

# Complex regional pain syndrome of the knee after COVID-19 Vaccine in an adult patient

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**Title: Complex regional pain syndrome of the knee after COVID-19 Vaccine in an adult patient**

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## ABSTRACT

Several vaccines were developed and approved after the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) or COVID 19 pandemic in a relatively short period. However many side effects are still reported and the safety profile of all vaccines remains an area of concern. Complex regional pain syndrome is a rare and uncommon adverse effect to COVID-19 vaccination.

Herein, we describe the case of a patient with complex regional pain syndrome (CRPS) of the right knee that occurred after the second dose of mRNA COVID-19 vaccination.

We discuss this case and tried to clarify the association between CRPS and COVID-19 vaccination which is more likely explained by an immune-mediated inflammatory response to the vaccine component or antigen. Treatment requires a multidisciplinary management, including many medications, physiotherapy and psychological approach. More data were needed on the pathogenesis and the treatment of this unusual complication.

**Keywords :** COVID-19 vaccine ; complex regional pain syndrome ; reflex sympathetic dystrophy syndrome

## Key clinical message

We report a new case of the literature Complex regional pain syndrome of the knee after COVID-19 Vaccine in an adult tunisian patient showing the possible development of CRPS following COVID-19 vaccination and that this rare side effect should not be ignored.

## 1.INTRODUCTION

Complex regional pain syndrome (CRPS) is a common and disabling persistent pain condition results from an abnormal tissue response to injury, and increased sensitization of the central and peripheral nervous systems with various symptoms including swelling, limited joint range of motion, autonomic dysregulation and trophic changes in the affected limb. Several cases of CRPS have been reported after vaccination [1,2].

After the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) pandemic, several new and effective vaccines were approved in a relatively short period. However, the safety profile has been subject of concern.

This report describes a young man patient who developed complex regional pain syndrome (CRPS) of the right knee after receiving the second dose of messenger RNA— BNT162b2 (Pfizer–BioNTech) COVID-19 vaccine.

## 2.CASE PRESENTATION

A previously healthy 28-year-old Tunisian man was admitted to our Department of internal medicine on april 2022 with a painful swelling of her right knee with more than twelve month history of persistent pain, stiffness and functional disability. Her history revealed that symptoms occurred two weeks after the second shot of coronavirus mRNA BNT162b2 (Comirnaty Pfizer–BioNTech) COVID-19 vaccine (the first dose was also Comirnaty)

He was treated with nonsteroidal anti-inflammatory drugs (NSAIDs) without any relief. His pain and disability were worsened to the point that his daily activities were restricted (walk, managing stairs. . .), and his work was badly compromised.

He reported that pain and weakness were evident the night with an average intensity of 9 on a numeric rating scale (NRS) of 0 to 10.

On examination, the right knee showed mild not pitting edema with tactile allodynia, extreme restriction of knee joint on active and passive movement and major atrophy of the right muscles. There was tactile allodynic response to any palpation on anterior and medial area of the knee The left knee and the upper limbs were both normal.

Blood screening which include a sedimentation rate (4 mm first hour), C-reactive protein (18 mg/l), full blood counts (white blood cell count , hemoglobin level and platelet level) , electrolytes, creatinine, fasting glucose, liver function tests (including Total bilirubin , ASAT and ALAT GGT), creatine phosphokinase were all normal. Serum rheumatoid factor, anti-citrullinated peptides, antinuclear antibodies (ANA), Anti-neutrophil cytoplasmic antibodies (ANCA) and hepatitis B and C viral screening were all negative. The Thyroid stimulating hormone (TSH) value was normal at 0,69 mUI/L. 25-hydroxy vitamin D level was found to be low (17 ng/mL). There was no evidence of obvious infectious and all bacteriological studies were negative. An electromyography of the lower limbs was performed and did not show any pathologic findings.

MRI of the right knee was performed and showed extensive patchy bone marrow edema with high signal within the femur , the tibia and the patella in proton density weighted fat saturated sequences , with a mild joint effusion without fractures lines (**Figures 1 and 2**).

Therefore, the diagnosis of CRPS of the right knee after COVID-19 vaccination was made.

