Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Perspective

COVID toes: Where do we stand with the current evidence?

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ABSTRACT

Background: Numerous cases of chilblains have been observed, mainly in young subjects with no or mild symptoms compatible with COVID-19. The pathophysiology of these lesions is still widely debated, and an association with SARS-CoV-2 infection remains unconfirmed.
Objectives: This paper focuses on the unresolved issues about these *COVID toes* and, in particular, whether or not they are associated with COVID-19.
Arguments: The temporal link between the outbreak of chilblains and the COVID-19 pandemic suggests a link between the two events. Positive anti-SARS-CoV/SARS-CoV-2 immunostaining on skin biopsy of chilblains seems to confirm the presence of the virus in the lesions but lacks specificity and must be interpreted with caution. Conversely, RT-PCR and anti-SARS-CoV-2 serology were negative in the majority of patients with chilblains. Therefore, SARS-CoV-2 infection can be excluded, with relative certainty, even after accounting for possible lower immunization in mild/asymptomatic patients and for some differences in sensitivity/specificity between the tests used. Some authors hypothesize that chilblains could be the cutaneous expression of a strong type I interferon (IFN-I) response. High production of IFN-I is suggested to be associated with early viral control and may suppress antibody response. However, the absence of other cutaneous or extracutaneous symptoms, as observed in other interferonopathies, raises unanswered questions. To date, a direct link between chilblains and COVID-19 still seems impossible to confirm. A more indirect association due to lifestyle changes induced by lockdown is a possible explanation. Improvement of chilblains when protective measures were adopted and after lifting of lockdown supports this hypothesis.
Conclusion: Conflicting current evidence highlights the need for systematic and repeated testing of larger numbers of patients and the need for valid follow-up data that take into consideration epidemic curves and evolution of lockdown measures.

Skin manifestations are considered to be infrequent presentations of COVID-19, but no causal link has been formally demonstrated to date (Daneshgaran et al., 2020; Freeman et al., 2020a). A significant number of cases of chilblains have been observed, mainly in adolescents and young adults with no or mild symptoms compatible with SARS-CoV-2 infection. An association between chilblains and COVID-19 is suspected, but the pathophysiology of these lesions is still widely debated. Although numerous publications on *chilblains*, *pseudo-chilblains*, *chilblain-like lesions*, *covid-toes*, or *acral ischemic lesions* exist, an association with SARS-CoV-2 infection remains currently unconfirmed.

The prevalence of these *COVID-toes* observed in several European countries and in the United States is difficult to assess, with some authors drawing attention to possible *SALAMI publishing* and to overlapping cases reported in scientific literature and social networks (Kluger, 2020). These lesions seem to mainly affect the feet of children, adolescents, and young adults who are otherwise in good health and who have no particular medical history (Figure 1). However, in our series, blood tests revealed isolated positive anti-nuclear antibodies in one-third of patients, and these lesions seem to preferentially affect patients with a low BMI (Median:19.13) (Baeck et al., 2020c; Herman et al., 2020). Several patients report symptoms consistent with SARS-CoV-2 infection in the days and weeks prior to the onset of chilblains or report contact with people who experienced such symptoms.

In most reported series, other causes of chilblains such as coagulopathy or systemic diseases were excluded. Several authors performed histopathological and/or immunofluorescence analyses that confirmed the diagnosis of chilblains sometimes with vasculitis and microthromboses (Herman et al., 2020; Kanitakis et al., 2020). These features are classically encountered in

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Figure 1. Clinical aspect of the COVID toes in an otherwise healthy teenager, with purplish-erythematous macules located on the toes.

chilblains and should not be confused with the ischemic acral lesions due to thrombotic vasculopathy and systemic procoagulant state observed in patients with severe or critical COVID-19 and mainly triggered by endothelial damage (probably due to direct viral effect and perivascular inflammation) (Baeck et al., 2020a; Zhang et al., 2020; Magro et al., 2020).

