Cutaneous Adverse Drug Reactions (CADRs) to COVID19 Vaccines: A Case Series

Abstract

Viral vector vaccines (Covishield) and inactivated vaccines (Covaxin) are now being administered worldwide to reduce the impact of life-threatening corona virus disease 19 (COVID-19). Various cutaneous adverse drug reactions (CADRs) have been reported following COVID-19 vaccination. Here, we are reporting series of CADRs following COVID-19 vaccination. Among 18 CADRs, 4 each were of acute urticaria and pityriasis rosea, 2 each of leukocytoclastic vasculitis and herpes zoster, 3 exacerbation of psoriasis, and 1 each of exacerbation of eczema, reactivation of herpes simplex virus 1 infection, and COVID arm. However, in 1 case there was remission of psoriasis. These CADRs occurred between 6 hours and 20 days after vaccination and were mild to moderate in severity. Only 1 needed hospitalization. Of the 18 CADRs, 10 developed after first dose and 8 after second dose. Causality assessment was done using World Health Organization causality assessment classification. Mass COVID-19 vaccination program is in progress worldwide. Many CADRs like COVID arm, urticaria, pityriasis rosea, leukocytoclastic vasculitis, herpes zoster etc., have been reported following vaccination. In our series only 1 developed cutaneous adverse drug reaction (CADR) to Covaxin. It was Covishield that was administered during the vaccination drive; hence, more cases were seen to that vaccine. Most of the CADRs were mild to moderate in intensity. Awareness of these adverse effects enables the healthcare professionals to be better equipped to recognize and manage them correctly.

Keywords: *CADR, covaxin, covishield*

Manila Purushottam, Vinutha Rangappa, Jayadev B. Betkerur, Ashwini P. Kombettu, Veeranna Shastry

Department of Dermatology and Venereology, JSS Medical College, JSS Academy of Higher Education and Research Centre, Mysore, Karnataka, India

Introduction

The corona virus disease-19 (COVID-19) is a viral infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is a positive stranded RNA virus with spike glycoproteins on the envelope. Since its first outbreak in 2019, it has spread rapidly resulting in global pandemic.

The current COVID-19 pandemic has been largely disruptive affecting day-to-day normal life, socio-economic growth, and loss of human lives. Multiple drugs/therapies have been tried and tested to contain the condition. Various vaccines have been advanced globally and are being administered at fast pace for public immunization[1] and perhaps vaccines are the best hope for controlling the pandemic.

Protein subunit, mRNA, viral vector, and inactivated virus vaccines are the different types of COVID-19 vaccines available. In India, ChAdOx1 nCoV-19 corona virus vaccine recombinant (Covishield), Bharat Biotech COVID-19 vaccine (Covaxin), Sputnik V, AZD1222, Ad26.COV2.S, ZyCoV-D, and mRNA-1273 are approved for use. India started its vaccination drive against COVID-19 on January 16, 2021. As per the latest data, India has administered more than 1.51 billion COVID-19 doses overall.

Various cutaneous and systemic adverse events are reported following COVID-19 vaccination. Cutaneous adverse drug reactions (CADRs) are defined as any unfavourable or unintended sign, an abnormal laboratory finding, a symptom, or a disease which follows immunization. They are usually mild, including injection site reactions or morbilliform eruptions. However, few severe CADRs like rowell syndrome, acute generalized exanthematous pustulosis have also been reported.[2,3]

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Address for correspondence:
Dr. Vinutha Rangappa, Department of Dermatology, Venereology and Leprosy, JSS Medical College and Hospital, Mysore - 570 004, Karnataka, India.
E-mail: drvinutharangappa@gmail.com

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Spectrum of CADR have been reported worldwide following COVID-19 vaccination but are not very well characterized. A comprehensive data on CADRs following novel coronavirus vaccination in Indian population are lacking. We describe 18 cases of COVID-19 vaccine–induced CADRs encountered in a tertiary care hospital.

Case Series

We included all patients presented with cutaneous response within 30 days of receiving first or second dose of COVID-19 vaccine in the department of dermatology from April to December 2021.

We encountered 18 cases of CADRs following COVID-19 vaccination. Among them, 12 were females and 6 were males. Of 18, 17 patients had received Covishield and 1 Covaxin. Total of 10 cases were reported after first dose and 8 after second dose of vaccination.

These CADRs occurred between 6 hours and 20 days with majority being <7 days (15 cases) post vaccination.

Among 18 CADRs, 4 were acute urticaria, 4 developed pityriasis rosea, 2 each of leukocytoclastic vasculitis and herpes zoster, 3 exacerbations of psoriasis [Figure 1], and 1 each of exacerbation of eczema, reactivation of herpes simplex virus 1 infection, and COVID arm. Histopathological test was performed in selected cases [Figure 2, Table 1].

