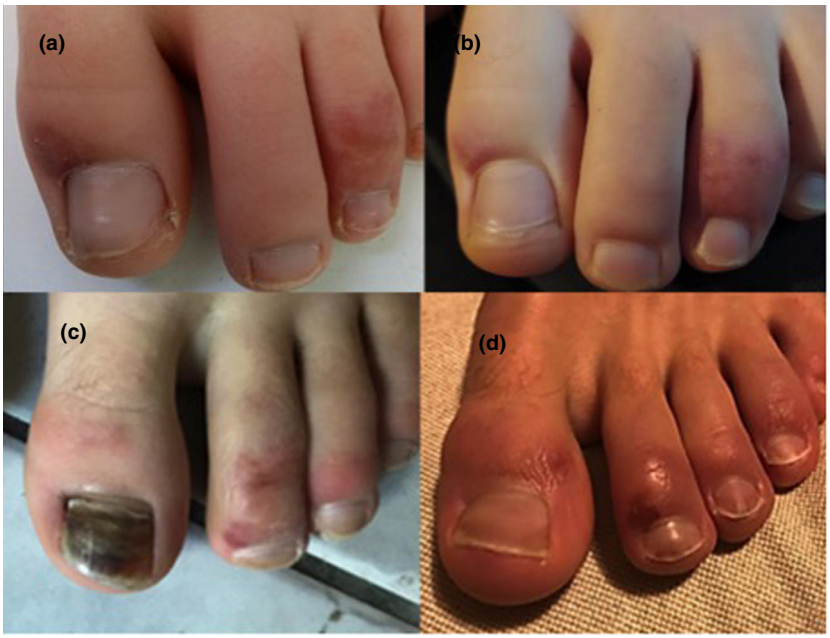

Figure 2 Clinical features of onset and reactivation of chilblain lesions in two patients: (a–b) Patient 1, 13-year-old girl: (a) first manifestation of chilblains in March 2020 spontaneously regressed at the end of April 2020. (b) reactivation of chilblains at the same anatomical site in December 2020. (c–d) Patient 2, 15-year-old boy: (c) in a foot with a pre-existing subungual haematoma, first manifestation of chilblains in March 2020 spontaneously regressed in June 2020. (d) reactivation of chilblain-like lesions at the same anatomical site in December 2020.

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The authors have no conflict of interest to declare.

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All procedures performed in studies involving human participants were in accordance with ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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COVID-19-triggered sarcoidal granulomas mimicking scar sarcoidosis

Editor

Diverse cutaneous manifestations of coronavirus disease-2019 (COVID-19) have been reported including morbilliform, pernio-like, urticarial, vesicular and papulosquamous eruptions.[1] In

