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Commentary

The Quasi Neurasthenic-Calcium Pyrophosphate Deposition Disease

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Preface

Calcium pyrophosphate deposition disease (CPPD) is an arthropathy engendered due to deposition of calcium pyrophosphate dihydrate crystals within the articular cartilage, synovium or periarticular tissues. The disorder may be asymptomatic or appears as an acute or chronic inflammatory arthritis. Crystal deposition disease is indicated with emergence of acute degenerative arthritis within weight bearing joints of elderly individuals. Comorbid joint diseases such as osteoarthritis demonstrate an enhanced possibility of acute arthritis due to calcium pyrophosphate deposition disease.

The disorder is additionally designated as chondrocalcinosis, pyrophosphate arthropathy, chondrocalcinosis articularis, acute calcium pyrophosphate (CPP) deposition arthritis or pseudo-gout. However, imaging manifestations of chondrocalcinosis may not be indicative of calcium pyrophosphate deposition disease as chondrocalcinosis characteristically delineates calcification of intra-articular fibrocartilage upon imaging.

Disease characteristics

Calcium pyrophosphate deposition disease simulates osteoarthritis with an unusual distribution as denominated by symmetric distribution of lesions, occurrence within non weight bearing joints or incrimination of inter-carpal and metacarpophalangeal joints of the hand, radiocarpal and scapho-lunate joints of the wrist, patellofemoral joint of the knee, shoulder joint or elbow joint [1,2].

Larger, weight bearing joints such as hip joint or knee joint are frequently incriminated. Enlarged subchondral cysts may be discerned. An estimated 50% of incriminated individuals demonstrate significant joint injury. Multiple joints may be implicated at initial disease representation [1,2].

Calcium pyrophosphate deposition disease can arise in specific sites such as medial meniscus and patellofemoral joint of the knee, triangular fibrocartilage complex and lunotriquetral ligaments of the wrist, pubic symphysis or intervertebral discs. In the vertebral column, the disorder may configure a chronic retro-odontoid pseudo-tumour or a crowded dens syndrome manifesting acute pain and systemic inflammatory syndrome [1,2].

Metacarpophalangeal joints, preferably second and third joints can exhibit hook like osteophytes. Generally, uninvolved, non weight bearing joints may exemplify features of osteoarthritis [1,2].

Significant proportion of individuals with concomitant joint disease or metabolic abnormalities such as osteoarthritis, trauma, surgery or rheumatoid arthritis depict a predilection for calcium pyrophosphate deposition disease [1,2].

Calcium pyrophosphate crystal deposition disease can be categorized as

- Idiopathic variant or
- Hereditary variant where clinical symptoms are discerned at a young age and disease may be concurrent with severe osteoarthritis.

Emergence of secondary calcium pyrophosphate deposition disease is contingent to disorders such as haemochromatosis, diabetes mellitus, hyperparathyroidism, hypothyroidism, hypomagnesemia, preceding joint injury and ochronosis [3,4].

Comorbid conditions associated with calcium pyrophosphate deposition disease are hyperparathyroidism, gout, osteoarthritis, rheumatoid arthritis, hemochromatosis, osteoporosis, hypomagnesemia, chronic renal disease and calcium supplementation [3,4].

Acute calcium pyrophosphate deposition arthritis is commonly observed beyond > 65 years wherein around ~50% subjects are above > 85 years. The disease is exceptional below < 60 years. Older population depicts a mild clinical course although subjects may manifest acute disease flares following traumatic joint injuries [3,4].

A male predominance is observed or an equivalent gender predisposition may be encountered [3,4].

Disease pathogenesis

The disorder depicts an autosomal dominant pattern of disease inheritance and is accompanied by a chromosomal mutation within the ANKH gene which encodes a transmembrane inorganic pyrophosphate transporter protein [3,4].