In all the aforementioned cases, temporal relationship between cutaneous response and vaccination was established using World Health Organization causality assessment classification. As per this scale, all our cases are classified under category B1, that is, temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing event.[4]

Discussion

Vaccine is a preparation used to stimulate body's immune response (acquired immunity) against particular diseases. Vaccines may contain attenuated live organisms, inactivated or killed organisms, inactivated toxins, or segments of the pathogen.[5] Vaccination against COVID-19 is very critical in ending the pandemic. Covishield and Covaxin are two vaccines produced in India.

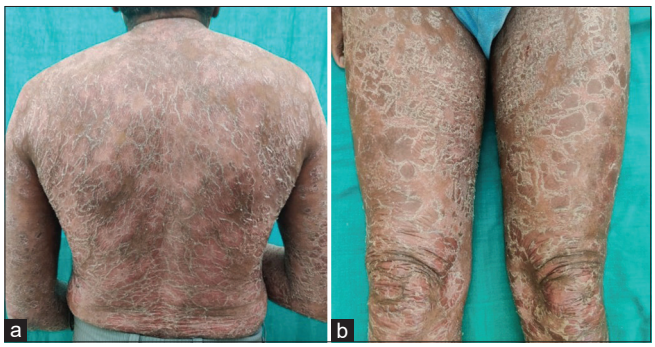

Figure 1: (a) and (b) exacerbation of psoriasis

Vaccines induce at least 4 different patterns of inflammatory skin reactions.[6]

1) Th1 polarized T helper cell profile immune response with key cytokine like TNFα, TNFγ, IL2, and IL6.
2) Th2 polarized inflammatory reaction with abundant IL4, IL5, and IL6.
3) Activation of cutaneous resident memory T lymphocytes which elicit Th17/Th22 response.
4) Vaccine-derived degradation of extracellular matrix triggering macrophages or histiocytes to form granulomas.

Covishield is a viral vector vaccine which uses genetically engineered chimpanzee DNA adenovirus. It encodes a protein which is similar to SARS-CoV2 s-peptide which generates cellular immune responses and neutralizing antibodies.[7,8]

Covaxin is a whole virion-inactivated vaccine containing SARS-CoV2 antigen. It generates the immune response without causing the disease.[8]

Majority of the patients in our study had received Covishield vaccine. This could probably be due to the fact that Covishield was used extensively during the initial vaccine drive.

The CADRs following COVID vaccination can be classified as new onset skin conditions and alteration of existing skin conditions [Table 2].

The most reported cutaneous responses were found to be acute urticaria and pityriasis rosea–like lesions. The onset of urticarial symptoms ranged from 5 to 48 hours following

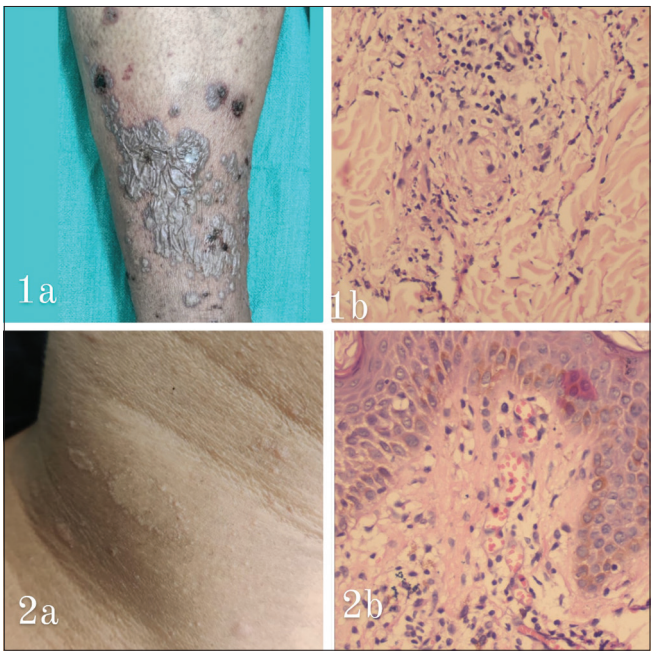

Figure 2: (1a) and (1b) clinical and histopathology of leukocytoclastic vasculitis (2a) and (2b) clinical (herald patch) and histopathology of pityriasis rosea

Table 1: Cutaneous response following COVID-19 vaccine.

