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SHORT PAPER

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Leukocytoclastic vasculitis as a cutaneous manifestation of ChAdOx1 nCoV-19 corona virus vaccine (recombinant)

Sunmeet Sandhu[1] | Anuj Bhatnagar[1] | Harish Kumar[2] | Prashant Kumar Dixit[2] | Gourang Paliwal[3] | Devinder Kumar Suhag[1] | Chetan Patil[1] | Debdeep Mitra[1]

[1]Department of Dermatology, Command Hospital Air Force Bangalore, Bangalore, Karnataka, India

[2]Department of Medicine, Command Hospital Air Force Bangalore, Bangalore, Karnataka, India

[3]Department of Pathology, Armed Forces Medical College, Pune, Maharashtra, India

Correspondence
Sunmeet Sandhu, Department of Dermatology, Command Hospital Air Force Bangalore, Bangalore, Karnataka 560007, India.
Email: sunmeet.sandhu@gmail.com

Abstract

With the present COVID-19 vaccination drive across the world, adverse skin reactions post COVID-19 vaccine is expected. Majority of these reactions seen were transient or local injection site reactions. However, as the larger population is being vaccinated, certain uncommon dermatological presentations including leukocytoclastic vasculitis, pityriasis rosea, and exacerbation of pre-existing autoimmune diseases are now being reported. Among all the COVID-19 vaccines, most of these reactions are seen with messenger ribonucleic acid-based Pfizer/BioNTech (BNT162b2) and Moderna (mRNA-1273) vaccine. We report two cases of leukocytoclastic vasculitis following ChAdOx1 nCoV-19 corona virus vaccine (recombinant) that bring out potential new dermatological manifestations of recombinant corona virus vaccine being administered across the European, South American, and Asian countries. It is important for all health care workers and patients to be aware of the corona virus vaccine associated adverse cutaneous reactions.

KEYWORDS
corona virus vaccine (recombinant), COVID-19, COVID-19 vaccination, leukocytoclastic vasculitis

1 | INTRODUCTION

Various dermatological manifestations of COVID-19 including leukocytoclastic and IgA vasculitis and Kawasaki-like multisystem inflammatory syndrome associated with COVID-19 have been reported.[1–3] With the ongoing widespread COVID-19 vaccination across all continents, a spectrum of cutaneous reactions are emerging. Majority of these being transient or local injection site reactions.[4–6] Dermatological manifestations similar to reported in COVID-19 infection are now being increasingly seen associated with COVID-19 vaccination. New onset or reactivation of cutaneous and IgA vasculitis has been observed in handful of cases associated with either messenger ribonucleic acid (mRNA) or inactivated SARS-CoV-2 vaccines but none with *ChAdOx1 nCoV-19 corona virus* vaccine (recombinant).[4,7–11] *ChAdOx1 nCoV-19 corona virus* vaccine (recombinant) is replication-deficient chimpanzee adenovirus vector vaccine that encodes SARS-CoV-2 Spike glycoprotein which is being extensively used in Indian subcontinent, European, and South American nations. We report two patients who developed leukocytoclastic vasculitis (LCV) following corona virus vaccine (recombinant) and its management. This further adds onto our growing knowledge about post COVID-19 vaccination dermatological manifestations.

2 | CASE SUMMARY

2.1 | Case 1

A 55-year-old female with no comorbidities presented with 3-day history of fever, myalgia, left wrist swelling, and palpable purpura over both ankles associated with burning sensation, 5 days following first dose of *ChAdOx1 nCoV-19 corona virus* vaccine (recombinant). Within

24 h, rash progressed proximally to involve both lower limbs (Figure 1A). Reverse transcriptase polymerase chain reaction (RT-PCR) for COVID-19 was negative. She was investigated for systemic involvement, including hematology, biochemistry, viral markers, antinuclear antibody (ANA), antineutrophilic antibody (ANCA), complement levels, ASO titer, urinalysis including 24-h urine protein, C-reactive-protein and ESR that were unremarkable. Anti-Spike SARS CoV-2 Antibody titer was raised to 322 AU/mL (<50.00). Skin biopsy from a lesion was suggestive of LCV with small vessels in dermis showing plump endothelial cells surrounded by perivascular mixed inflammatory infiltrate with karyorrhectic debris and extravasation of red blood cells (RBC) (Figure 1B,C). Direct immunofluorescence (DIF)

