## Reply to Pernio during the COVID-19 pandemic and review of inflammation patterns and mechanisms of hypercoagulability

*To the Editor*: We thank Cavanagh et al for giving us the opportunity to further comment on our case report[1] and to clarify all relevant misconceptions. Numerous additional case reports and case series of the coronavirus (COVID-19)-induced chilblains, or the so-called *COVID-toes*, have been published since our initial publication, and they confirm the following key concepts:

1. Most of the reports of this cutaneous findings do not originate from northern latitude counties, as Cavanagh et al assert, but rather Spain[2,3] followed by Italy and France.[4,5] All authors agree that the outbreak of chilblains suspected to be induced by COVID-19 appeared in the springtime, with temperatures in Spain being greater than 20°C, in patients with no history of Raynaud phenomenon, chilblains, or exposure to cold, and concomitant with the COVID-19 crisis. In fact, some family clusters have been reported. Our reported patient had never experienced chilblains, denied any cold exposure, and had the lesions during a particularly warm springtime in Belgium. Although causality between COVID-19 and chilblains has not been confirmed, we can certainly affirm that the reported chilblains are not related to cold exposure.

2. Pathogenesis of the COVID-induced chilblains should not be confused with the hypercoagulability and risk for thrombosis[6,7] being seen in severely affected patients who have livedoid necrotic lesions.[3,8] We already stressed that the significance of COVID-toes is exactly the opposite portending an indolent clinical course. The pathogenetic mechanisms described by the authors in this letter are irrelevant, as the patients with chilblains do not show increased coagulability or D-dimers. We already collected more than 30 biopsy specimens our institutions in Brussels and Portland, and, similar to our published case, we are observing lymphocytic vasculitis in all cases with no intraluminal thrombus formation (ongoing publication). The authors' misconception is partially from the numerous published case series based only on clinical pictures, in which hypercoagulability is suspected but not confirmed with blood testing.[9]

A probable explanation for the COVID-toes is that there is a COVID-19–induced endotheliitis, as the virus can enter endothelial cells with the angiotensin-converting enzyme 2 (ACE2) receptor. This has already been found in lungs, kidneys, and small bowel,[10] and we know that the endothelial cells in the skin also express ACE2. Cutaneous and histopathologic similarities with chilblain lupus suggest to us that activation of the type I interferon immune response is the basis for the pathogenesis.[11]

3. We disapprove of the practice of describing all of the reported cutaneous eruptions being seen in the COVID-19 epidemics as "viral-induced, nonspecific immunologic eruptions." Each cutaneous sign has a different pathogenesis, appears in a different subset of patients, appears at a different moment in the course of the disease, and has distinct prognostic significance for the patient and a distinct significance for the community (ie, contagiousness).

COVID-19–induced chilblains is a late-onset, cutaneous manifestation, seen in children and young adults portending an excellent disease course. The patients are either mildly or no longer contagious. This finding explains why COVID-19 nucleic acid amplification tests, including polymerase chain reaction on nasopharyngeal swabs, are usually negative in patients with COVID-toes.[2,3] The concept of a different pathogenesis for each COVID-19–related eruption explains why each patient does not show all of the cutaneous signs during the course of the disease but rather only one of them at a particular moment of the clinical course.

4. Finally, we disagree with 2 major assumptions of Cavanagh et al regarding testing for COVID-19. First, symptom-based screening is inadequate and should be extended to asymptomatic patients in congregate living situations.[12] Second, testing should not be restricted to nucleic acid amplification essays but should also be extended to include serologic testing as a further tool for investigation in the ongoing outbreak. Serologic testing will also allow a retrospective assessment of the attack rate or extent of an outbreak.[13] COVID-toes may represent one of the clinical indicators showing immunized patients, as we progress to "herd immunity." Identification of these patients could help us end the pandemic lockdown strategy in a more responsible manner.[14]

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