Acute Calcium Pyrophosphate Crystal Arthritis of the Wrist Elicited by Anti-COVID-19 Vaccination After Carpal Tunnel Release

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Patient: Male, 70-year-old
Final Diagnosis: CPPD wrist arthritis
Symptoms: Redness • edema of wrist
Medication: —
Clinical Procedure: —
Specialty: Plastic Surgery

Objective: Unusual clinical course

Background: Calcium pyrophosphate dihydrate deposition disease includes a variety of clinical syndromes, including acute calcium pyrophosphate (CPP) crystal arthritis. Most patients with CPP crystal arthritis have a primary/idiopathic form presenting with severe pain, swelling, and stiffness. COVID-19 infection, which originated in China in December 2019, required extraordinary efforts to develop and test new vaccines to halt the pandemic. The Vaxzervria vaccine has shown excellent safety and efficacy in phase 3 trials with a mechanism based on the expression of the SARS-CoV-2 spike protein gene coding for the S-antigen, which stimulates the immune response.

Case Report: We describe an acute event of crystal arthritis after a carpal tunnel syndrome release followed by administration of the second dose of anti-COVID-19 Vaccine Oxford-AstraZeneca (ChAdOx1 nCoV-19). Medical treatment resulted in full resolution of the symptoms in 2 weeks.

Conclusions: Although most episodes of acute arthritis happen spontaneously, certain factors may trigger the acute CPP crystal arthritis such as intercurrent illnesses or surgeries. Although the association between carpal tunnel syndrome and CPP arthritis has been known for over 40 years, surgical release of the carpal ligament has always been associated with full resolution of symptoms. This is the first case report describing an exacerbation after carpal canal release, concomitant with the administration of the vaccine. According to our opinion, the vaccination associated with a prior surgery in the same anatomical site could have synergically triggered the arthritis flare-up, in a predisposed patient, with a mechanism still unknown.

Keywords: Carpal Tunnel Syndrome • COVID-19 Vaccine • Drug-Related Side Effects and Adverse Reactions • Chondrocalcinosis

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Background

We present the case of a male patient, 71 years old, who was surgically treated for carpal tunnel syndrome and who developed acute calcium pyrophosphate (CPP) crystal arthritis of the wrist 2 weeks after surgery, 12 h after the administration of the second dose of Vaxzevria, an anti-COVID-19 vaccine.

Calcium pyrophosphate dihydrate deposition disease (CPPD) consists of a crystal deposition arthropathy characterized by a wide spectrum of clinical symptoms, with the acute phenomenon called acute CPP crystal arthritis, resembling gout flares, hence named in the past also “pseudo-gout”. Mostly, it presents as a primary/idiopathic form affecting the elderly population, with the majority of patients affected over the age of 65.

CPPD is an umbrella term that includes a broad spectrum of manifestations, in addition to acute arthritis: asymptomatic isolated chondrocalcinosis and chronic symptomatic pyrophosphate arthropathy (osteoarthritis with varying degrees of synovitis). More rare forms are represented by pseudo-rheumatoid arthritis and pseudo-neuropathic arthropathy [1]. Some patients can also be affected by hand flexors tenosynovitis with carpal tunnel syndrome [2].

The disease is believed to be caused by an imbalance between levels of pyrophosphate and pyrophosphatases: pyrophosphate deposits in the synovium and adjacent tissues combining with calcium to form CPP [3], which in turn causes activation of the immune system with consequent inflammation and tissue injury [4-6]. Crystal properties and individual reactivity both determine the intensity of the inflammatory response to crystals [7].

Although a definitive diagnosis of CPPD relies on synovial fluid analysis by polarized light microscopy identifying parallelepiped, predominantly intracellular crystals with absent or weak positive birefringence, due to its low cost and widespread availability, plain radiography is considered the first-line radiological investigation, providing a visualization of calcium-containing crystal deposits as well as features of osteoarthritis, although their absence does exclude the diagnosis [8].

