No antibody response in acral cutaneous manifestations associated with COVID-19?

Editor,

Skins symptoms during COVID-19 have been recently described, but their relation to SARS-CoV-2 is unclear while results for real-time reverse transcriptase polymerase chain reaction (rRT-PCR) testing were variable.[1–3] Recalcati *et al.*[2] reported 14 cases of patients with skin symptoms consistent with previous described COVID-19 lesions, but all the patients were tested negative. They asked for a serology to validate the hypothesis that these lesions are related to COVID-19.[2]

We identified ten patients (median age 27 years) with acral cutaneous manifestations suggestive of COVID-19 and

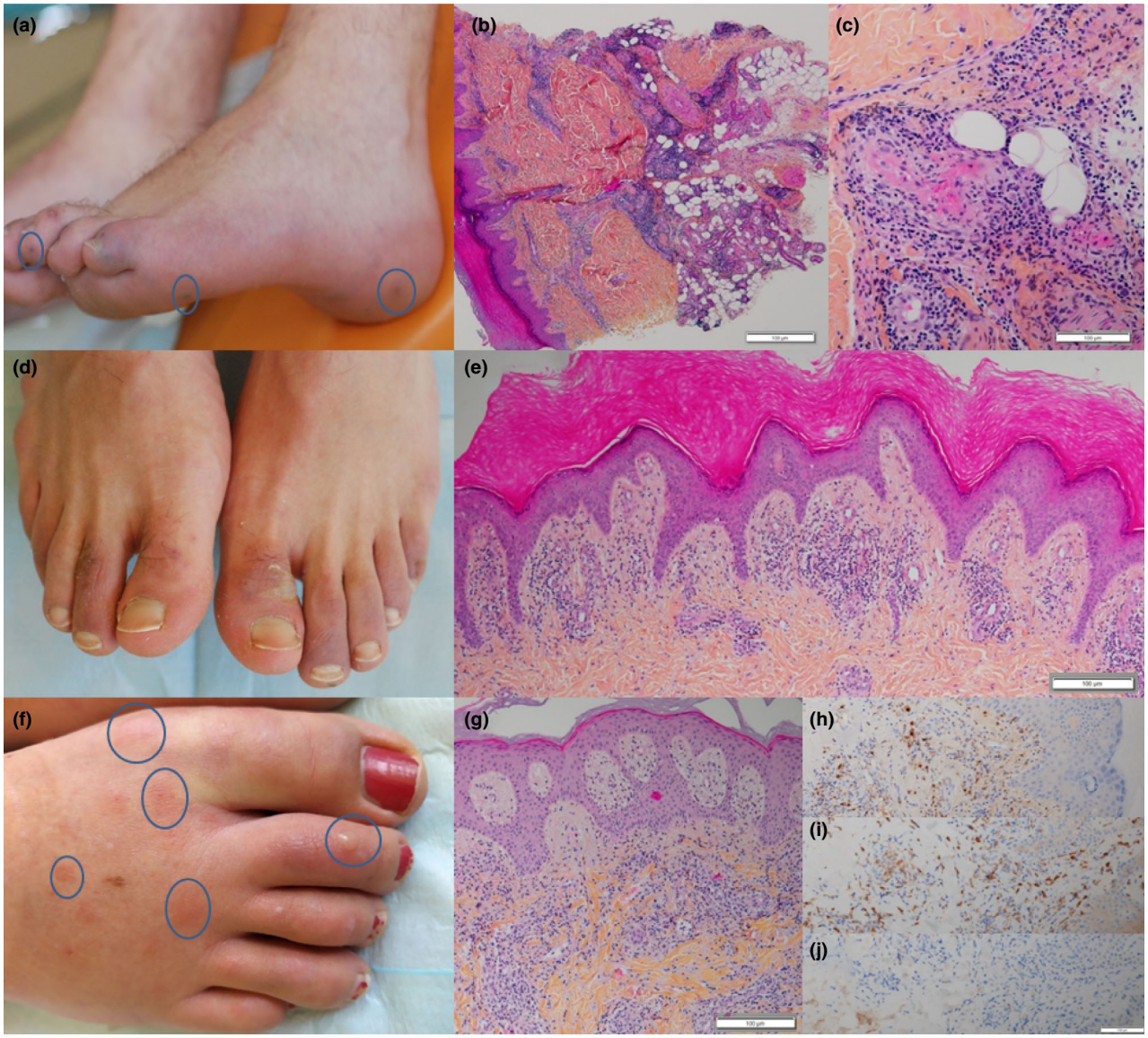

Figure 1 Acral cutaneous manifestation and associated histological findings in three patients. (a) Chilblain-like lesions of the tips of the toes with associated lesions on the soles. (b) Superficial and deep perivascular and perisudoral lymphoide infiltrates (HPS). (c) Parietal fibrinoid necrosis in a deep dermal arteriole (HE&S). (d) Violaceous chilblain-like lesions. (e) Superficial and deep perivascular lymphoide infiltrates slightly lichenoid (HE&S). (f) Chilblain-like lesions with vesiculo-bullous lesion and forefoot involvement. (g) Oedema of the papillary dermis, lymphocytes, histiocytes and histiocytoid cells infiltrates with caryoclasia (HE&S). (h–j) Immunohistochemistry staining: histiocytoid cells marked with myeloperoxydase (h), anti CD163 (i), and not CD15 (j)

serological assay, rRT-PCR on nasopharyngeal swab (n = 10), skin biopsy (n = 3) with PCR (n = 4) on histological material were performed. All patients had acral chilblain-like lesions (Fig. 1d). Two patients had non-specific symptoms (asthenia, shiver, conjunctivitis and headache) 6–7 days before skin lesions. The cutaneous lesions consisted in erythemato-violaceous, infiltrated papules or macules, located on the dorsum or the tips of the toes, associated with a mild swelling. They were slightly painful or pruriginous. A bullous evolution occurred in five patients (Fig. 1f). The dorsal aspect of the forefoot (Fig. 1f), the lateral sides of the feet or the heel were also frequently involved. One patient displayed similar lesions on the soles (Fig. 1a). These cutaneous manifestations affected both feet except in one patient. Two patients displayed fingers associated lesions. All of them had favourable outcome without specific treatment within 2–4 weeks. Skin biopsy showed a superficial and deep perivascular and perisudoral infiltrate of lymphocytes and histiocytes (Fig. 1b,e). The infiltrate was slightly lichenoid. In one biopsy, parietal fibrinoid necrosis was seen in a deep dermal arteriole (Fig. 1c). In another one, oedema of the papillary dermis was obvious and histiocytoid cells and caryoclasia accompanied lymphocytes in the dermis (Fig. 1g).

