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Letter-to-the-Editor

SARS-CoV-2 spike protein is present in both endothelial and eccrine cells of a chilblain-like skin lesion

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Dear Editor,

Data on SARS-CoV-2 detection in lesional skin is controversial.[1-8] We report a PCR-proven COVID-19 patient with a chilblain-like SARS-CoV-2 positive skin lesion. An 80-year-old woman presented to the emergency department at the End of March 2020. She reported an onset of fever (38.4 C°) several days before admission, along with cough and shortness of breath. RT-PCR from a nasopharyngeal swab was positive for SARS-CoV-2. An X-ray showed evidence for right-sided pneumonic infiltrates. A blood collection revealed increased leukocyte count, C-reactive protein, ferritin, and decreased sodium. She was treated with nasal oxygen, intravenous sodium chloride infusions, and transient hydrocortisone to substitute possible hypocortisolism. After 3 weeks the patient showed an asymptomatic violaceous scaly patch on the left thumb without a history of preceding trauma etc. On discharge after 4 weeks, the patient was fully recovered from her respiratory illness. Consecutive nasopharyngeal swabs were negative for SARS-CoV-2. A fortnight after the discharge blood test revealed anti-SARS-CoV-2 IgG and IgA positivity. Histology, immunohistochemistry, and RT-PCR data of two skin biopsy specimens are displayed in **Figs 1** and **2**.

From the clinicopathologica point of view, the appearance of the lesion described in the present case would fit at best into the chilblain-like acral pattern of COVID-19 associated skin changes.[1] Reports on direct or indirect SARS-CoV-2 investigation in skin lesions of COVID-19 patients are relatively rare yet.[4-8] Santonja et al.[5] recently found granular positivity of spike protein in dermal endothelial cells and epithelial cells of eccrine glands of a RT-PCR-negative patient with chilblain-like lesions. Trellu et al.[6] and Ahuoach et al. [7] performed RT-PCR for SARS-CoV-2 in two COVID-19 patients with skin eruptions. However, SARS-CoV-2 RT-PCR was negative in these cases. Moreover, Kanitakis et al.[3] and Herman et al.[8] performed RT-PCR in chilblain-like lesions of 25 COVID-19 patients and did not find evidence for SARS-CoV-19 skin infection. Interestingly, chilblain-like lesions have frequently been reported to be associated with COVID-19, although a causal relationship is often difficult to prove since SARS-CoV-2 infection has not been detected in many cases.[1-5] Similar to the reports of Torello et al.[4] and Santonja et al.,[5] the positivity for SARS-CoV-2 assessed in our case by RT-PCR as well as immunohistochemistry strongly suggest a pathogenetic link between the SARS-CoV-2 infection and the chilblain-like lesion observed. COVID-19 infection robustly stimulates the expression of interferon-inducible genes significantly assisting in anti-viral responses of the host. Similar to the rare monogenic auto-inflammatory interferonopathies, characterized by chilblain-producing microangiopathy, the SARS-CoV-2-triggered interferon stimulation may result in chilblain-like lesions in COVID-19 patients as well.[4-8] A notion further corroborated by the detection of increased expression of

kallikrein and SDF-1 mRNA in lesional skin. A function of angiotensin-converting enzyme 2 (ACE2) is to decrease levels of bradykinin, thus affecting the renin-angiotensin system (RAS) and the kallikrein-kinin system (KKS). A systemic decrease in ACE2 function impacts the RA-KK systems increasing clotting. Given the direct participation of ACE2 in RAS as well as KKS, it is probable that those systems directly contribute to local and systemic inflammation and prothrombotic effects in COVID-19, as also supported by our histology.[9] Increased protein as well as gene expression of ACE2 has recently been reported in the review by Zhao et al.[10] In conclusion, SARS-CoV-2 can be detected in COVID-19 associated skin lesions and may be directly involved in the pathogenesis of cutaneous manifestations of COVID-19. Enhanced expression of kallikrein and SDF-1 mRNA in lesional skin indicates an ongoing inflammatory and prothrombotic local response. The detection of SARS-CoV-2 components in eccrine glands – corroborated by the notion that the closely related SARS-CoV is also present in sweat glands [5] - indicates sweat as a possible source of contagion.

