Erythema multiforme-like papules after COVID vaccine administration

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Abstract

A unique dermatopathology incident arose after administration of the mRNA-1273 SARS-CoV-2 (Moderna) vaccine. Specifically, a transient purpuric interface dermatitis occurred 5 days post-second vaccine with the presentation of erythematous papules with erythema multiforme-type findings. A patient developed purpuric interface dermatitis with micro-vesiculation post-vaccination which ultimately resolved without sequelae.

Keywords: COVID-19, interface dermatitis, micro-vesiculation, purpuric, vaccine reaction

Introduction

To date, over 1,000,000 people in the United States have succumbed to SARS-CoV-2 with more than 33 million diagnoses being reported [1]. The administration of the BNT162b2 (Pfizer) and mRNA-1273 SARS-CoV-2 (Moderna) vaccine, which are generally regarded as safe, should be monitored closely for possible cutaneous reactions. We are becoming more familiar with the dermatologic manifestations of SARS-CoV-2, but there is a paucity of information regarding any adverse cutaneous manifestations from the aforementioned vaccines. This report will describe a new eruption secondary to the mRNA-1273 SARS-CoV-2 vaccine with an atypical pathologic picture—that of a purpuric interface dermatitis with micro-vesiculation.

Case Synopsis

A 51-year-old woman ophthalmologist presented with approximately 20 erythematous, 2-4mm papules of both legs and right lower thigh (**Figure 1**) which began their appearance 5 days after her second dose of the mRNA-1273 SARS-CoV-2 vaccine. Six days later she sought dermatologic consultation for these asymptomatic lesions. She had a low-grade fever and myalgias for 24 hours after her vaccine administration but otherwise was in good health and her only medication was levothyroxine for hypothyroidism for many years. She denied any other medications, allergies, or significant past medical history. Review of systems was unremarkable.

A dermatological examination revealed multiple, nontender, erythematous papules of the legs and right thigh. There was no lymphadenopathy. A shave biopsy was performed on the right posterior ankle (**Figure 2**). H&E staining revealed purpuric interface dermatitis with extravasated erythrocytes in dermal papillae and an infiltrate of lymphocytes and neutrophils, vacuolar alteration of basal

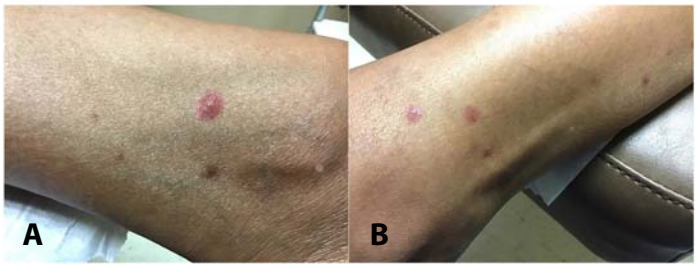

Figure 1. *Lesions on **A)** right ankle; **B)** left ankle-leg.*

keratinocytes, and necrosis of single and clustered squamous keratinocytes surrounding a 1.2mm vesicle. Deeper level sections and melanoma-associated antigen recognized by T cells 1 (MART1) staining failed to demonstrate melanocyte proliferation or neoplasm. Periodic acid-Schiff-Alcian blue stains failed to reveal fungal hyphae. The basement membrane was normal. Immunohistochemical stain to SARS-CoV-2 spike protein failed to react (SARS-CoV-2 Antibody Bio SB catalog# BSB-3701-3 Mouse Monoclonal Clone: BSB-134, Santa Barbara, CA).

Treatment options including topical corticosteroids, topical immunomodulators, oral corticosteroids, or antihistamines were declined by the patient as the lesions were asymptomatic. She subsequently chose to use topical halobetasol lotion daily which had no demonstrable effect. Several lesions continued to develop but over the course of three weeks the lesions slowly resolved without scarring or residua.

Case Discussion

The erythema multiforme-like pathological findings were atypical given the morphology of the lesions. Erythema multiforme frequently occurs due to an infiltrate of lymphocytes, as a result of medications and also from vaccines [2]. There have been documented cases of erythema multiforme presenting as both a dermatological manifestation of SARS-CoV-2 as well as from other vaccines, but a similar reaction for a SARS-CoV-2 vaccine has yet to be reported until now [2,3], to the best of our knowledge.

The mechanism of a vaccine-induced erythema multiforme-like reaction is not well understood [4,5].

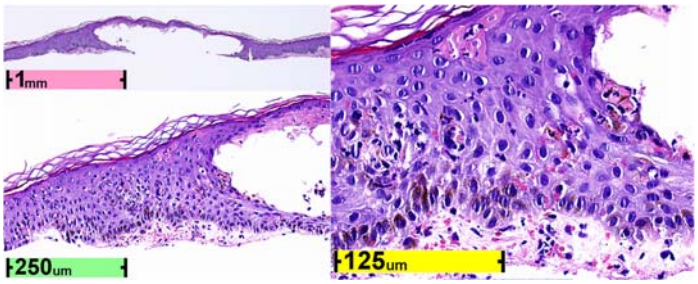

Figure 2. *H&E histopathology. Right ankle shave biopsy with 1.2mm intra-epidermal vesicle with exocytosis of lymphocytes and single necrotic keratinocytes.*

Erythema multiforme has been studied in the context of herpes simplex virus (HSV); specifically in HSV, a nonspecific pro-inflammatory cascade is initiated by autoreactive T cells, leading to cytokine production that causes a histopathological appearance of hypersensitivity-like reaction [6]. Within the context of HSV, the viral DNA is trafficked into the epidermis by viral DNA fragment-containing immune cells such as $CD34^+$ Langerhans cell precursors, monocytes, and macrophages [6]. The $CD34^+$ Langerhans cell precursors can upregulate cutaneous lymphocyte-associated (CLA) antigen, an epitope that interacts with, and binds to vascular lectin endothelial cell-leukocyte adhesion molecule one (ELAM-1), possibly leading to T cell infiltration to dermal endothelial cells causing a subsequent inflammatory response [6-8]. Although speculative, it may be possible a similar mechanism is occurring with cutaneous mRNA vaccine reactions whereby viral mRNA could be trafficked, and reacted to, with similar mechanisms. Conversely, it may be possible that there is an antigen-antibody complex deposition leading to a type III hypersensitivity reaction.