Ultrasonography is emerging as a complementary tool to perform a multi-planar and multi-tissue assessment with the possibility to evaluate both crystal deposits and soft tissues inflammatory abnormalities, identifying the exact anatomic site where synovial fluid collects, guiding its aspiration if needed [8,9]. Further investigations, such as dual-energy computed tomography (DECT) and MRI (magnetic resonance imaging), can be considered in cases with inconclusive findings on first-line examinations [9].

As there is no substance known capable of limiting the formation of calcium pyrophosphate crystals, the available treatment strategies are aimed at reducing inflammation, relieving only the symptoms in acute and chronic CPPD [10,11]. Commonly used treatments are NSAIDs, colchicine, and systemic corticosteroids, depending on patient's comorbidities and response to previous treatments. Biologic drugs like IL-1 receptor antagonist anakinra appear promising in the management of CPPD, especially in acute refractory CPPD or when standard treatments are contraindicated [10,12].

Case Report

The patient reported about 3 months of numbness and tingling in the 4 lateral fingers of his left hand, with symptoms exacerbated by weightlifting and driving. He woke up at night due to paresthesias in the 4 lateral fingers and pain in his left wrist. He also reported weakness in hand movements and loss of sensation.

Since these manifestations were consistent with the diagnosis of carpal tunnel syndrome (CTS), he underwent an electrodiagnostic study, which documented the presence of an estimated severe neuropathy of the median nerve, which confirmed the diagnosis of CTS.

The physical examination revealed the presence of mild atrophy of the thenar muscles, with reduced sensitivity on the volar surface of the first, second, and third finger of the left hand. Tinel’s sign was positive on his left wrist.

Referring to his past medical history, the patient had been diagnosed with acute CPP crystal arthritis a year earlier. This initially presented with nocturnal low back pain with a fever of 39°C, followed the next day by acute arthritis pain of the left wrist joint. The patient was quickly subjected to appropriate investigations, including CT of the spine and radiographs of the spine and wrist, which showed diffuse calcifications both in the intervertebral discs and in the wrist, and synovial fluid (SF) analysis revealed numerous intra- and extracellular CPP crystals in an inflammatory SF (35 000 WBC/mm³). Metabolic and other disorders associated with CPPD were excluded by comprehensive blood laboratory tests. He was treated with low-dose colchicine and glucocorticoids tapered from 25 mg prednisone/day to 0 in 2 weeks, with rapid remission. There were no other painful symptoms until 3 months ago, when those related to CTS began.

At the first visit, because his symptoms of CTS were disabling and conservative therapy consisting of a wrist splint and non-steroidal anti-inflammatory drugs failed to improve his condition, he underwent surgical sectioning of the left transverse carpal ligament.
When he was reevaluated in the clinic 5 days after surgery, he was asymptomatic with a clean wound. The patient benefited from the surgery and after 10 days the stitches were removed.

Fourteen days after surgery, the patient was inoculated in the morning with the second dose of 0.5 ml of Vaxzevria COVID-19 vaccine by intramuscular injection into the left deltoid.

Twelve hours later, during the night, the patient began having increasing pain in his left wrist, swelling with erythema, warmth, stiffness, and tenderness, and all findings were consistent with an acute CPP crystal arthritis flare-up. Symptoms included chills, fatigue, and weakness, with concomitant low-grade fever.

Later, he decided to contact us for a visit. After the physical examination, blood tests and radiographs of the hand and wrist joints were done. There was a slight increase in serum C-reactive protein (6.80 mg/L, upper reference limit: 6.0 mg/L); peripheral white blood cell counts and all serum ion levels were within normal range, including, in particular, serum magnesium concentration. Radiographs showed narrowing of the radio-carpal space associated with sclerosis and calcification of the distal radio-ulnar joint (Figure 1).

We asked for the opinion of the treating rheumatologist, who, based on a well-documented diagnosis of CPP arthritis made a year earlier and the peculiar findings, decided not to perform arthrocentesis to avoid possible infection risks. Then, he was pharmacologically treated with colchicine 1 mg per day combined with celecoxib 200 mg per day, which resulted in a full recovery in 2 weeks.