Age/sex	Vaccine type	First dose	Second dose	Time gap (days)	Cutaneous response
21/F	Covishield		√	4	Pityriasis Rosea like
54/M	Covishield	√		20	Exacerbation of Psoriasis
22/F	Covishield	√		7	Pityriasis Rosea like
37/F	Covishield	√		2	Acute urticaria
48/F	Covishield		√	1	Acute urticaria
32/M	Covishield	√		< 1	Leukocytoclastic vasculitis (LCV)
37/M	Covaxin	√		21	Pityriasis Rosea like
61/F	Covishield	√		< 1	Acute urticaria
69/F	Covishield		√	2	Right Herpes zoster Ophthalmicus (HZO)
50/M	Covishield		√	2	Exacerbation of Eczema
55/M	Covishield	√		3	Exacerbation of Psoriasis
20/F	Covishield		√	< 1	Acute urticaria
25/M	Covishield		√	4	Herpes zoster (HZ) left T10 dermatome
18/F	Covishield	√		4	Pityriasis Rosea like
63/F	Covishield		√	3	Leukocytoclastic vasculitis (LCV)
43/F	Covishield	√		2	Exacerbation of psoriasis
28/F	Covishield	√		2	COVID arm
30/F	Covishield		√	7	Reactivation of HSV1 with dissemination

√ - indicates the dose of vaccine received by the patient

Table 2: Classification of cutaneous response following covid vaccination.

New onset skin condition	Alteration in existing skin condition (Exacerbation/remission)
1) Urticarial rash – Acute urticaria	Papulosquamous disorder- Psoriasis
2) Papulosquamous disorder- Pityriasis Rosea	Eczematous disorder
3) Vasculitic lesions- Leukocytoclastic vasculitis (LCV)	
4) Vesicular lesions- Herpes zoster	
5) COVID arm	

vaccination. Urticarial rash may represent type 1 immediate hypersensitivity reaction against vaccine excipient polysorbate 80.[9]

Pityriasis rosea is a self-limiting papulo-squamous eruption of probable viral aetiology. It has also been reported after influenza and human papillomavirus vaccines. Pityriasis rosea–like lesions were recorded after Covishield and Covaxin vaccine.[10,11] All the patients had herald patch which is in contrast to Leerunyakul K *et al*.[10] It has also been reported after mRNA-1273[12] and other inactivated virus vaccine of COVID-19.[11] The exact mechanism is unclear; plausible theories include disruption of T-cell mediated control of latent infections, viral epitope molecular mimicry, and delayed type 4 hypersensitivity reaction.[13]

We report two cases of histopathologically confirmed leukocytoclastic vasculitis after the Covishield vaccine. It has been hypothesized that vaccine proteins induce proinflammatory cascade similar to viral protein as they are structurally analogous leading to vaccine-induced endothelial inflammation and dysfunction.[14] It has also been reported following mRNA COVID vaccine.[15]

Reactivation of varicella-zoster virus usually occurs in immunocompromised status. Vaccination could be a possible trigger in relatively young patients on immunosuppressants. However, in our study, one patient was diabetic under control with medications and other case had no known comorbidities and not on any immunosuppressants. Henry D *et al*. have reported a case of HZ following Covishield similar to our cases.[16] Vaccine-induced lymphocytopenia could trigger HZ in both immunocompromised and immunocompetent individuals.[17]

We also report a case of reactivation of herpes simplex virus 1 with dissemination presented for the first time after second dose of Covishield vaccine.

Three patients with chronic plaque psoriasis who were under remission for more than 4 months with systemic antipsoriatic medications presented with exacerbation within 2 to 20 days after first dose of Covishield vaccination. Nagrani P and Sotiriou E *et al* had observed similar exacerbation.[18,19] An increased secretion of cytokines like TNF-α and IFN γ by $CD4^+$ T cells (Th1 type) is seen on day 14 following Covishield vaccination similar to psoriatic pathomechanism.[18]

A case of exacerbation of eczema over legs and palms after the second dose of vaccine in nonatopic individual can be explained due to type I or IV allergic reaction to vaccine component due to prior sensitization, with abundance release of IL4 and IL13.[6]

Local reaction presenting as COVID arm was also encountered in the study. It may represent delayed hypersensitivity reaction presenting as erythema, swelling, and itching near the vaccination site.[20] Less reported cases of COVID arm could possibly be due to the less severity of the condition.

An online questionnaire-based study from India reported mucocutaneous adverse effects in 19.6% participants. Most predominant finding was local injection site reaction followed by urticarial, morbilliform, pityriasis rosea–like exacerbation of pre-existing dermatoses, aphthous ulcers, telogen effluvium, herpes zoster, purpuric rash, erythema multiforme, and others.[21] Similar reactions were reported from a Spanish study following BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), and AZD1222 (AstraZeneca) vaccines.[22] These findings are in concordance with our study.

Most of the CADRs were mild to moderate in intensity which responded well to the treatment.

Conclusion

The ongoing global vaccination is a giant step to end COVID-19 pandemic. Variety of CADRs following vaccination have been reported worldwide. Some of them mimic the cutaneous manifestations of COVID-19 infection itself. It also warrants the importance of assessment of vaccine safety in clinical trials, considering that these were developed in a short period of time.

Although CADRs are mild, awareness of these adverse effects enables the healthcare professionals to be better equipped to recognize and manage them correctly.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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