



Cases of Pernio-Like Lesions after mRNA-1273 Vaccination with Clinical and Pathological Features: A Single-Center Experience

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The currently available coronavirus disease 2019 (COVID-19) vaccines in South Korea include mRNA (Moderna[®] and Pfizer[®]) and adenoviral vector (AstraZeneca[®] and Janssen[®]) vaccines. Dermatologic side effects of COVID-19 vaccines range from local injection site reactions to systemic eruptions, including morbilliform rashes or erythema multiforme. Pernio-like lesions, one of the most common cutaneous manifestations of COVID-19, have been rarely reported post-vaccination. Herein, we report four cases of pernio-like lesions, which were detected in a single tertiary hospital within 2 months, after the first dose of mRNA-1273 (Moderna[®]) vaccination was administered. In this study, we discuss the clinical and pathological features of our cases and compare them with those of previously reported cases of pernio-like lesions after COVID-19 vaccination. It is pivotal to realize that pernio-like lesions can be a possible side effect of COVID-19 vaccination and that the number of patients experiencing this side effect is bound to be quite high in real-world clinical settings.

Keywords: Adverse drug reactions, Chilblains, COVID-19, mRNA-1273

INTRODUCTION

Various types of safe and effective severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines have been developed in response to the novel coronavirus disease 2019 (COVID-19) pandemic¹. However, their extended use has been associated with diverse adverse reactions². COVID-19 vaccines reportedly cause localized symptoms, such as pain, erythema, or swelling at the injection site, and systemic symptoms, such as fever, fatigue, headache, muscle pain, joint pain, and, in some cases, anaphylactic shock^{2,3}. Dermatologic adverse reactions, including urticaria, morbilliform rashes, erythema nodosum, and erythema multiforme, have been rarely reported^{2,4,5}.

Pernio-like lesions, usually referred to as “COVID toes,” are one of the most commonly described cutaneous manifestations of COVID-19⁶. Their occurrence after COVID-19 vaccination, however, has rarely been reported^{2,4}. Herein, we report cases of

four young patients with pernio-like lesions, which were detected in a single tertiary hospital within 2 months, after the first dose of mRNA-1273 (Moderna[®]) vaccination was administered.

The study was approved by the Institutional Review Board of the Keimyung University Dongsan Medical Center (IRB no. 2021-12-040). We received the patient’s consent form about publishing all photographic materials.

CASE REPORT

From September 2021 to October 2021, four patients (aged 24~31 years; three were females, and one was male) visited our dermatological clinic with painful or pruritic annular or round erythematous swollen patches on their hands and feet, particularly around the joints (Table 1, Fig. 1). The lesions developed 7~9 days after the first dose of mRNA-1273 vaccination, without mucous membrane involvement. The patients



Table 1. Comparison of clinical and pathological features among our cases

Case	1	2	3	4
Sex/age (yr)	F/30	F/24	M/31	F/30
Clinical manifestations	Painful erythematous swollen patches	Pruritic erythematous round-shaped patches	Pruritic erythematous targetoid patches	Painful erythematous round-shaped patches
Distribution	Both hands and feet	Both hands and feet	Both hands and feet	Both hands and first toes
Onset of lesions after vaccination	8 days	9 days	7 days	8 days
Histopathology	Dense perivascular lymphocytic infiltration and vasculitis	Exocytosis Basement membrane change Dense perivascular and periadnexal lymphocytic infiltration with eosinophils	Spongiosis Basal vacuolar degeneration Dense perivascular lymphocytic infiltration with eosinophils	Toe: Epidermal, periadnexal and perivascular lymphocytic infiltration Hand: Dense perivascular lymphocytic infiltration with eosinophils
Laboratory test	ANA 1:640	ANA 1:160	UR	IgE 231
Treatment	Systemic and topical corticosteroids Antihistamines	Systemic and topical corticosteroids Antihistamines	Systemic and topical corticosteroids Antihistamines	Systemic and topical corticosteroids Antihistamines
Time for resolution	2 weeks	Wax and wane	2 weeks	2 weeks
2nd vaccination	No adverse effects	No vaccination	No vaccination	Mild pernio-like lesions 22 days after vaccination

F: female, M: male, ANA: antinuclear antibody, UR: unremarkable.