Calcium pyrophosphate deposition disease is posited to arise due to an imbalance between pyrophosphate levels and proportion of pyro-phosphatases within the degenerated cartilage. Consequently, pyrophosphate is deposited within the synovium and adjacent tissues which combines with calcium to configure calcium pyrophosphate [3,4].

Deposition of calcium pyrophosphate stimulates the immune system with emergence of inflammation and soft tissue injury. Accumulated calcium pyrophosphate crystals activate the immune system thereby stimulating inflammation and injury of fibrocartilage [3,4].

Clinical elucidation

The European League Against Rheumatism (EULAR) has formulated a systematic terminology for categorizing calcium pyrophosphate deposition disease concordant to clinical representation wherein

- Calcium pyrophosphate deposition disease depicts accumulation of calcium pyrophosphate crystals along with or in the absence of pertinent clinical symptoms
- Asymptomatic disease (CPPD) which is clinically asymptomatic and delineates a concordance of chondocalcinosis with osteoarthritis
- Acute crystal arthritis (CPPD) or pseudo-gout manifesting a self limiting synovitis along with deposition of calcium pyrophosphate crystals
- Osteoarthritis with crystal deposition (CPPD) which exhibits typical manifestations of osteoarthritis in concordance with calcium pyrophosphate crystal deposition disease

- Chronic inflammatory arthritis due to deposition of calcium pyrophosphate crystals [5,6].

Majority of subjects demonstrating disease evidence upon radiography are clinically asymptomatic [5,6].

Acute calcium pyrophosphate crystal arthritis or pseudo-gout is generally a self limiting disorder and is associated with severe, acute or subacute pain, swelling, erythema, warmth upon singular or multiple joints and acute synovitis as it simulates a classical attack of acute urate arthropathy or gout. However, the disease frequently incriminates weight bearing joints as the knee, shoulder, elbow, hip, wrist or pubic symphysis [5,6].

Acute calcium pyrophosphate arthritis may represent with joint oedema, joint tenderness and low-grade fever. The self limiting disease demonstrates resolution of joint inflammation within weeks of commencement of therapy [5,6].

Chronic inflammatory arthritis due to calcium pyrophosphate deposition disease or pseudo-rheumatoid arthritis may represent a concordance of clinical manifestations with rheumatoid arthritis which emerge as morning stiffness, localized joint oedema and decreased range of motion (ROM). Tenosynovitis with carpal or cubital tunnel syndrome may ensue. Commonly, multiple, non weight bearing joints as the wrist or metacarpophalangeal (MCP) joints are incriminated. Episodes of arthritis with joint inflammation are non-synchronous with a variable, undulating, gradually evolving clinical course extending over a duration of several months [5,6].

Chronic inflammatory arthritis due to deposition of calcium pyrophosphate crystals delineates chronic, intermittent, painful swelling of peripheral joints of upper and lower extremities. Incrimination of the vertebral column occurs within a subset of individuals with occasional clinical manifestations of stiffness of vertebral column and bony ankyloses, similar to ankylosing spondylitis [6,7].

Clinical symptoms resembling diffuse idiopathic skeletal hyperostosis (DISH) with calcification of posterior longitudinal ligament and consequent spinal cord compression may ensue [6,7].

Additionally, deposition of calcium pyrophosphate crystals may engender clinical symptoms resembling septic arthritis, polyarticular inflammatory arthritis or degenerative osteoarthritis [6,7].

Histological elucidation

Upon gross examination, articular tissue demonstrates chalky white deposits of calcium pyrophosphate crystals. Upon microscopy, miniature, weakly birefringent, rectangular or rhomboid crystals are observed with polarized light. Circumscribing soft tissue exemplifies an infiltration of histiocytic cells along with foreign body giant cell reaction which encompasses the crystals [5,6].

Molecular configuration of calcium pyrophosphate crystals is capable of initiating an inflammatory response. Crystals of calcium pyrophosphate accumulate within the joint and may engender an inflammatory exudate comprised predominantly of neutrophils [6,7].