The discussion focuses on whether or not chilblains are associated with COVID-19:

- The temporal link between the outbreak of chilblains and the COVID-19 pandemic (moreover, during an unusual season for this type of lesion) is a first argument to suggest a link between the two events.
- Some authors have also shown positive anti-SARS-CoV/SARS-CoV-2 immunostaining on skin biopsy specimens of chilblains, which seem to confirm the presence of the virus in the lesions (Colmenero et al., 2020; Santonja et al., 2020). However, due to lack of specificity, these immunostainings should be interpreted with caution (Baeck et al., 2020b; Ko et al., 2020).
- Conversely, RT-PCR and anti-SARS-CoV-2 serology were mostly negative (Baeck et al., 2020c; Caselli et al., 2020; Colonna et al., 2020; Denina et al., 2020; El Hachem et al., 2020; Freeman et al., 2020b; Garcia-Lara et al., 2020; García-Legaz Martínez et al., 2020; Herman et al., 2020; Le Cleach et al., 2020; Lesort et al., 2020; Mahieu et al., 2020; Neri et al., 2020; Rizzoli et al., 2020; Roca-Ginés et al., 2020; Rouanet et al., 2020; Stavert et al., 2020). Negative RT-PCR on nasopharyngeal swabs could suggest that chilblains are a late symptom of COVID-19. However, serological tests were often negative. A few publications reported positive serology for anti-SARS-CoV-2 IgA (El Hachem et al., 2020; Hubiche et al., 2020). However, the sensitivity of these antibodies is questionable, and false positives arising due to excessive sensitivity cannot be ruled out (Jääskeläinen et al., 2020). Negative RT-PCR and serological tests in the majority of patients with chilblains allow the exclusion of SARS-CoV-2 infection with relative certainty, even when accounting for possible lower immunization in mild/asymptomatic patients and for some differences in the sensitivity/specificity between the tests used. For a virus-associated phenomenon, the strikingly low rate of testing positivity raises questions.
- Some authors hypothesize that chilblains could be the cutaneous expression of a strong type I interferon (IFN-I) response (Lipsker, 2020; Battesti et al., 2020; Damsky et al., 2020; Rodríguez-Villa Lario et al., 2020). A high production of IFN-I is suggested to be associated with early viral control and mild course of SARS-CoV-2 infection. IFN-I may also suppress antibody response, which could explain why these patients would not develop antibodies and fail serologic detection. However, some questions remain unanswered with regard to the sometimes long delay between the suspected COVID-19 symptoms and the appearance of the skin lesions or with regard to the absence of other cutaneous or extracutaneous symptoms as observed in other interferonopathies (Rodero and Crow, 2016; Papa et al., 2020).
- To date, a direct link between chilblains and COVID-19 still seems impossible to confirm. Our study, like others, points towards a more indirect association between the outbreak of chilblains and the COVID-19 pandemic due to lifestyle changes induced by lockdown—in particular, in sedentary behaviours and bare-feet exposure to cool indoors (Baeck et al., 2020c; Herman et al., 2020, Neri et al., 2020, Roca-Ginés et al., 2020). Patient follow-up supports this hypothesis with the observed improvement of chilblains when protective and warm-up measures were adopted and containment restrictions were relaxed. It should also be noted that we have observed no new cases of chilblains since lifting of lockdown measures, despite recent new COVID-19 infections.

Shedding light on unanswered questions would be significant for patient management and information, testing strategies, and implementation of isolation measures. Only data on large series of patients with systematic and repeated testing, as well as follow-up information considering epidemic curves and evolution of lockdown measures, will enable to strengthen any one hypothesis.

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Ethical approval

The data have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Specific national laws have also been observed.

Authors' contribution

Marie Baeck and Anne Herman performed literature searches, prepared the manuscript, reviewed and approved the manuscript, and decided to submit the manuscript for publication.

Conflict of interest

The authors have no conflicts of interest.

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