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SHORT REPORT

DERMATOLOGIC THERAPY WILEY

An extremely rare mucocutaneous adverse reaction following COVID-19 vaccination: Toxic epidermal necrolysis

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Abstract

Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), is a type of delayed hypersensitivity reaction that requires urgent medical intervention. In the COVID-19 era, COVID-19 vaccines are currently being widely administered and mucocutaneous adverse reactions following vaccination have been reported; however, severe cutaneous adverse reactions associated with COVID-19 vaccines including SJS/TEN, are extremely rare. Herein, we describe a case of COVID-19 vaccination induced TEN which developed 1 day after receiving the first dose of Sinopharm COVID-19 vaccine with favorable clinical outcome.

KEYWORDS
COVID-19, erythema multiforme, Lyell's syndrome, Stevens-Johnson syndrome, vaccination

1 | INTRODUCTION

Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), a distinct form of erythema multiforme, is a rare and potentially life-threatening delayed hypersensitivity reaction that affect the skin and mucous membranes. This entity is often drug related, although infections such as *Mycoplasma pneumonia* can also be the cause. The incidence is estimated to be 0.4–1.9 cases per million population per year worldwide and the mortality rate is approximately 25%–30%.[1–3] SJS/TEN are characterized by mucocutaneous tenderness and hemorrhagic erosions with erythema and epidermal detachment presenting as blisters and areas of denuded skin.[3] Vaccination-induced SJS/TEN is much more rare and reported with a number of vaccination.[4] Herein; we described a very rare case of COVID-19 vaccination induced TEN that developed 1 day after receiving the first dose of Sinopharm COVID-19 vaccine.

2 | CASE PRESENTATION

A 76-year-old man hospitalized with a history of skin lesions. He has received Sinopharm COVID-19 vaccine 1 day before the development of skin lesions and had no symptoms on the day of the vaccine injection. Three days before admission he had chills and anorexia as prodromal symptoms. Skin lesions affected the upper and lower limbs, trunk, face and also oral mucosa. The patient drug history included atorvastatin 10 mg/day taken for several years and had no history of taking any new medication before the development of the skin lesions. The patient has no history of drug or food allergies. On physical examination he was hemodynamically stable and evidence of blisters on the face, trunk, upper and lower extremities, conjunctivitis and also ulceration and erythema of the oral mucosa in addition to hemorrhagic crusting of the lips were obvious (Figures 1 and 2).

The body surface affected was 42%. The complete blood count showed a leukocyte count of 6100 cells/μl, a hemoglobin level of 11 g/dl, and a platelet count of 241,000 platelets/μl. Liver enzymes including aspartate aminotransferase was 90 IU/L and alanine aminotransferase was 82 IU/L. Renal function test was in normal range. Chest computed tomography was normal. IgM anti-HBC-Ab, HBS-Ag, and HCV-Ab were checked and all were negative. The biopsy of skin lesion was performed and histopathologic examination revealed skin tissues with erosive and necrotic sub-epidermal blister containing dense fibrinous exudate which covered by totally necrotic epidermal roof. Upper dermis showed sparse infiltrate of lymphocytic inflammatory cells around superficial blood vessels. Direct immunofluorescence test on the skin biopsy was negative for anti IgG, anti IgA, anti IgM, and anti C3, which revealed that the disorder was not due to

