# Relapse of chilblain-like lesions during the second wave of coronavirus disease 19

*Dear Editor,*

The pandemic of coronavirus disease 19 (COVID-19) is ongoing. After a reduction of the spread during summer in Western Countries, a rise of incidence has been registered in the last few months. During the first pandemic wave we described an outbreak of chilblain-like lesions (CLL), affecting in particular children and young adults.[1,2] Similar lesions were also observed in many other dermatologic centres.[3,4] While in summer no more patients with CLL have been reported, during the second wave of infection we faced again new cases of CLL ($n$ = 10, F/M = 9/1, average age 16.6 years). In addition, interestingly, we could document a relapse of CLL in seven young patients previously observed in spring (F/M = 3/4, average age 15.3 years). These latter were otherwise healthy subjects and had no relevant medical history. Screening for autoimmune diseases was negative. Clinical manifestations were perfectly comparable to their first episode (Fig. 1). In these patients, nasopharyngeal swabs and serology for SARS-CoV-2 were performed in spring and showed negative results. Serology was repeated during the relapse, yielding again negative results. In one case we performed a biopsy consistent with histological pictures previously described (Fig. 2).[5] Therefore, both clinical and histological findings were similar to the first episode of CLL. Patients were treated with topical antibiotic and steroid cream with improvement, and follow-up is currently ongoing.

How can we explain this relapse? Common characteristics of CLL patients reported so far are the appearance of the lesions during active pandemic in otherwise healthy young subjects, the frequent history of contact with symptomatic affected patients and the lack, in the majority of patients, of laboratory evidence of SARS-CoV-2 infection. Even if most of the reports correlate CLL to COVID-19, the pathogenetic mechanisms which lead to CLL are, so far, speculative. Several reports link the appearance of CLL to the activation of a type I interferon (IFN) response in infected patients.[6–10] IFN is crucial in the early response to viral infections and its production is higher in infancy and young adulthood and then decreases with age.[6] Achoff *et al.* provided evidence for a role of type I IFN in the pathogenesis of CLL by using immunohistochemistry. They speculated that the direct infection of endothelial cells may be sufficient to induce local type I IFN induction and CLL.[7] This finding has been recently supported by Hubiche *et al.*[6], who demonstrated an increased IFN-alfa response in CLL patients as compared to non-CLL patients with acute COVID-19 infection. The hypothesis of a pathogenetic role of IFNs in the development of CLL is further supported by the observation that patients with chronic type I IFN activation due to rare genetic type I interferonopathies frequently develop chilblain lesions.[8] According to this hypothesis, a strong early type I IFN response would lead to a fast and efficient control of the viral infection by the innate immune system, thus protecting from progression to severe respiratory disease.[9,10] This might be the reason for the low positive rate of nasopharyngeal swabs and the lack of an antibody response in these young patients, who possibly cleared the infection before an antibody response occurs.[4] On this basis, the relapse of CLL would follow a new contact with SARS-CoV-2: the lack of anti-SARS-CoV-2 antibodies made these patients liable to reinfection and to a new IFN response. This new viral contact can be related to the resurgence of the pandemic we are now facing, especially if we consider that most of these patients are children of health workers.

