

Basic Calcium Phosphate Crystal Periarthritis Involving the Distal Interphalangeal Joints in a Patient with Systemic Lupus Erythematosus

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
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Patient: Female, 34
Final Diagnosis: Basic calcium phosphate arthropathy
Symptoms: —
Medication: —
Clinical Procedure: —
Specialty: Rheumatology

Objective: Rare co-existence of disease or pathology





Background: Increased serum levels of basic calcium phosphate (BCP) and calcium pyrophosphate (CPP) are found in patients on dialysis, following trauma, and are associated with connective tissue diseases (CTDs), including dermatomyositis, scleroderma, and systemic lupus erythematosus (SLE). The shoulder is the joint most commonly associated with BCP crystal periarthritis. A report is presented of a case of BCP crystal periarthritis involving the distal interphalangeal (DIP) joints in a patient with SLE.

Case Report: A 34-year-old woman with SLE presented with destructive arthritis of the DIP joints that developed during a two-year period, despite immunosuppressive therapy. Aspiration of synovial fluid from a DIP joint showed a lack of inflammatory cells, but the fluid was positive for the presence of crystals on alizarin red S histochemical staining.

Conclusions: A case of BCP crystal periarthritis is reported in a patient with SLE with chronic joint symptoms that were unresponsive to immunosuppressive therapy. This case has shown that chronic joint symptoms that are unresponsive to immunosuppressive therapy may be due to causes other than connective tissue disease (CTD) and that imaging studies and diagnostic workup that includes synovial fluid examination may support the diagnosis of BCP crystal periarthritis.

MeSH Keywords: Arthritis • Calcium Phosphates • Lupus Nephritis

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Background

Increased serum levels of basic calcium phosphate (BCP) and calcium pyrophosphate (CPP) are found in patients on dialysis, following trauma, and are associated with connective tissue diseases (CTDs), including dermatomyositis, scleroderma, and systemic lupus erythematosus (SLE) [1]. The shoulder joint is most commonly affected by the deposition of calcium crystals. For example, Milwaukee shoulder syndrome is a destructive arthropathy associated with the deposition of calcium hydroxyapatite crystals. However, the involvement of other joints has also been reported. A previously published case report described a 29-year-old patient with SLE who presented with acute elbow pain and swelling, and chronic destructive elbow arthropathy on X-ray imaging [1]. In this previous case, BCP crystals were identified alizarin red S histochemical staining of synovial fluid from the affected joint [1]. A further study of arthropathy involving the hands in seven out of 52 patients with a diagnosis of SLE, identified periarticular calcification around the distal interphalangeal (DIP) joints, proximal interphalangeal (PIP) joints, and metacarpophalangeal (MCP) joints [2]. A report is presented of a case of BCP crystal peri-arthritis involving the distal interphalangeal (DIP) joints in a 34-year-old woman with SLE.

Case Report

A 34-year-old woman from Haiti with history of anemia was admitted to hospital with acute kidney injury and polyarthritis with a positive antinuclear antibody (ANA) titer of 1: 2560, with a speckled pattern, consistent with systemic lupus erythematosus (SLE). She denied any hair loss, mouth sores, history of deep vein thrombosis (DVT), or symptoms of Raynaud's disease. She was found to have anemia of chronic disease, and positive antibodies to Smith, ribonucleoprotein (RNP), SSA, and SSB, and low C3 and C4. Urinalysis showed +2 proteinuria with +1 blood. Anti-citrullinated peptide antibodies (ACPA), double-stranded DNA (dsDNA), Scl-70 (anti-topoisomerase I), rheumatoid factor (RF), and antiphospholipid antibodies were negative.

On examination, she had normal vital signs, and examination of the heart, lung, and abdomen were normal. There was synovitis of both hand joints involving the distal interphalangeal (DIP) joints, proximal interphalangeal (PIP) joints, and metacarpophalangeal (MCP) joints and the wrists with right ankle swelling. She had bilateral third, fourth, and fifth digit reducible swan neck deformities (Figure 1). She also had mild lymphadenopathy of the axillary and cervical lymph nodes. Her skin did not show sclerodactyly or skin thickening, and there was no psoriatic rash.



Figure 1. Photograph of the hands of a 34-year-old woman with basic calcium phosphate (BCP) crystal peri-arthritis and systemic lupus erythematosus (SLE). Bilateral third, fourth, and fifth digits with 'swan neck' deformities.