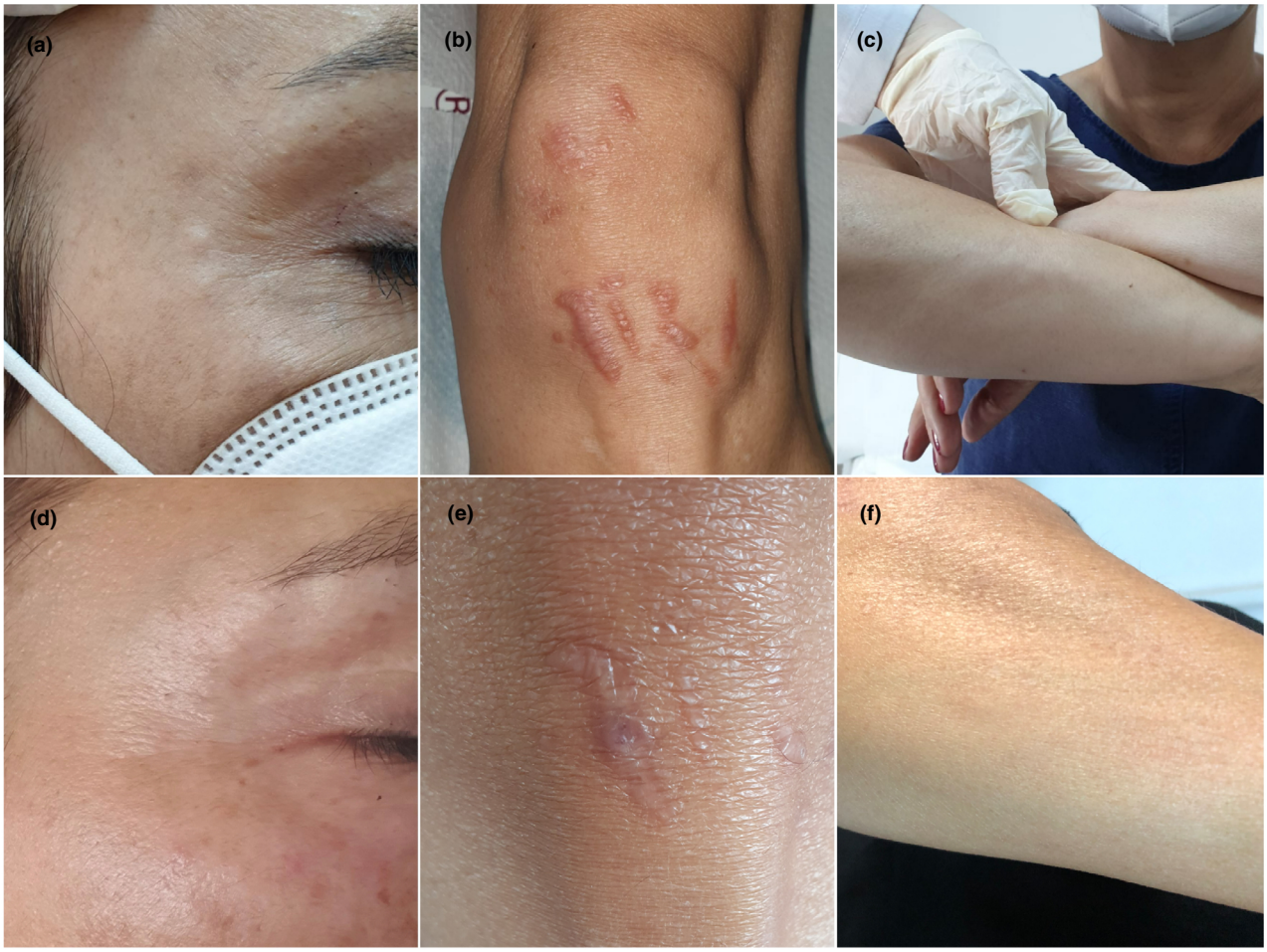

Figure 1 (a, b, c) Subcutaneous papules on periorbital areas at the sites of botulinum toxin-A injection (a), multiple, infiltrated and reddish plaques in old scar sites (b), and subcutaneous nodules on both arms (c); (d, e, f) all cutaneous sarcoidal lesions were almost completely resolved within four months.

the context of association between COVID-19 and sarcoidal granulomas, only one case of sarcoid-like granulomatous subcutaneous nodules was reported, which developed 2 to 3 weeks after the COVID-19 diagnosis.[2] We report on a case of sarcoidal granulomas mimicking scar sarcoidosis in a patient diagnosed with COVID-19.

A 55-year-old woman presented with infiltrated, reddish and tender plaques over old scar sites on both knees, multiple, rounded, mobile and tender subcutaneous nodules of 1–2 cm in diameter on both arms, three subcutaneous papules measuring 3–4 mm on periorbital areas and a single papule in the glabellar region (Fig. 1a–c). Papules on periorbital and glabellar areas corresponded to the sites of botulinum toxin-A injection that had been performed three months earlier. The patient had a history of hypertension, hyperlipidemia and hypothyroidism.

