Illuminating, through immunohistochemistry, the link between SARS-CoV-2 and pernio (chilblains)

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The association between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the acral skin eruption of pernio (chilblains) has been a leading topic of discussion among the global dermatology community during the coronavirus disease 2019 (COVID-19) pandemic. Although the majority of patients with pernio in our previous Mayo Clinic series (published 6 years prior to the current pandemic) did not have a serious underlying systemic disease association, a few patients were found to have Epstein–Barr virus infection.[1] Thus, it is not surprising that other viral infections (such as SARS-CoV-2) could be associated with pernio.

Recent large case series (predominantly from Europe and North America) suggest that SARS-CoV-2-associated pernio typically affects younger patients, is a late manifestation of COVID-19, and generally runs a benign course without associated systemic complications.[2,3] However, a limitation of these studies is that a direct causal link between SARS-CoV-2 and pernio could not be definitively established, due to either lack of, or negative confirmatory testing for SARS-CoV-2 [via nasopharyngeal polymerase chain reaction (PCR) or serum antibody testing] in the majority of patients. Perhaps the skin itself could provide critical insight regarding a causal role of SARS-CoV-2 in pernio?

In analogous fashion, a previous study detected herpes simplex virus (HSV) DNA within skin lesions of erythema multiforme (EM), demonstrating the pathogenic role of HSV in some cases.[4] This provided a clinical rationale for considering molecular testing for HSV DNA on skin biopsy specimens of patients with recurrent EM of unclear cause.

In this issue of the *BJD*, Colmenero *et al.*[5] provide important insight regarding a potential 'missing causal link' through the use of immunohistochemical studies of skin biopsy specimens of seven paediatric patients with pernio during the COVID-19 pandemic. Clinically, the seven patients had a benign course without systemic complications. SARS-CoV-2 PCR swabs were negative in six tested patients, and coagulation studies were normal in six tested patients. Routine microscopy of skin biopsy specimens demonstrated typical findings of pernio (including superficial and deep perivascular and perieccrine lymphocytic inflammation, dermal oedema and variable degrees of lymphocytic vasculitis), similar to previous studies.[3,6,7]

The unique importance of the study by Colmenero *et al.*[5] lies in its use of immunostaining of the spike protein of SARS-CoV-2 on skin biopsies of the seven patients, likely confirming the pathogenic role of SARS-CoV-2 in the development of pernio. All specimens demonstrated positivity for the SARS-CoV-2 spike protein in endothelial cells and eccrine epithelial cells. Electron microscopy was performed in one patient and demonstrated coronavirus-like particles within the cytoplasm of endothelial cells.

Future studies should aim to corroborate the findings of Colmenero *et al.*[5] in adult patients (and to correlate positive immunostaining with the timing of positive nasopharyngeal PCR and serum antibody results), and to develop a commercially available SARS-CoV-2 immunostain to be used in widespread clinical practice. Indeed, such a test would be a welcome addition to the clinician diagnostic toolkit when caring for patients with pernio due to suspected COVID-19 in the setting of negative PCR and antibody testing.

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