Fig. 1. Clinical presentation of pernio-like lesions after mRNA-1273 vaccination. (A, B) Case 1: erythematous swollen patches on both hands and (C) resolved skin lesions (2 weeks after systemic and topical corticosteroid treatment). (D~F) Case 2: erythematous round-shaped patches on both hands and feet. (G~I) Case 3: erythematous targetoid patches on both hands and feet. (J, K) Case 4: erythematous patches on fingers.

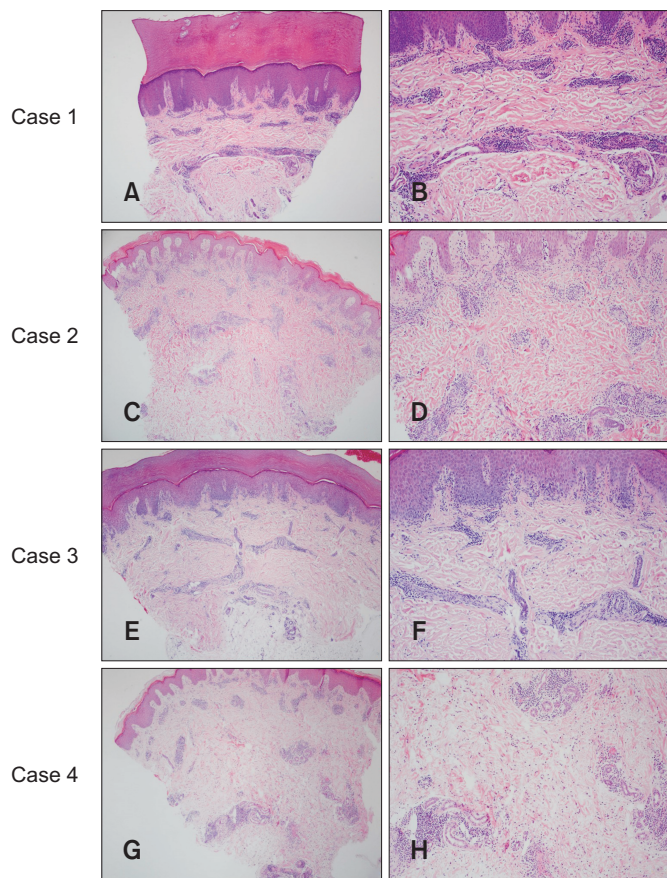


Fig. 2. Histopathological assessment of pernio-like lesions. (A, B) Dense superficial and deep perivascular lymphocytic infiltration with vasculitis (H&E, 40 \times and 100 \times). (C, D) Dense perivascular and periadnexal lymphocytic infiltration with eosinophils. Exocytosis and basement membrane change are evident (H&E, 40 \times and 100 \times). (E, F) Dense superficial and deep perivascular lymphocytic infiltrations with eosinophils. Spongiosis and basal vacuolar degeneration are evident (H&E, 40 \times and 100 \times). (G, H) Dense superficial and deep perivascular lymphocytic infiltrations with eosinophils (H&E, 40 \times and 100 \times).

reported neither general symptoms nor unusual exposure to cold and had no medical or allergic history. One patient had been taking an herbal medicine for 2 months (Case 2). Skin biopsies obtained from the hand or foot mostly showed dense perivascular lymphocytic infiltrate; in some cases, periadnexal lymphocytic infiltrate, eosinophils, spongiosis, exocytosis, and basement membrane change were evident (Fig. 2). Interestingly, the skin biopsy of Case 1 showed vasculitis with dense perivascular lymphocytic infiltrate (Fig. 2A, B). In Cases 1 and 2, laboratory tests showed positive antinuclear antibodies (1:640 and 1:160 titer, respectively), while the results of other tests, including serum complement and anti-dsDNA antibody

levels, were normal. Both Cases 1 and 2 were referred to the rheumatology department, but systemic autoimmune diseases were not diagnosed. Instead, they were scheduled for regular check-ups. In Case 3, the results of laboratory tests, including herpes simplex virus IgM, cytomegalovirus IgM, Epstein-Barr virus viral capsid antigen IgM, and anti-mycoplasma IgM, were found to be normal, whereas Case 4 showed elevated serum IgE levels (231 IU/ml).