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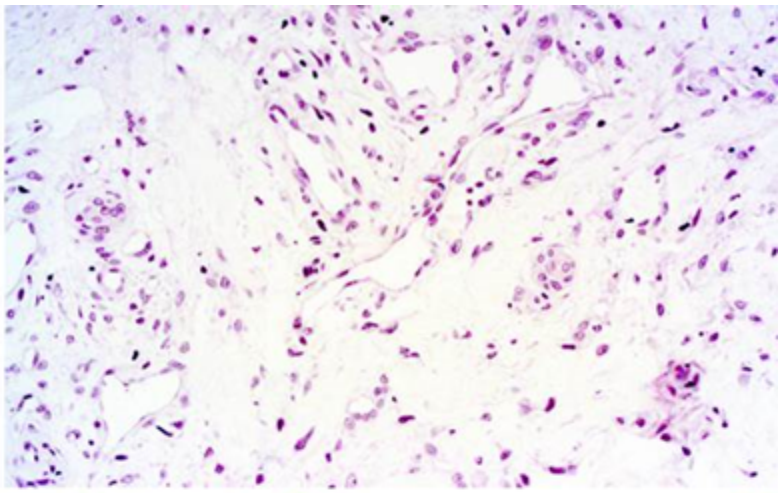
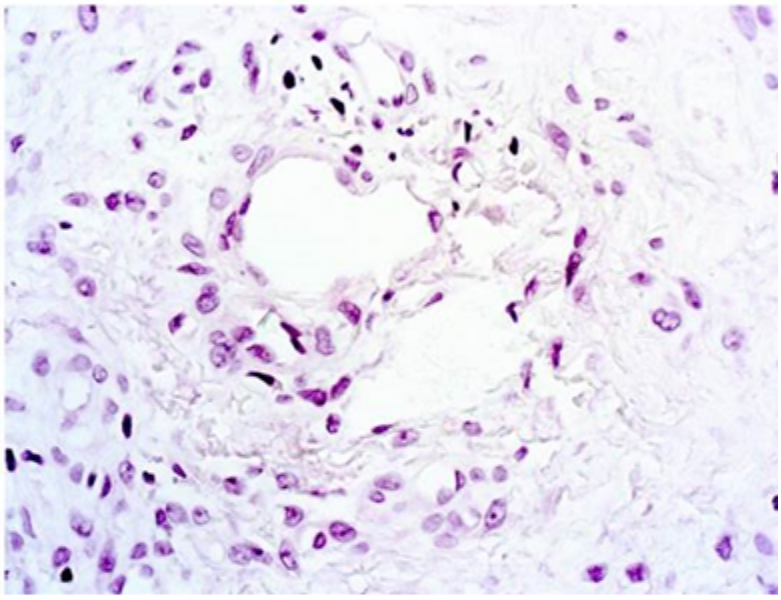
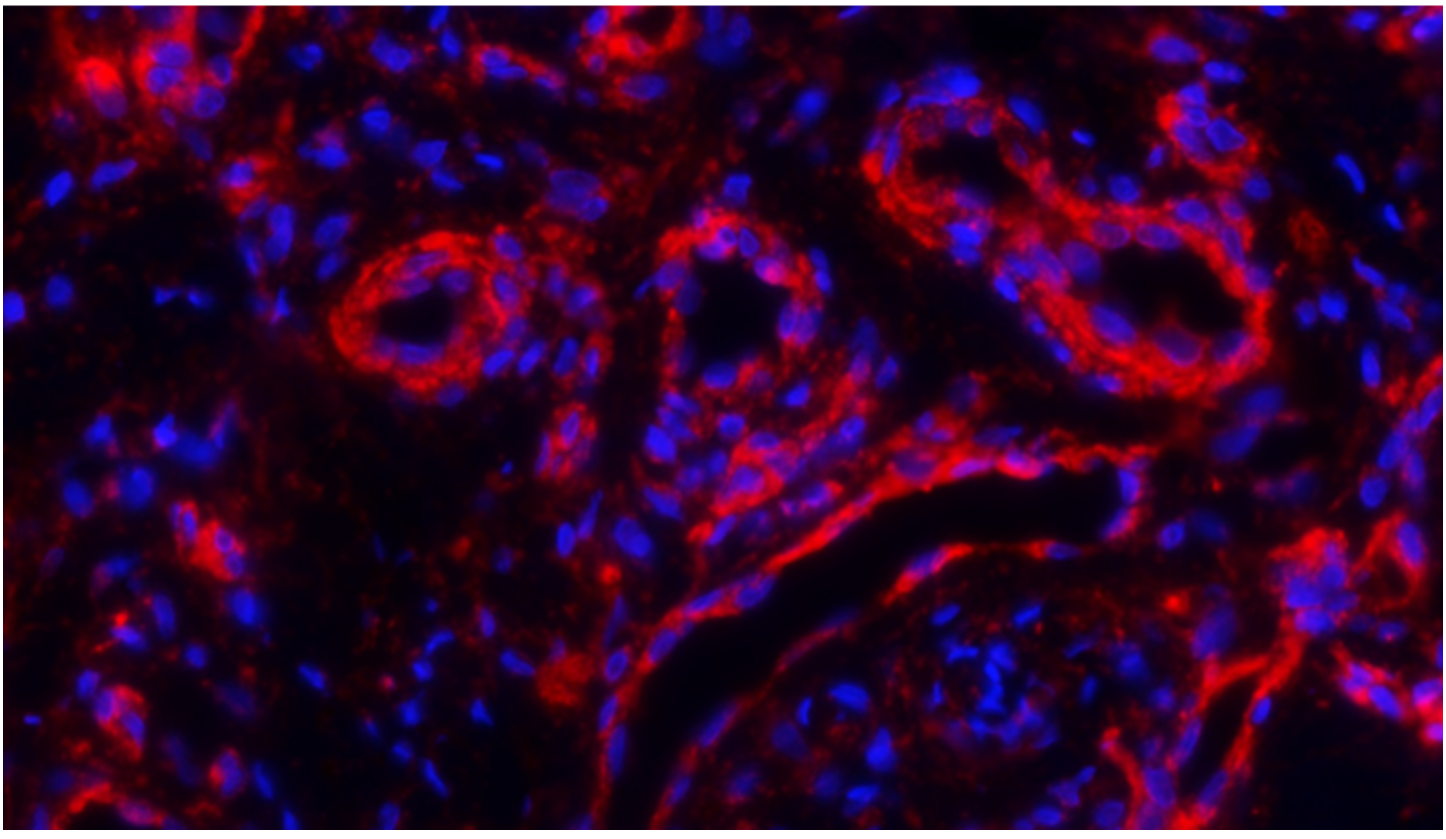
The patient in this manuscript have given written informed consent to the publication of her case details