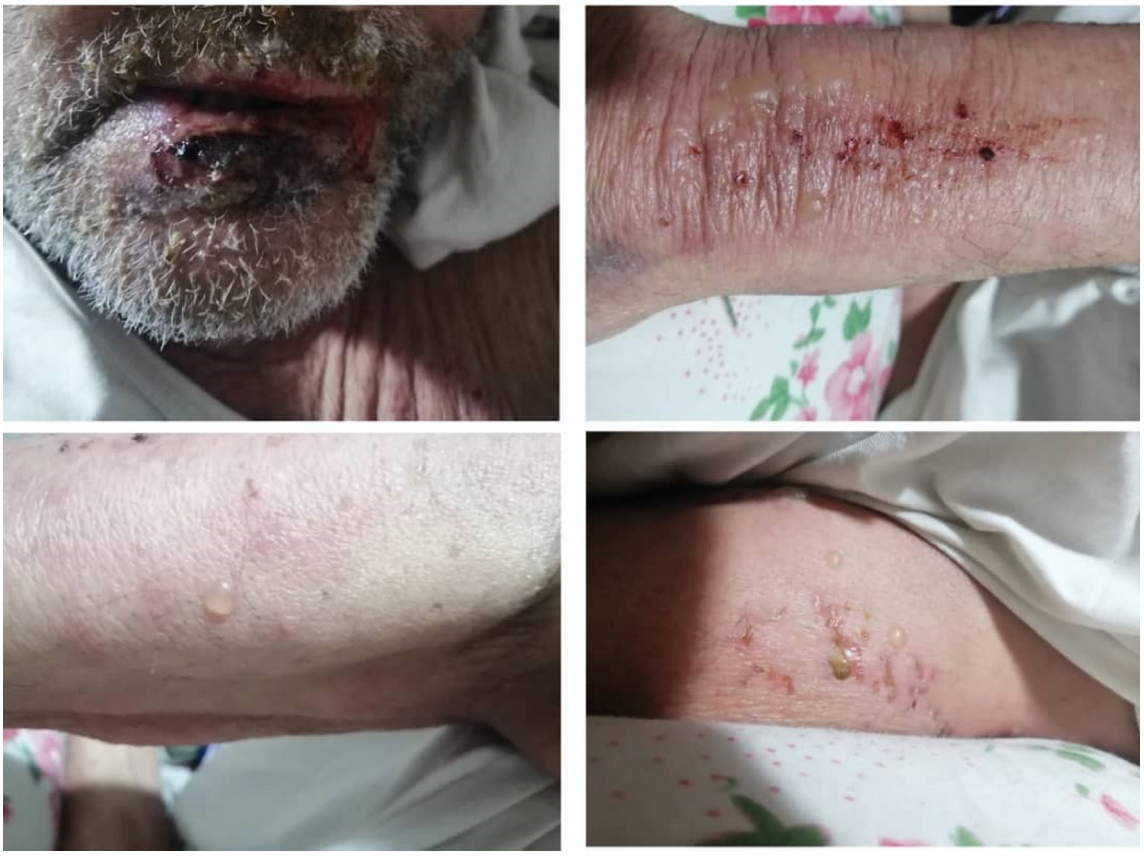

FIGURE 1 The figure shows blisters affecting the limbs and also ulceration in the oral cavity in addition to hemorrhagic crusting of the lips

