CHAPTER 13

Calcium Pyrophosphate Dihydrate, Hydroxyapatite, and Miscellaneous Crystals

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- The incidence and prevalence of calcium pyrophosphate dihydrate (CPPD) are unknown, though there is an increasing prevalence of radiographic chondrocalcinosis with age, and trauma may predispose to the disease. Several metabolic diseases are associated with CPPD.
- Overproduction of extracellular pyrophosphate in abnormal cartilage matrix contributes to CPPD.
- Acute pseudogout is the inflammatory host response to CPPD crystals shed from cartilaginous tissues. Because of the common occurrence of these crystals in osteoarthritic cartilage, there is a strong association of pseudogout with osteoarthritis (OA).
- There are multiple clinical manifestations of CPPD, including pseudogout, pseudo-osteoarthritis, pseudo–rheumatoid arthritis, pseudo–neuropathic arthropathy, and asymptomatic chondrocalcinosis (lanthanic CPPD).
- Diagnosis is made by identifying CPPD crystals in synovial fluid of affected joints.
- There is no practical way to remove calcium pyrophosphate crystals from the joints and symptomatic treatment is with nonsteroidal anti-inflammatory drugs (NSAIDs), colchicines, and local or systemic glucocorticoids.
- Basic calcium phosphate crystals (BCP) frequently deposit in articular tissues and may involve dysregulation of extracellular pyrophosphate homeostasis. BCP crystals can cause diverse clinical conditions including destructive arthritis (Milwaukee shoulder) and calcific periarthritis/tendonitis.

Deposition

Calcium pyrophosphate dihydrate (CPPD) and hydroxyapatite crystals are the most common calcium-containing crystals associated with joint and periarticular disorders. Deposition of these crystals is frequently asymptomatic or can be intermittently symptomatic. However, common clinical manifestations of calcium crystal deposition include acute or chronic inflammatory and degenerative arthritides, and certain forms of periarthritis. In addition to these, a number of other crystalline materials have been identified less commonly in synovial or bursal fluid. These include calcium oxalate, cholesterol, lipids, and synthetic corticosteroid crystals.

CALCIUM PYROPHOSPHATE DIHYDRATE DEPOSITION DISEASE

Specific identification of calcium pyrophosphate dihydrate (CPPD) crystals ($Ca_2P_2O_7.H_2O$) in synovial fluid (SF) or articular tissue allows the clinician to differentiate between CPPD crystal deposition disease and other inflammatory and degenerative arthritides. The term *chondrocalcinosis* generally refers to the characteristic radiographic features of CPPD deposition in articular cartilage. Calcium-containing crystals other than CPPD may also deposit in articular cartilage, producing radiographically detectable densities in cartilage as well as joint inflammation or degeneration. Deposition of CPPD crystals is not limited to articular cartilage. Less frequently, CPPD crystals are deposited in synovial lining, ligaments, tendons, and, on rare occasions, periarticular soft tissue, much like gouty tophi.

Calcium pyrophosphate dihydrate crystal deposition disease may be asymptomatic or may manifest in a variety of ways. The term *pseudogout* refers to the acute, goutlike attacks of inflammation that occur in some individuals with CPPD deposition disease. CPPD deposition may also cause symptoms similar to septic arthritis, polyarticular inflammatory arthritis (which can be mistaken for rheumatoid arthritis), or osteoarthritis (OA). The incidence and prevalence of clinically important CPPD deposition disease are unknown.

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Radiographic surveys show a steadily increasing prevalence of chondrocalcinosis with age. Data from the Framingham study showed an overall prevalence of radiographic chondrocalcinosis of 8.1% in the population over the age of 63, showed prevalence rates of 20% in knee joints of patients over the age of 60, and rates as high as 50% in patients over the age of 90 (1).

