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DERMATOLOGIC THERAPY WILEY

LETTER

Ulcerative injection site reaction after third COVID-19 vaccine dose with mRNA-1273

Dear Editor,

With the advent of vaccines against COronaVIrus Disease 2019 (COVID-19), associated local skin reactions are now largely reported.

We herein report the case of a 67-year-old Caucasian woman who presented with a local ulcerative reaction to mRNA-1273 (Spikevax®; Moderna) vaccine about 1 month after the injection. The patient had her first two doses of BNT162b2 (Comirnaty®; Pfizer-BioNTech) vaccine, 7 and 6 months earlier. Previous vaccinations were not associated with remarkable injection site reactions. She was affected by chronic ischemic cardiopathy, hypothyroidism with multinodular goiter, hypertension, and Sjogren's disease and was taking doxazosin, clopidogrel, telmisartan, and rosuvastatin. Sjogren's disease was well-managed with the only use of topical oral (saliva substitutes) and ocular (artificial tear drops) therapy. A few days after the booster dose with mRNA-1273 vaccine, the patient noticed erythema and edema localized at the injection site (right arm) for which she was unsuccessfully treated by her general partitioner with Cefixime 400 mg daily for 5 days. Thirty days after the first clinical signs, she came to our department and the dermatological examination revealed two small ulcers covered by serous crusts at the site of inoculation surrounded by an eczematous area (Figure 1A). The patient complained of mild lesion-localized pain but denied any systemic symptoms and no other dermatological lesions were observed. Routine tests (complete blood count, liver and renal function) were normal, C-reactive protein was slightly elevated (2 mg/dl; reference value <0.5 mg/dl). The histopathological exam revealed a superficial ulceration with epidermal reactive hyperplasia on the borders, vasodilatation, neoangiogenesis, fibroplasia, perivascular mononuclear infiltrate with occasional histiocytes and eosinophils. No signs of vasculitis or thrombosis were seen (Figure 1B). In the suspicion of a delayed cutaneous reaction to COVID-19 vaccine, we prescribed deflazacort 30 mg/day (tapered in 30 days) in order to accelerate the resolution of the ulcerative lesion and gentamicin cream twice a day to prevent a superinfection. A complete resolution was seen in 40 days.

Based on the mRNA-1273 Phase 3 trial, injection site events after the vaccination were mainly grade 1 (mild) or 2 (moderate) in severity and lasted only a few days later; the most common site event was pain.[1] Nevertheless, an increasing number of cases with delayed cutaneous reactions after mRNA-based vaccines against COVID19 have been reported. This delayed reaction is different from a local injection site reaction, characterized by local pain, redness, and swelling, usually observed the next few days after the injection. Instead, a delayed injection site reaction is characterized by erythema, pruritus, induration, and tenderness. In mRNA-1273 Phase 3 trial, delayed (defined as occurring on or after day 8) injection site reactions were reported only in 0.8% of the participants after the first dose and in 0.2% after the second dose.[1] Based on a case series of 414 patients with skin reactions to BNT162b2 and mRNA-1273 vaccines, the most common cutaneous reactions to mRNA-1273 were delayed large local reactions, followed by local injection site reactions, while no serious adverse event did develop. In this case series, 66% of the participants who received mRNA-1273 developed a delayed (with a mean of 7–8 days after the vaccination) large local reaction after the first dose, while second-dose delayed reactions generally occurred more quickly (mean of 1–3 days), were generally less intense and occurred only in 30% of the participants.[2] Differently, a smaller percentage of the participants who received BNT162b2 developed a delayed large cutaneous reaction, meaning only 15% after the first dose.[2] For now, there are no large studies in the literature describing skin reactions after the third dose, especially in patients who have received more than one type of vaccine. The etiopathogenesis of these delayed large local reactions due to the mRNA-1273 is still unclear. A T-c0ell-mediated delayed-type hypersensitivity reaction, as postulated by previous publications,[3,6] possibly related to a vaccine excipient, lipid nanoparticle, or mRNA component is a possible explanation.[2–5] As to our patient, she could have already been sensitized to mRNA component from her two previous doses; this could explain the more quickly and severe reaction after the third dose. Concerning the histopathological findings of these delayed large local reactions, one previous study described a mild predominantly perivascular and focal interstitial mixed infiltrate with lymphocytes and eosinophils.[3] Similar to our observation, other two papers demonstrated a perivascular and interstitial inflammatory infiltrate composed mainly by lymphocytes with rare eosinophils.[6,7]

Francesca Barei and Dario A. Marletta contributed equally to this work.

