

CLINICAL VIGNETTE

A Case of Fever and Altered Mental Status Caused by Calcium Pyrophosphate Dehydrate (CPPD) Deposition Disease

Pei-Fen Lin, M.D., Nicholas Tangchaivang, M.D.

Introduction

Calcium pyrophosphate dehydrate (CPPD) deposition disease is a clinical syndrome in which CPPD crystals deposit in joints and soft tissue, resulting in inflammation and tissue damage. CPPD can manifest as an acute inflammatory process involving single or multiple joints, lasting days to weeks¹. Synovitis with joint tenderness typically affects the knees, elbows, shoulders, wrists and metacarpophalangeal joints. Often CPPD deposition disease can be associated with systemic symptoms such as fevers, malaise, leukocytosis and elevated acute phase reactants (such as erythrocyte sedimentation rate and c-reactive protein) but more rarely altered mental status¹⁻². Since CPPD deposition disease can mimic other rheumatic diseases as well as systemic disease, diagnosis may be delayed. We describe an elderly patient with fever and altered mental status felt to be secondary to CPPD deposition disease.

Case Report

An 80-year-old woman with a history of osteoarthritis, hypertension and chronic kidney disease presented to the Emergency Department with fever and severe lower extremity pain and edema, initially involving the left leg then progressing to the right. She was discharged two days earlier following a seven-day hospitalization for a subdural hemorrhage requiring craniotomy after a fall. She was without any localizing signs of infection except for pyuria. Blood and urine cultures were collected and the patient was given empiric vancomycin and ceftriaxone and admitted for possible urinary tract infection.

After 24 hours cultures remained negative and antibiotics were discontinued. Bilateral lower extremity doppler and CT venograms were negative for deep vein thrombosis and hip films were also negative for occult fracture. The patient's lower extremity edema and pain spontaneously resolved,

however, fevers persisted and the patient became acutely altered.

Repeat head CT scan showed stable post craniotomy changes and EEG was without evidence of seizure activity. Empiric vancomycin and cefepime were started for possible post-operative neurosurgical infection. Lumbar puncture was without evidence for infection and all cultures remained negative and antibiotics were again discontinued.

The patient's mental status waxed and waned but improved over the next 48 hours, and lower extremity edema and pain did not recur, however, she continued to be febrile up to 39.0C and she developed left upper extremity pain and swelling. The pain was so severe that the patient refused to move her arm. Physical examination revealed mild synovitis of the left elbow and wrist and Rheumatology reviewed prior radiologic studies which showed chondrocalcinosis and osteoarthritis of the left first carpometacarpal joint one year prior to admission. Given the presence of chondrocalcinosis on prior imaging and fevers with mild synovitis on examination, this was felt to be an acute flare of CPPD disease. The clinical picture was not consistent with septic arthritis with good range of motion of the affected joints with no associated warmth or erythema. She was given Colchicine 0.6mg PO BID with complete resolution of fever, altered mental status and significant improvement in her left upper extremity pain and swelling within 24 hours. Additional labs revealed an elevated erythrocyte sedimentation rate at 98 mm/hr (normal range 0-22 mm/hr), elevated c-reactive protein at 40.8 mg/dL (normal range <0.8 mg/dL), normal uric acid, negative ANA, negative Rheumatoid Factor, and normal CK.

Discussion

The prevalence of CPPD in the general population is unknown but the prevalence of chondrocalcinosis on radiographs in the general population is 0.9 per 1000¹. CPPD crystal deposition begins in cartilage near the surface of chondrocytes embedded in the cartilage matrix. Formation and deposition of CPPD crystals is thought to be secondary to aberrations in metabolism of calcium and pyrophosphate¹. The majority of cases of CPPD deposition disease are idiopathic. Risk factors include joint trauma, familial chondrocalcinosis, hemochromatosis, hyperparathyroidism, Gitelman's syndrome, hypomagnesemia and hypophosphatemia².

Diagnostic criteria for CPPD deposition disease proposed by McCarty and colleagues³ requires the demonstration of CPPD crystals in tissue or synovial fluid by documenting the presence of both positively (but weakly) birefringent crystals by polarized light microscopy or x-ray diffraction and typical cartilage or joint capsule calcification on x-ray examination. Since it is difficult to access x-ray diffraction unless, the most common method to diagnose CPPD deposition disease is the evaluation of synovial fluid and radiographic findings. The presence of positively, weakly birefringent crystals by polarized light microscopy or typical cartilage or joint capsule calcification on radiographic examination make CPPD deposition disease probable.

CPPD disease typically presents in the elderly with symptoms of acute or chronic arthritis. Patients may also present with asymptomatic CPPD deposition. There are case reports of atypical manifestations of CPPD deposition disease including altered mental status, nuchal rigidity and fevers of unknown origin⁴⁻¹⁰. Fever in patients with CPPD deposition disease has been attributed to interleukin-1 produced by monocytes, stimulated by calcium pyrophosphate crystals⁸. Interleukin-1 has also been shown to affect the central nervous system producing somnolence and slowing of sleep waves⁸. Fever in the elderly can lead to altered mental status, but the exact mechanism remains unclear.

There are several treatment options available for acute flares of CPPD deposition disease¹¹. These treatments mirror treatment of acute gout. Joint aspiration for diagnosis coupled with intra-articular corticosteroids can be use with large joints. For smaller or multiple affected joints, oral nonsteroidals or colchicine is preferred. If patients are unable to take these oral therapies, systemic glucocorticoids or

ACTH can be given. Interleukin-1 inhibitors have shown promise for suppressing crystal-induced inflammation, but there are no data supporting use in acute flares of CPPD deposition disease. Patients with three or more attacks/year may benefit from colchicine prophylaxis if there are no contraindications.

Our patient presented with fever and developed altered mental status. However, because of her recent history of subdural hematoma as well as urinalysis suggestive of infection, CPPD deposition disease was not considered on the initial differential. The patient did complain of migratory joint pains, however, clinically subtle synovitis was not initially recognized. For that reason the patient underwent extensive testing including CT scans, lumbar puncture and multiple blood and urine cultures; all of which were unrevealing. There was a delay of at least four days before CPPD deposition disease was recognized and treated appropriately. Because our patient had only mild synovitis, it was felt that a joint aspiration would be of low yield. The diagnosis of probable CPPD deposition disease was made by the combination of clinical presentation and findings on previous x-rays of chondrocalcinosis. Once treatment with colchicine was initiated, the patient defervesced and her altered mental status completely resolved. CPPD deposition disease should be considered in the differential diagnosis of fevers and altered mental status. Awareness that CPPD deposition disease can present with systemic symptoms including altered mental status and fevers may prevent diagnostic delay and unnecessary testing.

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Submitted on June 17, 2012