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Chilblains in a child with confirmed SARS-CoV-2 infection: a red flag for late-onset skin manifestation in previously infected individuals

Dear Editor,

During the COVID-19 pandemic, an outbreak of chilblain lesions has been described worldwide. The relationship with SARS-CoV-2 infection is still debated.^{1–3} Emerging literature regarding this possible correlation focuses on two hypotheses: an endothelial infection or the result of an IFN type I-mediated immune response.^{4,5}

We present the case of a 6-year-old girl with confirmed mild COVID-19 and late-onset chilblains.

Asymptomatic SARS-CoV-2 infection occurred 2 months before our first examination. Nasopharyngeal swab RT-PCR-based SARS-CoV-2 detection was performed because both parents resulted COVID-19 positive. Three weeks after molecular testing, the patient was hospitalized for 5 days due to the onset of diffuse papulopustular rash on the trunk and upper thighs, chilblains associated with severe pain, low-grade fever and marked asthenia. At that time, nasopharyngeal swab for SARS-CoV-2 was negative, routine blood tests were within normal range including C-reactive protein (CRP) and coagulation profile, while IL-6 serum levels were slightly increased. The skin lesions disappeared within 2 weeks.

Three weeks later, on August 2020, the girl was referred to our dermatology unit because of a relapse of the painful lesions on the feet, associated with gait impairment, low-grade fever (37.2°C) and marked asthenia. Clinical examination revealed painful red-purple nodular lesions on the toes and lateral sides of the feet, associated with palmar and fingertips erythema with slight desquamation (Fig. 1). The clinical picture was suggestive of chilblain. Furthermore, the mother reported that her daughter often presented cold and sweating extremities.

RT-PCR nasopharyngeal swab for SARS-CoV-2 was repeated, being negative, while serology test confirmed the positivity of the specific SARS-CoV-2 IgG.

A 4 mm punch biopsy of a right foot lesion showed superficial and deep perivascular dermatitis. Oedema, slight perivascular lymphocytic infiltrate, some thick-walled vessels and proliferation of thin-walled vessels with swollen endothelial cells (endothelialitis) were detected in the dermis (Fig. 2). RT-PCR performed on tissue was negative for SARS-CoV-2. Laboratory assessment was normal, including routine blood test, CRP, coagulation profile (PT, aPTT, INR, fibrinogen, D-dimer), ferritin and inflammatory cytokines profile (including IL6, IL8).

The skin manifestations cleared spontaneously in 3 weeks. A chilblain relapse was observed after 3 months and negative nasopharyngeal swab RT-PCR ruled out virus re-infection.

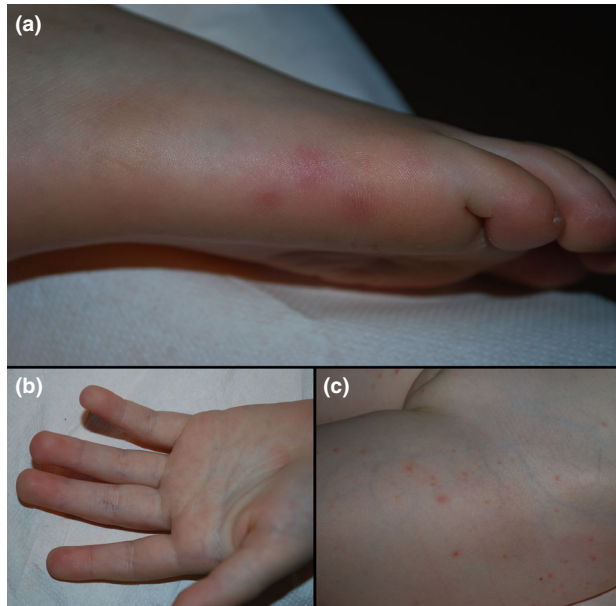


Figure 1 (a) Red-purple nodular lesions on the lateral sides of the foot (chilblains). (b, c) Palmar and fingertips erythema with slight desquamation, and papulopustular rash on the trunk and upper thighs.

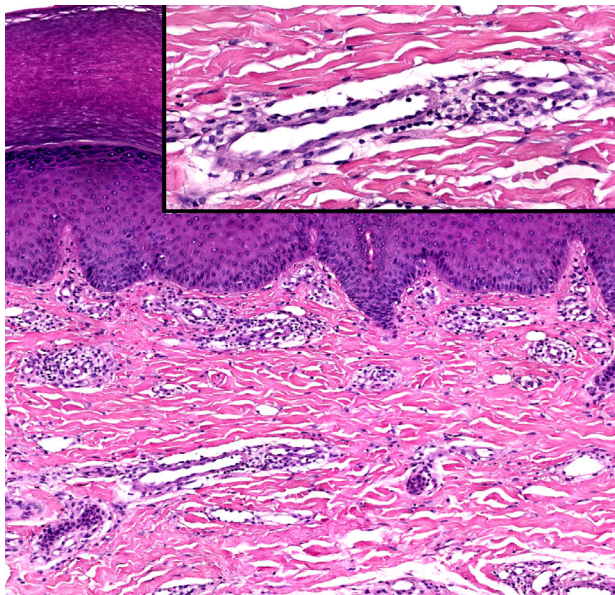


Figure 2 Oedema, slight perivascular lymphocytic infiltrate, some thick-walled vessels and proliferation of thin-walled vessels in the dermis (H&E 10 \times). Inset: Proliferation of thin-walled vessels with swollen endothelial cells (endothelialitis) in the dermis (H&E 20 \times).

