

Review

Stevens–Johnson syndrome precipitated by Moderna Inc. COVID-19 vaccine: a case-based review of literature comparing vaccine and drug-induced Stevens–Johnson syndrome/toxic epidermal necrolysis

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Introduction

The Moderna COVID-19 vaccination was approved for use in the United States in December of 2020¹ and since that time massive public health efforts have been made to vaccinate patients against COVID-19 infection. Adverse reactions from the vaccination are well-reported and include both local skin reactions, such as pain, swelling, and erythema at the injection site, as well as systemic reactions including fever, malaise, headache, muscle aches, drowsiness, nausea, and vomiting. Rarely, anaphylaxis and myocarditis have occurred. Although serious adverse events such as Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) are rare, two cases have now been reported after the COVID-19 vaccination. We

Abstract

The Moderna COVID-19 vaccination was approved for use in the United States in December of 2020¹ and since that time massive public health efforts have been made to vaccinate patients against the COVID-19 infection. Adverse reactions from the vaccination are well-reported and include both local skin reactions, such as pain, swelling, and erythema at the injection site, as well as systemic reactions including fever, malaise, headache, muscle aches, drowsiness, nausea, and vomiting. While severe serious cutaneous adverse reactions, such as Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), remain rare; two cases of SJS/TEN related to COVID-19 vaccination have been reported. We herein review the two previously reported cases of SJS/TEN and report the first case of SJS precipitated by the Moderna Inc., MRNA 1273 COVID-19 vaccination in the United States. Although we review potential adverse reactions to vaccination, the benefits of COVID-19 vaccination outweigh the risks based on current data. Cases should be reported to the Vaccine Adverse Event Reporting System (<https://vaers.hhs.gov/>) to help public health officials recognize and track these severe but rare adverse events.

present the third case and perform a case-based review of vaccine vs. drug-induced SJS/TEN.

Case

A 46-year-old Ethiopian female with a medical history of diabetes mellitus type 2, hyperlipidemia, and obesity on chronic metformin and atorvastatin therapy received her first dose of COVID-19 vaccination (Moderna Inc., MRNA 1273). She remained asymptomatic the day of vaccination but the following day developed oral discomfort and mucosal sloughing. She presented to an outside hospital 3 days after vaccination with erosions of the mucous membranes. She received cetirizine 10 mg daily and prednisone 60 mg daily and was transferred to our

hospital. On arrival, she was afebrile, and her vitals were stable. Physical exam revealed: dusky, pink-purple plaques on her eyelids and cheeks; nasal and oral mucosal sloughing (Fig. 1a,b); small, dusky, purple papules coalescing into plaques across her trunk and arms (Fig. 2a,b); and violaceous annular lesions on her palms and soles (Fig. 3a,b) totaling roughly 20% body surface area. There was no obvious vaginal sloughing, but she did report vaginal discomfort. She denied any other recent illnesses, fever, chills, congestion, sore throat, or cough. She had no history of HSV infection or cold sores. She denied any changes to chronic medications, having been on the same regimen for several years, and reported no other supplemental/as-needed medications, vitamins, nutritional supplements, or NSAID use in the preceding month.

Laboratory workup included BMP and CBC, which were entirely within the reference range. CBC revealed WBC: 7.9 (*N* 4.00–10.00 k/cmm), Abs Neutrophil: 5.5 (*N* 1.70–7.0 k/cmm), Abs Lymphocyte: 1.7, (*N* 0.90–2.9 k/cmm), Abs Eosinophil: 0.01 (*N* < 0.50 k/cmm) and Abs Basophil: 0.020 (*N* < 0.30 k/cmm). Labs otherwise revealed an elevated CRP at 91.38 (*N* < 5.0), negative HIV, hepatitis B, hepatitis C, and tuberculosis screenings. HSV IgM antibody titers were negative with detectable IgG antibody titers. Oral swabs for HSV-1, HSV-2, and varicella were negative. Mycoplasma antibody profile similarly returned negative for IgM antibody and positive IgG

antibody suggesting prior exposure. COVID-19 PCR nasal swab was negative. Chest x-ray was normal without infiltrates.

