

progressive improvement of pruritus was noted. The eruption regressed spontaneously after 3 weeks.

Among the cutaneous manifestations of COVID-19 infection, maculopapular rashes account for almost 50% of cases.³ Rarely, these may resemble or are identical to PR. Ehsanixi *et al.* recently reported an otherwise healthy young man with a typical PR eruption concurrent with COVID-19 pneumonia.⁴ Isolated reports of PR developing in asymptomatic patients have also been described.⁵

Drug-induced PR-like eruptions (PR-LE), in contrast to typical PR, often lack the herald patch, tend to be itchy, more diffuse and confluent, and the mucous membranes can be involved. Patients do not experience prodromal symptoms, and blood or/and dermal eosinophilia may be found, and there are no signs of HHV-6/7 systemic reactivation.²

Pityriasis rosea and PR-like eruptions have rarely been observed to develop after vaccinations. Cases of PR/PR-LE after vaccination for smallpox, tuberculosis, influenza, influenza A (H1N1), diphtheria, tetanus, diphtheria-pertussis-tetanus (DTP), papillomaviruses, yellow fever, hepatitis B and pneumococcus have been reported in the literature.^{2,6} In such instances, the average time lapse between vaccination and eruption onset ranged from 5 to 17 days, and the exanthema lasted from 2 to 6 weeks. Differentiation between 'true' PR and PR-LE was difficult and virological investigations for HHV-6/7 reactivation were performed only in a minority of cases. In cases of vaccine-induced PR, a high cytokine response to the vaccine leading to an immune deregulation and reactivation of latent viral infections, such as HHV6 and HHV7, has been hypothesized.⁷ As far as we are concerned, no previous reports of PR developing after COVID-19 vaccination have been reported.

In our cases, prodromal symptoms were absent; the presence of herald patch was present in one case; exacerbation after the second dose administration was observed in one patient; and histopathological findings were consistent with typical PR. Therefore, we suggest that COVID-19 vaccination should be included in the list of potential triggers of PR. Development of PR/PR-LE after COVID-19 vaccination seems to be a rare event. Only further additional reports will demonstrate the real significance and prevalence of this potential side effect of COVID-19 vaccination.

Patient consent for publication

Yes.

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The patients in this manuscript have given written informed consent to the publication of their case details.






Conflict of interests

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Development of eruptive pseudoangiomatosis following COVID-19 immunization – Apropos of 5 cases

To the editor,

In the midst of the trying times whilst the world has come to a standstill by the novel coronavirus disease 2019 (COVID-19) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-

