LETTER TO THE EDITOR

A spectrum of leprosy reactions triggered by Covid-19 vaccination: a series of four cases

Dear Editor,

The vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to expand across the globe. Concurrently, a large number of dermatological adverse effects related to vaccination are vigorously reported. A study conducted by Rerknimitr *et al* encompassing over 35 000 vaccine receiving healthcare workers stated the incidence of cutaneous adverse effects to be <1%. India launched its vaccination drive on 16 January 2021 and has vaccinated over 320 million individuals (23.4% of the total population) by July 2021.[1,2] Amongst various vaccine-related adverse effects, leprosy reactions have sparse mention in the literature limited to mere case reports and case series. We report a series of four cases of Hansen's disease with leprosy reactions spanning across the entire spectrum after being administered the vaccine from a leprosy care centre in India.

Of the four cases included in the series, three were borderline tuberculoid (BT) leprosy while one was of borderline lepromatous (BL) pole of the Ridley–Jopling classification. Of the three BT leprosy cases, two were released from treatment (RFT) after completing 6 months and one year of MDT, respectively. Two kinds of vaccines were administered, covishield (Recombinant ChAdOx1-S) vaccine manufactured by the serum institute of

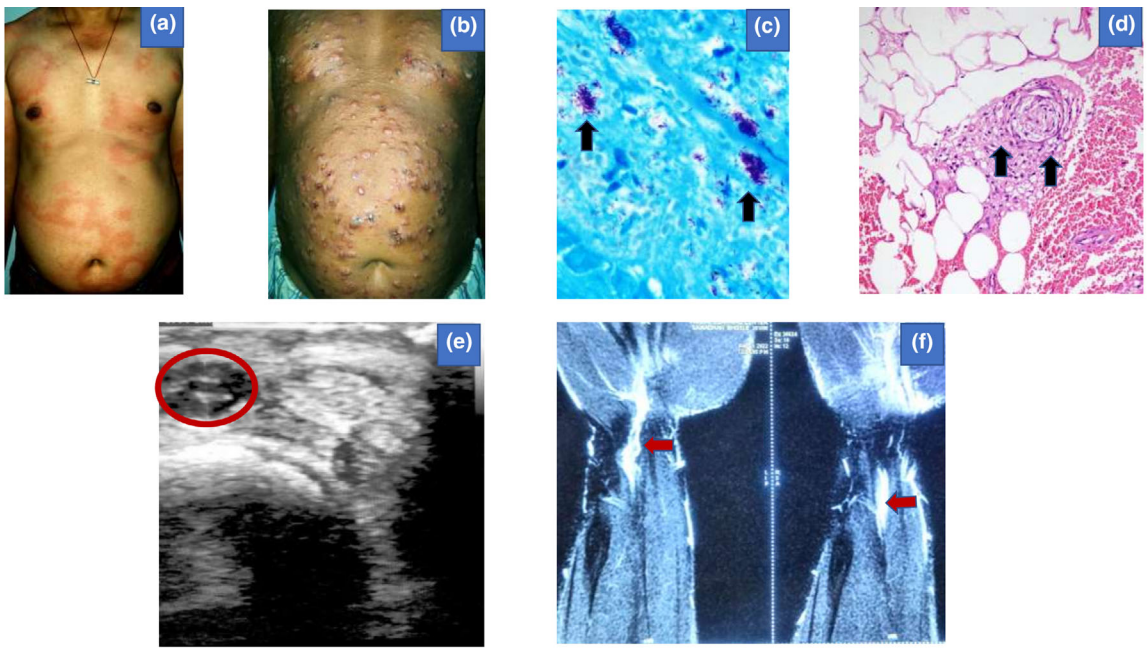

Figure 1 (a) Erythema and oedema over pre-existing patches distributed over trunk and back (Patient 1). (b) Crops of multiple erythematous tender nodules with subsequent ulceration distributed symmetrically over trunk and extremities (Patient 4). (c) Multiple acid-fast lepra bacilli in globi suggestive of multibacillary leprosy indicated by black arrows (Patient 4) (Fite Faraco stain of tissue for AFB [L], 40×). (d) Histopathology revealed infiltration of neutrophils and sparse lymphocytes of the subcutaneous tissue suggestive of lobular panniculitis with vasculitis indicated by black arrows (Patient 4) (H & E, 40×). (e) Ultrasonography of right upper limb suggestive of ulnar nerve thickening with surrounding edematous changes suggesting acute neuritis indicated by the red circle and red arrows (Patient 2). (f) Contrast-enhanced magnetic resonance imaging (MRI) of the left forearm and wrist region suggestive of median nerve neuritis with focal granuloma/abscess indicated by red arrows (Patient 3).

Table 1 Demographic and clinical characteristics of cases.

