SHORT COMMUNICATION

COVID-19 Vaccination-related Complex Regional Pain Syndrome Masquerading as Erythromelalgia: A Case Report

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Complex regional pain syndrome (CRPS) is a rare and poorly understood chronic pain disorder of the extremities, which is characterized by intense pain, hyperalgesia, allodynia, oedema and skin discolouration (1). Other clinical manifestations include change of temperature, anhidrosis/hyperhidrosis and hypotrichosis/hypertrichosis and, in later stages, the skin may become atrophic and sclerotic with concurrent nail dystrophy (2). The aetiology of CRPS is not well understood, but it often follows trauma or surgery to the affected limb (1). Reports of CRPS following vaccination, and recently also following SARS-CoV-2 coronavirus disease (COVID-19) vaccination, have been documented (3–6). We report here the first published case from Scandinavia of possible COVID-19 vaccination-induced CRPS with prominent dermatological manifestations.

CASE REPORT

A 56-year-old woman was referred to a private practice dermatologist due to painful discoloration of her feet. She had daily attacks of very painful acrocyanosis of her feet, which could be provoked by standing and walking. Moreover, she experienced constant pain in the soles of her feet (visual analogue scale (VAS) for pain ~5) that worsened notably when she stood up (VAS pain 10; feeling her feet were going to burst). She recently became dependent on using a wheelchair, as the intense pain in her feet made her unable to walk and stand. By objective examination, her feet were red and tender to touch with no trophic disturbances.

Her history revealed that these disabling symptoms had manifested following her COVID-19 vaccinations in 2021. Previously she had been physically very active and usually walked 10–15 km daily. In March 2021 she was diagnosed with mild plantar fasciitis due to her active lifestyle. After receiving her first COVID-19 vaccine (Pfizer-BioNTech mRNA) in June 2021 there was a slight worsening of the existing foot pain. The day after her second vaccination in July 2021, she experienced a sudden worsening, with notable pain in her feet accompanied by swelling and a violaceous discoloration (**Fig. 1**a).

Since then she has experienced a constant, throbbing sensation in the soles of both feet as well as episodic oedema and discolouration ranging from red to dark-purple and anaemic white. The pain and skin discoloration could be worsened/triggered by various stimuli, such as standing, walking, touching the skin, use of footwear, and cold temperature/water. After receiving her third COVID-19 vaccine in December 2021, the symptoms worsened further.

Initially she had been evaluated by a private practice dermatologist who suspected erythromelalgia and referred her to a department of dermatology, confirming the suggested diagnosis. She also received a second opinion from another dermatology department where redness and purple discoloration of her feet were verified by submersion in lukewarm water. A punch biopsy was performed, showing a discrete and unspecific superficial perivascular lymphocytic inflammation.

During the disease course she underwent intensive investigations to provide a diagnosis and was also seen by the department of vascular surgery, rheumatology, neurology (3 different public hospitals and a private hospital) and orthopaedics (3 different public hospitals and a private hospital). Extensive diagnostic tests were performed, including blood tests, genetic testing for erythromelalgia, lumbar puncture, computed tomography of the chest and abdomen, magnetic resonance imaging of the total columnar spine, positron emission tomography-computed tomography and magnetic resonance imaging of the feet without any relevant findings. Electroneuronography did not show any signs of polyneuropathy, a normal sweat response was demonstrated by a quantitative sudomotor axon reflex test, and a skin biopsy for small fibre neuropathy revealed normal intraepidermal nerve fibre density. Differential diagnoses considered were plantar fasciitis and/or heel spur and erythromelalgia. Finally, she was referred to a specialist CRPS clinic, which currently manages her condition.

Throughout the disease course a multitude of different pain-relieving modalities, such as pregabalin, ibuprofen, paracetamol, low-dose naltrexone and opioids were tried without success. Oral prednisone 37.5 mg daily had been tried for 4 days without effect and a regimen of nifedipine for 14 days also provided no relief.