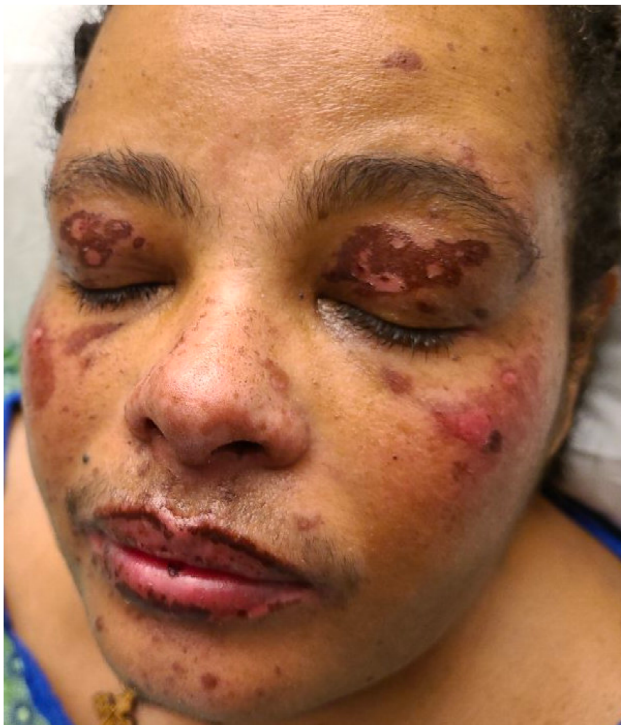
Biopsy of the right forearm revealed confluent and full-thickness necrosis of the epidermis with a basket weave-type stratum corneum, sparse mild perivascular infiltrate of lymphocytes in the dermis, consistent with SJS/TEN (Fig. 4a–c). She was started on prednisone 80 mg daily and clobetasol 0.05% ointment twice daily. She began to see improvement on this regimen and after 6 days was discharged to home on a prednisone taper and continued topical clobetasol 0.05% ointment.

After obtaining written consent from the patient for publication of the case and photos, a literature review was performed. A literature review was conducted using the NCBI database (PMC and PubMed filters) using the keywords “Stevens Johnson Syndrome,” “SJS,” “SJS/TEN,” “TEN,” “bullous,” and “COVID vaccination.” Parameters were expanded to include literature from any date. The literature review identified two previously documented cases of SJS/TEN related to COVID vaccination.

Discussion and case review

The COVID-19 pandemic has resulted in mass fatalities while efforts for prompt, global vaccinations remain underway. Skin reactions related to COVID-19 vaccinations are uncommon. McMahon et al. reviewed cutaneous reactions in 414 patients

(a)



(b)

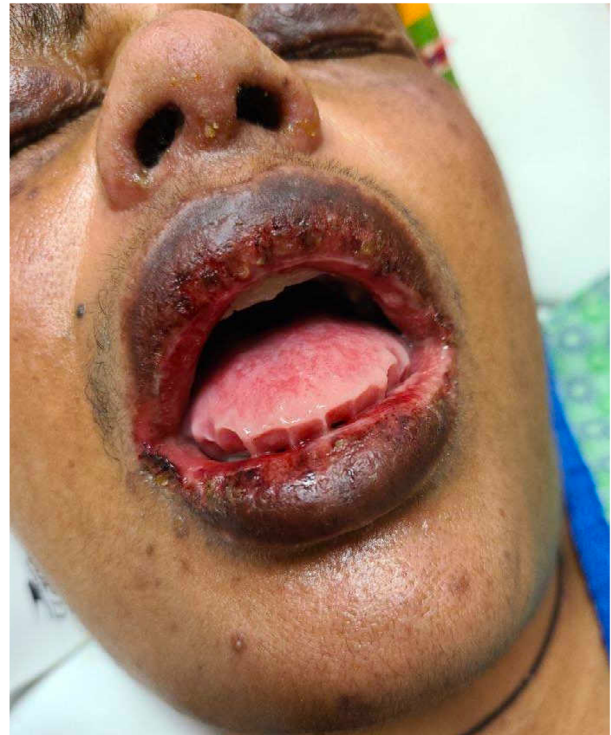


Figure 1 (a) Clinical photograph of patient's face showing dusky, pink-purple plaques on her eyelids and cheeks with nasal and oral mucosal sloughing. (b) Clinical photograph of patient's face revealing nasal and oral mucosal sloughing