**Figure 1.** Anteroposterior (AP) and lateral projections radiographs of the left hand, showing narrowing of the radio-carpal space associated with sclerosis and calcification of the distal radio-ulnar joint.
Discussion

Hyperparathyroidism, gout, osteoarthritis, rheumatoid arthritis, hemochromatosis, hypomagnesemia, chronic kidney disease, and calcium supplementation have been reported to be associated with an increased risk of CPPD [13-16].

Most acute CPP crystal arthritis episodes are of spontaneous origin, but certain situations such as traumas, acute medical conditions, or surgery (especially post-parathyroidectomy [17] or hip-fracture repair [18]) can elicit and precede the acute arthritis [3,11]. There are no known dietary associations of CPPD [11].

Although still controversial, several medications can also precipitate acute CPP crystal arthritis, such as administration of intraarticular hyaluronan preparations [19], use of loop diuretics [20], granulocyte-macrophage colony-stimulating factor [21], and pamidronate [22].

Even though the association between carpal tunnel syndrome and CPPD has been known for over 40 years, surgical release of the carpal ligament has always been associated with resolution of symptoms without any exacerbation. We therefore excluded any possible association with a minimally invasive surgery such as the liberation of the carpal canal and the acute event [23-25]. However, the global pandemic from COVID-19 has led to the development of several new vaccines that are inevitably associated with possible adverse reactions, which are emerging in recent times [26].

In particular, the Vaxzervria (formerly AstraZeneca) vaccine for preventing COVID-19 consists of a single vector of recombinant and replication-deficient chimpanzee adenovirus (ChAdOx1) encoding the SARS-CoV-2 glycoprotein S. The most frequently reported adverse reactions are tenderness and pain at the injection site, headache, fatigue, myalgia, malaise, pyrexia, chills, arthralgia, and nausea, usually improving within a few days [27].

Our patient was asymptomatic prior to vaccination and the only previous symptoms related to his rheumatic disease were 1 year earlier. There are 3 possible explanations for the correlation between vaccination and an arthritis flare-up: (1) 2 common conditions such as vaccination and arthritis happen concurrently by chance; (2) the vaccine is the etiology of a specific form of arthritis distinct from CPPD (post-immunization arthritis); or (3) the vaccine is one of the factors eliciting the development of CPPD arthritis.

On 8 Feb 2021, the American College of Rheumatology, regarding COVID-19 vaccination, acknowledged a theoretical risk of autoimmune disease flare after vaccination [28]. A flare of rheumatoid arthritis after COVID-19 vaccination with BNT162b2 (BioNTech-Pfizer) has also been recently reported [29].

The non-aluminum adjuvant contained in the recombinant zoster vaccine (RZV) is associated with a higher risk of developing a gout flare after vaccination because of activation of the NLRP3 inflammasome [30]. Aluminum adjuvants can also trigger the same reaction with a similar mechanism [31].

CPP crystals can stimulate the innate immune system. In particular, NLRP3 (NALP3) inflammasome through caspase-1 affects inflammatory cytokine IL-1β maturation [32]. Once released, this cytokine leads to a cascade of events leading to endothelial cell activation and neutrophil recruitment, and, ultimately, to crystal arthritis flares. A possible mechanism can thus be attributed to a component of the vaccine stimulating a significant inflammatory response.

Conclusions

This is the first case of acute CPP crystal arthritis occurring soon after SARS-CoV-2 vaccination.

It is our opinion that the vaccination associated with a prior surgery in the same anatomical site could have synergically triggered the arthritis flare, with a mechanism still unknown. A chance association cannot definitely be excluded, and more reports and studies are needed to establish a clear correlation.

It is of extreme importance to report all adverse effects related to all types of vaccines to be able to review existing guidelines and recommendations in order to establish the most appropriate vaccine for a specific patient and what kind of adverse effects could be expected.

Even though vaccines may be associated with acute CPP crystal arthritis, the benefits of vaccination, especially for the more fragile population, immensely outweigh its potential risks, especially during the current COVID-19 pandemic.

Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.
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