On 9 March 2020, she had had sore throat, cough, fatigue, arthralgia and anosmia, for which a nasal swab test by reverse transcriptase real-time polymerase chain reaction (RT-rtPCR) yielded a positive result for COVID-19 infection. She had been followed up without treatment for 10 days. One month after the first manifestations of COVID-19, she had noticed swelling of her old scars. One month later, small papules appeared at the sites of the botulinum toxin-A injection as well as multiple larger subcutaneous nodules in both elbows.

Histopathological examination of a punch biopsy from an infiltrated plaque on old scar showed non-necrotic, naked granulomas in the superficial and deep dermis suggestive of a sarcoidal granuloma (Fig. 2). An excisional biopsy of a subcutaneous nodule showed similar findings. We then investigated some possible viral traits through subjecting both specimens of sarcoidal granulomas to RT-rtPCR testing to detect viral RNA from blood. Two sets of RNA samples were extracted from formalin-fixed paraffin-embedded (FFPE) tissue specimens using the FFPE RNA kit (Qiagen RNeasy, Germany). RT-rtPCR was performed using Bio-Speedy®

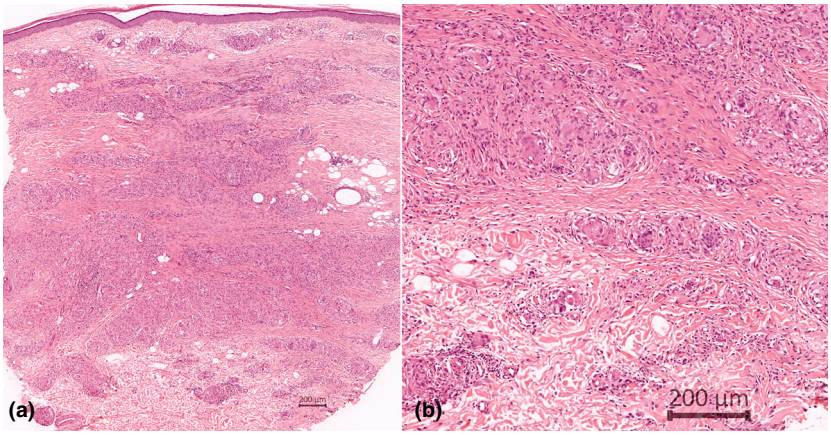

Figure 2 (a) Panoramic view of punch biopsy shows granulomatous inflammation in the entire dermis, especially in the lower half (HE [haematoxylin–eosin]); (b) well-delimited granulomas formed by histiocytes and many giant cells. Few lymphocytes participate (HE).

COVID-19 RT-qPCR Detection Kit (Bioeksen, Turkey) on a Rotor-Gene Q 5plex real-time PCR device (Qiagen, Germany). Both samples were negative for COVID-19.

A biopsy from the labial minor salivary gland, a chest X-ray, blood chemistry tests and pulmonary and ophthalmologic examinations showed no involvement of sarcoidosis. Serum antibody testing including immunoglobulin (Ig) M and IgG against nucleocapsid proteins of COVID-19 yielded positive results four months after the infection. As there was no evidence for systemic sarcoidosis, the patient was followed up without treatment. Her lesions began to regress spontaneously within one month. At the next visit, which corresponded to 8 months after the diagnosis of COVID-19, facial lesions had resolved, subcutaneous nodules substantially diminished, and the scar lesions become paler with a slight induration (Fig. 1d–f). Serologic testing was negative for IgM, but positive for IgG with an increase by 30% from the baseline, the latter was still positive at high titers at 13 months.

