

Calcium pyrophosphate deposition disease

A disorder with multiple presentations

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Calcium pyrophosphate arthropathy is associated with various clinical scenarios and can mimic other conditions. Investigation requires consideration of life-threatening alternative diagnoses.

Calcium pyrophosphate (CPP) crystals are frequently present in joints, particularly in the elderly, and are associated with several different clinical scenarios including acute CPP crystal arthritis, osteoarthritis with CPP deposition and chronic CPP crystal inflammatory arthritis. The various types of presentation potentially mimic other conditions. The nomenclature in this article is as recommended by EULAR (European League Against Rheumatism).¹ Chondrocalcinosis is a radiological finding of calcification within cartilage that is most commonly caused by CPP crystal deposition.^{1,2}

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Pathogenesis

There are two key concepts in the pathogenesis of CPP arthropathy:

- the formation and accumulation of CPP crystals in the joint space and tendons;
- the occurrence of acute and chronic inflammation in this setting.

Crystal formation occurs slowly. CPP crystals are formed by the binding of calcium ions with inorganic pyrophosphate in the pericellular matrix of joint cartilage. Inorganic pyrophosphate is produced by metabolism of adenosine triphosphate in chondrocytes and is then extruded into the extracellular space by ANKH protein, a multi-pass pyrophosphate membrane transport protein.³ Key risk factors for CPP deposition are age and joint damage that is due to osteoarthritis or previous trauma. Hyperparathyroidism, hypomagnesaemia, haemochromatosis and hypophosphatasia (confirmed by low alkaline phosphatase activity) are less common causes but are of greater importance in younger patients.^{2,4}

The interaction between the crystals and the inflammatory system can occur abruptly or chronically. Many components are involved, but it appears that a key driver is the NLRP3 inflammasome, a cluster of proteins that produces a cascade of proinflammatory enzymes leading to activation of interleukin-1, an important driver in this process.⁵

Clinical presentations, investigation and management

We will use clinical cases to outline the various presentations of CPP arthropathy and highlight specific recommendations for investigation, diagnosis and management.

Case scenario 1

An 89-year-old man presented with a three-day history of left lower quadrant abdominal pain and an acutely painful swollen right knee.

He had pre-existing, functionally limiting osteoarthritis of the right knee, small joint osteoarthritis of the right hand and multiple comorbidities (hypertension, type 2 diabetes, congestive cardiac failure and benign prostatic hypertrophy). His medications included glucosamine, vitamin D, enalapril, metoprolol, aspirin, spironolactone, atorvastatin, dutasteride/tamsulosin and metformin. On examination, he was febrile, with left lower quadrant abdominal tenderness without peritonism and a warm and tender right knee with a prominent effusion.

Investigations showed an elevated white blood cell count ($12.1 \times 10^9/L$; reference interval [RI], $4-10 \times 10^9/L$) and an elevated C-reactive protein (CRP) level (peak of 262 mg/L ; RI, $<5.0 \text{ mg/L}$). A CT scan of his abdomen showed diverticulitis.

Aspiration of his right knee provided 45 mL of cloudy fluid. The fluid was negative on Gram staining and had a white blood cell count of $24,300 \times 10^6/L$. Calcium pyrophosphate crystals were seen in the fluid, and culture test results remained negative after five days.

The patient's diverticulitis resolved with intravenous antibiotics and his knee symptoms settled with a 10-day tapering course of prednisone, commencing at 15 mg daily. Six months later, he had acute CPP arthritis of the left knee, which settled with a brief course of meloxicam. His attacks have not been sufficiently frequent to warrant prophylaxis.

Commentary

Acute CPP arthritis often presents with rapid-onset large-joint synovitis, such as in the knee, wrist, ankle or shoulder, but can also involve the metacarpophalangeal (MCP) joints and extensor tendon sheaths of the hand and wrist. It may be associated with fever and chills and can occur in the context of an apparently unrelated acute illness or sudden metabolic derangement. A large-joint crystal monoarthritis is difficult to differentiate from septic arthritis and cellulitis. In patients with cognitive impairment or language deficits, it has been confused with limb paralysis.

Acute inflammatory monoarthritis is a diagnostic (not therapeutic) emergency and the key investigation is joint aspiration followed by prompt examination of the synovial fluid (cell count, Gram stain, polarised light microscopy for crystals, culture). If sepsis is possible, blood cultures should be ordered. Antibiotics must not be used until all relevant culture results (including synovial fluid and blood cultures) have been obtained. Identification of CPP crystals is achieved either by polarised light microscopy or by chondrocalcinosis, typically seen on an x-ray (Figure 1). If a Gram stain is negative and CPP crystals are identified, treatment should be influenced by the patient's comorbidities and may include corticosteroid injection of the joint, or an oral NSAID, colchicine or low-dose oral prednisone as appropriate.

Although recurrent attacks of acute CPP arthritis are common, frequent recurrences are not and, in the absence of any proof of efficacy from controlled trials, prophylactic therapy is usually not indicated.⁶ Low-dose colchicine (0.5 mg twice daily) or methotrexate may have efficacy in some patients.