Many treatments were tried with unsatisfactory pain relief : intra-articular knee injections, pregabalin, opioids. The patient was managed with extensive and regular physiotherapy including muscle strengthening and functional training. He was started alendronate 70 mg orally twice a week , calcium carbonate - cholecalciferol supplementation with psychotherapy to reduce anxiety

The patient responded very slowly to the treatment and began to show marked improvement in pain, range of movement and function but without complete recovery.

A second MRI was performed 8 months after the diagnosis (**Figure 3**). It showed a mild decrease of the signal of the bone marrow edema within the femur and tibia, marked improvement of the edema within the patella; Persistence of the joint effusion. A bone resorption and muscle hypotrophy were observed.

### 3.DISCUSSION

This paper presents a case that developed a complex regional pain syndrome (CRPS) of the knee after the Pfizer-BioNTech vaccine, an mRNA-based vaccine administered against the COVID-19 virus.

Vaccines are the most effective ways to stop the spread of the coronavirus disease-2019 (COVID-19) and as the vaccination continue, more patients are likely to present with complications.

Various types of vaccines have been approved worldwide and have been shown to be safe and effective in preventing severe cases of COVID-19 especially in the elderly and patients with comorbidities [3]. Until now, 13.34 billion doses have been administered worldwide and approximately 69.8 % of the global population has received at least one dose [<https://ourworldindata.org/covid-vaccinations>]. The common side effects following COVID-19 vaccines include tenderness at the injection site, headache, fatigue, fever or myalgia. More serious events including life threatening allergic reactions, neurological manifestations, thrombocytopenia and myocarditis have been reported [4,5].

However, some uncommon and rare events after COVID-19 vaccination have been also reported and should not be ignored for early diagnosis and management. Recently, probable association between COVID-19 vaccine administration and CRPS has been shown by few cases [2, 6,7,8]. Clinically, Complex regional pain syndrome (CRPS), previously described as reflex sympathetic dystrophy (RSD) or algoneurodystrophy, is a disabling condition characterized by some clinical features :continuing regional pain with allodynia, hyperalgesia, autonomic changes, trophic changes, vasomotor edema, joint stiffness and functional loss [1, 9] that frequently affects the limbs. The upper extremities are more likely affected than the lower extremities and clinical manifestations are often most severe in the extremity that has experienced acute injury, but any part of the body can be affected. The symptoms can manifest on the right side like our case , on the left side or bilaterally in few cases [1].

Like our patient, most patients with CRPS experience many motor dysfunction, including restricted range of motion, muscle weakness, some patients complain from tremor or dystonia.

The current knowledge of CRPS remains insufficient, but it is now believed that the aetiology of CRPS involves a variety of pathological processes with an exaggeration of physiological responses (central and peripheral sensitization, sympathetic dysfunction, overproduction of proinflammatory cytokines ) leading to enhanced bone resorption. The current taxonomy classify two types of CRPS : type I (occurring in the absence of nerve injury) and type II formerly named  $\text{ii}$  causalgia  $\text{ii}$  (occurring in the presence of nerve injury). This condition often develops after trauma even minor, blunt traumatic injuries excluding fractures (e.g., sprains), or surgery, stroke, myocardial infarction. Female gender (reported female-to-male ratio ranged from 2:1 to 4:1 [1]), inflammatory chronic diseases and vaccinations also increase risk of developing CRPS [10].

The contribution of psychological factors including anxiety and depression to the development of CRPS is controversial. However, many research found a correlation between psychological factors and CRPS [1].

The pathophysiological mechanisms that lead to CRPS after COVID-19 vaccines are thought to be the same and can be explicated by injection trauma leading to CRPS of the upper limb, nerve damage by invasion of the virus or may be an hypersensitivity reaction to the component of the vaccine [2]. In a case-series of CRPS after HPV, the authors described peripheral sympathetic nerve dysfunction in 40 Japanese girls [11]. It remains difficult to know whether CRPS could occur as an indirect effect of tissue injury following the intramuscular injection, or caused by auto-inflammatory response triggered by the vaccine antigens or the two mechanisms in predisposing individuals. In our case, the causative mechanism of CRPS may be immune hyperactivity to a vaccine constituent supporting an immune-mediated mechanism as the CRPS affected the lower extremity.

The diagnosis of CRPS is based on clinical manifestations and there are criteria developed by The International Association for the Study of Pain (IASP) known as The Budapest criteria with a sensitivity and a specificity of 99 % and 68 % respectively [12].