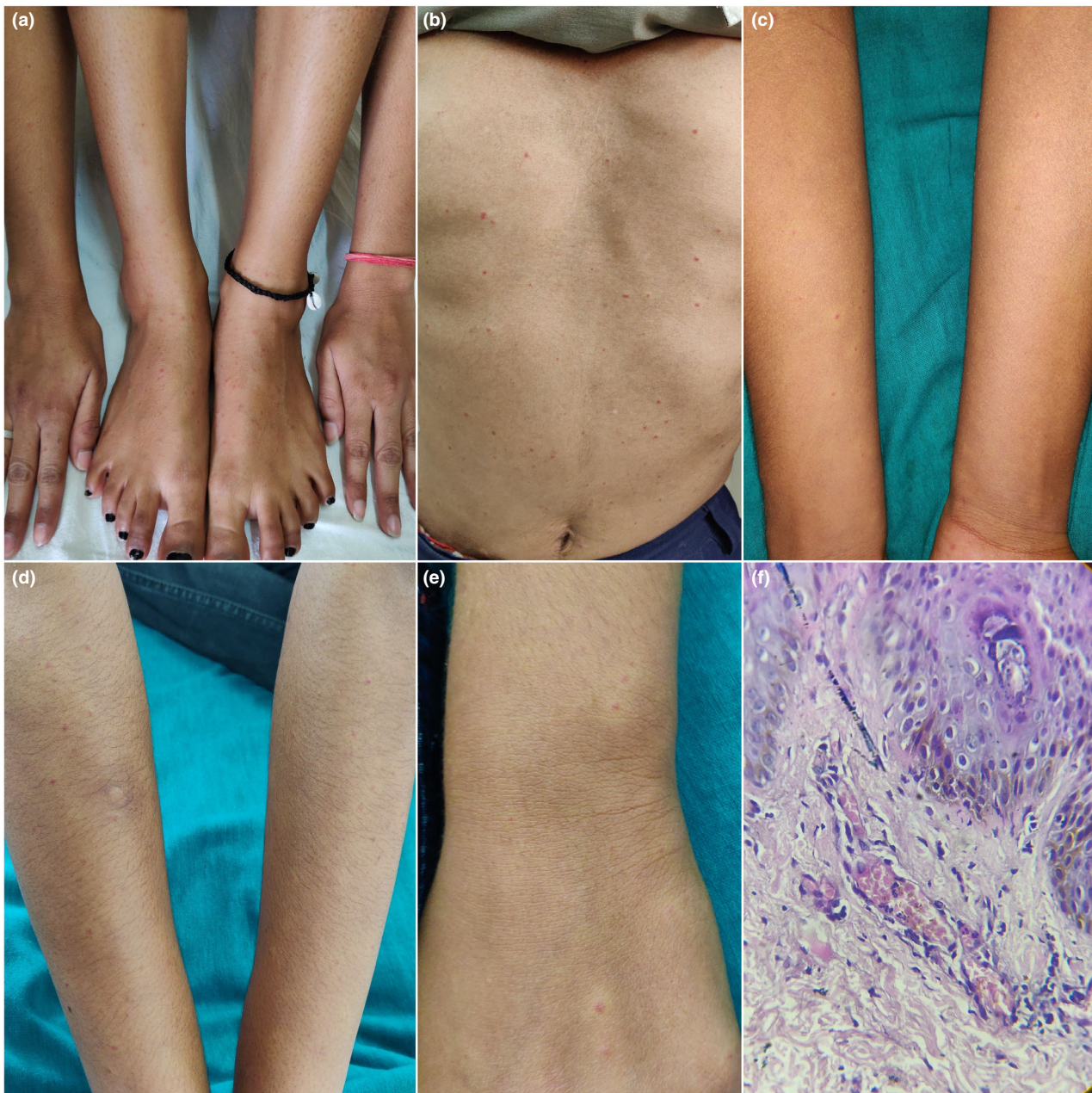


Figure 1 (a) Discrete erythematous papules with blanching perilesional halos around some of the lesions over bilateral limbs in case 1. (b) Another patient with multiple pruritic bright red macules and surrounding pale halo over trunk, which developed 3 days after vaccination. (c) A patient with acral eruptive pseudoangioma having pruritic pinhead-sized erythematous macules and surrounding pallor in all the lesions. (d) Multiple bright red papules with perilesional halo in a patient with generalized eruptive pseudoangioma. (e) Close-up image of the hand in another patient with characteristics lesions. On diascopic examination, the lesions blanched completely and refilled from the centre after the release of pressure. (f) Histopathological analysis of a typical lesion revealing perivascular lymphocytic and histiocytic infiltration, plump endothelial cells, dilated vessels, and absence of RBC extravasation (H and E staining, $\times 400$).

2), there exists an urgent need for safe and effective vaccination against this deadly virus.¹ Currently, there are 93 vaccine candidates against COVID-19 under clinical trial, of which at least 14

vaccines have been approved or authorized.² India started its national vaccination programme against COVID-19 on 16 January 2021 by immunizing health care workers as a priority,

Table 1 Details of patients

Serial number	Age in years/sex	Duration between vaccination and eruption	Associated fever	Site of onset and sites involved	Time taken for resolution (in days)
Case 1	24 years/female	5 d	+	Onset – left hand; followed by generalized involvement	7 d
Case 2	47 years/male	3 d	+	Onset – face; followed by generalized involvement	8 d
Case 3	35 years/male	6 d	-	Onset – forearms; confined to forearms	2 d
Case 4	27 years/male	5 d	+	Onset-trunk; followed by generalized involvement	6 d
Case 5	25 years/male	7 d	-	Onset – legs; confined to bilateral legs and forearms	3 d

followed by those over 60 years of age, and as of 3 May 2021, more than 28 million individuals have been fully vaccinated in India, accounting for 2% of the total population of the country.³ Herein, we report a series of 5 healthcare workers with negative polymerase chain reaction (PCR) testing, who developed eruptive pseudoangiomatosis following Covishield™ vaccination.

Five healthcare workers present to us between the months of January and March 2021, with complaints of multiple eruptive erythematous lesions ranging from size 2–5 mm. All the patients gave a consistent history of onset of eruptions within one week of vaccination. At least 3 patients had complaints of pruritus. The typical papular lesions were erythematous in centre with a pale perilesional halo (Fig. 1a–e). On diascopy, these lesions were completely blanchable and would fill from the centre on release of pressure.

A detailed description of these patients has been provided in Table 1. All 5 patients had received the recombinant ChAdOx1 nCoV-19 coronavirus vaccine (recombinant), also known as Covishield™. The mean duration between vaccination and development of eruptions was 5.2 days. The most common variant was generalized ($n = 3$) followed by acral ($n = 2$). None of the patients had any prodrome of sore throat, gastrointestinal upset or a recallable history of insect bite prior to the onset of lesions. None of the patients had any lymphadenopathy. Whilst cases 1, 2 and 5 had already undergone COVID-19 PCR tests prior to vaccination, we subjected cases 3 and 4 to PCR testing after they presented to us. The investigation reports of all 5 patients turned out to be negative. The cases also denied development of any adverse events after the vaccination. Routine investigations revealed raised ESR in case 2 and leukocytopenia in case 4. Punch biopsy specimen revealed a distinct histology of perivascular lymphocytic and histiocytic infiltration, plump endothelial cells, dilated vessels and absence of RBC extravasation (Fig. 1f).

Based on classical clinical appearance supported by histopathology and a strong temporal association with COVID-19 vaccination, all 5 patients were diagnosed with eruptive pseudoangiomatosis secondary to COVID-19 vaccination. Oral antihistaminics and emollients were advised to patients, followed by complete recovery within 10 days with no recurrence during the follow-up period.