A kidney biopsy showed mesangial proliferation on light microscopy with one fibrous crescent. Immunofluorescence staining was positive for mesangial IgG. Electron microscopy showed subendothelial, subepithelial, and mesangial deposits consistent with Class IIIc active and chronic proliferative and sclerosing focal lupus nephritis. A computed tomography (CT) scan of her chest showed bilateral small pleural effusions without hilar lymphadenopathy or interstitial lung disease.

The patient was treated with prednisone 60 mg, hydroxychloroquine 400 mg, and azathioprine 100 mg daily, which resulted in normalization of her creatinine, complement levels, and resolution of her proteinuria over the next few weeks. Although the synovitis of her PIP and MCP joints and wrists resolved, the synovitis of her DIP joints persisted. X-rays of the hands showed bilateral periarticular osteopenia, DIP joint space narrowing, and swan neck deformities of the third, fourth, and fifth digits (Figure 2). Given her DIP joint synovitis, she commenced methotrexate 7.5 mg weekly with uptitration to 20 mg weekly, as the arthritis was presumed to be secondary to her SLE. Synovitis of her DIP joints continued despite treatment with methotrexate for several months.

Repeat X-rays of her hands two years later showed a destructive erosive process with the fragmentation of multiple DIP joints bilaterally, and calcification of the DIP joints and the soft tissues (Figure 2). Ultrasound imaging of her left hand showed a small DIP joint effusion of her third and fourth fingers amenable to aspiration (Figure 3), as well as hyperechoic densities in and around the joint capsule and surrounding tendons. About 0.1 ml of clear fluid was aspirated, with a non-inflammatory white cell count of 10^3 leukocytes per μL , with no birefringent crystals on polarized microscopy. Alizarin red S staining of the fluid showed many crystals with a surrounding halo, consistent with basic calcium phosphate (BCP) crystals (Figure 4). Her serum calcium, phosphorus, magnesium,



Figure 2. X-rays of the hands of a 34-year-old woman with basic calcium phosphate (BCP) crystal peri-arthritis and systemic lupus erythematosus (SLE) on presentation and two years later. **The top panel** shows the initial radiograph of the left and right hand. **The bottom panel** shows the hand X-rays two years later. **The top panel** shows periarticular osteopenia, distal interphalangeal (DIP) joint space narrowing, and 'swan neck' deformities of the third, fourth, and fifth digits. **The bottom panel** shows progressive destruction of multiple DIP joints with further DIP joint space narrowing, fragmentation, and bone lysis. Periarticular calcification is seen, especially around the left second, third, and fifth DIP joints and the right third DIP joint.

and parathyroid hormone (PTH) were all normal. She had no evidence of calcium pyrophosphate disease (CPPD) on her hand X-rays. Although treatment options included colchicine, intra-articular steroid injections, and nonsteroidal anti-inflammatory drugs (NSAIDs), due to her history of lupus nephritis, she received no additional medication. She was given the option of using figure-of-eight splints to support her PIP joints.

Discussion

This report presented a case of basic calcium phosphate (BCP) crystal peri-arthritis involving the distal interphalangeal (DIP) joints in a patient with systemic lupus erythematosus (SLE).

BCP crystals are composed of hydroxyapatite, octacalcium phosphate, and tricalcium phosphate [3]. The crystals aggregate and cause calcific peri-arthritis, chronic arthropathy, and soft tissue calcification. In an acute flare, BCP crystal peri-arthritis can mimic calcium pyrophosphate disease (CPPD) and gout, with erythema, warmth, and swelling of the joints [4].

Chronic destructive arthropathy associated with crystal deposition also includes Milwaukee shoulder syndrome, a destructive arthropathy associated with the deposition of calcium hydroxyapatite crystals, which is associated with a hemorrhagic non-inflammatory synovial fluid [5]. The term Philadelphia finger has been used to describe the destructive process of BCP crystals in the fingers [6]. The pathophysiology of these crystal