Figure 2 (a) Clinical photograph of patient's trunk showing small, dusky, purple papules coalescing into plaques. (b) Clinical photograph of patient's arms showing small, dusky, purple papules coalescing into plaques across arms

who received either the Moderna (83%) or Pfizer-BioNTech (17%) mRNA vaccine.² The most common reactions, in order, included delayed large local reactions, local injection site reactions, urticarial eruptions, and morbilliform eruptions.^{2,3} Gambichler et al. reported a case of erythema multiforme (EM) in an elderly patient after receiving the BNT162b2 mRNA COVID-19 vaccination in Germany.⁴ No other cases of EM post COVID-19 vaccination have been reported. Kong et al. reported a case of a bullous eruption post second dose of the Moderna vaccination that did not meet diagnostic criteria for SJS/TEN given no mucosal involvement.⁵ Elborae et al. and Dash et al. both reported cases of SJS post COVID vaccination (Table 1).^{6,7}

In assessing the three cases noted in Table 1, the age of patients affected ranged from 46 to 60, and time to diagnosis ranged from 3 to 5 days with an average time to the diagnosis of about 3.5 days. Two cases had no new exposure to medications while one case did not specifically comment on any new

exposures. In terms of clinical and histological findings, all cases had mucosal involvement, although there was no cutaneous involvement in the case reported by Elborae et al., and the pathologic findings outlined by Dash et al. are also not classic for SJS/TEN. Two cases were treated with prednisone while one case was treated with cyclosporine. All patients improved after treatment (Table 1).^{6,7}

Vaccine-induced SJS/TEN to any vaccine is exceedingly rare with cases in the literature consisting mostly of single case reports or very small case series. Many vaccines have been implicated: Influenza, smallpox, anthrax, tetanus, measles-mumps-rubella (MMR), hepatitis B (HepB), human papillomavirus (HPV), varicella, meningococcal B, Hemophilus influenzae type B (HiB), diphtheria-pertussis-tetanus (DPT), polio, rabies, H1N1, and hantavirus vaccines.⁸⁻¹¹ It has not been elucidated whether the antigen (active ingredient) is responsible for the reaction or if other vaccine components play a primary role



Figure 3 (a) Clinical photographs of palms showing violaceous annular lesions. (b) Clinical photographs of soles showing violaceous annular lesions

(inactive ingredients). Vaccine adjuvants, preservatives, and tissue fixatives, such as aluminum, thimerosal, and formaldehyde/formaldehyde-releasing preservatives, have been reported to cause allergic contact dermatitis-type delayed hypersensitivity reactions from vaccines⁸ but not SJS/TEN.^{12,13} The Moderna vaccine contains none of these aforementioned inactive ingredients; moreover, none of the ingredients in the vaccine have been previously reported as causing SJS/TEN (Table 2).

There are similarities but also notable differences between drug-induced SJS/TEN and vaccination-induced SJS/TEN. The clinical presentation of drug-induced and vaccine-induced SJS/TEN is similar with dusty red macules coalescing into patches, skin, and mucosal erosions.⁹ The least common manifestation of vaccine-induced SJS/TEN is a targetoid rash.⁹ Compared to drug-induced SJS/TEN where SJS is more common than TEN, in vaccine-induced, SJS and TEN appear to be equally likely to occur.^{12,13,16,17} The measles vaccine has been reported in cases of both SJS and TEN, and varicella, smallpox, anthrax, tetanus, and influenza vaccinations have been implicated in cases of SJS while MMR, hantavirus, and meningococcal B vaccinations have been implicated in cases of TEN,^{12,13,16,17} although it is difficult to definitively conclude this given the low number of vaccine-induced cases.^{9,16} In Chahlal, et al.'s review of 29 cases of vaccine-induced reactions after meningococcal B

