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The Simultaneous Occurrence of Monosodium Urate and Calcium Pyrophosphate Dihydrate Crystals in an Arthritic Joint

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Gout and pseudogout, two metabolically different diseases, occur rarely in the same individual. A patient is reported who featured calcium pyrophosphate dihydrate and monosodium urate crystals simultaneously in the synovial fluid exudate which was removed during an acute arthritic attack of the left knee. The patient represents the seventh such case reported in the literature. The pathogenetic differences of gout and pseudogout are reviewed as they relate to the role of the crystal.

Crystalline deposition within or near a tendon, bursa or joint may cause an acute inflammatory reaction with pain, swelling, redness and heat. The clinical onset, symptoms and signs of arthritis may be so similar in gout and pseudogout that a definitive diagnosis must rely upon the laboratory. The exudative synovial fluid in both diseases contains inflammatory cells with crystals. These crystals of different chemical composition can be differentiated from one another by a simple microscopic observation utilizing compensated polarizing light microscopy. The monosodium urate (MSU) crystal, which is associated with the arthritis of gout, is negatively birefringent when identified by compensated polarizing light microscopy (CPM). The calcium pyrophosphate dihydrate (CPPD) crystal which is seen with the arthritis of pseudogout is positively birefringent.

Gout and pseudogout are metabolically unrelated diseases. Considering the available data, the occurrence of one type of crystal in the joint would not exclude the presence of another crystalline type in the same individual. However, the presence concurrently of MSU and CPPD crystals in an arthritic joint may be decidedly rare since only six cases are reported in the literature. Our purpose is to add another case report and review the pathogenetic differences of these two crystalline deposition diseases.

Case Report:

A 66-year-old white man, admitted to Henry Ford Hospital in April, 1970, reported having episodes of painful feet for 20 years. For 6 months prior to admission, he had continuous discomfort in the feet and knees. The right knee became acutely painful and swollen, then just prior to admission the left knee became involved. Anti-inflammatory medications usually re-
X-rays of the patient's knees showed the articular calcification—(A) right knee (B) left knee.

Figure 1

The patient had passed a renal calculus 20 years ago but its composition was unknown. There was no familial history for arthritis.

Admission examination revealed an obese patient in mild discomfort. Blood pressure was 130/90 mm Hg. A soft Grade I/VI early systolic ejection murmur was heard at the cardiac apex. Skin tophi were absent. The general examination was normal except for the joints. Only the knees were abnormal; both showed an effusion, more marked in the left knee, with no local heat about the joint.

Laboratory studies included a hemoglobin of 11.6 gm\%, total white blood cell count of 7,700/cu mm with a normal differential white blood cell count. Normal tests included a urinalysis, a two-hour postprandial blood sugar, serum cholesterol, creatinine, calcium, phosphorus, alkaline and acid phosphatases, sodium, potassium, chloride and CO₂ and bilirubin. Total serum protein, albumin and globulin fractions were normal. Serum uric acid was 8.7 mg\%; content of a 24-hour urine collection for uric acid was 510 mg and for creatinine 1500 mg.

Chest x-ray was normal. X-ray of the knees revealed bilaterally calcification in the articular cartilages (Figure 1). Roentgenographs of the hands demonstrated calcification of the articular disc in both wrists, and minor degenerative changes of the distal interphalangeal joints of both hands (Figure 2). Narrowing of the metatarsal phalangeal joint of the great toe was noted bilaterally, with osteophyte formation.

Intravenous pyelography raised the possibility of a mass in the upper pole of the left kidney. Nephrotomograms and renal arteriography characterized an avascular mass in the upper pole of the left kidney.

The left knee aspirate was yellow and turbid. Total leucocyte count was 4,950 per cu mm, with 72\% polymorphonuclear leucocytes. Compensated polarizing light microscopy showed intracellular and extracellular elongated crystals both negatively and positively birefringent. Interestingly, a single cell contained only one type of crystal, as determined by CPM. The differential rheumatoid agglutination titer of the synovial fluid was negative.

Colchicine 0.6 mg was prescribed three times a day, but prompt relief of the joint
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Figure 2
PA films of hands from our patient illustrating articular disc calcification at the ulnocarpal areas of both wrists.

On May 1, 1970 a partial excision of the left renal cyst was carried out under general anesthesia. The patient was discharged on May 12, 1970 with a regimen of colchicine 0.6 mg twice a day. On May 19, 1970, Allopurinol 100 mg twice a day was prescribed, because the serum uric acid was consistently at a level greater than 8 mg%. The patient has continued to be asymptomatic and without arthritis for 20 months.

Discussion
Gout or Pseudogout?
McCarty et al in 1962 described one patient with an acute arthritis in the knee where both MSU and CPPD crystals were found. Not enough material was present to do X-ray diffraction studies. The same situation prevailed with our patient. Sometimes intra-articular corticosteroid preparations mimic the CPM characteristics and morphological appearance of CPPD or MSU crystals. However, our patient had not received intra-articular installations of corticosteroids nor had he experienced arthrocentesis of any joint prior to the one we performed for purposes of synovial analysis. However, before an
assessment of birefringency can be made without error by compensated polarizing light microscopy it is imperative to align accurately the long axis of the biaxial crystal. The acicular form of a monosodium urate crystal provides little difficulty in alignment of its long axis in order to determine its negative birefringency property (Figure 3). However, the pleomorphism of the CPPD crystal often prevents accurate assessment of the sign of birefringency particularly when the crystal is rhomboidal or cuboidal in configuration (Figure 4). Consequently, it may be mistakenly interpreted as negative when in reality the crystal is positively birefringent. Realizing this pitfall we were cautious in making the CPM assessment in our patient.

