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CASE REPORT

Post-COVID-19 vaccination arm pain diagnosed as complex regional pain syndrome: A case report

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Abstract
As the vaccination efforts against the coronavirus disease-2019 (COVID-19) continue, more patients are likely to present with complications related to COVID-19 vaccination. We describe the first reported case of complex regional pain syndrome (CRPS), involving the upper extremities, that occurred after COVID-19 vaccination. The patient presented with acute-onset severe arm pain and swelling following vaccine administration. Based on the clinical, electrodiagnostic, and radionuclide three-phase bone scan findings, the patient was diagnosed with postvaccination CRPS. The COVID-19 vaccine possibly elicited an immune-mediated inflammatory response to the injected antigen in the patient, who was predisposed to CRPS due to inflammatory immunity. The COVID-19 vaccine elicited an immune-mediated inflammatory response to the injected antigen, resulting in CRPS following COVID-19 vaccination.

KEYWORDS
case report, complex regional pain syndrome, COVID-19, immune system, vaccination

INTRODUCTION

Mass vaccination against the coronavirus disease-2019 (COVID-19) is crucial for achieving herd immunity against the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection.[1] However, the trial follow-up periods for monitoring vaccine-related complications have been brief.[2]

Complex regional pain syndrome (CRPS) is a persistent pain condition, characterized by allodynia, hyperalgesia, and autonomic and trophic changes in the affected limb.[3] CRPS reportedly results from an abnormal tissue response to injury, and increased sensitization of the central and peripheral nervous systems, accompanied by inflammatory changes and autonomic dysregulation.[3] Since it is a life-altering disease, many patients with CRPS experience refractory pain that limits their capacity to perform activities of daily living.[3,4] The risk factors for CRPS include a history of injury, sprain, fracture, immobilization, and surgery.[4] Injections, specifically vaccinations, have rarely been reported to cause CRPS.[3,5]

Herein, we describe the clinical presentation of CRPS in a patient who received the COVID-19 vaccine. Currently, there are no published reports of CRPS following COVID-19 vaccination. We sought to analyze the potential complications of COVID-19 vaccination.

CASE REPORT

This study was approved by the institutional review board (IRB number: 2021-12-006), and written informed consent was obtained from the patient.

The patient was a healthy 32-year-old woman with hypothyroidism, controlled via levothyroxine (0.05 mg). The patient received the Pfizer BioNTech (BNT162b2) COVID-19 vaccine in her left upper arm after passing the civil service examination at 11 AM on September 7, 2021. Three hours later, the patient experienced pain and hyperesthesia in her left arm and consequently self-medicated with acetaminophen (650 mg) multiple times. After 12 h, the patient experienced severe and persistent pain (numeric rating scale [NRS]: 9), increased temperature, sweating, and edema in the left arm (Figure 1A). This was accompanied by chest discomfort.

Furthermore, the patient had decreased active range of motion at left shoulder abduction and elbow flexion,

and was unable to control her grip due to severe left arm pain. Although the non-dominant arm was affected, the patient's ability to perform activities of daily living, such as typing, writing, grooming, and toileting, was hindered. Additionally, it affected on sleep disturbance and psychological symptoms such as anxiety and depressive mood. After 14 h, the patient visited the emergency department because the symptoms were persistent. Blood testing revealed an aspartate transaminase (AST) of 64 U/L and alanine transferase (ALT) of 59 U/L. Computed tomographic angiography of the left upper extremity revealed no abnormal findings in the vascular system. Moreover, cardiology, rheumatology, and vascular surgery consultations were conducted to identify other possible causes. No abnormalities were identified.

On September 16, 2021, the patient visited the Department of Rehabilitation Medicine as an outpatient (NRS 8–9). The nerve conduction and electromyography findings of the upper extremities were unremarkable. A radionuclide three-phase bone scan of the wrist and a whole-body bone scan with 800 MBq Tc-99 m hydroxymethylene diphosphonate were performed. Increased uptake was observed at periarticular areas of the left hand with increased perfusion and blood pool (Figure 1B). The Budapest criteria were used to rule in the diagnosis of CRPS.[6–8] The patient had sensory symptoms, such as hyperesthesia and allodynia; vasomotor symptoms, including skin redness and increased temperature; edema and sweating on the left arm; and motor symptoms, such as difficulty in moving her left arm and controlling her grip. She had sensory signs, which were hyperalgesia to pinprick and allodynia to light touch; vasomotor sign (ie, asymmetric skin color change); edema and sweating on the left arm; and motor sign, such as decreased active range of motion at the left arm. However, no trophic change was observed in the left arm. Thus, there were continuing pain, four symptoms, and signs compatible with CRPS in the patient. The signs and symptoms could be explained CRPS, no other diagnosis that better. Based on the Budapest criteria, electrodiagnostic, and radionuclide three-phase bone scan findings, the patient was diagnosed with CRPS (Table 1).[8]