vaccine, 22 presented as EM, six as SJS, and four as TEN.⁹ Perhaps the most notable difference is in the timeline of symptom development between drug-induced versus vaccine-induced SJS/TEN. Symptoms of drug-induced SJS/TEN typically begin 2–3 weeks post medication administration; however, in post-vaccine exposure, the timeline is shorter with the eruption beginning 1–8 days after administration, with 3–5 days being typical.^{9,14,18} To date, cases reported of SJS/TEN presented on average ~3.5 days post vaccination fitting this timeline.

Lastly, patients have been reported to progress from an EM-like presentation to full TEN with vaccine-induced SJS/TEN, which is considered unlikely to occur with drug-induced SJS/TEN.⁹ We present a case of Stevens-Johnson Syndrome occurring after COVID-19 vaccination to increase awareness of this exceedingly rare potential adverse event. The benefits of vaccination outweigh risks based on current data, and patients should continue to be vaccinated. Adverse events, however, should be reported to the Vaccine Adverse Event Reporting System (<https://vaers.hhs.gov/>) to help public health officials recognize and track these severe but rare adverse events.^{11,14,15}

Conflict of interest

None declared.

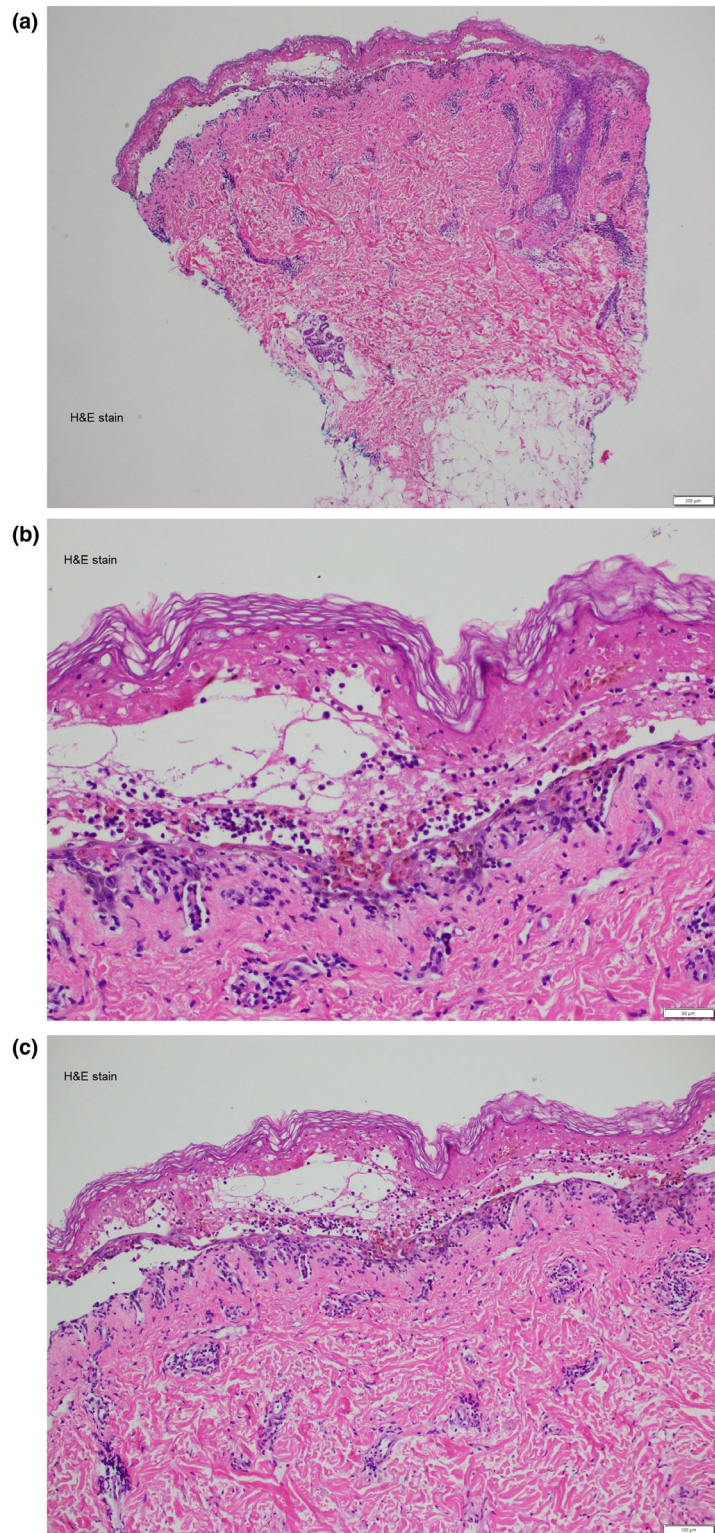


Figure 4 Histopathologic examination of right forearm skin biopsy. (a) Histopathologic slide from right forearm showing separation of the epidermis and dermis with mild chronic inflammation composed predominately of lymphocytes (hematoxylin and eosin stain x20). (b) Histopathologic slide from right forearm (hematoxylin and eosin, x100). (c) Histopathologic slide from right forearm (hematoxylin and eosin, x200). (b, c) reveal overlying confluent and full-thickness necrosis of epidermis associated with mild perivascular infiltrate of lymphocytes and a basket weave-type stratum corneum.

Table 1 Summary of demographics and clinical picture of patients with SJS/TEN reported post COVID-19 vaccination

Author	Elboraey et al. ⁶	Dash et al. ⁷	Present case, Padniewski et al.
Age	Middle aged	60	46
Gender	Female	Male	Female
Vaccine received	Pfizer-BioNTech	Not discussed	Moderna