Patient #	1	2	3	4
Age (in years)	35	28	25	45
Gender	Male	Male	Male	Male
Spectrum of Hansen's disease	Borderline tuberculoid (BT)	Borderline tuberculoid (BT)	Borderline tuberculoid (BT)	Borderline lepromatous (BL)
Status of Multidrug therapy (MDT)	On multibacillary MDT since the past 05 months	Release from therapy 06 months back after 12 months of MDT	Release from therapy one year back after 12 months of MDT	On multibacillary MDT since the past 04 months
Type of lepra reaction	Type I reaction (cutaneous)	Type I reaction (right ulnar nerve neuritis)	Type I reaction (left median nerve abscess)	Type II reaction (necrotic erythema nodosum leprosum)
Clinical characteristics	Presented with few light-coloured numb patches over trunk and back. Slit skin smear (SSS) for acid-fast bacilli (AFB-L) - 1 + .	Sudden onset sharp shooting pain down right elbow	Sudden onset pain and swelling over volar aspect of left forearm around wrist joint	Crops of multiple erythematous tender nodules with subsequent ulceration distributed symmetrically over trunk and extremities (Fig. 1)
	Acute onset erythema and oedema over these pre-existing patches (Fig. 1)	Right ulnar nerve grade III thickened and grade II tender	Left median nerve grade III thickened and grade II tender	Associated fever and joint pains. No features of organ involvement. SSS for AFB- 4+
	Histopathology revealed multiple ill-defined epithelioid granulomas centred around nerve twigs and appendages with neutrophilic infiltrate and dermal oedema	USG of right upper limb suggestive of ulnar nerve thickening with surrounding edematous changes suggesting acute neuritis (Fig. 1)	Contrast-enhanced MRI suggestive of median nerve neuritis with focal granuloma/abscess (Fig. 1)	Histopathology revealed infiltration of neutrophils and sparse lymphocytes extending to subcutaneous tissue with vasculitis (Fig. 1). Special stains for AFB (L): Globi teeming with lepra bacilli (Fig. 1)
Treatment	Tapering doses of oral steroids that was started at 0.75 mg/kg/day of prednisolone	Tapering doses of oral steroids that was started at 1 mg/kg/day of prednisolone	Tapering doses of oral steroids that was started at 1 mg/kg/day of prednisolone	Managed with thalidomide 100 mg four times a day tapered monthly
Details of vaccine and dose	First dose of covishield (recombinant ChAdOx1-S vaccine)	Second dose of covishield (recombinant ChAdOx1-S vaccine)	Second dose of covishield (recombinant ChAdOx1-S vaccine)	Second dose of covaxin (whole virion inactivated vaccine NIV-2020-770 strain)
Duration between onset of reaction and Covid-19 vaccine administration	11 days	5 days	8 days	7 days

India and covaxin (the whole virion inactivated vaccine NIV-2020-770 strain) by Bharat biotech, India. The BL leprosy case was administered covaxin while the other three cases were given covishield. The duration between the administration of the vaccine and the onset of leprosy reactions ranged from 5 to 11 days. The clinical profile of the cases was varied, and precipitation of the entire spectrum of leprosy reactions was noted which included cutaneous type I reaction, ulnar nerve neuritis, median nerve neuritis with nerve abscess and type II reaction in the form of necrotic erythema nodosum leprosum (ENL). The diagnosis was established with corroborating radiological and histopathological findings in a background of characteristic clinical presentation. The demographic, clinical profile and details of vaccination are summarized in Table 1.

Leprosy reactions are immunologically mediated episodes of acute or subacute inflammation interrupting a relatively uneventful disease process and are classified as type 1 and type 2 reactions. Initiation of multidrug therapy (MDT) is the primary trigger for these reactions, but they are known to be influenced by pregnancy, infections, stress and vaccinations. Barring vaccination, there were no identifiable triggers of reactions in the four cases reported. Amongst vaccines, influenza, pneumococcal, Bacillus Calmette and Guerin (BCG), and hepatitis-B vaccines have been implicated with leprosy reactions. Covid-19 vaccines after administration are known to increase TNF-α, IFN-γ and IL-8 levels stimulated by glycoprotein-S.[2] Panda *et al.* have proposed a hypothesis of increased neutrophil–lymphocyte ratio postcovid infection and vaccination. A conglomeration of neutrophilic inflammation with increased TNF-α, IFN-γ and IL-8 could trigger leprosy reactions. An average interval of 5.1 to 11.5 days is mentioned for onset of reactions postvaccination which in our study was 7.5 days.[3] Moreover, neurological complications of Covid-19 vaccination have been reported such as Guillian-Barre syndrome (GBS), ischaemic stroke, facial nerve palsy and acute transverse myelitis.. Enhanced IL-6 and IL-12B gene expressions, inherent to Covid-19 infection, are key mediators of neuritis in lepra reactions. The vaccines possess enhanced immunostimulatory effects, and it could be contemplated that IL-6 and IL-12B expressions result in subsequent leprous neuritis in our cases.[4]

Covid-19 vaccine-associated ENL and foot drop in Hansen's disease have been reported previously, but type I reaction with cutaneous flare and acute neuritis has probably not been reported so far.[3,5] The four cases reported are from a leprosy care centre in India where the disease is endemic. CXCL10 and IL-6 along with cortisone–cortisol shuttle enzymes are potential laboratory markers of type 1 reactions, and IL-17 and platelet-derived growth factor BB (PDGF-BB) are for type 2 reactions. The sheer versatility of clinical presentation of leprosy reactions following Covid-19 vaccination warrants further large-scale molecular studies including assays of potential laboratory inflammatory markers to establish the exact pathogenesis of vaccine-related adverse effects.

Acknowledgement

The patient in the manuscript has given written informed consent to the publication of case details and photographs.

Conflicts of Interests

None declared.

Author contribution

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

Data availability statement

The authors declare that data supporting the findings of this case are available within the article and its supplementary information file.

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