Corticosteroids systemically may likely clear the lesions but may also impair the immune response. Topical corticosteroids or topical immunomodulators are a suitable treatment if desired by the patient. Similar eruptions due to mRNA vaccines are likely and being aware that these can mimic erythema multiforme histopathologically may allow a prompt diagnosis, and minimize the medical expense of pursuing a diagnosis of erythema multiforme.

Cutaneous reactions to the COVID-19 vaccine have been reviewed recently by McMahon et al. (2022) and have documented these presentations as vaccine-related eruption of papules and plaques "V-REPP" [9]. Our case fits under the category of V-REPP based on the timing and clinical papules in this patient despite the histopathological features of erythema multiforme.

In the review by McMahon et al. (2022), the authors reviewed 58 biopsy reports and made the classifications of 1) robust, 2) moderate, and 3) mild V-REPP [9]. Respectively, these classifications were

determined by: 1) "marked spongiosis with intra-epidermal vesicles with little to no interface changes;" 2) "moderate spongiosis occurring more frequently than interface changes;" and 3) "mild spongiosis with more interface changes" [9]. Moreover, the authors found that of the patients with erythema multiforme (N=1) and Stevens-Johnson Syndrome (N=1), both received the mRNA-1273 SARS-CoV-2 vaccine, as did our patient [9]. The reactions while widespread, involved arms and hands especially [9]. Our case is a papular presentation with prominent spongiosis, 1.2mm microvesicles, and single cell keratinocyte necrosis-like erythema multiforme which does not fit neatly in the criteria of V-REPP.

In 2021, McMahon et al. also reported cases of erythema multiforme, among other dermatological manifestations from the mRNA-1273/BNT162b2 vaccines [10]. In this review, 1.1% of cases (N=3) developed erythema multiforme after the first dose of mRNA-1273 while 0 cases were reported after the second dose [10]. There were no reports of erythema multiforme from the BNT162b2 vaccine [10]. Conversely, Lavery et al. (2021) reported a case of erythema multiforme 12 hours after the first BNT162b2 vaccine [11]. This patient had a history of prior erythema multiforme eruptions coinciding with herpes labialis episodes [11]. Following the BNT162b2 vaccine, the patient developed bilateral erythematous concentric targetoid plaques on plantar surface of the hands and feet [11]. A similar reaction took place 24 hours after administration of the second dose of BNT162b2 [11].

Another case series showing erythema multiforme-like reactions from the mRNA-1273/BNT162b2 vaccines was also performed by Karatas et al. (2022), [5]. The four patients reviewed developed: 1) scattered, nontender erythematous targetoid plaques across the extremities, trunk, and face 10 days post-first mRNA-1273 vaccine; 2) erythematous targetoid lesions across the extremities three days post-second BNT162b2 vaccine; 3) erythematous targetoid plaques across the extremities and trunk 5 days post-second BNT162b2 vaccine; and 4) erythematous targetoid plaques across the extremities two days post-second mRNA-1273 vaccine [5]. Histopathological findings from the first and fourth patient revealed a vacuolar interface dermatitis with necrotic keratinocytes and interface dermatitis, respectively [5]. These cases also did not report microvesiculation as a feature of the erythema multiforme reactions [5].

Similar to the case described by Lavery et al. (2021), Kim et al. (2021) reported a targetoid, pruritic erythematous rash that erupted 10 days post-first BNT162b2 vaccination [4]. These reported plaques were diffuse across the patient's entire body [4]. Necrotic keratinocytes, lymphocytic infiltrate into the dermal-epidermal junction, and subepidermal blistering were revealed upon histopathological examination [4]. On the other hand, Bujan Bonino et al. (2021) reported an atypical erythema multiforme 6 days post-second BNT162b2 vaccination [12]. The patient developed erythematous plaques over the injection site at the left deltoid which spread to the back and extremities [12]. Histopathological examination revealed superficial dermal and intraepidermal lymphocytic infiltrate and dyskeratosis of grouped keratinocytes that were not confined to the basal layer [12]. Interestingly, microvesiculation was not a feature of these reported cases [4,12].

Overall, this case is among the first to include micro-vesiculation and histopathological erythema multiforme with a papular presentation following administration of the mRNA-1273 vaccine. The presence of necrotic keratinocytes and neutrophils in the epidermal layer supports the erythema multiforme pathology. The interface changes of the microvesiculation appear to fit, at least partially, the characteristics of the robust V-REPP reaction suggested by McMahon et al. (2022), [9].

Conclusion

This case sheds light on a novel dermatological vaccine reaction with unique characteristics to the best of our knowledge was not previously reported elsewhere. The eventual resolution of these lesions, its onset at 5 days post-vaccination, and the lack of symptoms hopefully will allow the physician to assure the patient that these lesions may not progress like erythema multiforme or Stevens-Johnson syndrome/toxic epidermal necrolysis but

are an atypical pathologic response to the mRNA vaccine and will likely resolve without sequelae.

Potential conflicts of interest

The authors declare no conflicts of interest.

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