In view of the above, we continue to support our study conclusion that skin cancer risk is increased in Korean patients with vitiligo compared with the general public.

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Negative tests for SARS-CoV-2 infection do not rule out its responsibility for chilblains

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Dear Editor, We read with great interest the report of Le Cleach *et al.* discussing chilblains as a manifestation of the COVID-19 pandemic.[1] They reported 311 patients with acral lesions occurring during the COVID-19 lockdown in France. The most frequent clinical presentation of these acral lesions was typical chilblains. Among the 150 patients with reverse transcription polymerase chain reaction (RT-PCR) testing and/or serology, only 10 had confirmed COVID-19. They concluded that there is no evidence of SARS-CoV-2 infection in the large majority of patients with acral lesions. They hypothesized that the situation could be due to the media stating that chilblains were caused by SARS-CoV-2 infection and leading to a higher rate of consultation or the lockdown leading to more inactivity and long periods at home barefoot on a cold floor.[1]

We do not agree with this explanation. We recently published cases of chilblains enrolled during the COVID-19 pandemic.[2] We performed the same virological tests, which were also mostly negative, but our conclusion was different. We demonstrated in skin biopsies a high expression of MxA [interferon type I induced (IFN-I) protein] and CD123 (a marker of plasmacytoid dendritic cells, known as the major producer of IFN-I). Histochemical results were comparable to those found in our chilblain lupus erythematosus group. We concluded that chilblain was a manifestation of IFN-I upregulation as observed in genetic interferonopathies. Active viral replication is not necessary to mount an efficient IFN response in SARS-CoV infection. IFN-induced transmembrane protein may inhibit coronavirus replication.[3] This inhibition may be one of the reasons why PCR tests were negative. It was also demonstrated that high expression of IFN-I at the onset of viral infection may induce a depletion of B cells and may explain the negativity of serologies.[4] Moreover, subcutaneous injection of β-interferon is known to induce vasculopathy. We concluded that chilblains reflect a strong antiviral response in patients that are potentially genetically predisposed for high production of IFN-I.

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Negative tests for SARS-CoV-2 infection do not rule out its responsibility for chilblains: reply from the authors

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Dear Editor, With great interest, we read the comment by Battesti and Descamps[1] on our recently published study in the BJD.[2] Their comment is based on their findings that

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