Calcium pyrophosphate deposition disease is constituted of calcium pyrophosphate dihydrate crystals which appear as rhomboid, rod shaped or paralleleliped and minimally birefringent upon examination with polarized light [6,7].

Palpable nodules or masses simulating gouty tophi are exceptionally delineated following several episodes of acute calcium pyrophosphate crystal arthritis. The nodules amalgamate within periarticular soft tissue and can represent as aggregates of calcium pyrophosphate crystals within the synovium or adjacent soft tissue, thereby engendering degradation of incriminated joint [6,7].

Chondrocalcinosis demonstrates deterioration of menisci and synovial tissue [7].

Differential diagnosis

Calcium pyrophosphate deposition disease requires a segregation from diverse joint diseases such as gout, rheumatoid arthritis, ankylosing spondylitis and erosive arthritis. Differentiation of pertinent disease is contingent to clinical representation [1,2].

Deposition of monosodium urate crystals within joints and cartilage is encountered in gout. Talc or methyl methacrylate deposition may occur in prosthetic joints [1,2].

Calcium pyrophosphate deposition disease requires a segregation from

- Osteoarthritis which typically incriminates weight bearing joints. Cartilaginous degeneration induces deterioration of collagen matrix with consequent proliferation and aggregation of chondrocytes. Phenotypic alteration into hypertrophic chondrocytes may ensue with cartilaginous outgrowths which ossify to configure osteophytes. Perpetual injury to collagen matrix initiates apoptosis of chondrocytes. Inadequate mineralization of collagen engenders thickening of subchondral bone. Advanced disease may occasionally demonstrate bone cysts [1,2].

- Giant cell tumour is composed of numerous uniformly disseminated osteoclast-like giant cells admixed with spindle shaped cells or spherical to elliptical mononuclear cells along with macrophage-like and primitive mesenchymal cells with inadequately defined cytoplasm. Several giant cells exceed the magnitude of normal osteoclasts and are imbued with nuclei beyond > 50. Foci of paucity of giant cells may be observed. Mitotic activity is minimal. Circumscribing stroma is significantly vascular and demonstrates foci of fibrosis or reactive woven bone. Foci of acute haemorrhage, hemosiderin pigment deposition, accumulated xanthomatous histiocytes, necrosis or secondary aneurysmal bone cyst -like areas may be discerned. Enlarged subchondral cysts of calcium pyrophosphate deposition disease can simulate subchondral giant cell tumour [1,2].

Investigative assay

A comprehensive physical examination is indicated along with pertinent radiographic examination of incriminated joints. Arthrocentesis with analysis of synovial fluid is necessitated for confirming calcium pyrophosphate deposition disease [7,8].

Synovial fluid exhibits an elevated white cell count between 2000 cells/mm^3 to 8000 cells/mm^3. An estimated 80% neutrophils exhibit intracellular crystals. Subsequent infiltration of mononuclear cells is associated with intracellular or extracellular crystals of calcium pyrophosphate [8,9].

Diagnostic confirmation can be obtained with microscopic appearance of birefringent rhomboid crystals of calcium pyrophosphate within the synovial fluid aspirate, as discerned with examination upon polarized light microscopy [8,9].

Step ladder pattern of joint contractility delineates a gradually enhancing disease severity from mid-carpal joint to radiocarpal joint. Disease progression is accompanied by scapho-lunate advanced collapse (SLAC) of the wrist [8,9].

Intra-articular calcification as denominated by radiographic assessment is characteristic in calcium pyrophosphate deposition disease. Symptomatic joint disease associated with characteristic radiographic features of chondrocalcinosis is indicative of concurrent calcium pyrophosphate deposition disease [8,9].

Imaging features consistent with chondrocalcinosis or calcification of joint cartilage are indicative of calcium pyrophosphate deposition disease. Chondrocalcinosis of the knee appears as attenuated, dense zone of intra-articular opacification which is parallel and disparate from adjoining bone cortex or may emerge as a calcified opacification of the menisci [8,9].

