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CLINICAL COMMENTARY

Development of severe pemphigus vulgaris following ChAdOx1 nCoV-19 vaccination and review of literature

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Abstract

Vaccines are indeed a boon for tackling the present COVID-19 pandemic. In India, ChAdOx1 nCoV-19 (Covishield) is the most commonly used vaccine in the government vaccination program for adults more than 18 years of age. It is a recombinant vaccine developed by Oxford-Astra Zeneca and manufactured in India by Serum Institute of India (SSI). Here, we report a case of severe pemphigus vulgaris following the second dose of ChAdOx1 nCoV-19 vaccination in an adult male. The patient developed septicemia during the course of hospital stay, and he was managed with systemic steroids, parenteral antibiotics, and intravenous immunoglobulins (IVIg) along with proper wound care. Patient started improving within 1 month of therapy. This case is being reported in view of the rarity of pemphigus vulgaris following ChAdOx1 nCoV-19 vaccine.

KEYWORDS
COVID-19 pandemic, ChAdOx1 nCoV-19, pemphigus vulgaris, recombinant vaccine

INTRODUCTION

ChAdOx1 nCoV-19 is a recombinant vaccine developed by Oxford-Astra Zeneca and manufactured in India by Serum Institute of India (SSI) under the name of Covishield®. It is the main contributor in India's COVID-19 vaccination program with more than 1-billion doses administered in India alone, till date. It has been granted Emergency Use Listing (EUL) by WHO for active immunization in individuals more than 18 years old.[1] Phase 2 and 3 clinical trials in India have shown it to be safe and well tolerated with no life-threatening adverse events or deaths related to vaccination.[2] Here, we report a rare case of pemphigus vulgaris following ChAdOx1 nCoV-19 vaccination during the present pandemic of COVID-19 infection. This case and similar reported cases prod us to research for better understanding of the etiopathogenesis of pemphigus vulgaris.

1 | CASE REPORT

A 44-year-old man presented with complaints of painful oral lesions for 2 months and multiple, recurrent, fluid-filled blisters, and erosions for 45 days. The patient initially developed painful, oral erosions 1 week after administration of 2nd dose of ChAdOx1 nCoV-19 vaccine. Few days later, flaccid blisters developed over the abdomen, upper back, and face, which burst spontaneously to form raw, painful erosions and progressed to involve the whole body in the next 15–20 days. There was no history of any drug intake or itching prior to the onset of erosions. His past medical history was unremarkable.

Examination of the oral mucosa revealed multiple ulcers of varying sizes with irregular jagged overhanging margins present over hard palate, bilateral buccal mucosa, gingiva, and labial mucosa. On cutaneous examination, multiple, irregular, and crusted erosions were seen all over the body (body surface area 20%), predominantly