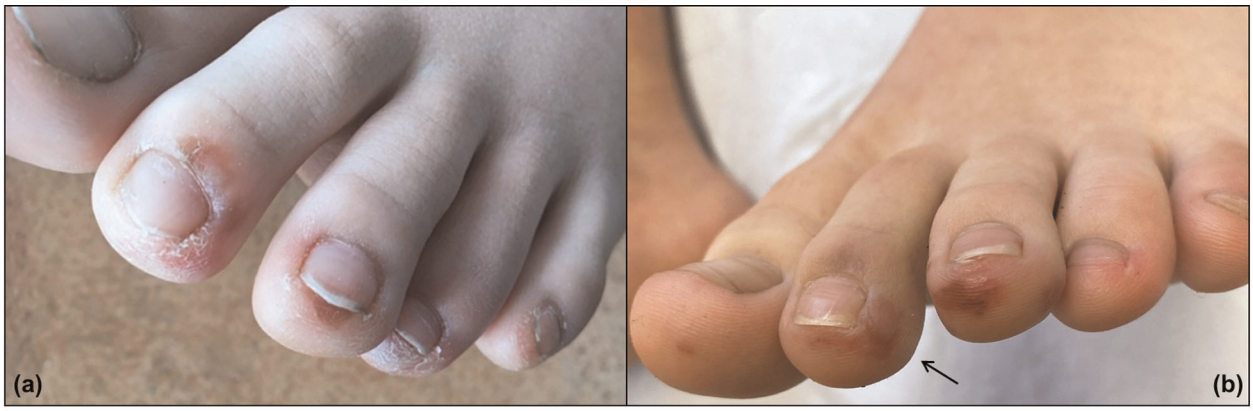


**Figure 1** Clinical presentation of chilblain-like lesions on a feet of a 14-year-old male. (a) First presentation on April 2020. (b) Relapsing lesions on December 2020. Arrow indicates site of biopsy.

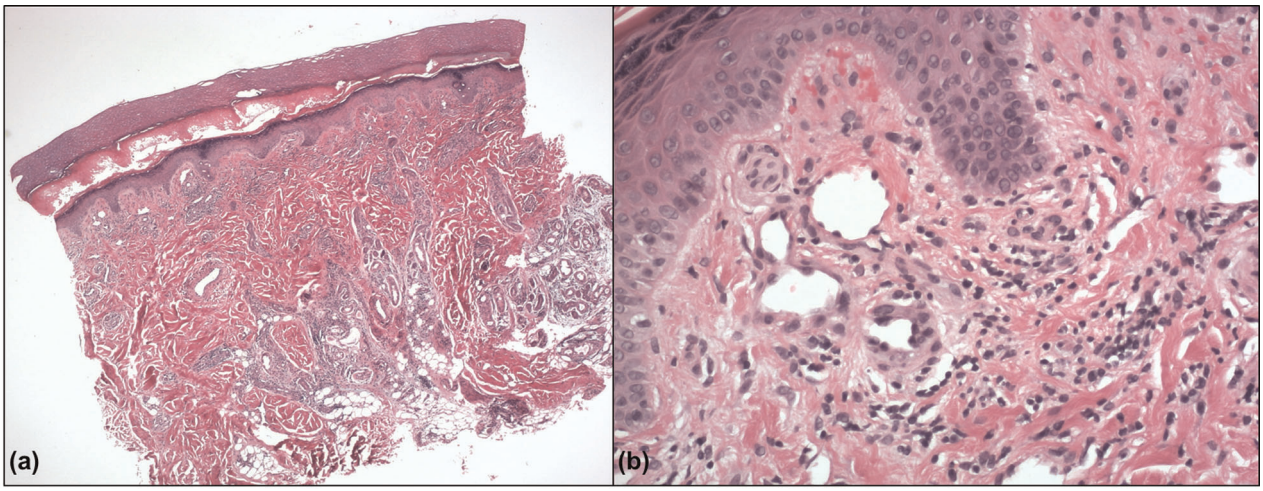


**Figure 2** Histologic findings of patient of Fig. 1. (a) Diffuse perivascular and periadnexal involvement of the dermis and hypodermis by a dense lymphoid infiltrate (H&E, 2,5×). (b) Thickening of the vessel wall and activation of the endothelium with nuclear enlargement (H&E, 20×).

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## Conflict of interest

The authors have no conflicts of interest to declare.

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# Chilblain-like lesions and COVID-19: second wave, second outbreak

*Dear Editor,*

During the first phase of European epidemic of COVID-19, a contemporary outbreak of chilblain-like lesions (CLL) has been reported.[1] After that, hundreds of similar cases have been described in the world. CLL typically appeared in young otherwise healthy patients with no proven SARS-CoV-2 infection, and most studies did not show positivity of PCR of serology. In

 