Ultrasonography of preliminary crystal deposition disease delineates abnormalities of joint cartilage [8,9].

Upon ultrasonography, calcium pyrophosphate deposition disease is accompanied with echogenic crystal deposition within the cartilage, in contrast to gout where echogenic monosodium urate crystals layer the surface of articular cartilage [8,9].

Magnetic resonance imaging (MRI) can be gainfully employed for evaluation of estimated calcium pyrophosphate crystal deposition within the joint cartilage [8,9].

Therapeutic options

Appropriate treatment of calcium pyrophosphate deposition disease is directed towards decimating inflammation and stabilizing associated, predisposing metabolic disorders. Acute flare of calcium pyrophosphate crystal deposition within a singular or dual joints can be optimally managed with joint aspiration and intra-articular glucocorticoids in pertinent instances [9,10].

Acute inflammation occurring within three or exceeding joints mandates systemic therapy with nonsteroidal anti inflammatory drugs (NSAIDs). Alternatively, colchicine or systemic glucocorticoids may be adopted although glucocorticoid therapy may be circumvented in instances with culture- positive septic arthritis [9,10].

Joint aspiration can be performed following exclusion of septic arthritis. Adjuvant therapeutic manoeuvers are comprised of application of ice packs and joint rest with restricted weight bearing in order to decimate joint inflammation [9,10].

Repetitive episodes of acute arthritis with calcium pyrophosphate deposition disease can be managed with singular, minimal dose of colchicine [9,10].

Additionally, treatment of concurrent predisposing metabolic disorders, soft tissue inflammation and alleviation of pertinent clinical symptoms is recommended [9,10].

Currently, a cogent therapeutic strategy directly influencing genesis of calcium pyrophosphate deposition disease remains elusive [9,10].

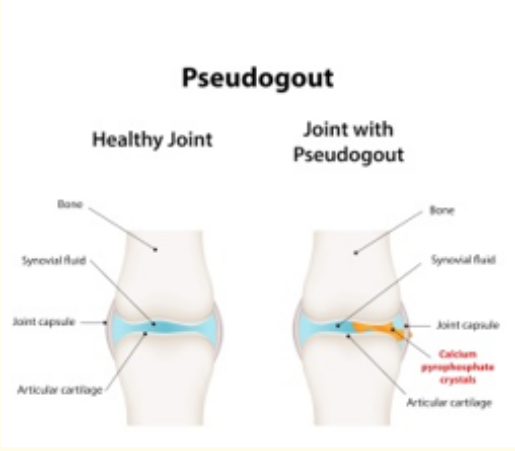

Figure 1: *Calcium pyrophosphate deposition disease displaying deposition of calcium pyrophosphate crystals within the articular cartilage and joint capsule [11].*

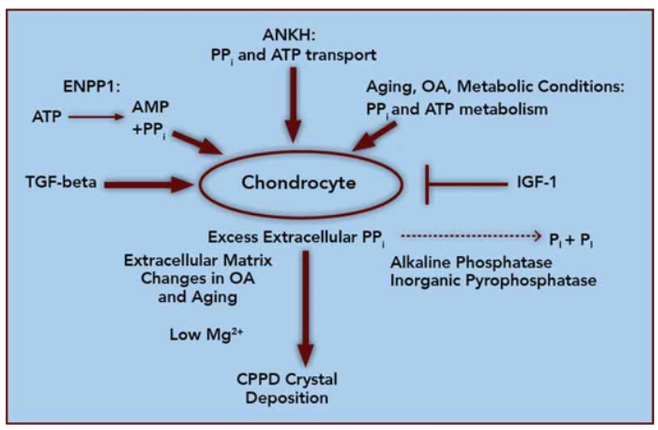

Figure 2: *Calcium pyrophosphate deposition disease demonstrating various molecules and factors engaged in deposition of calcium pyrophosphate within the chondrocyte [12].*