Classification

Categorization based on etiology results in four patient groups: hereditary, sporadic/idiopathic, associated with a metabolic abnormality, or post-traumatic. Although most cases of CPPD deposition disease are nonfamilial, many multicase families with CPPD deposition disease have been reported in the literature. Most familial cases appear to be inherited in an autosomal dominant manner, with early onset and varying severity (2). Susceptibility to familial CPPD deposition disease has been most commonly localized to the short arm of chromosome 5. Of particular interest is the gene located at the CCAL2 locus on chromosome 5p, the ANKH gene. The ANKH gene codes for the multipass transmembrane protein AHKH, which transports inorganic pyrophosphate (PPi) from the cell. Gain-of-function mutations in ANKH causes familial autosomal dominant CPPD deposition, of which several variants have been reported. Other genetic conditions are associated with chondrocalcinosis. Gitelman's and Bartter's diseases are both associated with CPPD deposition, possibly due to their association with chronic hypomagnesemia. Magnesium is a cofactor of alkaline phosphatase, and it is postulated that these conditions lead to mild functional hypophosphatasia. Iron and copper overload, associated with haemochromatosis and Wilson's disease, respectively, are thought to favor calcium crystal nucleation as well as inhibiting alkaline phosphatase activity. Genetic factors could also participate in so-called sporadic cases, as a familial pattern has been identified in some case series of apparently sporadic CPPD deposition disease. However, the late onset of the arthritis phenotype makes family studies of CPPD deposition disease difficult.

A number of metabolic disease and physiologic stresses, such as aging and trauma, have been associated with CPPD crystal deposition (Table 13-1). Only aging and previous joint surgery have been proven to be associated. Nonetheless, circumstantial evidence suggests that many of these other associations are valid. Therefore, the routine study of a patient newly diagnosed with CPPD crystal deposition should include evaluation of serum calcium, ferritin, magnesium, phosphorus, alkaline phosphatase, and thyroid-stimulating hormone. Further studies should be obtained if abnormal values are found.

TABLE 13-1. CONDITIONS ASSOCIATED WITH CALCIUM PYROPHOSPHATE DIHYDRATE CRYSTAL DEPOSITION DISEASE.

Strongly associated
Age
Previous joint surgery
Osteoarthritis
Trauma
Gout
Hyperparathyroidism
Hemochromatosis
Hypophosphatasia
Hypomagnesemia
Weakly associated
Hypothyroidism
Potentially associated
Wilson's disease
Acromegaly
Hyaluronidase deficiency
X-linked hypophosphatemic rickets
Familial hypocalciuric hypercalcemia
Ochronosis

Pathogenesis of Inflammation and Cartilage Degeneration

Acute pseudogout is believed to represent a dose-related inflammatory host response to CPPD crystals shed from cartilaginous tissues contiguous to the synovial cavity. Phagocytosis of crystals by neutrophils, as invariably demonstrated by compensated polarized light microscopy in fluids removed from acutely inflamed joints of patients with pseudogout, results in the release of lysosomal enzymes and cell-derived chemotactic factors. Phagocytosis by synovial-lining cells leads to cell proliferation and release of prostaglandins, cytokines, and matrix metalloproteases capable of matrix degradation, such as collagenase and stromelysin.

The relationship between OA and CPPD deposition is complex. A study of SF sampled at the time of knee replacement demonstrated that 60% of 53 unselected patients with a preoperative diagnosis of OA contained either CPPD or hydroxyapatite or both (3). It has been suggested that most SF from patients with OA may contain CPPD or hydroxyapatite too small or too infrequent to detect by routine microscopy. The frequency of association of CPPD crystal deposits may result from the biological effects of CPPD crystals as they interact with fibroblasts or mononuclear synovial lining cells. These include a well-documented mitogenic response, resulting in tissue hypertrophy. Stimulated lining cells secrete proteolytic enzymes and cytokine release. Proteolytic enzymes may damage cartilage and other articular structures and cytokine release can enhance further

immune attack

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