Immunohistochemistry showed a massive infiltrate of both $CD4^+$ and $CD8^+$ T cell, some being granzyme B^+, and of $CD68^+$ $CD163^+$ $CD15^-$ myeloid precursors cells (histiocytoid cells; Fig. 1i,j) that expressed myeloperoxydase in one patient (Fig. 1h), as described in the histiocytoid Sweet Syndrome.[4]

Real-time reverse transcriptase-PCR for SARS-CoV-2 on skin biopsies and nasopharyngeal swabs were all negative. SARS-CoV-2-specific IgA and IgG antibodies (EUROIMMUN, Luebeck, Germany) were undetectable in all patients. Complete blood count, hepatic and kidney functions, C-reactive protein, immunoglobulins blood levels, cryoglobulinaemia, complement system exploration and antiphospholipid antibodies were normal, and HBV, HCV and HIV serology were negative.

Most of dermatological manifestations during the COVID-19 involved the cutaneous microvascular system with acral eruption with possible bullous evolution, chilblain-like lesions, transient livido reticularis and acrocyanosis.[1–3,5] Because endothelial cells express ACE2, a receptor for SARS-CoV-2, microvascular lesion is consistent with pathophysiology of COVID-19. While evidence of SARS-CoV-2 in the lung during the acute phase has been provided through electron microscope, immunohistochemical staining and rRT-PCR, only inflammatory lesions were found in other organs and tissues.[6] In support, none of our patients were positive for SARS-CoV-2 on rRT-PCR on skin biopsy nor had detectable anti-SARS-CoV-2 antibodies, despite an overall sensitivity of serological assay above 80%.[7] We propose that these skin lesions could be due to cytotoxic CD8 T cells, locally recruited to kill some infected keratinocytes and/or endothelial cells. Accordingly, SARS-CoV-2 proteins have been previously evidenced in a COVID-19 patient with similar cutaneous manifestations.[8] During COVID-19, lower levels of specific antibodies have been reported in patients with mild compared to severe disease[9] suggesting that T-cell exhaustion and viral-associated immunosuppression may dampen the production of SARS-CoV-2 specific antibodies.[10] Inability of the host immune system during mild form of the disease to completely clear the virus may contribute to explain these delayed cutaneous lesions without detectable antibody production.

Acknowledgement

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

Conflict of interest

We declare no conflicts of interest.