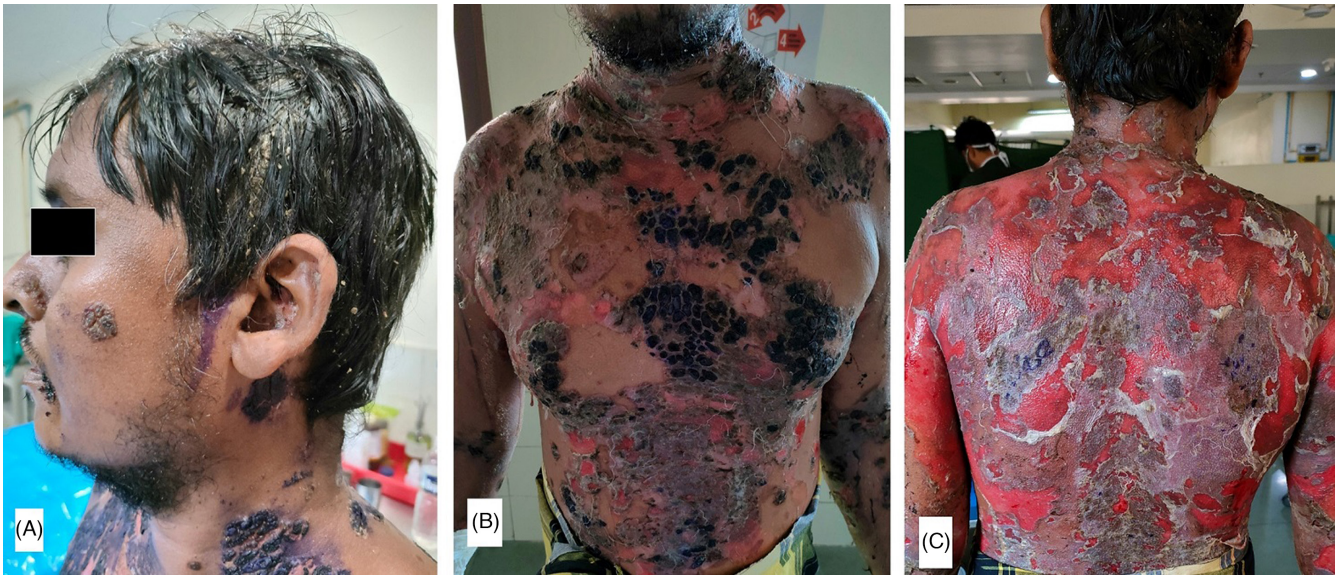

FIGURE 1 (A) Multiple crusted erosions over face and left ear along with matted hairs over scalp; (B) multiple crusted erosions with overlying gentian violet seen on chest and abdomen; **(C):** extensive erosions with some islands of normal skin present over whole back

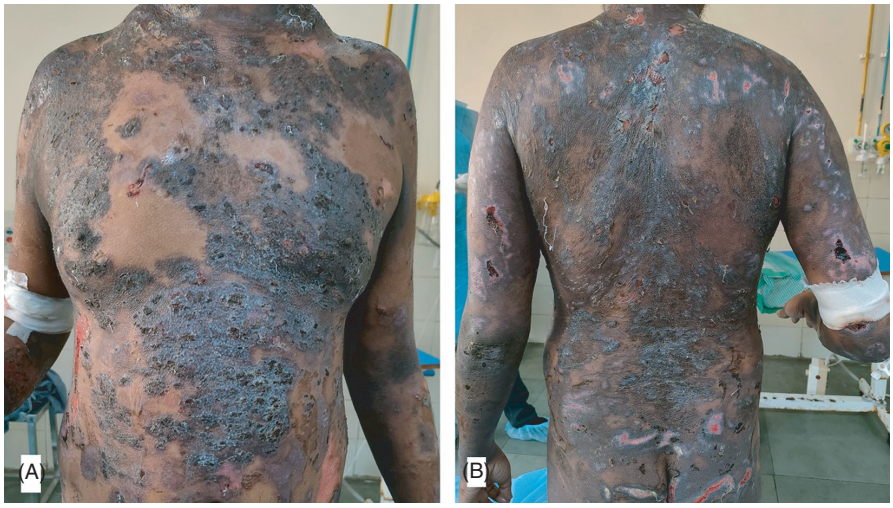

FIGURE 2 (A) Healed erosions with post inflammatory hyperpigmentation (PIH) seen on chest and abdomen; (B) erosions in the healing phase along with PIH present over back, buttocks and upper extremities

over the trunk, neck, and face and proximal extremities with a few intact bullae on the back and feet (Figure 1A–C). Both direct and indirect Nikolsky signs were positive. The Pemphigus disease area index (PDAI) was 73 denoting severe disease. Tzanck smear from an intact bulla showed numerous acantholytic cells. Histopathological examination showing the suprabasal blister and higher Desmoglein 3 levels (>200 U/ml) measured by enzyme-linked immunoassay (ELISA) confirmed the diagnosis of pemphigus vulgaris. The patient was started on injectable steroids, intravenous antibiotics, and other symptomatic treatment. After relevant work-up, pulse steroid therapy was administered in the dose of 100 mg dexamethasone IV over 3 days along with Azathioprine 50 mg daily as the adjuvant. IVIg at the dose of 2 g/kg dosage over 4 days was given in view of poor response to steroid therapy. In the next 1-month following treatment, new bullae ceased to appear and the existing erosions started to heal and PDAI decreased to 24 (Figure 2A,B).

2 | DISCUSSION

ChAdOx1 nCoV-19 (Covishield®) is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2.[1] The current recommendations are two doses of 0.5 ml of vaccine to be given intramuscularly 12 weeks apart. It is approved for use in adults >18 years of age in India. Phase 3 trials have shown the vaccine efficacy to be 78% for symptomatic illness and 100% for severe or critical symptomatic COVID-19 infection.[2] The most frequently detected adverse effects were injection site tenderness (>60%); injection site pain, headache, fatigue (>50%); myalgia, malaise (>40%); pyrexia, chills (>30%), arthralgia, and nausea (>20%). Most of the side effects were milder and less frequent after the second dose of vaccination when compared with the first dose.[2]