Sarcoidal granulomas are characterized by compact, epithelioid, non-necrotizing lesions with varying degrees of lymphocytic inflammation, resulting from an excessive immune response through activation of mainly T helper-1 (Th1) and, in part, Th17 cells and release of cytokines including interleukin 2 (IL-2), IL-12, IL-17, IL-22, interferon γ (IFN-γ) and tumour necrosis factor-α (TNF-α).[3] At earlier phases of granuloma formation, a higher production of TNF-α, IFN-γ and IFN-γ-mediated activation of signal transducer and activator of transcription 1 have been shown.[4]

In cases in which primary sarcoidosis is ruled out, sarcoidal granulomas may develop as a result of immune response and delayed-type hypersensitivity reaction to various antigenic stimuli.[3,5] Thus, COVID-19, where type-I IFN is considered to play an essential role in the first-line antiviral defence, might well have served as an antigenic trigger in our case.[6] Moreover, IFN-γ has been reported to play a central role in COVID-19-related cytokine storms.[7] Increased expression of IFN-γ in CD4+ T cells followed by activation of adaptive immune responses may have initiated sarcoidal granuloma formation. Trauma areas, i.e. scar and injection sites, which are of high antigenic content, might be primarily affected from COVID-19-triggered immunologic reactions, particularly cytokine storms.

Currently, cutaneous sarcoidal granulomas are not included among the skin lesions associated with the COVID-19 infection, possibly because of the rarity and late occurrence of the symptoms. The exact pathophysiology of late manifestations of COVID-19 is yet to be clarified. A delayed immunologic response triggered by prolonged or late cytokine storms might give rise to granulomatous lesions which might be challenging, if localized over old scar sites mimicking scar sarcoidosis, as in the present case. This case may suggest a causal relationship between viral infections and sarcoidal granulomatous reactions.

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Conflict of interest

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Under-representation of people of African ancestry in publications on the cutaneous manifestations of COVID-19: coincidence or physiology?

To the Editor,

Recent publications have highlighted the rarity of patients with dark skin among COVID-19-related skin eruptions.[1] Indeed, very few patients of non-European descent were reported among 318 cases of COVID-19-related perniosis[2] and there was a virtual absence of 'Covid toes' among a large population of African-American and Hispanic patients during the COVID-19 outbreak in New York City.[3]

These results prompted us to review the clinical charts and photographs of 80 patients referred by general practitioner, private practice dermatologists or emergency services to our department for chilblain-like lesions during the first wave of COVID-19 outbreak in Paris, between 9 April and 16 April 2020. None of the patients were of sub-Saharan African descent or had Fitzpatrick's skin phototype of 5 or 6. These findings contrast with the usual visits to our institution – 30% of our outpatient population are of sub-Saharan African descent, with phototype 5 or 6.

Two recruitment biases may be cited as reasons for the 'ethnic' differences in relation to COVID-19-chilblain-like lesions, but none of them seems plausible. Poor visibility of erythema and inadequate training in recognizing skin manifestations in richly pigmented skin is unlikely to be pertinent in this setting, given that chilblain-like lesions are usually symptomatic and hence unlikely to be missed/neglected by either patients or doctors. Socio-economic factors precluding access to dermatological care cannot explain the virtual absence of chilblain-like lesions in African-American and Hispanic patients in New York.[4] Finally, data from all the published studies support ethnic differences in relation to the incidence of COVID-19-related chilblain-like lesions. Vascular skin reactions of poor prognosis, such as ecchymosis or necrosis, were not reported in the study by Lester *et al.*[1] nor in a short case series of COVID toes in people of Fitzpatrick skin types III to V.[5]

In most of the published series, chilblains appeared to affect young patients with discrete to mild symptoms of COVID-19 and no microbiological or serological evidence of SARS-CoV-2 infection. This has led Hebert et al. to refute any link between SARS-CoV-2 infection and such lesions.[6] According to these authors, several biases could contribute to the concomitance of COVID-19 and chilblains outbreaks; however, such biases could hardly account for the aforementioned differences between patients of diverse ethnic backgrounds.

It is noteworthy that patients of African descent not only show fewer, if any, chilblain-like lesions, but also have a poorer prognosis when infected by the SARS-CoV-2.[4] This could suggest a pathophysiological link between a more effective immune response to SARS-CoV-2 infection and the development of acral vascular lesions. According to this hypothesis, the restriction of chilblain outbreaks primarily to people of European ancestry may be due to genetic factors (e.g. those impacting immune response) that predispose to the development of both chilblains and milder forms of COVID-19.

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