Fig. 1. (a) Right foot showing red/purple discolouration. (b) Feet after regional block with ropivacaine of left foot prior to cryoneurolysis, which triggered worsening of the symptoms. Note the redness and oedema of the left foot compared with the right foot.

Table I. Budapest Criteria for complex reginal pain syndrome diagnosis

All of the following 4 criteria must be met:	
I. At least 1 sign in 2 or more of the categories below	III. Continuing pain, which is disproportionate to any inciting event
II. At least 1 symptom in 3 or more of the categories below	IV. No other diagnosis can better explain the signs and symptoms
CATEGORY	SIGNS/SYMPTOMS
Sensory	*Hyperalgesia/hyperesthesia* and/or *allodynia*
Vasomotor	*Temperature asymmetry* and/or *skin colour changes* and/or *skin colour asymmetry*
Sudomotor/Oedema	*Oedema* and/or *sweating changes* and/or *sweating asymmetry*
Motor/Trophic	*Decreased range of motion* and/or *motor dysfunction* and/or *trophic changes (nail, skin)*

Furthermore, treatment with fexofenadine and topical capsaicin did not alleviate her symptoms, and in addition to pharmacological intervention, physiotherapy was instituted. The CRPS clinic planned off-label treatment with cryoneurolysis; however, a pre-test regional nerve block with ropivacaine of the tibial and sural nerves led to increased discoloration, oedema and pain (Fig. 1b). As a consequence, this procedure was cancelled. The patient is now awaiting treatment with botulinum toxin injections in her feet.

DISCUSSION

As no diagnostic test is available for CRPS, the Budapest Criteria (7) can be used (**Table I**). The current patient fulfils a diagnosis of CRPS based on the following Budapest Criteria: allodynia and hyperalgesia (sensory symptom and sign), skin colour changes (vasomotor symptom and sign), oedema, continuing pain and absence of a more obvious explanation. Also, it is probable, as the patient scored 7 points on the Naranjo Adverse Drug Reaction Probability Scale (8), that her symptoms and signs were provoked by COVID-19 vaccination. This is also supported by a literature search of recent case reports (4–6, 9). The published cases included 1 male and 5 females with symptoms from both upper and lower extremities. One of the published patients developed CRPS after the second vaccination (4), while the others experienced symptoms after their first injection (5, 6). Local trauma following injection or an autoimmune/inflammatory reaction induced by the vaccine were considered the most likely causative factors. The current patient experienced a slight worsening of existing pain in her feet following the first vaccine; however, the excruciating pain, discolouration and oedema occurred after her second vaccination. It is notable that there is also a case series from 2022 of 3 patients with CRPS that worsened after COVID-19 vaccination (9).

General awareness of CRPS is relatively low, as shown by Allen et al. (10). Even though CRPS often presents with prominent skin changes (11), the condition has not gained much recognition in the realm of dermatology and the number of publications in the dermatological literature is scarce (12).

In the current case, the most obvious dermatological differential diagnoses were chilblains and erythromelalgia (**Table II**). Chilblains however, are provoked by cold, involve the toes (COVID toes), are normally not that painful, and may also present with itching (13). Patients with erythromelalgia usually have more burning and episodic pain, and as a hallmark often try to relieve the pain with ice-cold water (14). In contrast, the current patient experienced worsening of her symptoms with cooling. Moreover, erythromelalgia does not usually cause patients to become dependent on using a wheelchair, whereas CRPS can be very debilitating, leading to severe loss of function and quality of life.

The pathophysiology of CRPS is not known in detail (1), but possible autoimmune and autonomic dysfunction have been considered and discussed in a recent paper on post-COVID syndrome (15). Early diagnosis and management are integral to patient prognosis using a multidisciplinary approach involving patient education, physical and occupational therapy, psychological support, pharmacotherapy and sometimes surgical intervention (1).

The current case highlights mRNA COVID-19 vaccination as a possible trigger for CRPS. Dermatologists should be on the lookout for regional dysesthesias with cutaneous findings, as early recognition and treatment of CRPS is paramount for the prognosis.