Case scenario 2

A 67-year-old farmer was referred to a rheumatology outpatient department with a six-month history of recurrent symmetrical synovitis of the hands, involving the wrists and MCP joints, without complete resolution between attacks. His wrist pain previously responded to bilateral intra-articular corticosteroid injections and, to a lesser extent, courses of oral prednisone. He had a past history of diabetes, ischaemic heart disease, bilateral ankle fractures, chronic cervical and lumbar spinal pain and previous acute synovitis of both great toes consistent with gout. On examination, he had bilateral synovitis of the MCP joints that was maximal at the index and middle fingers without visible tophi and there was restricted range of movement of both wrists, elbows and shoulder joints.

Blood test results from the previous six months showed mildly elevated



Figure 1. Osteoarthritis of the knee with chondrocalcinosis present in the medial and lateral joint spaces.

inflammatory markers (CRP peak, 13.1 mg/L ; erythrocyte sedimentation rate, 22 mm/hour [RI, $0-12 \text{ mm/hour}$]) and good glycaemic control (HbA_{1c} 6.6%). Results were negative for rheumatoid factor, anti-cyclic citrullinated peptide antibodies and human leukocyte antigen-B27.

X-rays showed advanced nonerosive MCP osteoarthritis that was most severe bilaterally at the index and middle MCP joints (a distribution typical of CPP arthropathy) with heavy chondrocalcinosis. An x-ray of the hips and pelvis showed mild to moderate osteoarthritis with chondrocalcinosis of both hip joints and at the pubic symphysis. Spinal x-rays showed degenerative cervical spine disease and an old L1 vertebral fracture.

Given the presence of chronic synovitis and the substantial joint damage seen on x-ray, the patient was treated with an NSAID followed by low-dose prednisone and then leflunomide (his alcohol intake precluded the use of methotrexate). This did not provide sufficient improvement and leflunomide was ceased. Paracetamol as needed was offered and he was referred for consideration of MCP joint replacement after retirement from his strenuous farming duties.

Commentary

Calcium pyrophosphate deposition can also manifest as a recurrent acute or chronic inflammatory polyarthropathy of the hands



Figure 2. Typical radiological findings in calcium pyrophosphate arthritis with chondrocalcinosis in the triangular fibrocartilage complex (arrow) and osteoarthritis of the index and middle metacarpophalangeal joints.

that resembles rheumatoid arthritis due to involvement of MCP joints (Figure 2); however, it is usually less symmetrical. It can also mimic osteoarthritis, with chronic small-joint or large-joint polyarthropathy. In comparison with osteoarthritis, CPP arthropathy has greater involvement of the radiocarpal, midcarpal, index and middle MCP, glenohumeral, hindfoot and midfoot joints, and more prominent cyst and osteophyte formation on x-ray.

The symmetrical small-joint distribution with MCP involvement in this patient warranted further investigation to exclude rheumatoid arthritis. X-rays confirmed widespread chondrocalcinosis, osteoarthritis and absence of erosions, in keeping with chronic CPP crystal inflammatory arthritis superimposed on osteoarthritis.

Treatment is similar to that for osteoarthritis and can include oral NSAIDs with a proton pump inhibitor to prevent peptic ulcer disease. In the absence of placebo-controlled trial evidence supporting prophylactic drug therapy, individual patient trials of longer courses of low-dose

oral prednisone, colchicine, methotrexate or similar following resolution of the acute episode should only be continued when the patient clearly responds to treatment and monitoring is in place to minimise risk.

Case scenario 3

A 74-year-old woman with a past history of hypertension, atrial fibrillation and treatment with warfarin, chronic kidney disease and renal calculi presented with acute cervical pain and stiffness radiating to both shoulders. The pain woke her from sleep and intensified over two days. Twenty-four hours after the onset of the neck pain, she developed bilateral knee pain. On examination, she had a low-grade fever and very restricted painful cervical movements. Her neurological examination was normal.

The patient's peripheral blood white cell count was elevated ($14.8 \times 10^9/L$), as was her CRP level (92.3 mg/L then 133.9 mg/L). Her creatinine level was unchanged from previous results (218 $\mu\text{mol/L}$; RI, 45-90 $\mu\text{mol/L}$) and calcium, phosphate and magnesium levels were normal.

A CT scan of the cervical spine showed calcification of the transverse ligament around the odontoid process of C2, consistent with crowned dens syndrome and multilevel degenerative disc disease with facet joint arthropathy. Bilateral meniscal chondrocalcinosis was seen on x-rays of the knees, involving the medial and lateral tibiofemoral compartments with preserved joint spaces.

The patient was commenced on prednisone 20 mg daily at diagnosis followed by weaning of the daily dose by 5 mg each week. Her symptoms dramatically improved and she was able to mobilise.