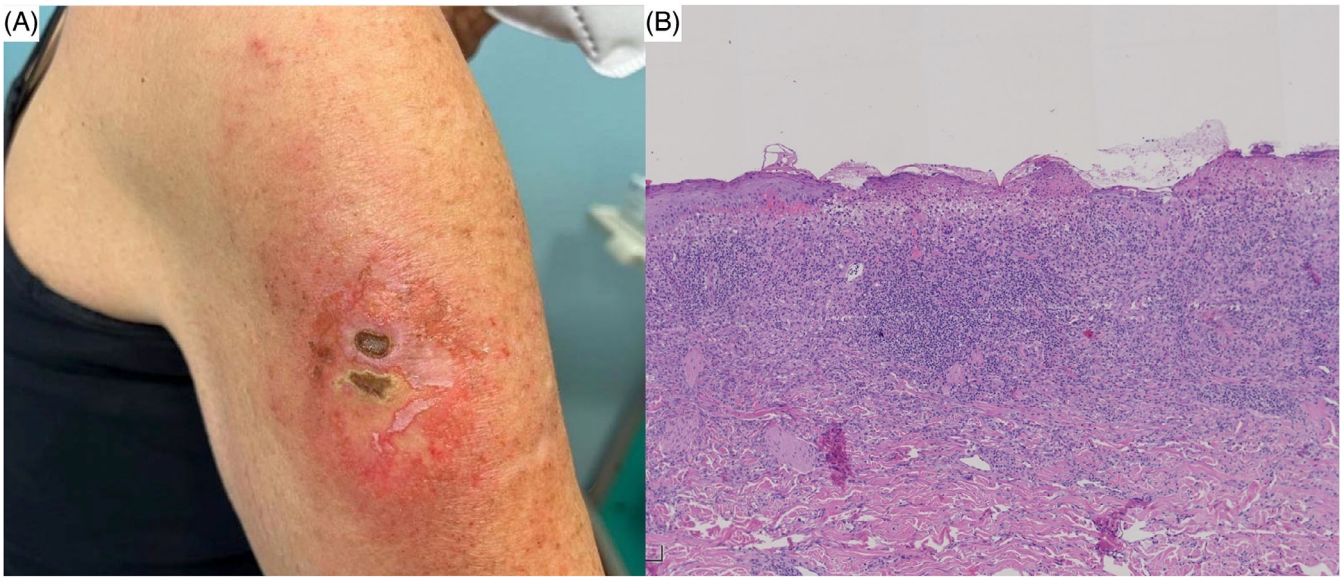

FIGURE 1 (A,B) Dermatological examination (about 30 days after the injection) revealed two small ulcerative lesions covered by serous crusts at the inoculation site associated with a surrounding eczematous reaction (A). Histopathological exam (H&E stain) reveling epidermal superficial ulceration with epidermal reactive hyperplasia on the borders, vasodilatation, neoangiogenesis, fibroplasia, perivascular mononucleous infiltrate with occasional histiocytes and eosinophils (B)

With regard to severe injection site reactions after COVID-19 vaccine, purpura fulminans-like lesions that occurred 4 weeks after mRNA-1273 in a 77-year-old woman and skin ulceration that occurred a few days after BNT162b2 in a 79-year-old man have been reported.[8,9] In the prior case, the patient suffered from rheumatoid arthritis, while a diagnosis of Sjögren's disease was reported in our anamnesis. Patients with a pre-existing autoimmune or inflammatory background could be more susceptible to more severe cutaneous reactions owing to a more overreactive immunologic system. Also, it is known that clinical trials showed that COVID-19 vaccination elicits a T-helper 1 (Th1) response, increasing the serum levels of interleukin 2, tumor necrosis factor-α and Interferon-c.[10–13] Obviously, further studies are needed to elucidate the underlying mechanisms responsible for COVID-19 vaccine-related cutaneous reactions. To the best of our knowledge, this is the first case of ulcerative injection site reaction after mRNA-1273. Nevertheless, cutaneous reactions associated with COVID-19 vaccines are generally minor and self-limited and should not discourage vaccinations.

AUTHOR CONTRIBUTIONS

Dario A. Marletta and Francesca Barei, both as first authors, have contributed equally to the conception, realization, and writing the paper; Giovanni Genovese and Angelo V. Marzano have revised the manuscript; Carlo A. Maronese and Ignasi Marti-Marti have contributed to collect data and participate to conception.

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Written informed consent from the patient, for the use of image and publication of his case detail, has been obtained.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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