Clinical spectrum of cervical involvement in calcium pyrophosphate deposition disease

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Submitted: 25/06/2025

Accepted: 03/09/2025

Abstract

Calcium pyrophosphate deposition (CPPD) disease is a common microcrystalline arthropathy in the elderly. The clinical spectrum includes both acute and chronic inflammatory arthritis, but crystals depositions may also occur without symptoms, with chondrocalcinosis identified incidentally on imaging. Axial involvement is less frequent than peripheral but has been increasingly recognized, particularly in the cervical spine. Its manifestations are heterogeneous and may mimic infectious, inflammatory, neoplastic or degenerative disorders, often leading to misdiagnosis. We report four cases of cervical CPPD disease that exemplify the main clinical phenotypes, from incidental crystals deposition to crowned dens syndrome, retro-odontoid pseudotumor and inflammatory discitis. They illustrate the diversity of cervical involvement and its potential for severe neurological complications. Diagnosis relies on clinical evaluation supported by imaging, with CT being the modality of choice for detecting calcifications, and MRI useful for assessing soft tissue masses, cord compression, or discitis changes. Management remains symptomatic, mainly with colchicine, glucocorticoids or NSAIDs, while surgery may be required in severe myelopathy. Awareness of cervical CPPD is essential to avoid unnecessary antibiotics or invasive procedures and to ensure timely and targeted management.

Keywords: Crystal arthropathies; Differential diagnosis; Calcium pyrophosphate deposition disease; Spinal disorders; Calcified tissue.

Introduction

Calcium pyrophosphate deposition (CPPD) disease is a microcrystalline arthropathy common in the elderly[1] and rare before the age of 50. Aging and the presence of other conditions, such as osteoarthritis[1], previous joint injury[2], and metabolic diseases (including hemochromatosis, hyperparathyroidism, hypophosphatasia, and hypomagnesemia[3]) are known risk factors for CPPD disease. The prevalence of CPPD disease is difficult to ascertain, as validated classification criteria were only introduced in 2023 by the European League Against Rheumatism and the American College of Rheumatology[4]. In the absence of such criteria, the prevalence of chondrocalcinosis has historically been used as a surrogate estimate for CPPD disease, and is reported to be around 10%[5].

Calcium pyrophosphate dihydrate (CPP) crystals predominantly deposit in fibrocartilage and hyaline cartilage, though they can also be found in periarticular tissues like ligaments[6]. CCP crystals interact with inflammatory cells and synovial fibroblasts, triggering the release of inflammatory mediators that contribute to joint inflammation and destruction[7].

The clinical spectrum of CPPD disease includes both acute and chronic inflammatory arthritis. CPP crystals deposition may also occur without symptoms, with chondrocalcinosis identified incidentally on imaging[4,7].

Although axial involvement in CPPD disease is less common than peripheral disease, it is increasingly recognized, with the cervical spine being the most frequently affected segment[8]. Clinical presentations are diverse and may mimic infectious, inflammatory, neoplastic or degenerative conditions, leading to diagnostic uncertainty[9]. Despite its potential severity, cervical CPPD disease is frequently underrecognized and underreported in literature. In this article we present four illustrative cases of cervical CPPD disease, each illustrating a distinct clinical phenotype, aiming to highlight the heterogeneity of presentation and emphasize the importance of considering CPPD disease in the differential diagnosis of cervical spine pathology.

Case Reports

Case 1 - Asymptomatic: A 68-year-old woman previously diagnosed with CPPD disease following an episode of knee monoarthritis. Diagnosis was confirmed by the identification of blunt crystals with weak birefringence and positive elongation in the knee synovial fluid analysis via polarized light microscopy. Later, a brain computed tomography (CT) performed after head trauma revealed calcification of the atlas transverse ligament (Figure 1) without current or past associated symptoms.