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Retiform purpura as a dermatological sign of coronavirus disease 2019 (COVID-19) coagulopathy

Dear editor,

Since December 2019, coronavirus disease 2019 (COVID-19) has spread worldwide to become a pandemic. Multiple skin manifestations related to the infection have been described progressively. Recalcati[1] asserted that 20.4% of infected patients developed cutaneous manifestations, and Galván-Casas *et al.*[2] have recently proposed five clinical patterns (pseudo-chilblain, vesicular, urticarial, maculopapular and livedo/necrosis). We report a case of COVID-19 with retiform purpura and its histopathological correlation.

A 79-year-old woman presented to the Emergency Department with a 7-day history of high temperature (up to 39°C), asthenia, cough, shortness of breath and livedoid skin lesions on her legs. Physical examination showed painful retiform purpuric-violaceous patches of 15 cm with some haemorrhagic blisters and crusts on both legs (Fig. 1) suggestive of retiform purpura. Two punch biopsies were performed. Conventional histology showed multiple thrombi occluding most small-sized vessels of the superficial and mid-dermis (Fig. 2a). Direct immunofluorescence showed the deposition of IgM, C3 and fibrinogen within superficial-to-deep dermal blood vessel walls (Fig. 2b). In addition, C9 deposition was also revealed on the vessel walls by immunohistochemistry (Fig. 2c). Blood tests showed elevation of acute phase reactants, leukopenia and D-Dimer of >10 000 ng/mL (reference value, <500). RT-PCR from a nasopharyngeal swab specimen confirmed a SARS-CoV-2 infection. The patient was hospitalized and treated with hydroxychloroquine (200 mg bid), azithromycin (250 mg/day), lopinavir-ritonavir (200 mg/50 mg bid) and low-molecular-weight heparin. After some days, given the lack of clinical improvement and the need for oxygen therapy a chest CT was performed, showing a segmental pulmonary thromboembolism in the right lower lobe. Anticoagulation was changed to fondaparinux due to progressive thrombocytopenia. Anti-platelet factor IV, antiphospholipid antibodies, lupus anticoagulant, crioglobulinemia and serum and urine immunofixation were all negative. Three weeks after hospital discharge, the patient continues with anticoagulation treatment and her cutaneous lesions are slowly recovering.

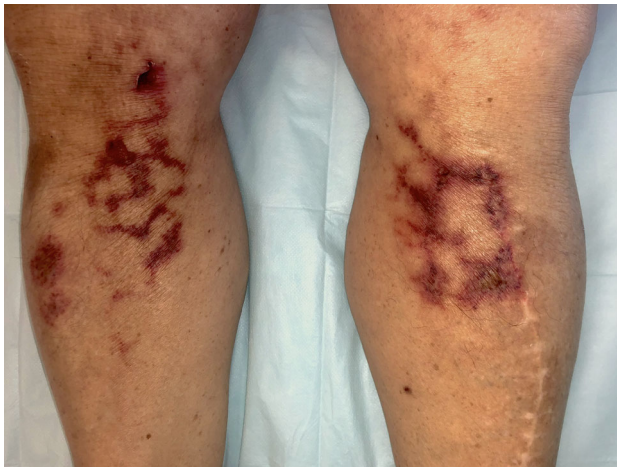

Figure 1 Bilateral retiform purpura in both legs.

COVID-19 can be associated with coagulopathy which indicates a worse prognosis.[3] The activation of both alternative and lectin-based complement pathways plays a key role in this procoagulant state and microvascular injury,[4] but the exact pathophysiology is still unclear. Skin manifestations of COVID-19 coagulopathy can vary from transient unilateral livedo reticularis in mild cases[5] to disseminated intravascular coagulation with true-ischemic lesions in critically ill patients.[6] Purpura, Raynaud's phenomenon, chilblain-like and erythema multiforme-like lesions in young asymptomatic patients have also been observed with this infection, although the connection with coagulopathy is unknown.[7,8] Our patient presented with retiform purpura as a cutaneous manifestation of COVID-19 coagulopathy. Galván-Casas *et al.*[2] linked the livedoid/necrotic lesions to older patients and severe disease (10% mortality) but no biopsies were performed. In the present case, histology showed thrombi in small cutaneous vessels, with complement pathway activation as demonstrated by C3 and C9 deposition. Heparin was changed to fondaparinux after suspecting heparin-induced thrombocytopenia, but Fan *et al.*[9] described mild thrombocytopenia (100–150 $\times$ 10^9/L) in 20% of COVID-19 patients.

Our case highlights the concomitant presentation of cutaneous microthrombi presenting as retiform purpura and macrothrombi presenting as pulmonary thromboembolism in the setting of COVID-19 coagulopathy. To our knowledge, there have been no histologically proven cases describing this phenomenon. We hope that in the coming months, pathophysiology of skin manifestations secondary to coagulation alterations will be better understood. From now on, we will have to include