Pernio-like lesions in response to mRNA-1273 vaccination were then suspected, and they were thus treated with systemic and topical corticosteroids and antihistamines; most lesions resolved within 2 weeks. However, in Case 2, the lesions relapsed after a week of complete remission and these symptoms were found to wax and wane.

Among the four cases, only two received the second dose of mRNA-1273 vaccination. In Case 4, a similar shaped but mild eruption limited to her right hand occurred 22 days after the second dose. She was treated with systemic and topical corticosteroids and antihistamines for a week, but these symptoms were found to wax and wane. Case 1 showed no adverse reactions after the second dose.

DISCUSSION

The currently available COVID-19 vaccines in South Korea include mRNA (Moderna[®] and Pfizer[®]) and adenoviral vector (AstraZeneca[®] and Janssen[®]) vaccines. According to a recently published register-based study covering 414 skin reactions following mRNA COVID-19 vaccination, delayed large local reactions were the most common, followed by local injection site reactions, urticarial eruptions, and morbilliform eruptions⁴. Pernio-like lesions after COVID-19 vaccination have been rarely reported⁴.

Among the case reports of pernio-like lesions after COVID-19 vaccination across the globe, Table 2⁶⁻¹² summarizes seven distinctive cases of pernio-like lesions that were found to occur 1-14 days after COVID-19 vaccination. Skin biopsy showed dense superficial and deep lymphocytic aggregates usually around the blood vessels and eccrine gland. Two cases showed remission 2 weeks after topical corticosteroid treatment, while in one case, the lesions tended to wax and wane despite treatment with topical corticosteroids. Among seven cases, only three received the second dose of COVID-19 vaccine; one case showed similar lesions 3 days after the second

Table 2. Reported cases of pernio-like lesions after mRNA COVID-19 vaccination worldwide

Case	1 ⁶	2 ⁷	3 ⁸	4 ⁹	5 ¹⁰	6 ¹¹	7 ¹²
Sex/age (yr)	F/82	M/42	M/64	NR/60	F/41	F/70	F/48
Medical history	Psoriasis (MTX treatment)	NR	UR	NR	UR	Pityriasis lichenoides chronica	Allergic contact dermatitis*
Type of vaccine	1st BNT162b2 mRNA	1st BNT162b2 mRNA	2nd BNT162b2 mRNA	2nd BNT162b2 mRNA	2nd BNT162b2 mRNA	1st mRNA-1273	1st mRNA-1273
Clinical feature	Painful erythematous patches	Non-painful erythematous to purplish patches	Violaceous patch	Pruritic and burning erythematous swollen patches	Painful erythematous patches	Painful erythematous papules and patches	Pruritic and painful erythematous swollen patches
Distribution	Both hands and feet	Both hands	Both feet	Both hands	Right hand	Both hands	Both hands and feet
Onset of lesion	1 day	12 days	3 days	14 days	1 day	2 days	10 days
Histopathology	Dense lymphocytic aggregates around the vessels and eccrine gland	NR	Superficial and deep lymphocytic aggregates around the vessels and eccrine gland	NR	NR	Dense superficial and deep perivascular lymphocytic infiltration	Spongiosis Superficial and deep perivascular lymphocytic infiltration with eosinophils
Laboratory test	UR	NR	UR	UR	IgG	UR	Positive ANA
Treatment	NR	NR	Topical corticosteroids	NR	NR	Topical corticosteroids	Topical corticosteroids
Time for resolution	NR	NR	Wax and wane	NR	NR	2 weeks	13 days
2nd vaccination	NR	No adverse effects	-	-	-	Similar lesions 3 days after	No adverse effects

F: female, M: male, MTX: methotrexate, NR: not reported, UR: unremarkable, ANA: antinuclear antibody. *Allergy to fragrances.

dose, which occurred at similar intervals as with the first dose, while no adverse reactions were found after the second dose in two cases. On the other hand, three cases showed pernio-like lesions only after the second dose; no adverse reactions were observed in them after the first dose of COVID-19 vaccination.