Oral corticosteroids (30 mg of prednisolone, followed by a reduction of 10 mg every 2 days) and pregabalin 100 mg/day (50 mg, twice a day) were prescribed. One week after treatment, the patient's increased temperature and edema improved, however the arm pain (NRS 7) and allodynia persisted. The pregabalin dose was increased to 150 mg/day (75 mg, twice a day), and duloxetine (30 mg/day) was added. A ganglion stellatum block with 1 ml of ropivacaine (7.5 mg/ml), 1 ml of dexamethasone (5 mg/ml), and 2 ml of normal saline was performed via ultrasonography. The presence of signs of Horner's syndrome confirmed a successful block. Two weeks later, the patient reported partial pain relief (NRS 4–5). However, the patient still had difficulty sleeping due to nocturnal episodes of pain (3–4 times, 1–2 hours, NRS 7–8). She then received 10 mg of amitriptyline. After 3 weeks of taking amitriptyline, the nocturnal pain reportedly decreased to an NRS of 3. Non-pharmacological treatment methods were not used due to the patient's refusal. The patient is currently undergoing follow-up, and a higher medication dose and additional procedures may be considered depending on the symptoms.

DISCUSSION

Injuries to the extremities, such as fractures, sprains, and surgical injuries, have been commonly proposed as precipitating factors for CRPS.[3,4] Post-vaccination CRPS rarely occurs, and its overall incidence is unknown.[5,9]

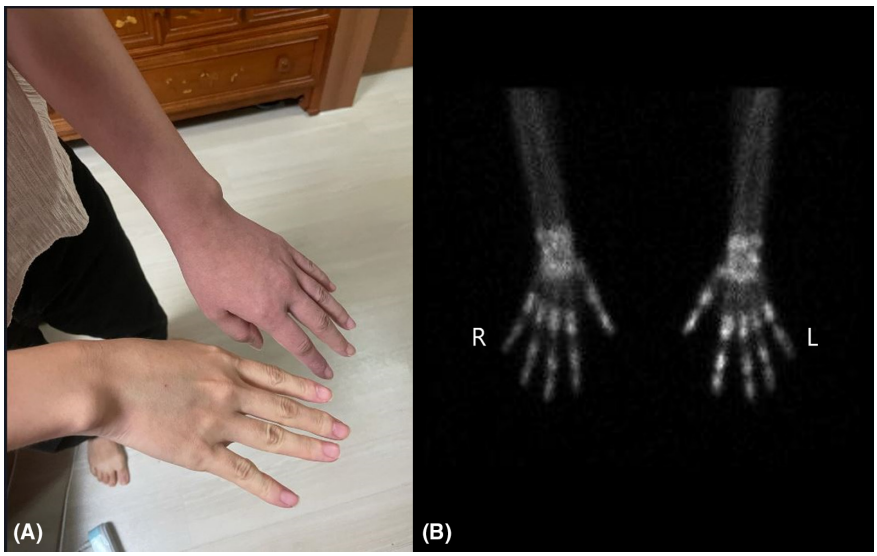

FIGURE 1 (A) The patient's appearance at the onset of symptoms; (B) The regional bone scan of the wrist revealing increased uptake at periarticular areas of the left hand in the delay phase (R: right, L: left)

TABLE 1 Budapest clinical diagnostic criteria for CRPS and patient's clinical presentation