Case 2 - Crowned Dens Syndrome: A 59-year-old woman presented for urgent evaluation due to inflammatory neck pain with sudden onset during the night, cervical mobility restriction, and fever (38.1ºC) for three days. Her medical history was notable for CPPD disease secondary to iatrogenic hypomagnesemia induced by proton pump inhibitor use. The patient had discontinued her medication (colchicine and oral magnesium) one month before symptom onset without medical advice. Laboratory workup revealed elevated acute-phase reactants, and cervical spine CT revealed calcification of the transverse atlas and alar ligaments (Figure 2). The patient was treated with a low dose of glucocorticoids and restarted her usual medication, achieving rapid and complete recovery.

Case 3 - Retro-odontoid Pseudotumor: An 85-year-old woman presented to the rheumatology outpatient clinic with longstanding episodes of cervical pain with mixed rhythm characteristics and clinical signs of cervical myelopathy. She denied any history of peripheral arthritis. Imaging studies (CT and Magnetic Resonance (MRI)) of the cervical spine and skull revealed calcification and marked thickening of the atlantoaxial ligament complex and peri-odontoid soft tissues, with anterior dislocation of the odontoid process and vertebral canal stenosis at the medullary bulb transition (Figures 3 and 4). Radiographic and ultrasound studies demonstrated chondrocalcinosis in the triangular fibrocartilage of the carpus and knee menisci, along with intracartilaginous hyperechoic images at multiple sites, consistent with CPP crystals deposition. After discussion with neurosurgery, the patient began therapy with colchicine 1mg/day and cervical orthosis for symptomatic control.

Case 4 - Inflammatory Discitis: A 78-year-old man was admitted with inflammatory neck pain, arthritis of the wrist and metacarpophalangeal joints, dysphagia, dyspnea, urinary incontinence, and fever. His personal history was notable for chronic kidney disease. Laboratory analysis showed elevated acute-phase reactants without leukocytosis. CT imaging revealed C4-C5 and C5-C6 discitis with prominent osteophytosis, causing pharyngeal anatomical distortion, and calcification of the periodontal and posterior longitudinal ligament (Figure 5). After an extensive investigation for infectious causes and failure to respond to multiple antibiotics, the patient was treated with high-dose corticosteroids and colchicine, resulting in rapid symptom resolution.

Discussion

Axial involvement in CPPD disease, although less common than peripheral manifestations, has been increasingly recognized in recent years, with the cervical spine as the most frequently affected spinal segment[8]. Clinical phenotypes range from asymptomatic incidental findings to overt acute or chronic presentations with neurological compromise. The four cases reported here exemplify this heterogeneity.

Axial CPP crystals deposition is probably underestimated. Previous studies have shown that, in patients with a prior diagnosis of peripheral CPPD disease, the prevalence of CPP crystal deposition in the atlanto-axial region cervical CT ranged from 51 to 70%, with up to 30% of these patients denying neck pain[10-12]. Despite this high prevalence, the clinical implications of asymptomatic cervical CPP crystals deposition remain uncertain. This was exemplified by our

first case, in which calcification of the transverse ligament was discovered incidentally on a CT scan performed after head trauma, in an otherwise asymptomatic patient with no prior cervical complaints.

Crowned Dens Syndrome (CDS) represents the classic presentation of cervical CPPD disease, resulting from crystals deposition around the dens[13]. It is characterized by acute-onset inflammatory cervico-occipital pain, accompanied by neck stiffness, fever, and elevated inflammatory markers[13,14]. Symptoms may last from several days to weeks, with pain radiating from the suboccipital region to the lower cervical spine and ranging from mild discomfort to severe, sleep-disturbing pain[13]. The diversity and nonspecificity of symptoms and laboratory findings may lead to misdiagnosis, particularly as polymyalgia rheumatica, giant cell arteritis, spondylodiscitis or meningitis[13,14]. Careful evaluation of the atlanto-axial region on CT is therefore essential, while a history of CPPD disease or peripheral chondrocalcinosis may provide important diagnostic clues, as illustrated by the second case.