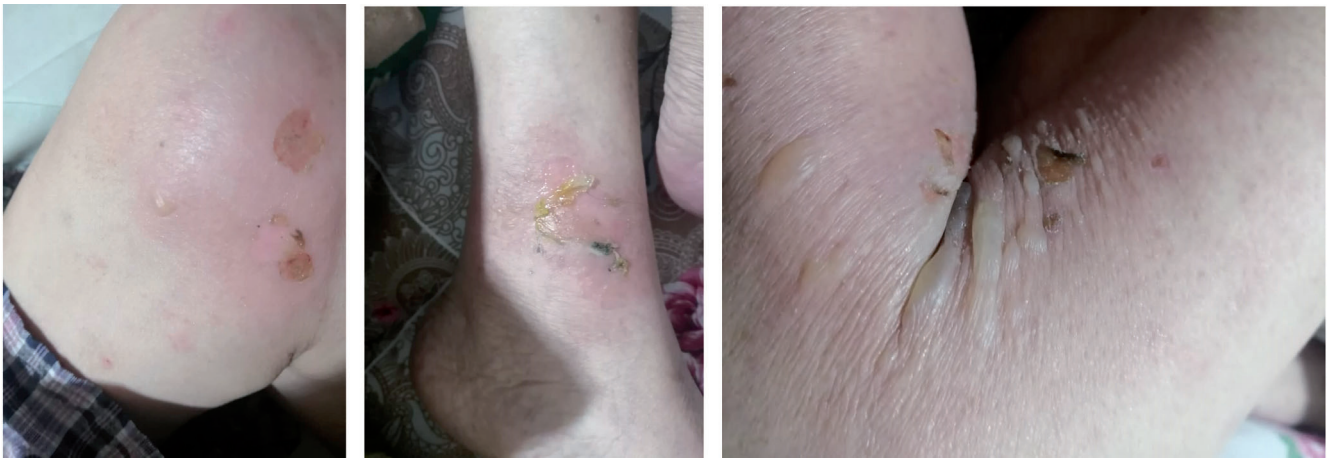

FIGURE 2 The figure shows flaccid blisters and areas of epidermal detachment

deposition of antibodies in the skin. According to the clinical examination and histopathologic result, the diagnosis of TEN was made (Figure 3). In addition to intravenous fluid replacement, the treatment was consisted of prednisolone and prepared mouthwash. Diphenhydramine-lidocaine-aluminum magnesium mouthwash and nystatin oral suspension prescribed as a conservative treatment for stomatitis. In addition, topical ointment consisted of clotrimazole, triamcinolone and mupirocin combination used for lip ulcer. The patient was discharged after 11 days. The mucocutaneous lesions were markedly resolved within 2 weeks.

3 | DISCUSSION

TEN is a medical emergency that requires urgent medical intervention. Lesions consist of targetoid lesions, diffuse erythema or macules with

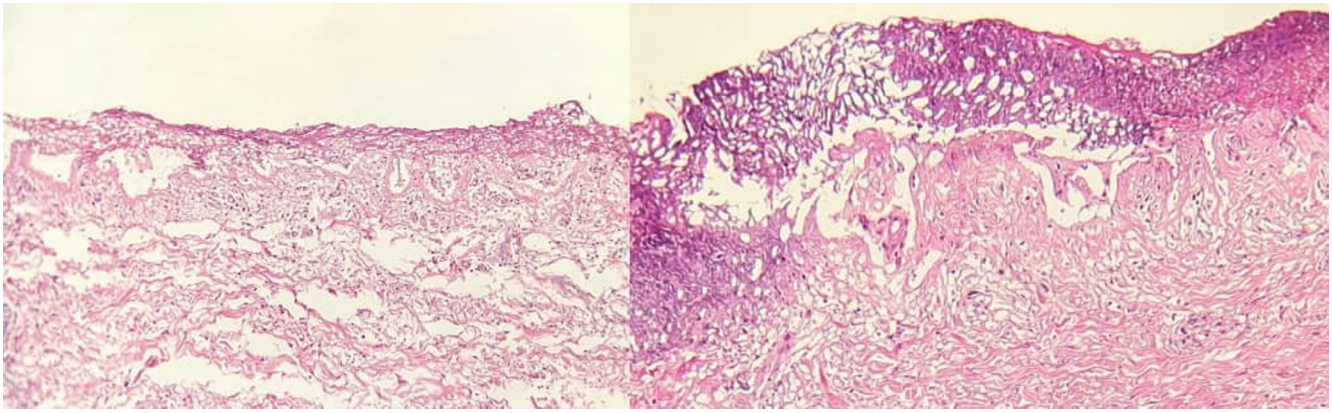

FIGURE 3 Histopathologic examination revealed skin tissues with erosive and necrotic sub-epidermal blister containing dense fibrinous exudate which covered by totally necrotic epidermal roof. Sparse infiltrate of lymphocytic inflammatory cells around superficial blood vessels are shown in upper dermis. Direct immunofluorescence test on the skin biopsy was negative

full-thickness epidermal necrosis, along with mucous membrane involvement. In SJS and TEN, less than 10% and more than 30% of the body surface are involved respectively.[3,5] SJS/TEN are now accepted as having the similar etiologies and pathogenesis and believed to be variants of the same spectrum of disease. The difference between these two entities is determined by the severity measurement which is characterized by percent body surface involvement.[6] SJS/TEN is typically secondary to medications including sulfonamides, certain antibiotics and anticonvulsants.[7]