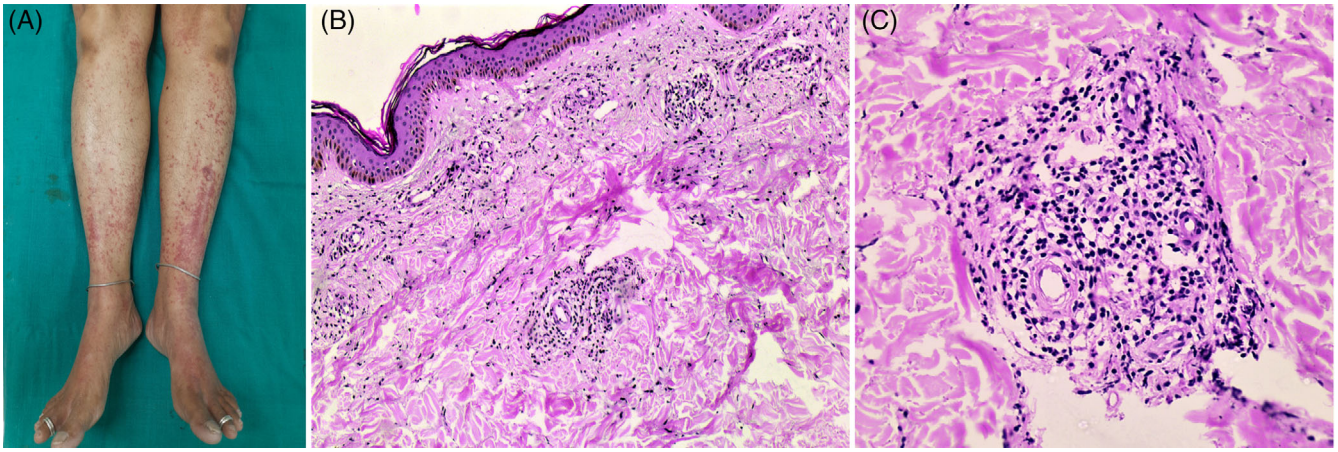

FIGURE 1 (A) Dermatological examination of case 1 revealing multiple, discrete to confluent palpable purpura distributed symmetrically over both lower limbs (B) Histopathology of a lesion in case 1 was suggestive of leukocytoclastic vasculitis with small vessels in dermis showing plump endothelial cells surrounded by perivascular mixed inflammatory infiltrate with karyorrhectic debris and extravasation of RBCs. (H&E, 200×). (C) Inflammatory cells consisting of neutrophils and lymphocytes infiltrating the vessel wall. Leukocytoclasia seen. (H&E, 400×)

