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CASE SERIES

Erythema multiforme reactions after Pfizer/BioNTech (BNT162b2) and Moderna (mRNA-1273) COVID-19 vaccination: A case series

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Key words: COVID-19 vaccination; cutaneous adverse events; erythema multiforme.

INTRODUCTION

Pfizer/BioNTech (BNT162b2) and Moderna (mRNA-1273) COVID-19 vaccines were approved for emergency use by the Food and Drug Administration in December 2020. Clinical trials of both vaccines reported no safety concerns other than a few local and systemic reactions.[1,2] Overall, these reported reactions were transient and resolved within a couple of days.[2] The most common cutaneous reaction reported was a delayed local injection-site reaction after the first vaccine dose, primarily after the mRNA-1273 COVID-19 vaccine (94%).[3]

Here we present 4 cases of erythema multiforme (EM) after administration of COVID-19 vaccines.

Abbreviations used:

EM: erythema multiforme
HSV: herpes simplex virus
SJS: Stevens-Johnson syndrome
TEN: toxic epidermal necrolysis

CASE SERIES

Case 1

A 61-year–old man with a past medical history of Crohn's disease who was taking 6-mercaptopurine and adalimumab presented with a rash that started with bilateral periorbital swelling associated with redness in both eyes and nontender red lesions on the face with painful sores on the lips and mouth. His rash progressed to involve the trunk and extremities, including the palms. He had painful mouth lesions that caused dysphagia but denied having any other pain or pruritus. The genital mucosa was not affected. He denied having fever, chills, recent illness, new medications, or sick contacts. He received the first dose of the mRNA-1273 COVID-19 vaccine 10 days before the onset of symptoms.

Physical examination revealed scattered, nontender, erythematous, targetoid plaques on the face, trunk, and extremities, including the palms and soles (Fig 1). He also had bilateral conjunctival erythema with multiple vesicles and erosions in the oral mucosa.

Laboratory findings were notable for negative COVID-19 polymerase chain reaction, syphilis serology, HIV antibody, herpes simplex virus (HSV) and varicella zoster virus polymerase chain reaction, antinuclear antibody panel, and serologic antibody tests consistent with previous HSV and coxsackievirus infections. Histopathologic analysis revealed a vacuolar interface dermatitis with occasional necrotic keratinocytes and a superficial perivascular inflammatory infiltrate with scattered eosinophils (Fig 2).

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Funding sources: None.

IRB approval status:

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JAAD Case Reports 2022;■■:■-■.
2352-5126

https://doi.org/10.1016/j.jdcr.2021.12.002

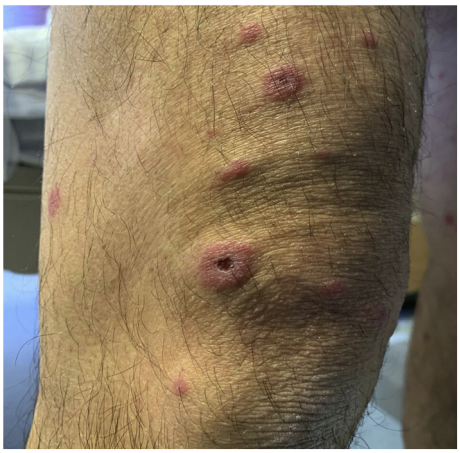

Fig 1. Well-demarcated, edematous targetoid papules and plaques around the knee.

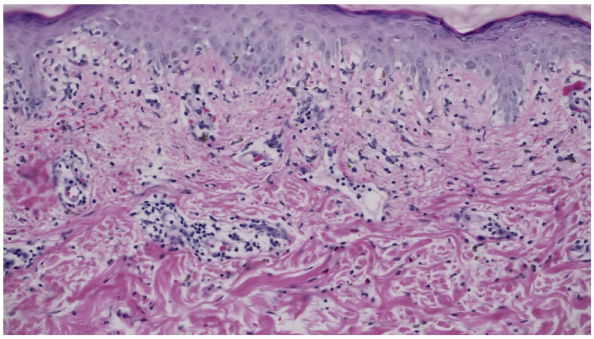

Fig 2. Punch biopsy specimen from the trunk showing vacuolar interface changes with occasional eosinophils. (Hematoxylin-eosin stain; original magnification: ×20.)