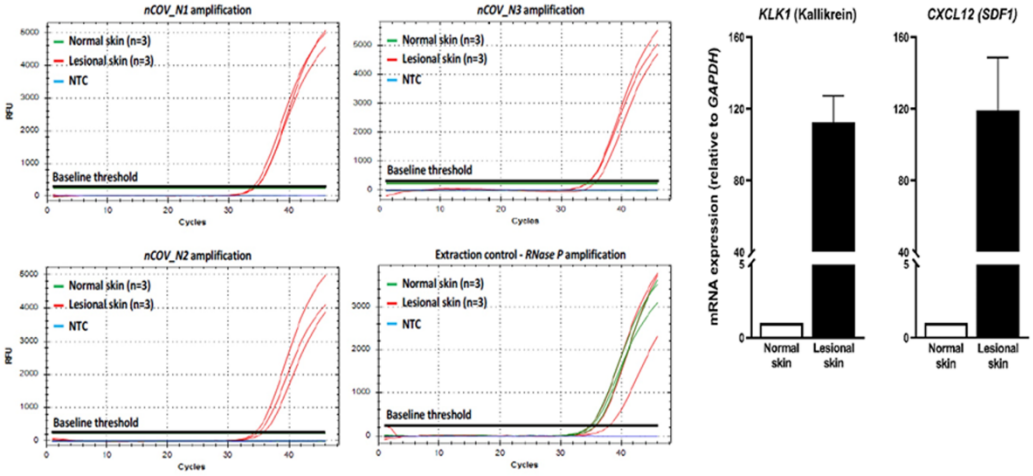
Fig. 1. On the left upper side of the figure, clinical appearance of an erythematous-violaceous desquamative patch on the left thumb (arrow: site of skin biopsies) - chilblain-like skin lesion in a COVID-19 patient. Haematoxylin-eosin staining revealed focal parakeratosis and acanthosis in the epidermis. The dermis contained mild perivascular as well as in part diffuse lymphohistiocytic infiltrates. In some small mid-dermal vessels there were fibrinoid deposits and occlusions (right upper side). Detection of SARS-CoV2 spike protein by fluorescence immunohistochemistry in Opal-technology using Clone [1A9]) from Gene Tex, GTX632604 (lower part of the pic).

Fig. 2. Detection of SARS-CoV2 using the 2019-nCOV CDC EUA authorized qPCR probe assay primer/probe mix (Cat No: 10006770; IDT, Iowa, USA) according to manufacturer's instructions (left side). Right part of the figure showing mRNA expression levels of KLK1 (kallikrein), stromal cell-derived factor 1 (SDF1) and GAPDH was measured by SYBR green assay using specific primers (*KLK1*, AGGCGGCTCTGTACCATTTC, GCACACCATCACACATCAGC; *CXCL12*, AAGGTCGTGGTCGTGCTG, TAGCTTCGGGTCAATGCACA; and *GAPDH*, ACCACAGTCCATGCCATCAC, TCCACCACCCTGTTGCTGTA).









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