulder.

Milwaukee shoulder is an extremely destructive BCP-associated arthropathy that occurs more commonly in elderly women. It is characterized by a large noninflammatory effusion (i.e. <2000 white blood cells per microliter) and results in destruction of the rotator cuff with subsequent marked instability and destruction of glenohumeral cartilage.

Other manifestations include acute reversible inflammatory arthropathies that resemble gout, referred to as *pseudo-pseudogout*, and ossifications along the anterolateral aspect of spinal vertebrae, termed *diffuse idiopathic skeletal hyperostosis* (DISH). Acute attacks of arthritis or bursitis may be self-limited. Intraarticular or periarticular injection of corticosteroids or the use of NSAIDs may shorten the duration and intensity of symptoms.

CALCIUM OXALATE DEPOSITION DISEASE

In calcium oxalate deposition disease, or oxalosis, calcium oxalate crystals are deposited in tissue. In primary oxalosis, a hereditary metabolic disorder, this deposition leads to nephrocalcinosis, renal failure, and early mortality. Secondary oxalosis complicates long-term hemodialysis or peritoneal dialysis; crystals are deposited in bone, cartilage, synovium, and periarticular tissue. Crystal shedding into the joint space may result in inflammatory arthritis of peripheral joints. Chondrocalcinosis or soft tissue calcifications can be seen on plain radiographs. The presence of strongly birefringent bipyramidal crystals is characteristic. Treatment with NSAIDS, intraarticular corticosteroids, or colchicine usually results in moderate improvement.