Another form of cervical CPPD disease presentation is the retro-odontoid pseudotumor, defined as soft tissue proliferation at the atlantoaxial junction surrounding the transverse ligament[15]. Retro-odontoid pseudotumors have also been described in other conditions, including rheumatoid arthritis, degenerative spinal disease, infection, trauma, neoplastic and congenital disorders[15,16]. In a study evaluating 105 cervical MRIs reporting the presence of atlanto-axial pannus, 32% of patients had a previous diagnosis of CPPD disease or imaging evidence of chondrocalcinosis[17]. The mass effect of retro-odontoid pseudotumors on the spinal cord may result in compressive myelopathy, manifesting as weakness or sensory deficits[18,19]. Our third case illustrates this phenotype, in which a retro-odontoid pseudotumor produces significant spinal cord compression and neurological symptoms, prompting neurosurgical evaluation.

Lower cervical spine involvement in CPPD disease appears to be less common than atlantoaxial involvement[8]. CPPD-related inflammatory discitis is characterized by cervical pain, limited range of motion, elevated inflammatory markers, and may be accompanied by fever and systemic symptoms[20]. Because the clinical picture closely resembles infectious discitis, patients are frequently treated empirically with antibiotics[20]. Our fourth case exemplifies this diagnostic challenge, as the patient received antibiotics without clinical improvement. Glucocorticoid and colchicine therapy was only initiated after an extensive investigation excluded infection. Biopsy was not performed because, after multidisciplinary discussion, the procedural risk outweighed the potential benefit.

The diagnosis of axial CPPD disease relies on the integration of clinical history, laboratory findings of systemic inflammation, and characteristic imaging features[14]. Cervical CT is the imaging modality of choice for detecting calcifications in the cervical spine and is more sensitive than conventional radiography[8]. Typical atlanto-axial findings include calcification of the peri-odontoid ligaments (transverse, alar, and apical)[8,13]. In our series, CT was essential in all four patients, either revealing incidental calcifications (Figure 1), confirming peri-odontoid deposits in CDS (Figure 2), identifying retro-odontoid calcifications (Figure 3) or supporting the diagnosis in the fourth case (Figure 5). Although MRI has low sensitivity for detecting CPP crystal deposits, it is valuable for soft tissue assessment, particularly in retro-odontoid pseudotumors, evaluation of spinal cord compression, and detection of bone marrow edema in discitis[8]. On MRI, retro-odontoid pseudotumor typically appears as soft tissue mass, isointense on T1-weighted sequences and showing iso- to hyperintense signal on T2[16]. CPPD-related discitis can be suspected based on CT, which often shows disc space narrowing with disc calcifications. A vacuum phenomenon within the disc, when present, may suggest a non-infectious etiology, although it is inconsistently observed. On MRI, CPPD-related discitis may demonstrate inflammatory changes resembling Modic type 1 lesions and gadolinium enhancement of the vertebral endplates. These features can strongly mimic septic discitis. However, unlike infection, CPPD-related discitis usually lacks extensive soft-tissue involvement or abscess formation. The coexistence of multiple affected disc levels of variable severity also favors a crystal-induced inflammatory process. Helpful features supporting CPPD-related discitis over infection include the presence of calcification of the anterior and posterior longitudinal ligaments (orange arrow in Figure 5), the ligamentum flavum and the interspinous ligaments. Needle biopsy may be required to rule out infection and, when positive for CPP crystals, can confirm the diagnosis[8]. Concomitant presence of degenerative changes, such as osteophytes and bone sclerosis, have been previously described, but it remains unclear whether their frequency and severity are increased compared to age-matched controls without CPPD disease[8,20]. The detection of chondrocalcinosis in the triangular fibrocartilage of the wrist or in the menisci of the knee by radiography or ultrasound may serve as a useful diagnostic clue in suspected cases of cervical CPPD disease, even in the absence of prior arthritis, as in the third case. The clinical phenotypes of cervical CPPD disease, along with their typical clinical presentations and imaging features, are summarized in Table I.