TABLE 1 List of immunobullous disorders induced or exacerbated post COVID-19 vaccination

Researcher	Disease	Age/sex	Vaccine	Dose	Flare/new onset
Knechtl et al[20]	Pemphigus vulgaris	89/M	BNT162b2	2nd	New
Koutlas et al[21]	Pemphigus vulgaris	60/M	mRNA-1273	2nd	New
Thongprasom et al[22]	Pemphigus vulgaris	38/F	AZD1222	1st	New
Angelyn et al[23]	Pemphigus foliaceus	83/M	BNT162b2	2nd	New
Solimani et al[24]	Pemphigus vulgaris	40/F	BNT162b2	1st	New
Damiani et al[25]	Bullous pemphigoid	75/M	mRNA-1273	2nd	Flare
	Pemphigus vulgaris	40/M	mRNA-1273	2nd	Flare
	Bullous pemphigoid	84/M	mRNA-1273	2nd	Flare
	Bullous pemphigoid	82/M	BNT162b2	2nd	Flare
	Pemphigus vulgaris	80/M	BNT162b2	2nd	Flare

Cutaneous adverse reactions like hyperhidrosis, pruritis, urticaria, angioedema, post-vaccination herpes zoster, pityriasis rosea, pityriasis rubra pilaris, erythema multiforme, erythema nodosum, generalized bullous-fixed drug eruption, toxic epidermal necrolysis, and sweet syndrome have been reported following ChAdOx1 nCoV-19 vaccine.[3–10]

Immunological mechanisms underlying pemphigus vulgaris include T- and B-cell dependent autoantibody production, Th2 predominant response with elevated levels of IL-6, IL-10, Tumor necrosis factor-α and reduced levels of Interferon-γ (Th1 cytokine), immune dysregulation and dysfunction of Treg and Breg cells.[11] Although the cause of autoimmunity is not clearly understood, the disease can be induced and/or exacerbated by several exogenous factors like drugs, malignancy, infections, and vaccines in a genetically predisposed individual.[12] In past, pemphigus vulgaris has been reported following vaccination with rabies, hepatitis B, Influenza, and anthrax vaccines.[13–16] Molecular mimicry, in which a vaccine or its components resemble a self-antigen and induce immune cross-reactivity, has been proposed as a possible mechanism for the development of autoimmunity following vaccination. Another possible mechanism is non-specific activation of innate immune response which can precipitate latent pemphigus in a susceptible individual.[17]

ChAdOx1 nCoV-19 vaccine targets spike (S)—glycoprotein present on the surface of the virus, producing neutralizing autoantibodies against it, which hampers the ability of the virus to bind to ACE-2 receptor on pneumocytes. This response is achieved via the stimulation of both humoral and cellular immune responses which leads to an alteration in the cytokines and chemokines levels in the body and activation of wide variety of immune cells, which, in turn, can cause induction or precipitation of a wide range of immune mediated diseases.[18] However, a recent case series by Kasperkiewicz et al[19] has shown that there was no cross-reactivity among anti-SARS COV-2 antibodies and pemphigus or pemphigoid autoantigens.

There are numerous case reports of new onset or flare of immunobullous disorders following administration of various COVID-19 vaccines from multiple countries, as summarized in Table 1. Till date, only four cases of new onset pemphigus vulgaris following COVID-19 vaccination have been reported. Our patient presented with multiple oral and cutaneous erosions 7 days after 2nd dose of vaccination with ChAdOx1 nCoV-19 vaccine and in addition, the disease was very severe in our patient, and he did not respond to pulse dose of IV steroids, and he had to be administered IVIg to achieve disease control over a period of more than 45 days of hospital admission. To the best of our knowledge, this is the first reported case of development of pemphigus vulgaris following ChAdOx1 nCoV-19 (Covishield®) vaccination. While this case could represent a coincidence, however, the temporal association, rarity of the disease, absence of any trigger factors like drugs or infections and similar reported cases of pemphigus onset following COVID-19 vaccines point toward the likelihood of causality.

In conclusion, COVID-19 vaccines are undoubtedly the single most important life-saving modality against the deadly COVID pandemic that we are going through and have proven to be effective and safe. Most of the adverse events following the vaccination are mild and easily manageable, although there are reports of a few serious adverse reactions. There should be research on the immunopathogenesis of immunobullous disorders such as pemphigus vulgaris following COVID-19 vaccines so as the incidence of such diseases/immune mediated cutaneous reactions post vaccination do not act as detrimental to the vaccination program.

CONFLICT OF INTEREST

None.

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