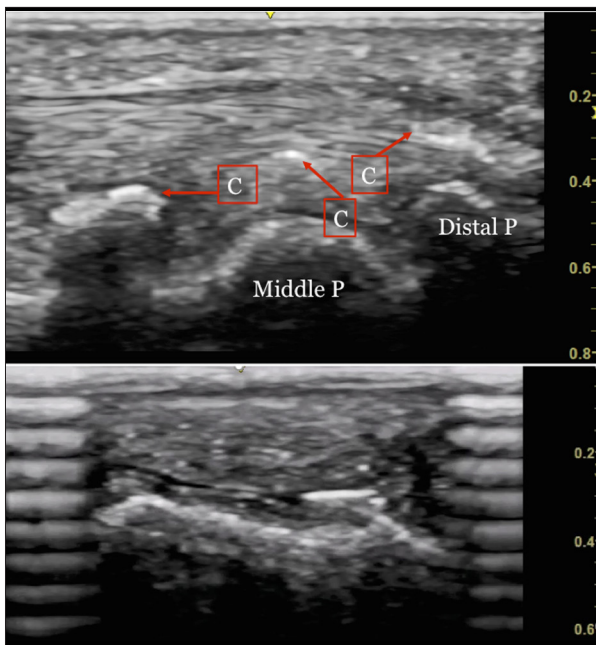


Figure 3. Ultrasound of the distal interphalangeal (DIP) joint of the hand of a 34-year-old woman with basic calcium phosphate (BCP) crystal peri-arthritis and systemic lupus erythematosus (SLE) **The top panel** shows the ultrasound image of the distal interphalangeal (DIP) joint in the longitudinal view. Distal P=distal phalanx. Middle P=middle phalanx. C=calcific deposits. There is calcification in the soft tissue and flexor tendon. **The bottom panel** shows the ultrasound image of the DIP joint in the transverse view, with a hyperechoic structure with the aspiration needle in place.

arthropathies involves their destructive effects that involve interactions with chondrocytes, fibroblasts, and macrophages. Joint crystals trigger the release of proteases, including matrix metalloproteinases (MMPs), as shown by *in vitro* studies following exposure to BCP crystals [7]. BCP crystals also reduce tissue inhibitors of metalloproteinases and can induce prostaglandin E2 and IL-1beta release from fibroblasts, leading to synovial proliferation, and further protease and cytokine release [3]. In osteoarthritis, hydroxyapatite crystal formation results in IL-6 production from chondrocytes and IL-6 can up-regulate MMPs, ankylosis protein homolog (ANKH), pituitary-specific positive transcription factor (PIT1), and annexin A5 (ANXA5) leading to calcification [8]. The S100A8 protein is also involved in upregulating MMPs in chondrocytes but downregulates aggrecan and type II collagen [8].

Treatment of BCP crystal peri-arthritis varies. In an acute flare, colchicine and nonsteroidal anti-inflammatory drugs (NSAIDs) have been used. In the setting of chronic arthropathy, joint lavage, corticosteroid injections, and joint replacement have been described [8]. In the diagnosis of BCP crystal peri-arthritis, although alizarin red S is a histochemical stain for calcium, it is

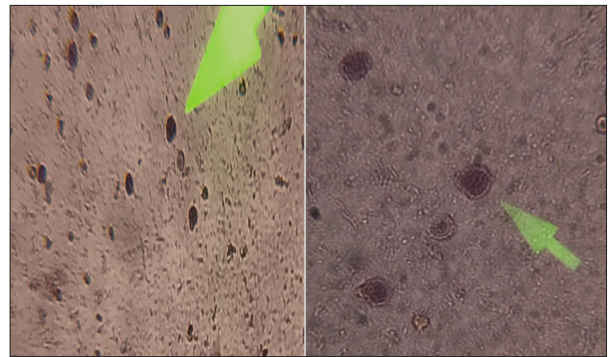


Figure 4. Photomicrograph of the distal interphalangeal (DIP) joint synovial fluid under light microscopy from a 34-year-old woman with basic calcium phosphate (BCP) crystal peri-arthritis and systemic lupus erythematosus (SLE). The synovial fluid is stained with alizarin red S. **The left image** is magnified $\times 10$. **The right image** is magnified $\times 40$. The arrows indicate globular aggregates of crystals that appear as 'shiny coins.' **The right image** shows a halo around the crystal aggregate, which is typical for alizarin red S staining of basic calcium phosphate (BCP) aggregates.

not specific for BCP crystals. Alizarin red S can also identify calcium pyrophosphate crystals, but BCP crystals have a different morphology. Individual BCP crystals are not readily visualized on light microscopy or polarized microscopy, as they are small (20–100 nm), non-birefringent, and needle-shaped [8]. Under light microscopy, BCP crystals may aggregate to form clusters that mimic 'shiny coins.' Following the addition of alizarin red S, clumps of crystals have a halo surrounding the stained crystals [3]. Alizarin red S stained BCP crystals have been reported in 100% of patients with BCP arthropathy, 37% of patients with osteoarthritis (OA), 89% in patients with CPPD, and 8–35% of patients with other forms of inflammatory arthritis [9,10]. Therefore, the identification of BCP crystals does not establish the diagnosis of BCP crystal peri-arthritis, but the absence of BCP crystals helps to exclude this diagnosis.