Eruptive pseudoangiomatosis (EP) is a rare, self-resolving exanthem characterized by the sudden appearance of 2–4 mm, asymptomatic blanchable erythematous papules surrounded by a 1–2 mm pale halo resembling angiomata. The disorder results from transitory dermal blood vessel dilation and therefore blanches on pressure. It was first described in 1969 by Cherry *et al.* in four children with high grade fever who were infected with ECHO (enteric cytopathogenic human orphan) virus.⁴ Various other viruses including coxsackievirus, Epstein-Barr virus, adenovirus, cytomegalovirus, insect bite, as well as vaccination, have been proposed as potential etiological agents.^{5,6} The disease has an excellent prognosis and resolves spontaneously within 2–18 days without any residual scarring.

In 2007, Chainotakis *et al.* had proposed a unifying hypothesis of pathogenesis of EP. According to them, EP in children and adults is caused by the same infective agent, presumably a virus that infects the pericytes of small vessels.⁷ Primary infection with the virus, after the first contact, is followed by haematogenous dissemination. Development of EP following vaccination has been reported sparsely in literature.⁶

The development of EP has also been observed after SARS-CoV-2 (COVID-19) infection. This could potentially suggest that the COVID-19 vaccination works by stimulating host's cellular and humoral response against the spike-protein of virus in the same way as the SARS-CoV-2 infection itself. Secondly, it can be hypothesized that the development of EP occurs secondary to an immunological reaction to a viral component and not due to the direct effect of virus on blood vessels.

Our series exemplifies the importance of identifying EP as a potential mild adverse event of COVID-19 immunization. A dermatologist must always be on the lookout for differentiating this underdiagnosed entity from similar spotters such as viral rash, papular urticaria, insect bite reaction and morbilliform rash.

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Pernio-like skin lesions after the second dose of Pfizer-BioNTech COVID-19 vaccine

Dear Editor,

We present the case of a 60-year-old patient who reported the onset of pernio-like lesions on both hands, approximately 14 days after the administration of the second dose of the Pfizer-BioNTech vaccine. Local and systemic symptoms such as pain at the injection site, asthenia and headache of mild-to-moderate severity also appeared following the administration of the first and second doses and resolved within 2 days. Physical examination showed erythematous-violaceous patches and swelling on the fingers, accompanied by itching and burning sensation (Fig. 1). The occasional appearance of livedo reticularis-like manifestations on the lower limbs was also referred.

Laboratory tests (complete blood count, antinuclear antibodies, antiphospholipid antibodies, C-reactive protein, erythrocyte sedimentation rate, serum protein electrophoresis and serum cryoglobulins) were normal, excluding the presence of concomitant systemic diseases.

Given the association between the new onset of pernio-like manifestations and COVID-19 infection,¹ a polymerase chain reaction test for COVID-19 was performed with a negative result.

Pernio or chilblains is an inflammatory condition, frequently affecting women, characterized by erythema and swelling that commonly occur in response to cold on acral regions.

Pernio lesions are generally idiopathic and, in some cases, secondary to other diseases such as systemic lupus erythematosus. Skin biopsy is generally not performed as this clinical condition is not characterized by specific histopathology. In fact, in the reported case no skin biopsy was performed and the diagnosis was clinical. Raynaud's phenomenon, cryoglobulinemia, acrocyanosis and cold panniculitis should be considered in the differential diagnosis.²

Management of pernio skin lesions consists of avoiding exposure to cold and the use of corticosteroids and vasodilatory agents such as nifedipine.³

During the COVID-19 pandemic, an increase in the occurrence of pernio-like acral lesions was highlighted,⁴ and therefore, a correlation between COVID-19 infection and this cutaneous eruption has been hypothesized.⁵

A large international registry-based case series of 318 patients with pernio-like lesions and confirmed or suspected COVID-19 infection showed that skin manifestations were only on the feet in 84% of patients and only on the hands in 5.1% of patients.⁶

The pathogenetic mechanisms that have been proposed to explain the association between COVID-19 and pernio-like eruptions suggest an increase in vasospasm, and pro-inflammatory and prothrombotic activity of the angiotensin II pathway, triggered by cellular infection; furthermore, a massive release of type I interferon could be involved.³

In the reported case, the pernio-like manifestations occurred 2 weeks after the administration of the second dose of the Pfizer-BioNTech vaccine. The patient had never experienced chilblain-like eruptions before; therefore, it cannot be excluded that these manifestations were related to the vaccine.

Pfizer-BioNTech vaccine, administered intramuscularly in two injections 21 days apart, is a nucleoside-modified RNA encoding the SARS-CoV-2 spike protein, which stimulates the production of SARS-CoV-2 neutralizing antibodies and an immune response mediated by antigen-specific Th1-type CD4⁺ T cells and CD8⁺ T cells.^{7–9} The main cutaneous reactions reported in patients who received the mRNA COVID-19 vaccines were reactions at the injection site, urticaria and morbilliform eruption; more rarely have been observed cosmetic filler reactions, zoster and herpes simplex flares, pityriasis rosea-like reactions and pernio eruptions.¹⁰