Our cases presented with erythematous patches limited to their hands and feet. Skin biopsies showed dense perivascular lymphocytic infiltration, diagnosed as pernio-like lesions clinically and pathologically. However, Case 3 showed targetoid patches, which were similar to erythema multiforme. Histopathologically, Case 3 showed dense perivascular lymphocytic infiltration without necrotic keratinocytes, which is different from erythema multiforme but similar to previously reported pernio-like lesions after COVID-19 vaccination. Further, Case 1 showed vasculitis, with positive antinuclear antibodies. She did not meet any diagnostic criteria for systemic autoimmune diseases, but the presence of an autoimmune disease, such as cutaneous lupus erythematosus cannot be excluded; therefore regular follow-ups may be needed. Moreover, considering that two of our cases showed positive antinuclear antibodies, it seems that COVID-19 vaccination triggers immune responses, particularly in patients with autoimmune tendency. It is notable that in several cases, autoimmune diseases, including cutaneous lupus erythematosus, have been found to be induced or exacerbated after COVID-19 vaccination^{13,14}.

In worldwide, pernio-like lesions mostly occur after mRNA vaccination, and only one case of pernio-like lesions following an inactivated COVID-19 vaccine has been reported^{1,15}. Moreover, of the ten cases of pernio-like lesions described across three observation studies, 60% were found to be associated with BNT162b2 (Pfizer[®]) vaccination, whereas the remaining were linked with mRNA-1273 (Moderna[®]) vaccination¹⁵. Herein, however, all cases in whom pernio-like lesions were observed had received mRNA-1273 vaccination and all cases occurred in young patients. It is challenging to determine whether these lesions occur more commonly in young patients or after mRNA-1273 vaccination as there are currently no statistics on vaccination rate according to vaccine type and age in South Korea; further evaluation is thus warranted.

The pathogenesis of pernio-like lesions after COVID-19 vaccination remains uncertain¹³. These lesions are believed to be more likely triggered by the immune response to SARS-CoV-2, rather than being a direct cytopathogenic viral effect¹⁶. First, COVID-19 vaccines, particularly the mRNA-based ones,

elicit a CD4+ type 1 T-helper cell responses as well as strong interferon-gamma and interleukin-2 producing CD8+ cytotoxic T-cell responses⁸. This suggests that COVID-19 vaccines elicit a similar immune response in the skin as that observed in response to COVID-19, which also triggers pernio-like lesions, usually in mild to asymptomatic patients during the late stages of the infection⁸. In addition, COVID-19 vaccines trigger the production of type 1 interferons, which are known to play a key role in the pathogenesis of various autoimmune diseases by elevating levels of nuclear antigen-containing immune complexes¹⁴. Moreover, the spike protein in COVID-19 vaccine shares genetic similarities with human proteins, potentially triggering autoimmune responses due to molecular mimicry post-vaccination¹³. Nevertheless, further studies are warranted to assess the correlation between COVID-19 vaccines and pernio-like lesions.

To summarize, we herein report four cases of young healthy patients showing pernio-like lesions after the first dose of mRNA-1273 vaccination. These lesions mostly resolved after treatment with systemic and topical corticosteroids and systemic involvements were not observed; therefore, vaccine administration should not be delayed. It is noteworthy that these four cases were encountered just within 2 months at our clinic in South Korea; thus, awareness regarding pernio-like lesions occurring after COVID-19 vaccination needs to increase, as the number of patients experiencing this side effect is bound to be quite high in real-world clinical settings.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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