Treatment of CPPD disease depends on the clinical phenotype. In cases of asymptomatic CPP crystal deposition, no treatment is recommended[7], as no therapy has proven capable of dissolving crystals[6]. In symptomatic axial CPP crystals deposition, the therapeutic goal is pain and inflammation control, and the use of colchicine, glucocorticoids, and/or nonsteroidal anti-

inflammatory drugs (NSAIDs) is recommended[6,7]. NSAID use is often limited in these patients due to advanced age and the presence of comorbidities. In most studies, the combination of colchicine with NSAIDs or glucocorticoids has resulted in rapid clinical and laboratory improvement[13,14], as observed in cases 2 to 4 in our series, although the doses used in different studies vary. Moshrif et al.[8] also reported effective use of anakinra in three patients with CDS refractory to conventional therapy[8]. In patients with severe neurological impairment, particularly in cases presenting with retro-odontoid pseudotumor, surgical decompression may be required[18,19].

This series of four cases emphasizes the heterogeneous clinical spectrum of cervical CPPD disease, a condition that is likely underrecognized and underdiagnosed, despite its potential to present severe manifestations. Awareness of its characteristic CT and MRI findings, together with the recognition of peripheral chondrocalcinosis, can facilitate diagnosis and prevent diagnostic delay. Recognizing cervical CPPD disease as a potential cause of acute or chronic neck pain in elderly patients is essential to avoid unnecessary antibiotic use or invasive procedures and to ensure timely and targeted management.

Tables and Figures

Table I - Clinical phenotypes of cervical CPPD disease, with typical clinical presentation and characteristic imaging findings.

Subtype of cervical CPPD	Clinical presentation	Imaging findings
Asymptomatic deposition of CPP crystals	None, incidental finding.	CT: calcification of the peri-odontoid ligaments (transverse, alar, and apical)[8,13].
Crowned dens syndrome	Acute neck pain, stiffness, fever and elevation of inflammatory markers[13,14]	CT: calcification of the peri-odontoid ligaments (transverse, alar, and apical)[8,13].
Retro-odontoid pseudotumor	Subacute/chronic neck pain, neurological symptoms[18,19]	MRI: retro-odontoid soft tissue mass, isointense on T1-weighted sequences and showing iso- to hyperintense signal on T2[16].
Inflammatory discitis	Acute/subacute neck pain, elevation of inflammatory markers, with/without fever[20]	CT: disc space narrowing with disc calcifications and vacuum phenomenon[8] MRI: disc edema and endplate gadolinium enhancement; absence of extensive soft-tissue involvement or abscess formation[8].

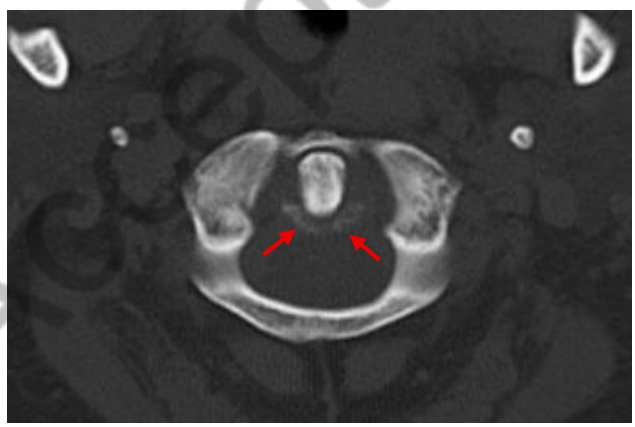

Figure 1 – Case 1 (asymptomatic) - Transverse cervical CT scan showing linear calcifications of the atlas transverse ligament (arrows).