Commentary

Crowned dens syndrome is a rare presentation of CPP arthropathy and occurs due to CPP deposition affecting the atlanto-axial joint and surrounding ligaments. On CT, the CPP is seen to be distributed in a crown-like configuration around the odontoid process. The condition is predominantly seen in elderly women and most patients have chondrocalcinosis at other common

sites of CPP deposition such as the knee, wrist or pubic symphysis.⁷

Similar to acute crystal-induced inflammation in other regions, the inflammatory response to the crystals in cervical ligaments leads to rapid onset, severe cervico-occipital or bitemporal pain, often with associated neck stiffness, shoulder girdle involvement and systemic symptoms including fever.⁸ Examination reveals markedly restricted neck rotation (a movement that predominantly occurs at the atlanto-axial joint) and is commonly accompanied by a raised white cell count and CRP level. Sinister complications that have been reported include cervical myelopathy due to large CPP deposits or destruction at the atlanto-axial joint.⁴

The differential diagnoses for acute neck pain, stiffness, systemic symptoms and raised inflammatory markers include meningitis, cervical osteomyelitis or discitis, giant cell arteritis and polymyalgia rheumatica, and hence these diagnoses need to be considered and excluded.

Periodontoid calcification is seen best with CT scanning (Figure 3) and is not usually apparent on x-ray or MRI (and hence the diagnosis can be missed), but MRI can be important for excluding differential diagnoses such as cervical discitis or malignancy and for assessing neural compression. Peripheral joint aspiration providing evidence of CPP crystals can support the diagnosis. Treatment includes a short course of oral corticosteroid, colchicine or NSAID or combined therapy, and supportive treatment such as a soft collar.

Case scenario 4

A 52-year-old woman presented with bilateral knee pain and swelling that was causing her difficulty in walking up and down stairs. She had a history of hypertension and orthotopic liver transplantation for cryptogenic cirrhosis and was taking regular prednisone and tacrolimus for immunosuppression. Her symptoms were consistently alleviated by meloxicam 7.5 mg daily; however, her knee pain and swelling would return upon cessation of treatment. On examination, she had moderate knee



Figure 3. Calcium pyrophosphate deposition seen in the transverse ligament posterior to the odontoid process.

effusions with marked patello-femoral crepitus but full range of movement.

X-rays showed severe patello-femoral joint osteoarthritis but with preserved joint space at the tibio-femoral joints as well as chondrocalcinosis and calcified bodies consistent with osteochondromatosis. Her magnesium level was chronically low (0.55mmol/L; RI, 0.70-1.10 mmol/L) and calcium and phosphate levels were normal. Oral magnesium supplementation partially corrected her magnesium levels and she continued to use meloxicam 7.5 mg daily for management of recurrent CPP inflammatory arthritis of the knees.

Commentary

Hypomagnesaemia is a risk factor for CPP deposition and can be due to medications including tacrolimus and proton pump inhibitors, malabsorption or renal wasting.^{9,10} Magnesium increases the solubility of CPP crystals and acts as a cofactor for pyrophosphatases. Accordingly, hypomagnesaemia results in increased levels of inorganic pyrophosphate available to bind calcium to form CPP.¹¹

In patients with acute CPP arthritis who are under 55 years of age, it is reasonable to identify metabolic derangements by performing serum iron studies for haemochromatosis, alkaline phosphatase, calcium, magnesium and parathyroid hormone to help identify a specific, and sometimes reversible, cause of CPP arthropathy. If

PRACTICE POINTS

- Acute CPP arthritis presenting as a monoarthritis requires analysis of synovial fluid aspirate to differentiate from septic arthritis.
- CPPD disease can also manifest as a recurrent acute or chronic inflammatory polyarthropathy of the hands that resembles rheumatoid arthritis or osteoarthritis. The pattern of joint involvement (including index and middle metacarpophalangeal joints), presence of chondrocalcinosis in the triangular fibrocartilage, and absence of erosions suggests CPP arthritis.
- CPPD in the ligaments of the cervical spine can result in inflammation leading to the development of acute neck pain with constitutional symptoms and raised inflammatory markers, with diagnosis confirmed on CT of the cervical spine and on identification of CPP in peripheral joints.
- Consideration of meningitis, temporal arteritis and polymyalgia rheumatica is important, and often further investigation is required to exclude these diagnoses.
- Testing for metabolic disturbances such as abnormalities of calcium, magnesium, parathyroid hormone, alkaline phosphatase and ferritin should be considered in younger patients (<55 years of age) with calcium pyrophosphate deposition disease.
- Referral to a rheumatologist or for assessment in hospital is recommended in unwell patients or in the context of diagnostic uncertainty or complex management.

Abbreviations: CPP = calcium pyrophosphate; CPPD = calcium pyrophosphate deposition.

hypomagnesaemia is found, review of medications is worthwhile in addition to urinary tests for electrolyte wasting.^{4,2}

Conclusion

Calcium pyrophosphate deposition disease can manifest as an acute large-joint mono- or oligoarthritis with or without tenosynovitis. It can present as a relapsing or chronic small-joint polyarthropathy resembling an inflammatory arthritis and it can occur in less common places such as the atlanto-axial joint due to calcium pyrophosphate deposition in the spinal ligaments. Investigation requires consideration and exclusion of life-threatening alternative diagnoses, most importantly infection, and identification of risk factors for this condition in a younger age group. Management needs to take into account the patient's comorbidities and referral to a rheumatologist is recommended in cases of diagnostic uncertainty and complex management. **MT**

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