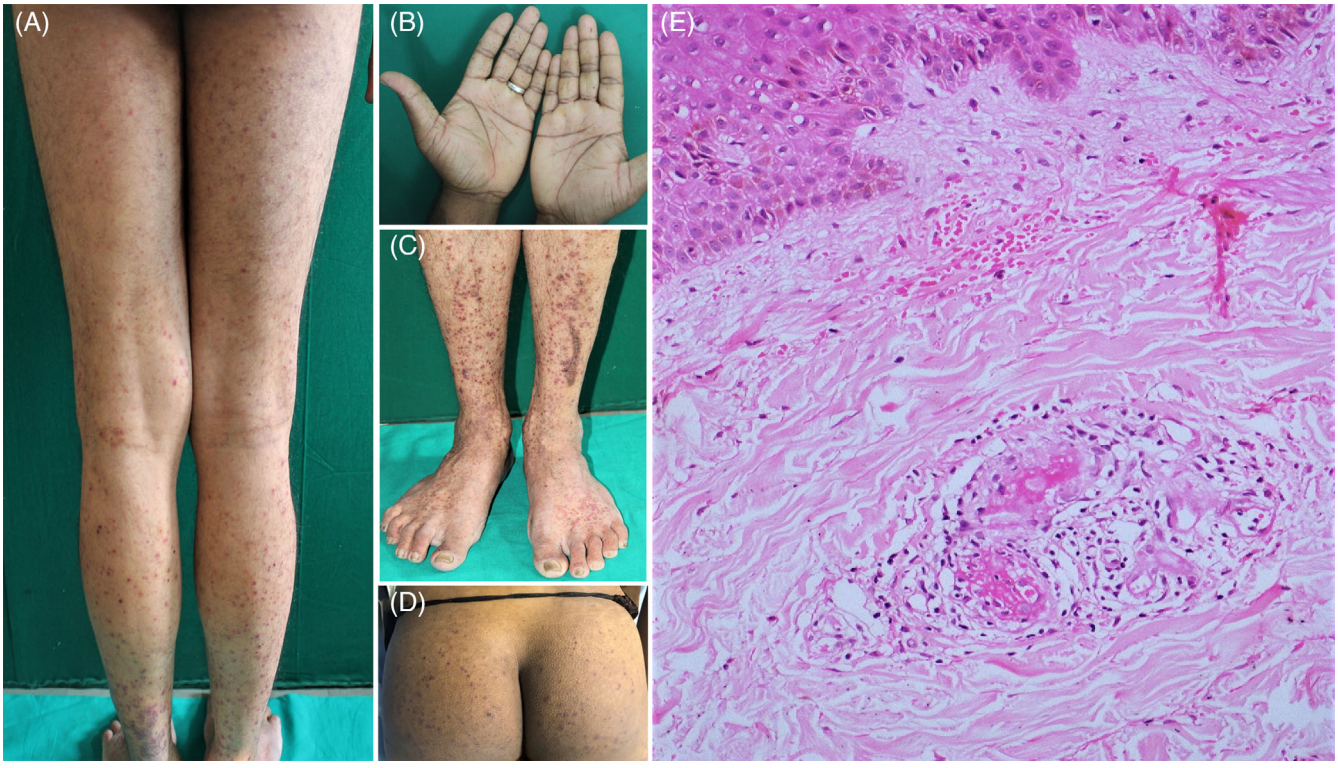

FIGURE 2 (A)–(D) Cutaneous findings in case 2 showing multiple, discrete to confluent palpable purpura distributed symmetrically over palms, gluteal region, and lower limbs. (E) Histopathology in case 2 revealed dermis with perivascular mixed inflammatory infiltrate of neutrophils and lymphocytes. Blood vessels show fibrinoid necrosis with infiltration by neutrophils. Marked extravasation of RBCs and karyorrhectic debris seen. (H&E, 400×)

from a lesion less than 24 h duration was negative. She was managed with oral prednisolone @0.5 mg/kg/day, tapered over 2 weeks with resolution of all symptoms. The patient was advised a repeat titer of anti-spike SARS CoV-2 antibody before the second scheduled dose of vaccine.

2.2 | Case 2

A 48-year-old hypertensive male, on medication presented with 2 days of fever, myalgia and 1 day of palpable purpura distributed symmetrically over hands, forearms, gluteal region, and lower limbs, 2 days after second dose of *ChAdOx1 nCoV-19 corona virus* vaccine (recombinant; Figure 2A–D). He had similar lesions limited to ankles without any constitutional symptoms 7 days after the first dose of vaccine that resolved within 7 days with topical corticosteroids. RT-PCR for COVID-19 was negative. Anti-spike SARS CoV-2 antibody titer was markedly raised to 1926.90 AU/mL (<50.00). Skin biopsy from a lesion was classical of LCV with dermal perivascular mixed inflammatory infiltrate of neutrophils and lymphocytes. Blood vessels showed fibrinoid necrosis with infiltration of vessel wall by neutrophils. Marked extravasation of RBCs and karyorrhectic debris were observed (Figure 2E). DIF was negative. Other relevant investigations and treatment profile were similar to case 1. Both patients denied history of COVID-19 or similar episodes in the past.

