Dear Editor, Pernio-like acral lesions are a common dermatological manifestation reported after SARS-CoV-2 (COVID-19) infection. The pernio-like eruption characteristically seen on the feet has been coined ‘COVID toes’. These lesions are more often seen in mild to asymptomatic patients and represent a late manifestation of COVID-19 infection. Here, we present a case of a patient with pernio that appeared after the Pfizer BNT162b1 COVID-19 vaccine, in an asymptomatic individual with negative polymerase chain reaction (PCR) testing.

A 64-year-old male presented to the emergency department in January 2021 with violaceous skin discoloration for 10 days that started on the left hallux and gradually spread to all toes on the bilateral feet. The patient received the second dose of the Pfizer COVID-19 vaccine 3 days prior to onset of the left toe discoloration. He denied hot or cold exposure, numbness, tingling or pain. He denied history of pernio or other similar lesions, Raynaud’s phenomenon, oral ulcers, photosensitivity, vascular disease, cardiac disease, hypercoagulable state, cardiac procedure or autoimmune diseases. He denied previous or current symptoms of COVID-19 or exposure to those with COVID symptoms or a positive test. The estimated local prevalence of the virus was 7.6%. The patient had three negative COVID-19 PCR tests in the 2 months prior to presentation, and negative testing at presentation. The patient denied any adverse reactions after the first dose of the vaccine.

The patient had painless, dark erythematous to violaceous discoloration of the bilateral toes, with an intact bulla on the left hallux. Abnormalities on initial laboratory studies included elevated C-reactive protein. The differential diagnosis included idiopathic pernio, connective tissue disease, hypercoagulable state, vasculitis/vasculopathy, COVID-19 infection or reaction to the vaccine. Laboratory workup including Hepatitis B, Hepatitis C, HIV, antinuclear antibody, antineutrophil cytoplasmic antibody, antiphospholipid antibodies, complements C3/C4/CH50, rheumatoid factor, and serum and urine protein electrophoresis was initiated to rule out other aetiologies in the differential diagnosis. The key differentiating feature between COVID-19-associated pernio and idiopathic pernio is the lack of association with cold exposure.

Idiopathic pernio was unlikely as the local weather was relatively mild; daily temperatures averaged 9–20 °C in the weeks before and after the lesions appeared. The patient was in a stable condition and was discharged with clobetasol 0.05% ointment for the affected toes with a plan to follow-up in the outpatient dermatology clinic in 2 weeks. At follow-up 15 days after initial presentation (28 days after vaccination), the clinical appearance of the toe discoloration was unchanged (Figure 1). The patient’s symptoms were now exacerbated by cold temperatures and improved with rewarming and leg elevation.

Laboratory workup was unrevealing. A punch biopsy of the left great toe was obtained, which revealed pathology consistent with pernio and immunohistochemistry (IHC) staining for SARS-CoV-2 of the tissue was negative (Figure 1). COVID infection remained a possibility. However, negative testing and lack of symptoms or contact with infected individuals argued against this. Thus, the final diagnosis was pernio, temporally associated with the second dose of Pfizer mRNA SARS-CoV-2 vaccine. The patient was counselled to use clobetasol as needed and avoiding cold exposure.

This presentation suggests possible attribution of the pernio-like lesions to an immune response triggered by the COVID-19 mRNA vaccine, potentially similar to the immune response described in COVID toes.

Figure 1 (a) and (b) Acral rash at follow-up visit on right foot and left foot, respectively; 28 days post vaccine. (c) and (d) There is a superficial and deep infiltrate of lymphocytes around vessels and eccrine glands, with papillary dermal oedema. No thrombi or vasculitis are seen. Haematoxylin and eosin stain, original magnification × 20 (c) and × 100 (d).
response after Sars-CoV-2 itself, which also triggers pernio. Notably, a similar but prolonged course of toe discoloration after the first dose of the Pfizer mRNA vaccine has been reported. The American Academy of Dermatology/International League of Dermatological Societies COVID-19 registry has noted eight of these pernio-like reactions after vaccination, but at present no cases of patients with biopsy confirmation have been reported.

Our understanding of the pathophysiology connecting COVID-19 and pernio is continuing to grow. A recent study demonstrated these lesions as part of the spectrum of COVID-19 by demonstrating IHC evidence of SARS-CoV-2 in endothelial cells of skin biopsies of patients with clinically diagnosed COVID-19-related pernio. Moreover, patients with pernio-like lesions observed during the pandemic demonstrated a significantly higher interferon-alpha response than those with moderate or severe COVID-19, characteristic of a viral-induced type I interferonopathy. The mRNA COVID-19 vaccine BNT162b1 elicits a CD4\(^+\) T helper cell response and strong interferon-gamma and interleukin-2 producing CD8\(^+\) cytotoxic T-cell responses. This could suggest that the vaccine is eliciting a similar response in the skin as the pernio-like lesions attributed to COVID-19.

This presentation raises considerations regarding the potential pathophysiology of COVID-19 and pernio as well as potential sequelae of the vaccine. Additional studies of host immune response in the skin after Sars-CoV-2 infection and COVID-19 vaccines are necessary for further understanding.

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