Confounding medications	Not discussed	Teneligliptin, metformin, amlodipine (on all medications for >6 months)	Atorvastatin, metformin (on all medications for >1 year)
Onset	5 days post second dose	No new confounding medications reported	No new confounding medications reported
Examination findings	Large, red, bullae ~3 × 1.5 cm in left retromolar area, white-yellow patches to dorsal tongue surface, upper and lower lips; multiple large ulcers at buccal and labial mucosa, tongue, and palate	3 days post first dose	3 days post first dose
		Multiple purpuric macules all over the body with perilesional erythema; lesions coalesced into large sheets of necrosed skin throughout the trunk; scattered bullae; oral erosions, hemorrhagic crusting over lips, eye congestion, and erosions to glans	Multiple dusky, pink-purple plaques on her eyelids and cheeks; nasal and oral mucosal sloughing. Fig. 1 (a,b): small, dusky, purple papules coalescing into plaques across her trunk and arms Fig. 2 (a,b): and violaceous annular lesions on her palms and soles Fig. 3 (a,b)
Histology	Not obtained	Orthokeratosis with epidermal atrophy, moderate intraepidermal infiltration of lymphocytes and neutrophils with spongiosis; scattered degenerated apoptotic keratinocytes; patchy areas of basal cell degeneration; interface dermatitis with perivascular and periadnexal inflammatory cell infiltrate along with extravasation of erythrocytes in dermis	Confluent and full-thickness necrosis of the epidermis with a basket weave-type stratum corneum, sparse mild perivascular infiltrate of lymphocytes in the dermis, consistent with SJS/TEN (Fig. 4)
Treatment course	Oral prednisone 30 mg/day	Oral cyclosporine 300 mg/day Improvement after 7 days	Prednisone 80 mg daily clobetasol 0.05% ointment twice daily Improvement after 6 days

Table 2 Ingredients in the Moderna COVID-19 vaccine^{14,15}

Messenger ribonucleic acid (mRNA)
Lipids (SM-102)
Polyethylene glycol (PEG) 2000 dimyristoyl glycerol (DMG)
Cholesterol
1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
Tromethamine
Tromethamine hydrochloride
Acetic acid
Sodium acetate trihydrate
Sucrose

Reprint requests

Jessica Padniewski.

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