The patient received a clinical and histologic diagnosis of EM major with extensive oral and nasal involvement. Other triggers of EM were ruled out, including recent HSV infection, and the vaccine was determined to be the most likely causative factor. Based on this conclusion and the severity of his reaction, he was advised not to get the second dose of the vaccine. The patient was managed with symptomatic treatment, and his rash and symptoms resolved.

Case 2

A 21-year−old woman with no past medical history presented with severe itching and a rash that started on the hands and feet and spread to the extremities 3 days after the second dose of BNT162b2 COVID-19 vaccine. It was accompanied by swelling of her hands and feet and some joint discomfort. The patient denied having a history of allergies, HSV infection, or new medications. The course after the first dose of vaccine was uneventful, and the patient reported multiple negative

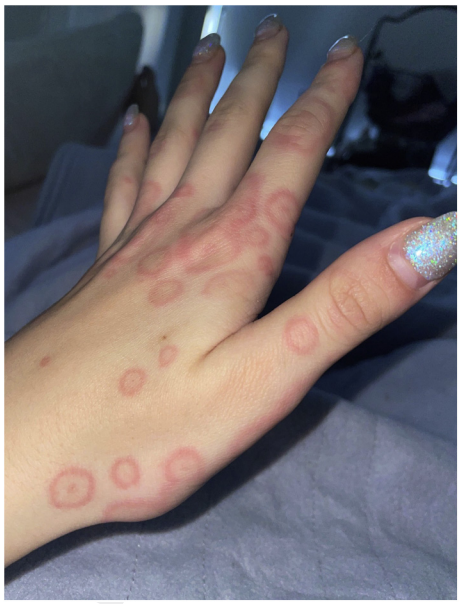

Fig 3. Erythematous targetoid plaques on the hand.

COVID-19 tests before and after the eruption. She was initially examined in urgent care and presumed to have a viral or bacterial infection, and she was treated with empiric doxycycline, azithromycin, and acetaminophen.

Physical examination revealed generalized targetoid lesions on the extremities, including the palms and soles, with rare lesions on the trunk (Fig 3). There was no mucosal or nail involvement.

The patient received a clinical diagnosis of EM secondary to the COVID-19 vaccine, given the classic targetoid skin lesions and temporal relationship to vaccination. She was started on a prednisone taper, and the antibiotics were discontinued; her rash and symptoms resolved.

Case 3

A 50-year−old man with a past medical history of hyperlipidemia and anxiety disorder presented with a worsening rash associated with pruritus for 4 days. The patient reported that he experienced changes in his voice, difficulty swallowing, shortness of breath, fatigue, a fever that improved with ibuprofen, and an episode of chest pain on the previous evening. He had been exposed to his son, who had tested positive for COVID-19 11 days previously, but multiple COVID-19 tests in the interim were negative. He had received the second dose of the BNT162b2 COVID-19 vaccine 5 days before the onset of symptoms.

Physical examination was significant for erythematous targetoid plaques on the trunk and extremities, bullae on the palmoplantar skin, and hemorrhagic Q9

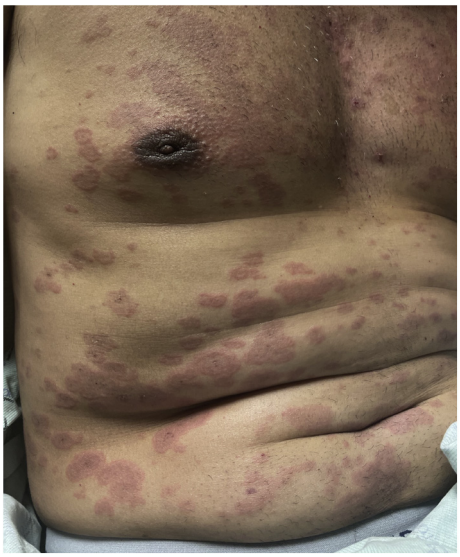

Fig 4. Erythematous targetoid plaques on the trunk.

crusts on the oral mucosa (Fig 4). Llaboratory findings were significant for elevated erythrocyte sedimentation rate and C-reactive protein, negative HSV and varicella zoster virus polymerase chain reaction, and negative mycoplasma immunoglobulin M. Serologic antibody tests were consistent with previous Epstein-Barr virus and HSV infections.

The patient received a diagnosis of EM secondary to the COVID-19 vaccine, given the recent exposure to the vaccine and no evidence of other etiologies. He was advised to start using a topical corticosteroid in addition to a prednisone taper that had been started 2 days earlier in the emergency department. His symptoms and rash subsequently resolved.