This case highlights the relationship between the chilblain manifestation and SARS-CoV-2 infection, confirmed by nasopharyngeal swab RT-PCR and serology test. Moreover, to

the best of our knowledge this is the first report of recurrent chilblains in a confirmed COVID-19-infected case. Skin lesions onset was accompanied by low-grade fever and asthenia, thus representing mild features of COVID-19, as similarly reported by other authors.⁶ Histopathology showed endothelialitis of the dermis vessels, which has been reported during the COVID-19 pandemic. The proliferation of thin-walled vessels with swollen endothelial cells represents a peculiar histological feature of toe chilblain. No fibrin, nuclear debris or neutrophils were detected in the vessels. No histological findings of leucocytoclastic vasculitis were observed.^{7,8}

The negative result of RT-PCR assay on the skin lesion, combined with the positivity of serology tests (IgG) performed during the chilblain relapse, supports the hypothesis that the acral skin injury might not be the result of endothelial infection, but of immune-mediated response triggered by SARS-CoV-2. A robust IFN-I response therefore explains the contemporary low viraemia (often with negative PCR testing) and the localized endothelial damage in the acral site with mild or no associated symptoms.⁵

Genetic, hormonal and environmental factors may also contribute to the development of SARS-CoV-2 chilblains.^{9,10} Further studies are needed to demonstrate this hypothesis in order to better clarify the biological processes underlying SARS-CoV-2-related chilblains.

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Conflict of interest

Nothing to disclose.

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Association between COVID-19 and chilblains: a case–control study

Editor

Chilblain-like lesions (CLL) were described early on the coronavirus disease 2019 (COVID-19) pandemic as red-to-violet macules, plaques or nodules typically appearing at the distal aspects of toes.¹ Although increasing evidence suggests they are COVID-19-related,² it is not supported by analytic controlled studies.

In order to provide a greater degree of evidence on this issue, a unicentre-matched case–control study was designed. Participants were recruited between August and November 2020 at Ramon y Cajal University Hospital, Spain. Cases were defined by a new clinical diagnosis of chilblains (incident cases) and compared with controls. Each control was recruited in the same time

frame and setting (concurrent sampling) and individually 1 : 1 matched by age and sex with cases. We calculated the sample size necessary to detect an OR = 4, which was 45 cases and 45 controls.³ We administered structured questionnaires to cases and controls and examined them in the same manner. A validated serological test was done to assess the presence of antibodies.⁴ A conditional logistic regression model was used to compare the prevalence of antibodies in both groups. All analyses were done with R software (version 4.0.3).

A total of 1347 patients were triaged to a dermatologist during the study period (Fig. 1), with 45 patients (3.34%) meeting the case definition and 522 patients meeting control definition. After 1 : 1 matching, baseline characteristics were well-balanced between cases and controls (Table 1). There were 5/45 (11.11%) positive patients among the controls and 17/45 (37.78%) positives among the cases. The odds ratio of a positive IgG against the receptor-binding domain of SARS-CoV-2 spike (S) protein was OR = 3.40 (95% CI, 1.25–9.22; *P* = 0.0162) in cases compared with controls. None of the cases required hospital admission.

There has been a wide controversy about the causal relation between COVID-19 and CLL as many patients do not show other symptoms and RT-PCR tests from skin specimens and even serological studies are often negative.^{2,5–8} Attending to the results of our study, IgG antibodies against SARS-CoV-2 appear to be indeed a risk factor for CLL that overall occur in asymptomatic or mildly symptomatic patients, as none of the patients required hospitalization. It should be noted that more than half of the cases were seronegative. They could correspond to CLL not caused by the virus. Nevertheless, specific T cells have been detected in antibody-seronegative individuals with a history of asymptomatic and mild COVID-19.⁹ Memory T-cell responses can occur in the absence or presence of circulating antibodies, consistent with a non-redundant role as key determinants of immune protection against COVID-19. T-cell responses are more common than circulating antibodies in mild and asymptomatic COVID-19 patients. Unfortunately, there are not T-cell activation tests available for clinical practice. We hypothesize that this skin manifestation could induce a weak antibody response but a robust cellular response, as it has been previously suggested triggering the release of IFN- γ .¹⁰ Our study has important limitations. The most obvious is the sample size. In addition, there may be a selection bias in patients who attend the emergency room for this reason leading to an overestimation of the seropositivity. We tried to overcome this limitation by being more restrictive in the case definition. Finally, histological confirmation was not required, but this allowed us not to further reduce the sample size. To conclude, we found a higher prevalence of IgG against SARS-CoV-2 in patients with CLL than in the control group, which suggests a causal relationship between both variables. However, further research is needed.