There are no specific tools with limited role of laboratory tests or image studies to fulfill these criteria. However, some general laboratory tests are recommended to help rule out infection, inflammatory/auto-immune diseases and vascular diseases, such as erythrocyte sedimentation rate, C-reactive protein, a full blood count, and serum autoantibodies [1].

Some imaging methods including conventional radiographs, bone scintigraphy, computed tomography, MRI may be beneficial for ruling out differential diagnoses.

MRI can reveal periarticular bone-marrow edema, soft-tissue swelling, joint effusions, and atrophy of peri-articular structures in later stages, same findings in our case.

To confirm post-vaccination CRPS diagnosis, requires the absence of other etiologies and beginning of the symptoms within few weeks after receiving the vaccine. In our case, the patient did not report any symptoms and all investigations were normal (no recent surgery or trauma, no infections, no metabolic or inflammatory disorders, no vascular disorders, no stress fracture, no nerve injury) except for a history of COVID-19 vaccination.

Reports of CRPS after a vaccine are extremely rare and only few cases of CRPS after vaccination such as the hepatitis B [13], influenza [14], rubella [15], and human papillomavirus [16] vaccines have been published.

Horisawa S et al [2] reported the case of a 17-year-old woman diagnosed with CRPS of her left hand after the second dose of the mRNA COVID-19 vaccine. Praveena Raman, an active 33-year-old dentist, reported her experience of living with CRPS of her left hand post COVID-19 vaccine shot [7].

The management includes a different therapeutic approaches (analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), local corticosteroids, calcitonin, opioids, analgesics, sympatholytic agents and sympathetic nerve and ganglion blockade, bisphosphonate in some refractory cases) and rehabilitation.

In our report, the patient was first treated with NSAIDs, local steroid injection and pregabalin and then with bisphosphonate (alendronate) with regular physiotherapy with partial response.

The natural history of CRPS is influenced by many factors and remains a challenge for most physicians especially for refractory cases. A good prognosis with successful outcome relies on early diagnosis and treatment. However, many patients have a poor prognosis with severe impact in their quality of life as CRPS affects daily function and activities, sleep with significant effect on mental health, like in our case.

In the literature, most of patients who developed CRPS after vaccination showed complete improvement of their symptoms within few months [2,13]. Many studies showed that pain and functional loss may last for a long time despite medications and physical therapy. In our case, range of motion of the right knee had improved, however, pain had not completely resolved eight months after diagnosis and different medications, which can be explained by a late diagnosis.

### **3.CONCLUSION :**

This case highlights possible development of CRPS following COVID-19 vaccination and that this rare side effect should not be ignored. In the other hand, anyone who is experiencing symptoms of CRPS after receiving any type of vaccine especially COVID-19 vaccine should mention their vaccination to their doctor.

Only early diagnosis and treatment with a multidisciplinary approach are effective to mitigate against poor prognosis and unsuccessful outcomes.

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## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

## AUTHOR CONTRIBUTIONS

**Frikha Faten** : Conceptualization; data curation; investigation; methodology; project administration; supervision; validation; visualization; writing –original

**Yosr Hentati, Anis Masmoudi , Chifa Damak , Rim Akrouit , Sofien Baklouti , Zouhir Bahloul** : Visualization; writing –original draft; writing –review and editing. draft.

## DATA AVAILABILITY STATEMENT

All data is available.

## ETHICAL APPROVAL

The patient has consented to publication the case, imaging and all data.

## CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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### **Figure 1 :**

#### **Coronal proton density weighted fat saturated MRI of the right knee :**

Extensive patchy bone marrow edema with high signal within the femur and tibia, , with a mild joint effusion without fractures lines .

### **Figure 2 :**

#### **Sagittal proton density weighted fat saturated MRI of the right knee :**

trabecular bone edema with high signal within the femur , the tibia and the patella with and joint effusion.

### **Figure 3 :**

#### **Coronal (A) and sagittal (B and C) proton density weighted fat saturated MRI of the right knee after 8 months :**

Decrease of the signal of the bone marrow edema within the femur and tibia, marked improvement of the edema within the patella (B and C); Persistence of the joint effusion. A bone resorption and muscle hypotrophy were observed.