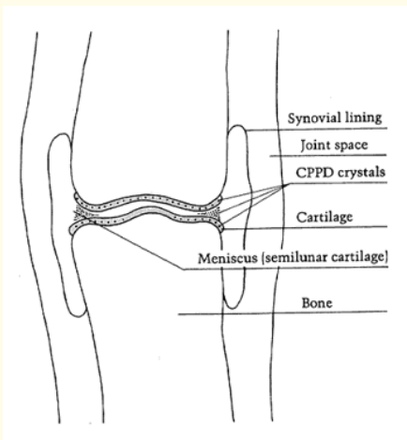

Figure 3: *Calcium pyrophosphate deposition disease enunciating deposition of calcium pyrophosphate crystals within the intra-articular cartilage and reducing joint space [13].*

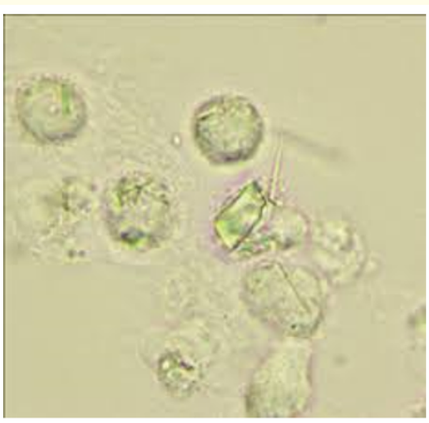

Figure 4: *Calcium pyrophosphate deposition disease exemplifying rhomboid and rectangular crystals of calcium pyrophosphate [14].*

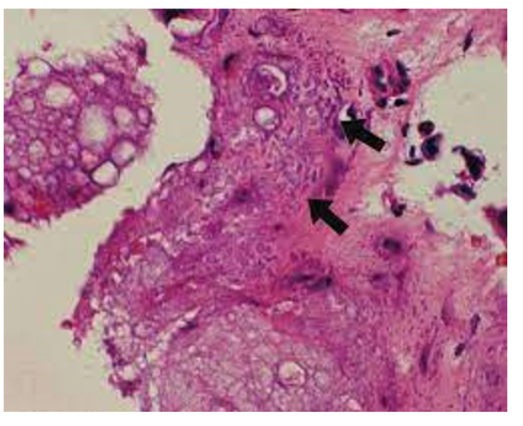

Figure 5: *Calcium pyrophosphate deposition disease exhibiting crystal deposition within the synovium and cartilage [15].*

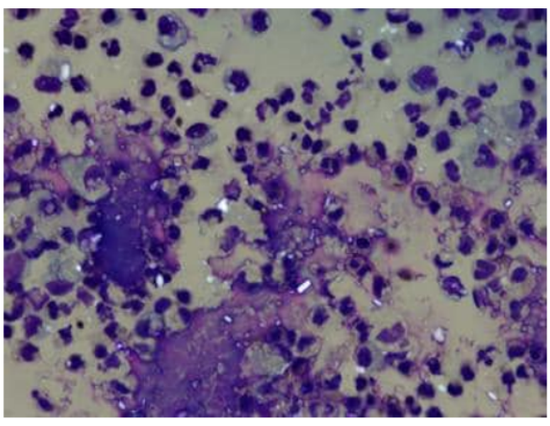

Figure 6: *Calcium pyrophosphate deposition disease exhibiting an exudate of neutrophils, histiocytes and few giant cells encompassing intra-articular crystals of calcium pyrophosphate [16].*