Case 4

A 53-year−old woman with a past medical history of diet-controlled type 2 diabetes mellitus and multinodular goiter presented with a 3-week history of a rash associated with pruritus on her hands, arms, and legs. She had no history of recent illness or new medications. She denied having a previous history of herpes infection. However, she had received the second dose of the mRNA-1273 COVID-19 vaccine 2 days before the onset of symptoms.

Physical examination revealed erythematous targetoid plaques on the dorsum of the hands and extremities (Fig 5). There was no mucosal involvement. Laboratory findings were significant for previous HSV-1 and HSV-2 infections. Histopathologic analysis revealed interface dermatitis.

Based on the clinical and histologic findings and the temporal association with the vaccine, the patient received a diagnosis of EM secondary to

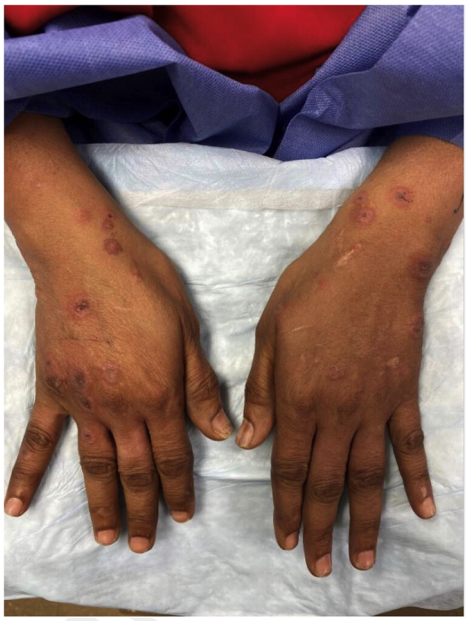

Fig 5. Erythematous targetoid plaques on the dorsum of the bilateral hands.

the COVID-19 vaccine. She was advised to start using a topical corticosteroid, and her rash and symptoms improved.

DISCUSSION

Cutaneous adverse events are among the most commonly reported adverse events after vaccination; however, they are typically limited to redness, swelling, and tenderness at the injection site. They can occur in up to 90% of people who receive vaccinations.[4]

EM is an acute, immune-mediated, mucocutaneous disorder.[5] Infections have been found to be the underlying cause in approximately 90% of cases, most commonly HSV infection in adults and *Mycoplasma pneumoniae* in children.[6]

Su et al[7] reviewed the Vaccine Adverse Event Reporting System in the United States for EM/Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) reactions from 1999 to 2017. Although over half (51%) of reported EM/SJS/TEN reactions were seen in children, with a median age of 3 years, it is notable that almost half occurred in adults, despite adults receiving far fewer vaccines than children. The most common vaccines associated with EM/SJS/TEN reactions were measles, mumps, and rubella vaccine (22%), diphtheria, tetanus toxoids, and acellular pertussis vaccine (18%), varicella zoster virus (18%), and 7-valent pneumococcal conjugate (13%) vaccines. Among the vaccines that require only a single dose, smallpox (16%), trivalent inactivated influenza (15%), and

varicella (7%) were the most common vaccines associated with an EM/SJS/TEN reaction.[7] EM cases were not reported separately from SJS/TEN.[7]

In addition to our cases, McMahon et al[3] reported 3 other cases of EM associated with the first dose of the mRNA-1273 COVID-19 vaccine. They reviewed 414 patients in whom cutaneous reactions developed after COVID-19 vaccine administration. The most commonly reported cutaneous reaction was a delayed, large, local-site reaction that was followed by erythromelalgia, a morbilliform eruption, and urticaria.[3] It should also be noted that Lavery et al[8] reported flaring of pre-existing EM after the BNT162b2 COVID-19 vaccine.

The pathogenic mechanism of EM after infection is thought to be a cell-mediated immune reaction with activation of T helper cells and cytokine production, resulting in a robust mucocutaneous inflammatory response.[9] The mechanism of EM after vaccination is not entirely clear, but it is likely to be a similar mechanism. It is not known if there is a specific vaccine antigen that triggers the eruption or if it is the effect of other ingredients within the vaccine. With widespread COVID-19 vaccination under way, more information will emerge about the relationship of EM to COVID-19 vaccination.

Conflicts of interest

None disclosed.

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