LETTER TO THE EDITOR

Development of delayed dermal hypersensitivity reaction following the second dose of COVID-19 vaccine – A series of 37 cases

To the Editor,

Delayed immunologic reactions are being increasingly reported following the administration of COVID-19 vaccines.[1,2] Dermal hypersensitivity reaction is one such reaction pattern. Clinically, the lesions of dermal hypersensitivity reaction are characterized by papular urticaria-like eruptions lasting for longer than 24 h.[3] Eruptive pseudoangiomatosis (EPA) is a variant of dermal hypersensitivity reaction consisting of benign, self-limiting exanthematous lesions. The lesions of EPA are pinpoint erythematous macules and urticarial papules having a blanched perilesional halo.[4] This series is an extension of our previously published work on post-COVID-19 vaccine EPA with special emphasis on histopathological changes.[5] Herein, we report a series of 37 cases of EPA developing following the administration of COVID-19 vaccine with typical features of dermal hypersensitivity on histopathology.

In our cases, EPA was clinically diagnosed on the basis of classical clinical features in 37 cases (Fig. 1a,b). The lesions clinically manifested as pinhead-sized bright, red maculopapular lesions, which blanch completely on pressure and refill from centre once the pressure is released. Histopathological and dermatoscopic features were noted in cases.

In our study, all patients developed EP following the second dose of COVID-19 vaccination. The most frequently affected age group was between 21 and 30 years (83.8% cases). While 29 (78.4%) cases were asymptomatic, the remaining 8 (21.6%) cases had mild-to-moderate pruritus. The average latency between second dose of vaccination and onset of eruptions was 6.8 days. The lesions resolved on their own within 2 weeks of onset without any postinflammatory dyspigmentation. The lesions occurred following a localized or distant solicited adverse event following immunization (AEFI) after first or both doses of vaccination in all cases. These solicited reactions included injection-site erythema, oedema, pruritus or systemic involvement like transient fever or myalgia.

Dermatoscopic features included central red dots, red globules and perilesional pale structureless areas (Fig. 1c). Histopathologically, there was the presence of moderately dense infiltration of perivascular and interstitial neutrophils, eosinophils and lymphocytes. Other features included papillary dermal oedema and plump endothelium with no RBC extravasation (Fig. 1d). Additionally, the epidermis was silent in all the specimens. On the basis of clinical and histopathological picture, a diagnosis of EPA with delayed dermal hypersensitivity reaction was made.

Localized and generalized delayed dermal hypersensitivity reactions following COVID-19 vaccine are still poorly understood. The prototype localized form of this reaction type is COVID-arm. The role of T-cell-mediated hypersensitivity at injection-site reactions has been observed by Blumenthal *et al.*[1] While we now understand the pathogenesis of COVID-arm, the mechanisms at play in disseminated hypersensitivity reaction are still elusive. However, according to a report by Myrdal *et al.*, these reactions are not a contraindication for subsequent doses of vaccination.[2]

According to our hypothesis, while the first dose of vaccination primes the immune cells, the second dose leads to the elicitation of a hypersensitivity reaction. The role of delayed hostel immunity has also been suggested in the case of urticarial eruptions following COVID-19 even by McMahon *et al.*[6]

In fact, EPA has been reported to develop following COVID-19 infection as well.[7] The latency between infection and onset of EPA further supports the role of delayed hypersensitivity reaction. This suggests that the viral mRNA mounts an immunological response or causes cytokinemia. While type I hypersensitivity reactions are immediate and manifest with anaphylactic reactions mediated by IgE, type IV reactions are T-cell driven and can manifest between 2 and 7 days. Although most delayed hypersensitivity reactions peak between 72 and 96 h after vaccination,[8] our report observed a very delayed onset of hypersensitivity response occurring within a week of vaccination. This finding is consistent with the various other COVID-19 vaccination-related skin hypersensitivity reactions.[2] A case series by Blumenthal *et al.*[1] observed a median latency of 8 days between vaccination and delayed hypersensitivity reactions. Subsequent studies by Ramos *et al.*,[9] Mc Mahon *et al.*,[6] and Johnston *et al.*[10] also observed a median duration of 7 days following vaccination. Such findings strongly suggest that, compared with other hypersensitivity reactions, vaccine-induced hypersensitivity often takes a longer duration to manifest.

Often, widespread vaccine-induced reactions can become a matter of concern for both the patients and the healthcare provider. In our series, delayed dermal hypersensitivity reaction was not associated with any systemic upset. This is consistent with McMahon *et al.*[6] and Myrdal *et al.*,[2] who had emphasized that delayed dermal hypersensitivity reactions are not associated with anaphylaxis.

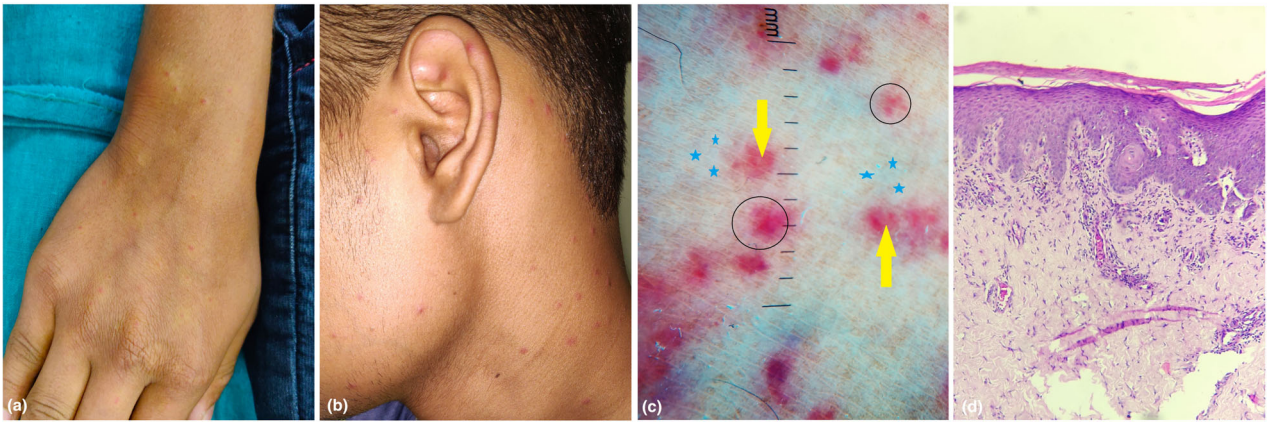

Figure 1 Multiple erythematous papules with perilesional halos (a) involving dorsum of hand in a 24-year-old man, which developed 7 days after vaccination, (b) over face and pinna of a 22-year-old man, which 6 days after vaccination. (c) Dermatoscopic features included red dots (black circles), surrounding dull red structureless-zones (yellow arrow), and pale zones at periphery of lesions (blue stars) seen on Dermlite DL3 10× magnification. (d) Silent epidermis, papillary dermal oedema and mixed infiltrates with dilated superficial vessels, plump endothelium, perivascular neutrophilic and lymphohistiocytic infiltration with absence of red blood cell extravasation (Haematoxylin and eosin stain, ×100).

In conclusion, cases of EPA following the second dose of vaccination commonly develop due to delayed dermal hypersensitivity reactions. However, there are still limited data regarding such reactions. There is a need to conduct larger clinic-histopathological studies over a longer duration for further characterization of these reactions. Owing to the benign and self-limiting nature of such eruptions, the development of EPA is not a contraindication for subsequent doses of COVID-19 vaccine.

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Data availability statement

Data available on request from the authors

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