histological and immunostaining of skin biopsies of seven cases of 'epidemic chilblains' with negative SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) testing and repeated serology was similar to those of a historical series of 11 cases of chilblains lupus, notably for high expression of CD123 and MxA [a type-I interferon (IFN-I)-induced protein] in both groups.[3] Thus, they hypothesized that chilblains observed during the COVID-19 outbreak are linked to a high IFN response to SARS-CoV-2, leading to both negative RT-PCR and serology due to this effective antiviral response and that development of chilblains is due to IFN production. Their hypothesis is notably based on recent publications showing that impaired IFN response is observed in patients who are critically ill with COVID-19.[4,5]

Even though we agree that it cannot be absolutely excluded, there is no evidence that their reported cases without RT-PCR or serological confirmation are really related to the infection. In our series, where most cases were negative for SARS-CoV-2 both by PCR and serology, it is highly unlikely that they are false-negatives as serology was performed an average of 3 weeks after the onset of manifestation. Secondly, their hypothesis warranted further exploration, notably to confirm the high IFN production in patients with chilblains and negative serology and PCR. Testing of IFN levels was performed in blood samples in two patients in our series and showed a low level of IFN production. In addition, to extrapolate that high IFN production would lead to negative PCR and serology, starting from the findings that profoundly impaired IFN-I response characterized by low interferon production is observed in critically ill patients, is a very speculative hypothesis. Indeed, such high IFN response could be expected to cause other clinical manifestations in addition to chilblains.

Finally, it was previously shown that CD123 immunostaining is not different between chilblain lupus erythematosus and idiopathic chilblains.[6] So, the fact of observing this expression in 'epidemic chilblain' is not an argument for attributing them to SARS-CoV-2. We also observed in five cases a high expression of CD123 in patients with negative serology and without any associated infectious signs.

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## Chilblains and COVID-19: why SARS-CoV-2 endothelial infection is questioned

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**Linked Article:** Colmenero *et al.* Br J Dermatol 2020; **183**:729–737.

Dear Editor, Chilblains observed during the COVID-19 pandemic have led to numerous reports and to a suggested link with COVID.

Recently, Colmenero *et al.*[1] demonstrated, by immunohistochemistry and by electron microscopy (EM), the presence of SARS-CoV-2 in endothelial cells of skin biopsy specimens of chilblains in seven patients. These results raise some questions.

The presence of the virus at cutaneous and vascular levels in otherwise asymptomatic patients with negative reverse-transcription polymerase chain reaction (RT-PCR) is unexpected. Vascular damage by direct viral effect is expected to be a sign of severity. It is also surprising that only feet are affected.

As mentioned by the authors, immunohistochemistry for detection of SARS-CoV/SARS-CoV-2 remains restricted and subject to cautious interpretation. It would be interesting to show the comparative images of controls. In our limited experience, the immunohistochemistry for SARS-CoV-2 (anti-SARS-CoV-2 NP Antibody, BioVision, Inc. Milpitas, CA, USA) in pulmonary specimens from patients with COVID-19 and those without COVID-19 shows similar diffuse and homogeneous nonspecific staining of the vascular endothelium (Figure 1a, b). The staining observed by Colmenero *et al.* concerns vessels that appear to be relatively healthy with no vasculitis or significant perivascular inflammatory infiltrates. Positive and identical immunohistochemistry for SARS-CoV-2 in all seven patients (despite time differences between chilblain onset and biopsies) is also puzzling. We compared SARS-CoV-2 immunostaining in skin biopsy specimens of chilblains

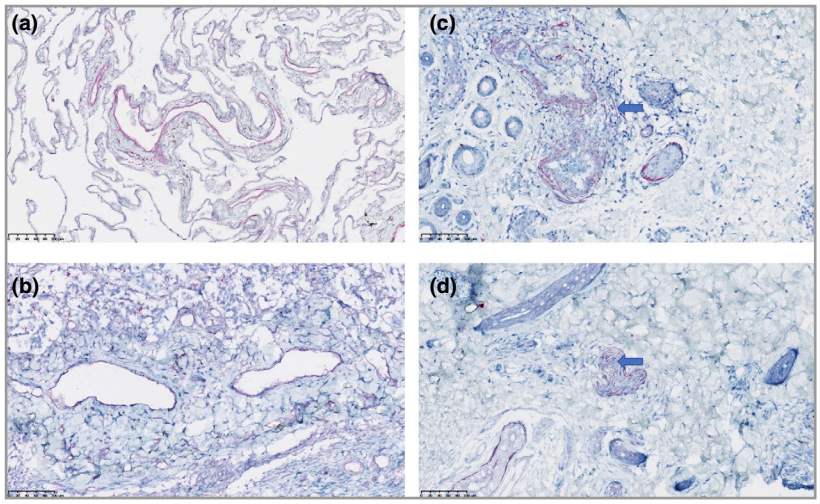


**Figure 1** Immunohistochemistry for SARS-CoV-2 [using anti-SARS-CoV-2 NP Antibody (Clone# 6F10) BioVision, Inc. Milpitas, CA, USA]. (a) Surgical pulmonary resection specimen of a patient without COVID-19 who underwent thoracic surgery in 2019 before the COVID-19 pandemic (original magnification × 20). (b) Autopsy pulmonary specimen of a patient with critical COVID-19 (original magnification × 20). Diffuse endothelial staining of pulmonary vessels can be observed in both cases. (c) Skin biopsy specimens of chilblain lesions during the COVID-19 pandemic (original magnification × 20). (d) Skin biopsy specimens of classical chilblains observed in 2015 prior to any cases of COVID-19 (original magnification × 20). Diffuse endothelial staining of dermal vessels is present in both cases.

observed in patients prior to and during the COVID-19 pandemic. The staining was similar in both cases (Figure 1c, d).

We feel that the EM image of a single patient presented by Colmenero *et al.* is not typical of coronavirus particles. Indeed, coronavirus particles have been described by Goldsmith *et al.* as spherical structures clustered within a membrane that separates them from the cytoplasm. Black dots, corresponding to cross-sections through the nucleocapsid, are affixed to the inside of the viral envelope, and the interior of the particles is usually eletron-lucent.[2,3] The structures observed by Colmenero *et al.* seem isolated and free within the cytoplasm, although we would expect to see accumulation of viral particles in membrane-bound areas. Moreover, they are surrounded by dark dots that may be interpreted as spikes of the coronavirus, whereas the spikes would normally be located on the inside of the cisternal space.[3]

Colmenero *et al.* argue that the negative nasopharyngeal and oropharyngeal PCR in six of their patients may be attributed to low positive rates of PCR in children with symptoms of COVID-19. However, several publications confirmed not only negative PCR, but also negative serological tests in patients with chilblains.[4] Additionally, RT-PCR performed on skin biopsy specimens from 21 patients with chilblains failed to detect SARS-CoV-2 RNA.[4]

In light of the questions raised, in our opinion, these findings seem insufficient to establish definitive infection by SARS-CoV-2 or a direct link with COVID-19 in patients with 'COVID toes'.

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## Chilblains and COVID-19: why SARS-CoV-2 endothelial infection is questioned. Reply from the authors

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Dear Editor, We thank Dr Baeck *et al.*[1] for their interest in our recent article published in the BJD.[2]

The negative reverse-transcription polymerase chain reaction (RT-PCR) in nasopharyngeal swabs in patients with