Since our patient meets the diagnostic criteria for gout and pseudogout, it is interesting to speculate which crystal may have been responsible for the acute attack. Chronic arthritis with acute exacerbation is seen in both gout and pseudogout. Our patient certainly had chondrocalcinosis articularis as demonstrated by the x-rays. His apparent response to colchicine during previous acute attacks of monarticular arthritis along with the established hyperuricemia suggests an intermittent arthritis due to gout. Nevertheless, we have observed a therapeutic response to colchicine in pseudogout and in calcium apatite deposition disease similar to that reported by Thompson et al.9

In our patient the acute arthritis of the left knee subsided after aspiration of the joint without intra-articular corticosteroid injection and after only one dose of colchicine. Such a response
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Figure 4

Synovial fluid exudative leucocytes contain pleomorphic CPPD crystals. Polarized light microscopy. Leishman stain. 500X

occurs in pseudogout after removal of synovial exudative fluid but not in gout. It suggests that at least in our patient the arthritis of the left knee was largely due to calcium pyrophosphate deposition despite the presence of urate crystals. However, since one of the diagnostic criteria of arthritis due to gout or pseudogout is dependent upon the demonstration of specific crystals in the synovial fluid, it is just as reasonable to conclude that the patient experienced a concurrent attack of gout and pseudogout.

Calcium pyrophosphate dihydrate crystals associated with an arthritis have been described with hyperparathyroidism as well as with degenerative joint disease. Usually abnormal calcium metabolism is not demonstrated in
patients with pseudogout or chondrocalcinosis articularis. Degenerative joint changes which may indicate aging or unusual joint stress are commonly seen in patients with pseudogout who are over 40 years of age. Our experience at Henry Ford Hospital has been similar. Our patient did not have hyperparathyroidism but did exhibit other signs of degenerative joint disease.

**Crystal Dynamics**

Gout, a disease described in antiquity, and pseudogout, described only recently, have at least one unifying characteristic, namely, from both, the synovial fluid exudate contains crystals. Pathogenetically, these diseases are quite dissimilar although both feature the presence of crystals. Faires & McCarty have shown that intra-articular injection of synthetic MSU crystals can produce an acute arthritis symptomatically identical with gout. Aspirates of synovial fluids from joints with acute inflammation induced by injecting MSU crystals showed intracellular and extracellular crystals. From these studies and the solubility properties of uric acid, it was assumed that the MSU crystals are the result of de novo formation extracellularly to explain the attacks of gouty arthritis. However, other evidence points to a cellular origin of the MSU crystal.

The study of exudative leucocytes from synovial fluids in patients with gout demonstrated that cytoplasmic lakes appeared only in the exudative neutrophils and these lakes had the same natural fluorescence as crystalline urate. Was this the degradation of MSU crystals or could it perhaps be non-crystalline MSU collections that occur intracellularly before crystallization? Evidence to suggest intracellular formation was obtained with the electron microscopic study of the exudative synovial leucocytes from patients with gout and pseudogout. Cytoplasmic MSU crystals were discovered to lie within the exudative synovial neutrophil devoid of a phagocytic membrane, while CPPD crystals were uniformly found within membrane-bound phagocytic vacuoles of synovial exudative neutrophils. Ultrastructurally, CPPD crystals were phagocytized by both neutrophils and macrophages, while the monosodium urate crystal was phagocytized by macrophages but only rarely by the exudative neutrophil. In the exudative neutrophil no limiting membrane is discerned and the MSU crystal lies in direct contact with the cytoplasm.

The capacity to form crystals intracellularly is not unique. Charcot-Leyden crystals develop intracellularly in exudative or peripheral blood eosinophils. Cystine crystals have been demonstrated in circulating peripheral blood leucocytes in a patient with cystinosis. Some patients with gout exhibit intracellular crystalline urate formation ex vivo in their peripheral blood neutrophils. Although debate still exists about extracellular de novo versus intracellular formation of MSU crystals as initiating inflammation in gout, it is generally agreed the crystal is capable of sustaining joint inflammation.

In contrast, there is current agreement that CPPD crystals are shed from the articular cartilage to initiate the arthritis seen in pseudogout. Phagocytosomal membranes are demonstrated regularly by electron microscopy to envelop the intracellular CPPD crystals in the cytoplasm of both exuda-
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monosodium urate crystals and macrophages. Even with ordinary light microscopy using a magnification of 1000X, the phagocytic vacuoles containing CPPD crystals often may be distinguished. Therefore, CPPD crystals are believed both to initiate and sustain the joint inflammation of pseudogout. However, why and how the CPPD crystals form in articular cartilage remains unsolved.

Summary

The seventh case of a crystalline arthritis which featured diagnostic criteria for both gout and pseudogout is described in an elderly man. A mildly symptomatic joint with calcification in the articular cartilage contained only a moderate number of cells but had both monosodium urate and calcium pyrophosphate dihydrate crystals within exudative synovial leukocytes. Emphasis is placed on the careful performance of compensated polarizing light microscopy to identify the crystals in synovial fluid. Furthermore, it is important to determine whether or not corticosteroids have been previously instilled into the joint that is being aspirated for crystalline identification. Speculations are offered regarding the pathogenetic role of these two chemically different crystals.

REFERENCES