Budapest clinical diagnostic criteria for CRPS		Patent's clinical presentation
1. Continuing pain, which is disproportionate to any inciting event		Yes
2. Must report at least one symptom in three of the following four categories		
Sensory	Reports of hyperesthesia and/or allodynia	Hyperesthesia and allodynia in the left arm
Vasomotor	Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry	Skin redness on the left arm
Sudomotor/Edema	Reports of edema and/or sweating changes and/or sweating asymmetry	Sweating on the left arm
Motor/Trophic	Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)	Difficulty in moving her left arm and controlling her grip.
3. Must display at least one sign at the time of evaluation in two or more of the following categories		
Sensory	Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)	Hyperalgesia to pinprick and allodynia to light touch in the left arm
Vasomotor	Evidence of temperature asymmetry and/or skin color changes and/or asymmetry	Left arm redness and asymmetric skin color
Sudomotor/Edema	Evidence of edema and/or sweating changes and/or sweating asymmetry	Left arm edema
Motor/Trophic	Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)	Decreased active range of motion at left shoulder abduction and elbow flexion
4. There is no other diagnosis that better explains the signs and symptoms		Yes

According to a cohort analysis, it affected 563 among 1,232,572 women, who received the human papillomavirus vaccine.[10] The COVID-19 vaccine elicits an immune response by inducing antibody formation against the SARS-CoV-2 virus.[1] The Pfizer-BioNTech (BNT162b2) COVID-19 vaccine, approved by the Food and Drug Administration, is a lipid nanoparticle–formulated nucleoside-modified RNA vaccine that encodes a prefusion-stabilized membrane-anchored SARS-CoV-2 full-length S protein.[11] Messenger RNA enters the human cell and directs cells to recognize the membrane-anchored SARS-CoV-2 spike protein. Subsequently, the host's immune system produces antibodies against the spike protein.[12] In such cases, the immune response can trigger autoimmune reactions, causing CRPS. However, no reports on the CRPS development following COVID-19 vaccination have been published.

CRPS is a chronic pain condition, characterized by sensory, motor, and autonomic changes, triggered by traumatic insult or autoimmune stress.[9] It is characterized by pain (neuropathic pain, allodynia, and hyperalgesia), autonomic abnormalities (local edema, sweating, skin temperature, and color changes), motor involvement (decreased strength and range of motion), and trophic changes.[4] Its pathophysiology remains unclear, but some mechanisms have been proposed. It is reportedly related to different factors, including central and peripheral nervous system sensitization, autonomic dysfunction, persistent neurogenic inflammatory changes, and autoimmunity.[6] Due to the complexity of its pathophysiology, CRPS is challenging to treat, and requires careful examination.

In the present case, the patient exhibited clinical symptoms of edema, increased temperature, allodynia, and severe pain in the left arm. A notable feature of this case is that there was no obvious trauma history except for vaccination, and symptoms appeared several hours after vaccination. Peripheral nerve diseases, including neuralgic amyotrophy, radiculopathy, entrapment neuropathy, and multifocal motor neuropathy, were excluded.[2] Among the various suggested pathophysiologic mechanisms of CRPS, the increased inflammatory mediators, such as pro-inflammatory cytokines, were reportedly a major factor in the pathophysiology of CRPS.[4] Vaccination possibly induced an immune-mediated inflammatory response against the injected antigen in our patient.[2] A COVID-19 vaccine-triggered immune reaction likely caused the patient's CRPS attack.

Corticosteroids were reportedly useful for managing CRPS due to their potent anti-inflammatory and immunomodulatory effects.[4] In the current case, a ganglion stellatum block was performed, and corticosteroids were also prescribed.[6,13] The concentrations of inflammatory markers were reportedly higher during the early phase of CRPS, compared to its later phase.[4]

To our knowledge, this is the first report of CRPS, following COVID-19 vaccination. Our report contributes to literature by stating that COVID-19 vaccinations could trigger CRPS, as this information had not been reported. As the mass vaccination efforts against COVID-19 continue, more patients with post-vaccination CRPS are expected. Although this probable COVID-19 vaccine induced CRPS, the causal relationship could not be completely confirmed, which was a

limitation of this case report. This study highlighted the importance of the clinical, electrodiagnostic, and radionuclide three-phase bone scan findings in the accurate diagnosis and early treatment of CRPS after COVID-19 vaccination. Clinicians should consider CRPS as a possible complication of COVID-19 vaccination and it might be helpful for early diagnosis and early therapeutic interventions of CRPS after COVID-19 vaccination. Further investigations are needed to compare the clinical features and course of COVID-19 vaccine-induced CRPS and typical CRPS. To achieve a definite conclusion on the precise pathophysiological process of COVID-19 vaccine-induced CRPS, it would be necessary to verify more cases.

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship, and or publication of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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