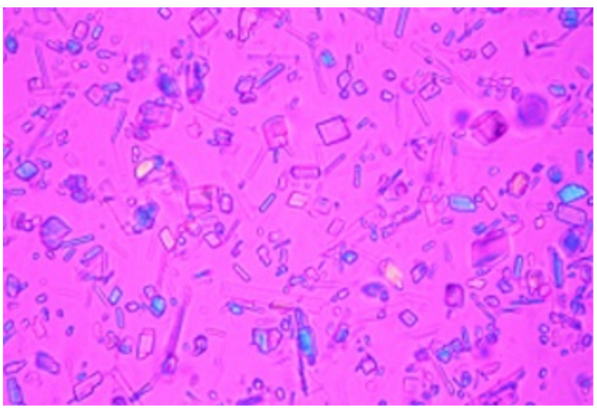

Figure 7: *Calcium pyrophosphate deposition disease delineating rhomboid and rod shaped crystals disseminated within the intra-articular cartilage [17].*

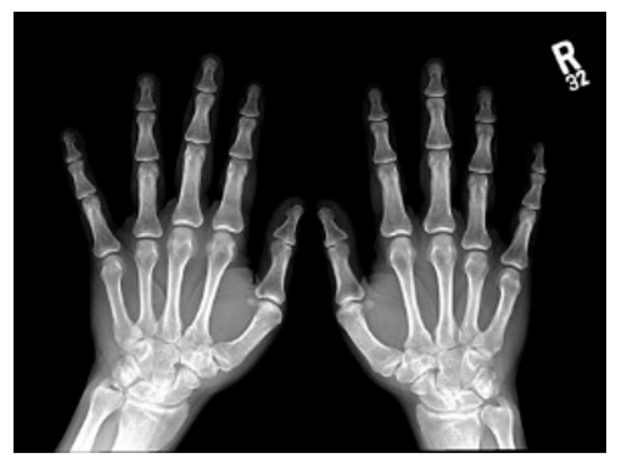

Figure 8: *Calcium pyrophosphate deposition disease depicting intra-articular opacification of metacarpophalangeal and interphalangeal joints [18].*

Bibliography

1. Zamora EA and Naik R. "Calcium Pyrophosphate Deposition Disease". Stat Pearls International 2021 Treasure Island, Florida (2021).
2. Rosales-Alexander JL., *et al*. "Calcium pyrophosphate crystal deposition disease: diagnosis and treatment". *The Open Rheumatology Journal* 6 (2014): 39-47.
3. Higgins PA. "Gout and pseudo-gout". *JAAPA: Journal of the American Academy of Physician Assistants* 29.3 (2016): 50-52.
4. Galozzi P., *et al*. "The prevalence of monosodium urate and calcium pyrophosphate crystals in synovial fluid from wrist and finger joints". *Rheumatology International* 36.3 (2016): 443-446.
5. Yamamura M. "Acute CPP Crystal Arthritis Causing Carpal Tunnel Syndrome". *Internal Medicine* 57.19 (2018): 2767-2768.
6. Schlee S., *et al*. "Crystal arthritides - gout and calcium pyrophosphate arthritis: Part 2: clinical features, diagnosis and differential diagnostics". *Zeitschrift für Gerontologie + Geriatrie* 51.5 (2018): 579-584.
7. Gersing AS., *et al*. "Evaluation of Chondrocalcinosis and Associated Knee Joint Degeneration Using MR Imaging: Data from the Osteoarthritis Initiative". *European Radiology* 27.6 (2017): 2497-2506.
8. Sidari A and Hill E. "Diagnosis and Treatment of Gout and Pseudogout for Everyday Practice". *Primary Care* 45.2 (2018): 213-236.
9. Shen G., *et al*. "A Case of Tophaceous Pseudogout on 18F-FDG PET/CT Imaging". *Clinical Nuclear Medicine* 44.2 (2019): e98-e100.
10. Stensby JD., *et al*. "Prevalence of asymptomatic chondrocalcinosis in the pelvis". *Skeletal Radiology* 45.7 (2016): 949-954.
11. Image 1 Courtesy: National Research Foundation.
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