The importance of recognizing the clinical presentation and correlating it with radiographic changes helps make the correct diagnosis and avoid unnecessary tests and procedures while allowing for more specific treatment [11]. On X-ray imaging, BCP crystals are demonstrated as homogenous, amorphous, round, or oval deposits that do not have trabeculae. The calcific deposit usually ranges from 2–10 mm and may change in shape or size [11].

On X-ray imaging, several connective tissue diseases (CTDs) can be associated with multiple areas of calcification but may have different radiologic changes than those of BCP crystal peri-arthritis. SLE is associated with subluxation, systemic sclerosis, and psoriatic arthritis, and acro-osteolysis and joint space loss. Musculoskeletal ultrasound has shown a wide spectrum

of pathological findings both at the articular and periarticular level in patients with SLE [12,13]. A literature review by Doumas et al. showed that acute calcific peri-arthritis more commonly affects one joint [11]. Arandas et al., described a 44-year-old woman with acute calcific peri-arthritis that improved with prednisone [4]. The authors described acute calcific peri-arthritis as a self-limited syndrome, whereby a painful inflammatory process was initiated after a calcific deposit ruptured into an adjacent soft-tissue space [4]. Macrophages then reabsorb the calcification, reducing inflammation, and although any tendon insertion can be involved, the most common are the shoulders and feet [4]. Pre-menopausal women with SLE compared with men are most commonly affected by arthropathy involving the hands in a 5: 1 ratio [4].

Acute calcific peri-arthritis has also been described in patients with scleroderma. A previous report from Canada described three patients with limited cutaneous scleroderma, which suggested that the resolution of acute attacks of arthritis were less frequent than those of acute calcific peri-arthritis [14]. Baron et al. described the radiologic abnormalities of hand X-rays studied in 38 patients with scleroderma and identified periarticular osteoporosis in 42% of patients, joint space narrowing in 34%, erosions in 40%, with seven patients who had involvement of the DIP joint [15]. Erosions did not correlate with disease duration, presence of rheumatoid factor (RF), a positive antinuclear antibody (ANA) titer, or scleroderma skin changes [15]. However, calcinosis was more frequent in patients with scleroderma and articular erosions [15]. Erosive changes were most often seen in MCP joints, usually in the form of an isolated, small, discrete lesion at the periarticular margin [15]. The joint space narrowing of DIP joints were characterized in five patients with an imaging appearance that was similar to classic primary OA, but the remainder resembled erosive OA with the fragmentation of articular structures and deformity, producing a 'gull wing' appearance [15].

Weissman et al. studied hand radiographs taken from 59 patients with SLE [16]. Twenty-five of these patients had normal X-rays, and the remaining 34 patients had a variety of findings, most commonly with periarticular demineralization and soft tissue swelling [16]. Five patients had soft-tissue calcification, and two had possible scleroderma overlap with one having renal failure [16]. Only one patient with SLE had joint erosion with cartilage loss [16]. The authors proposed that SLE should be considered when hand X-rays show findings of periarticular calcification, sclerosis, and joint deformity without erosion [16].

BCP crystals have been associated with erosive and destructive joint changes in individuals without CTD. Schumacher et al. described three patients, two who had idiopathic apatite crystal deposition, and one who had apatite deposition related to renal failure while on dialysis [17]. Examples of PIP joint and MCP joint calcification with marginal erosions and periosteal reaction were shown [17]. Dieppe et al. examined the destructive nature of apatite crystals in twelve patients (11 women, one man) aged 66–83 years, with the involvement of the shoulders and knees [18]. Calcific material was identified on synovial biopsy in four of these patients, and by X-radiography in seven patients, which showed loss of bone and cartilage with lack of reparative change [18].

Conclusions

This report presented a case of basic calcium phosphate (BCP) crystal peri-arthritis involving the distal interphalangeal (DIP) joints in a 34-year-old woman with systemic lupus erythematosus (SLE). This report has shown that chronic joint symptoms that are unresponsive to immunosuppressive therapy may be due to causes other than connective tissue disease (CTD). In this case, imaging studies and diagnostic workup that included examination of the synovial fluid supported the diagnosis of BCP crystal peri-arthritis.

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