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Are chilblains a skin expression of COVID-19 microangiopathy?

Dear Editor,

The unexpected outbreak of chilblains during the current coronavirus disease 2019 (COVID-19) pandemic has been causally linked to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1] The pathophysiology of these chilblains observed in otherwise healthy patients is widely discussed.

Acquired hypercoagulable states as reflected by markedly increased D-dimer, elevated concentrations of fibrinogen and fibrinogen degradation products (FDPs) and prolonged prothrombin time (PT), with disseminated intravascular coagulation (DIC) are responsible for acro-ischemia with cyanosis, livedo reticularis, and gangrene observed in severe forms of COVID-19.[2,3] Pathological observations have shown that microthrombi occur in the small vessels of the lungs of patients with COVID-19 pneumonia.[3] Endothelial cells were found to play a central role in these widespread alveolar capillary microthrombi seen in the lungs. Indeed, severe endothelial damage associated with significant new vessel growth through intussusceptive angiogenesis have been observed.[4] A SARS-CoV-2-induced microthrombotic mechanism has been suggested to account for chilblains observed in younger patients with no or mild symptoms of COVID-19.

Chilblains are usually cold-induced inflammatory lesions. They are typically a seasonal condition resulting from vasoconstriction of the deep cutaneous arterioles leading to anoxia, capillary damage, and dermal inflammation. Chilblain-like lesions have also been observed in association with autoimmune disorders or coagulopathy. Clinical presentation includes erythema and swelling on toes and/or digits followed by red-purple macules or patches. Blistering and necrosis may occur in more severe cases. Lymphocytic vasculitis, thrombi of the superficial small vessels, and endothelial swelling are common histopathologic findings.[5] Nevertheless, they do not result from severe endothelial injury and dysfunction as observed in the vascular phase of COVID-19.[4]

In our recently published case series of patients with chilblains,[6] histologic examination of skin biopsy specimens (22 patients) showed

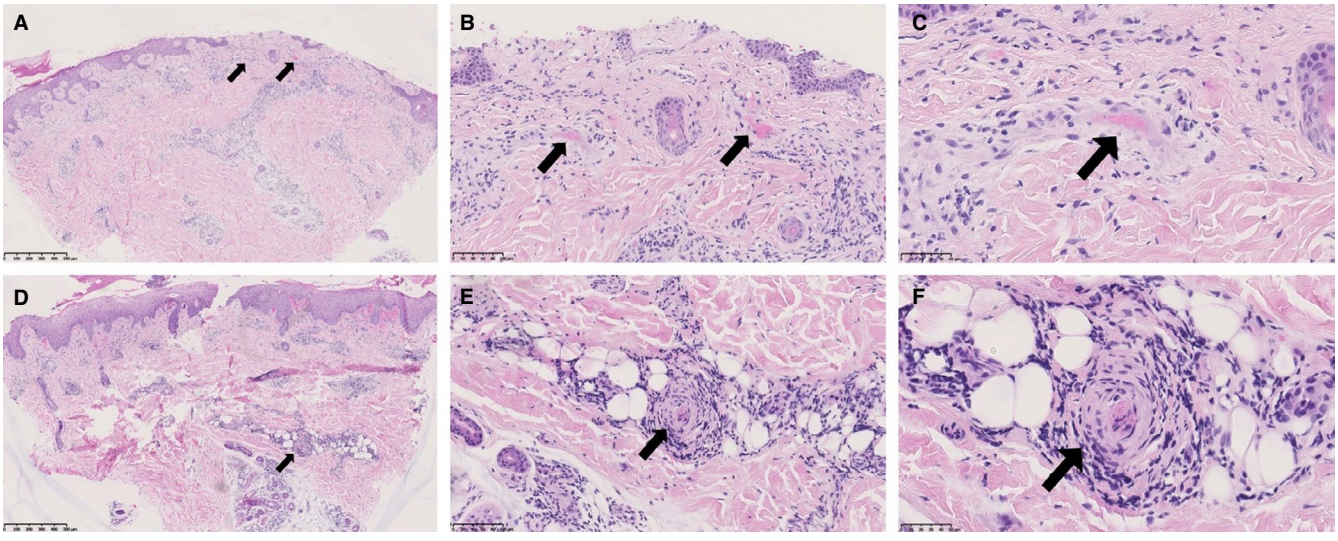

FIGURE 1 Histopathologic images of chilblain skin biopsy specimens, hematoxylin and eosin stain. Microthrombosis in the upper dermis; original magnification ×5 (A) ×20 (B) ×40 (C). Microthrombosis in the lower dermis; original magnification ×5 (D) ×20 (E) ×40 (F)

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microthrombotic phenomenon in six of them (Figure 1). Among these six patients, direct immunofluorescence (DIF) analyses revealed C3, immunoglobulin M (IgM), and/or immunoglobulin A (IgA) deposits in five cases. The presence of microthrombosis seems to be correlated with clinical severity of the lesions (bullous and necrotic lesions). No significant blood test abnormalities were suggestive of coagulopathy nor systemic diseases. Negative reverse transcription polymerase chain reaction (RT-PCR) SARS-CoV-2 in nasopharyngeal swabs and anti-SARS-CoV-2 specific IgM and immunoglobulin G (IgG) antibodies ruled out that these patients had been SARS-CoV-2 infected. SARS-CoV-2 virus was not detected by RT-PCR in skin biopsies of chilblains. Another recent study with histologic, immunofluorescence, and immunohistochemical study of 17 cases of chilblains lesions observed during the COVID-19 pandemic, also suggest that their pathological features are similar to those of idiopathic and autoimmune-associated chilblains, including vascular microthrombosis.[7]

Altogether, these findings confirm that chilblain lesions in healthy patients have no relationship with the microthrombotic vasculopathy, mainly triggered by endothelial damage (probably due to direct viral effect and perivascular inflammation), observed in critical COVID-19.

CONFLICTS OF INTEREST

There are no real or potential conflicts of interest for any author.

AUTHOR CONTRIBUTIONS

Marie Baeck prepared the manuscript. Marie Baeck, Anne Herman, Caroline Peeters, and Cedric Hermans reviewed or approved the manuscript; Marie Baeck and Cedric Hermans decided to submit the manuscript for publication.

KEYWORDS

chilblains, COVID-19, histopathological findings, hypercoagulable state, microthrombosis, thrombotic vasculopathy

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