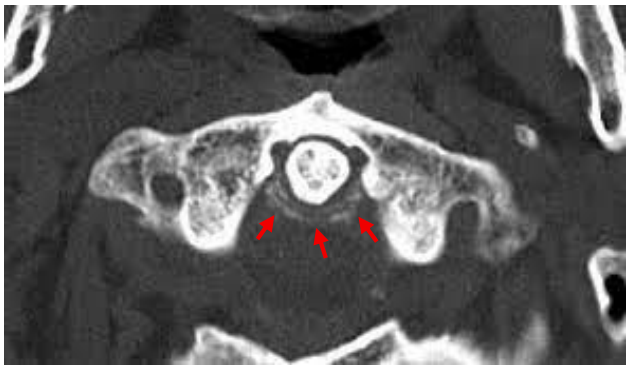

Figure 2 – Case 2 (Crowned Dens Syndrome) - Transverse cervical CT scan revealing calcification of the atlas transverse ligament (arrows).

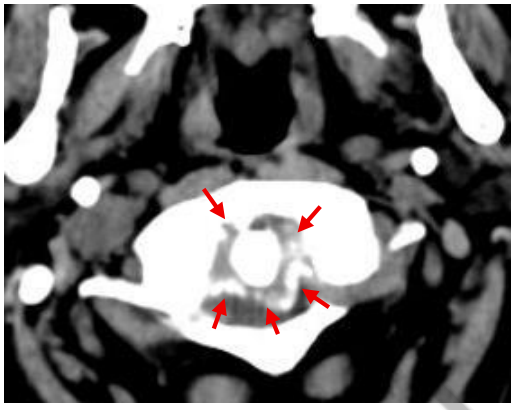

Figure 3 - Case 3 (Retro-odontoid Pseudotumor) - Transverse cervical CT scan demonstrating calcification of the atlantoaxial ligament complex (arrows).

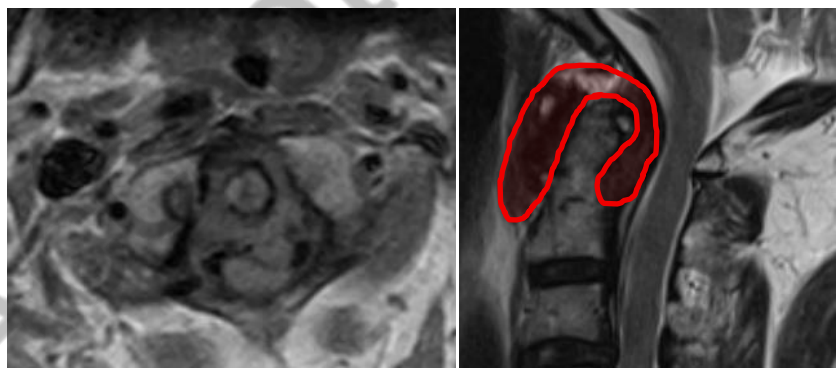

Figure 4 – Case 3 (Retro-odontoid Pseudotumor) – Transverse (left) and sagittal (right) cervical MRI, respectively, showing marked thickening of peri-odontoid soft tissues (red-shaded area), with anterior dislocation of the odontoid process and stenosis of the vertebral canal.

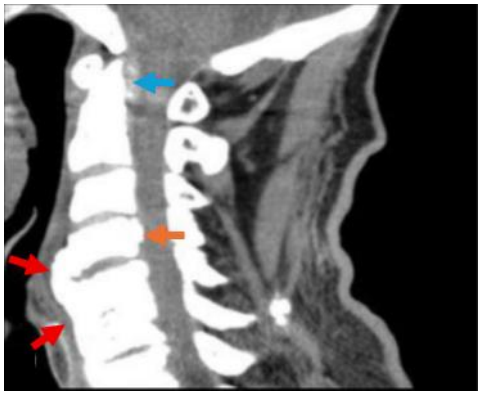

Figure 5 – Case 4 (Inflammatory Discitis) - Sagittal cervical CT scan revealing C4-C5 and C5-C6 discitis with prominent osteophytosis (red arrows), calcification of the periodontal (blue arrow) and posterior longitudinal ligaments (orange arrow).

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