COVID-19 vaccine platforms include virus-vectored vaccines, inactivated vaccines, protein subunit vaccines, virus-like particle vaccines, messenger RNA (mRNA) and DNA vaccines.[8] These vaccines are currently being widely administered and cutaneous adverse reactions following vaccination have been reported. However, immunologically mediated reactions are less common than the true infection. The cutaneous adverse reactions include cases of injection site reactions, exanthemas, eczematous dermatitis, urticarial, vascular lesions, autoimmune bullous diseases and also severe cutaneous adverse reactions (such as SJS/TEN), the latter of which has been reported rarely. The most of the cutaneous reactions are mild, limited to skin and with rapid resolution.[9,10] Anaphylaxis and severe cutaneous adverse reactions including SJS/TEN, are life-threatening and represent contraindications for a second vaccine dose.[11,12]

Till now few cases of SJS/TEN have been reported post COVID-19 vaccination. Bakir et al.[13] reported a case of TEN after the administration of Pfizer COVID-19 vaccine, with complete healing. The patient had a full recovery after receiving two doses of etanercept. Mansouri et al.[14] presented a case of SJS after the administration of Sinopharm COVID-19 vaccine, with markedly healing of lesions within 2 weeks and the therapy was consisted of prednisolone and fexofenadine. Dash et al.[15] reported a 60-year-old man who presented with complaints of fever and oral ulceration with skin rash, started 3 days after the first dose of the AstraZeneca COVID-19 vaccine. The diagnosis of SJS was confirmed and the patient was started on cyclosporine which led to complete resolution after 1 week. Elboraey et al.[16] reported a case of SJS 5 days after the administration of second dose of the Pfizer COVID-19 vaccine, presented with bullae at the left retro-molar area. In addition, the patient had whitish-yellow patches all over the tongue dorsal surface and upper and lower lips, in addition to multiple large ulcers found at the buccal mucosa, labial mucosa, tongue, and palate. The treatment consisted of prednisolone in addition to oral corticosteroid in the form of a mouthwash. We reported the case of COVID-19 vaccination induced TEN, which developed 1 day after receiving the first dose of Sinopharm COVID-19 vaccine. The treatment consisted of prednisolone and prepared mouthwash.

Immunological reactions to vaccines, can be divided to serum sickness, immediate hypersensitivity, and also delayed hypersensitivity reactions. Delayed-type hypersensitivity reactions are often T-cell mediated and SJS/TEN is one of the examples. In T-cell mediated reactions, the release of granzyme and perforin can lead to cell apoptosis.[17] Cytotoxic CD8+ T lymphocytes can be detected in the blister fluid and also perivascular superficial dermis. There is a strong evidence that the Fas ligand (FasL), a form of tumor necrosis factor secreted by lymphocytes, bind to the Fas receptor, which is expressed by keratinocyte. In addition, granulysin, a cytotoxic molecule, resulting in cytotoxicity. Hence; CD8+ T-cells in addition to these cytotoxic molecules are the key factors for the keratinocyte apoptosis in SJS/TEN.[3] Clinical manifestations of this type of hypersensitivity reaction, generally occurs within 6 h to weeks ranging from localized to disseminated mucocutaneous lesions.[18] It is believed that these events are the result of the response to virotopes antigen of vaccine in most of the cases. These virotopes antigen are preferentially expressed on the surface of keratinocytes, hence; lead to CD8+ T lymphocyte activation against epidermal cells and epidermal cells apoptosis with detachment at the dermal-epidermal junction occur.[19,20]

4 | CONCLUSION

Our case highlights a very rare COVID-19 vaccine associated mucocutaneous adverse reaction and physicians should be aware of this

reaction type following vaccination. However, because of an extremely rare adverse reaction, there should be no doubt about the COVID-19 vaccination.

CONFLICT OF INTEREST

The authors declare that they have no competing interest.

AUTHORS CONTRIBUTIONS

Masoud Mardani, Sayna Mardani, and Atousa Hakamifard: acquired and interpreted the data. Histopathologic result was provided by Zahra Asadi Kani. Atousa Hakamifard wrote the first draft of the manuscript. All authors have read and approved the final manuscript.

CONSENT

Written informed consent was obtained from the patient for the use of image and publication of case details in the manuscript.

DATA AVAILABILITY STATEMENT

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

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