The authors have no conflicts of interest to declare.

Table II. Characteristics of chronic regional pain syndrome (CRPS), erythromelalgia and chilblains

	CRPS	Erythromelalgia	Chilblains
Skin colour	Erythematous/white/purple (cyanotic)	Erythematous	Erythematous/purple (cyanotic)
Typical presentation	Limbs; usually unilateral, can be bilateral	Distal limbs; usually bilateral, can be unilateral	Fingers and toes; bilateral and symmetrical
Loss of functionality	Yes	Variable	No
Relieving factors	None	Cold	Heat
Provoking factors	Injury, temperature changes (cold and heat)	Heat	Cold
Course of pain	Extreme, constant	Intense, episodic	Variable, but remitting
Decreased neuronal activity	No	Can be seen	No
Associated conditions	Trauma/surgery	Myeloproliferative disorders, systemic lupus erythematosus, genetic	Systemic lupus erythematosus COVID-19
Selected other findings	Oedema, hyperalgesia, decreased range of motion, temperature differences of skin	Oedema, warmth	Erythrocyanotic lesions, oedema, ulcers
Skin biopsy	Unspecific	Unspecific	Diagnostic

REFERENCES

1. Taylor SS, Noor N, Urits I, Paladini A, Sadhu MS, Gibb C, et al. Complex regional pain syndrome: a comprehensive review. Pain Ther 2021; 10: 875–892.
2. Freeman R, Dover JS. Autonomic neurodermatology (Part I): erythromelalgia, reflex sympathetic dystrophy, and livedo reticularis. Semin Neurol 1992; 12: 385–393.
3. Jastaniah WA, Dobson S, Lugsdin JG, Petty RE. Complex regional pain syndrome after hepatitis B vaccine. J Pediatr 2003; 143: 802–804.
4. Horisawa S, Ando T, Kawamata T, Taira T. Complex regional pain syndrome after mRNA-based COVID-19 vaccination. Clin Neurol Neurosurg 2023; 224: 107578.
5. Cho JH, Ahn HC, Choi Y. Post-COVID-19 vaccination arm pain diagnosed as complex regional pain syndrome: a case report. Pain Pract 2023; 23: 313–316.
6. Raman P. Complex regional pain syndrome post COVID-19 vaccine shot: an autobiographical case report. Cureus 2021; 13: e20257.
7. Harden NR, Bruehl S, Perez R, Birklein F, Marinus J, Maihofner C, et al. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex regional pain syndrome. Pain 2010; 150: 268–274.
8. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239–245.
9. Zhang J, Gungor S. Acute worsening of clinical presentation in CRPS after SARS-CoV-2 (COVID-19) vaccination: a case series. Pain Manag 2022; 12: 249–254.
10. Allen G, Galer BS, Schwartz L. Epidemiology of complex regional pain syndrome: a retrospective chart review of 134 patients. Pain 1999; 80: 539–544.
11. Sundaram S, Webster GF. Vascular diseases are the most common cutaneous manifestations of reflex sympathetic dystrophy. J Am Acad Dermatol 2001; 44: 1050–1051.
12. Araki E, Tanioka M, Miyachi Y, Utani A. A case of complex regional pain syndrome: an underdiagnosed condition in dermatology. Acta Derm Venereol 2007; 87: 440–441.
13. Pratt M, Mahmood F, Kirchhof MG. Pharmacologic treatment of idiopathic chilblains (Pernio): a systematic review. J Cutan Med Surg 2021; 25: 530–542.
14. Jha SK, Karna B, Goodman MB. Erythromelalgia. StatPearls. Treasure Island, FL: StatPearls Publishing LLC; 2023.
15. Mahroum N, Shoenfeld Y. Autoimmune autonomic dysfunction syndromes: potential involvement and pathophysiology related to complex regional pain syndrome, fibromyalgia, chronic fatigue syndrome, silicone breast implant-related symptoms and post-COVID syndrome. Pathophysiology 2022; 29: 414–425.