3 | DISCUSSION

Leukocytoclastic vasculitis (LCV) as an adverse event to vaccination particularly to influenza vaccine has been reported.[12] The mechanism of vasculitis is uncertain; however, it may be associated with hypersensitivity or abnormal immunological activation due to trigger of an underlying autoimmune or inflammatory disorder.[12] Cutaneous vasculitis presenting with typical skin lesions were observed in mild as well as fulminant COVID-19 infection. Vasculitis in COVID-19 has been attributed to SARS-CoV-2 associated endotheliitis which could be either due to virus directly invading the endothelium or owing to inflammatory response that results in immune complex deposits in the vessels.[13] SARS-CoV-2 antigens and vaccine proteins share structural similarities. Hence, with recombinant COVID-19 vaccine, inflammatory response to vaccine component encoding SARS-CoV-2 spike glycoprotein targeting endothelium resulting in endotheliitis and subsequent vasculitis could be hypothesized.

This is the first report of cutaneous LCV in association with *ChAdOx1 nCoV-19 corona virus* vaccine (recombinant). Previous reported cases of post COVID-19 vaccine associated reactivated or new onset LCV or IgA vasculitis were seen with either mRNA or inactivated SARS-CoV-2 vaccines but none with recombinant corona virus vaccine (Table S1).[4,7–11] In both of our cases, a temporal association between vaccination and LCV could be established with a probable causal relationship in case 1 and definite relationship in case 2. Historically, first LCV episode in case 2 occurred 7 days after vaccination, which was mild with rash limited to ankles, resolving within a week and without any constitutional symptoms. However, second exposure to vaccine resulted in earlier onset and widespread rash with constitutional symptoms that required oral corticosteroids. This supports the existing data of recurrent and more robust cutaneous reaction on re-exposure to vaccine.[4] A registry-based study of 414 cases who received mRNA COVID-19 vaccine had 38 cases developing cutaneous reaction after first dose, 113 cases after second dose, and 29 cases to both doses. Of these 29 cases, 8 had milder reaction while 13 had more robust reaction on re-exposure but none were serious events, providing reassurance to continue vaccination.[4]

Cohen et al. showed fibrin deposition within the small vessel wall which is the hallmark feature of LCV.[8] We observed fibrinoid necrosis in case 2 only. Absence of fibrinoid necrosis in case 1 could be the result of skin biopsy done from the very early phase of LCV when fibrin deposition in the vessel wall was not fully developed.

Both the patients were managed with tapering doses of oral prednisolone. There is apprehension regarding use of immunosuppressants soon after vaccine. A dose-dependent variable effect on immunity has been reported with corticosteroids with adequate seroprotection with doses <20 mg/day. It is contemplated that systemic corticosteroids have "no or minimal risk" to patients' immune response irrespective of type of COVID-19 vaccine.[14]

Health care providers must be aware of the cutaneous manifestations of COVID-19 vaccine as it can potentially precipitate or exacerbate cutaneous inflammation. This is equally important while reassuring general population to continue vaccination if cutaneous reactions are not severe enough to discontinue vaccination, as potential benefits of COVID-19 vaccine are far more in this pandemic. Therapeutic options in such cases or events will depend on case-to-case basis in the best interest of each and every patient.

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CONFLICT OF INTEREST

There are no conflicts of interest.

AUTHOR CONTRIBUTIONS

The manuscript has been read and approved by all the authors. The requirements for authorship as stated earlier in this document have been met, and each author believes that the manuscript represents honest work.

PATIENT CONSENT STATEMENT

The authors certify that they have obtained all appropriate patient consent forms for use of patient photographs and data obtained.

DISCLAIMER STATEMENT

We confirm that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met and that each author believes that the manuscript represents honest work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Sunmeet Sandhu https://orcid.org/0000-0002-9222-4006

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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