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COVID toes: Pernio-like lesions

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Abstract More than 40 million people have been infected with the severe acute respiratory syndrome coronavirus 2 since the first infection was reported in December 2019 from Wuhan, China. Multiple reports of cutaneous manifestations of the virus have been described, including a pernio-like eruption, recently termed "COVID toes." We have reviewed the published case series on "COVID toes" in addition to studies identifying possible pathogenic mechanisms behind the eruption.

Introduction

The first cases of infection with the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were reported in December 2019 in Wuhan, China. Since then, the virus has spread to a pandemic level, with more than 40 million people infected worldwide. As the number of cases continues to grow, reports of cutaneous manifestations of the virus are coming to light, namely a pernio-like eruption. Recognizing cutaneous manifestations of the disease may provide a diagnostic clue to clinicians and patients to prompt further investigation and intervention.

Cutaneous manifestations

Case series in Europe and the United States have highlighted the major morphologies of Coronavirus Disease 2019 (COVID-19)-related eruptions, namely urticarial, morbilliform, vesicular, papulosquamous, livedo, acro-ischemic, retiform purpura, and pernio-like.[1] Many of these eruptions, such as morbilliform and urticarial, are nonspecific and can be seen in the setting of other viral infections or drug eruptions. A morphology that seems to be unique to COVID-19 is the development of pernio-like acral lesions, colloquially named "COVID toes" (Figures 1–3). One of the first reports from Spain highlighted 6 patients with pernio-like lesions on the distal aspect of the toes.[2] The majority of the patients either had no COVID-19 infection symptoms (cough, fever, body aches, headaches) at the time of the eruption or only mild symptoms that either preceded or followed the eruption weeks later. A larger cohort compiled from an international registry of eight countries reported 318 patients with pernio-like lesions. The majority of these patients were generally young and healthy and had mild or no symptoms related to COVID-19 (55% otherwise asymptomatic). In those who exhibited viral symptoms, pernio lesions typically appeared weeks later.[3] This was consistent with an earlier report from Spain, where 69% of those with pseudo-chilblains (pernio) developed the eruption weeks after the initial viral symptoms.[4] Unfortunately, complete viral testing was not available for all patients in either of these studies, as the mild symptoms associated with the eruption did not meet clinical testing criteria in most countries at that time. Only 7% of patients in the largest international cohort with pernio were confirmed as COVID-19 positive

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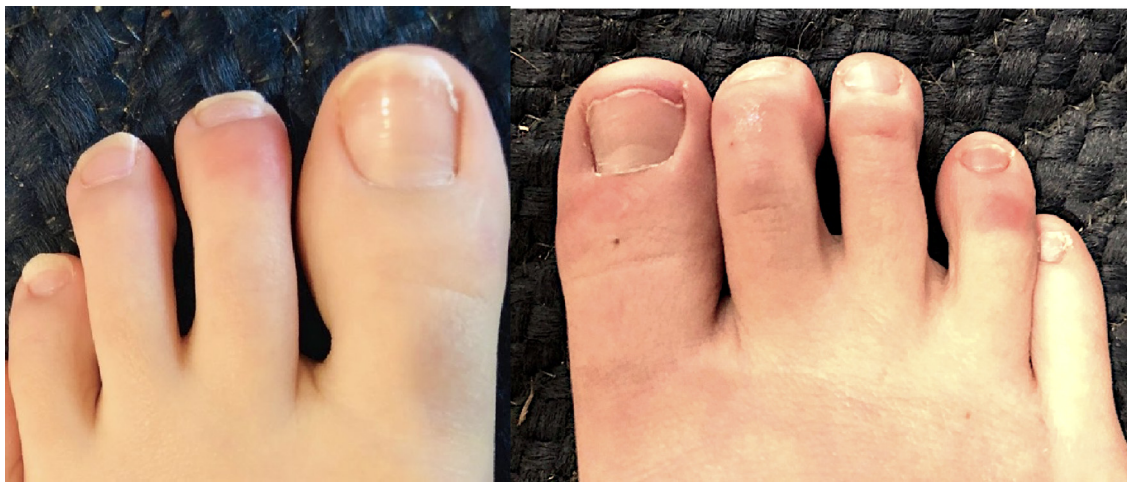

Fig. 1 Erythematous to purpuric macules and thin papules on distal aspect of the dorsal toes.

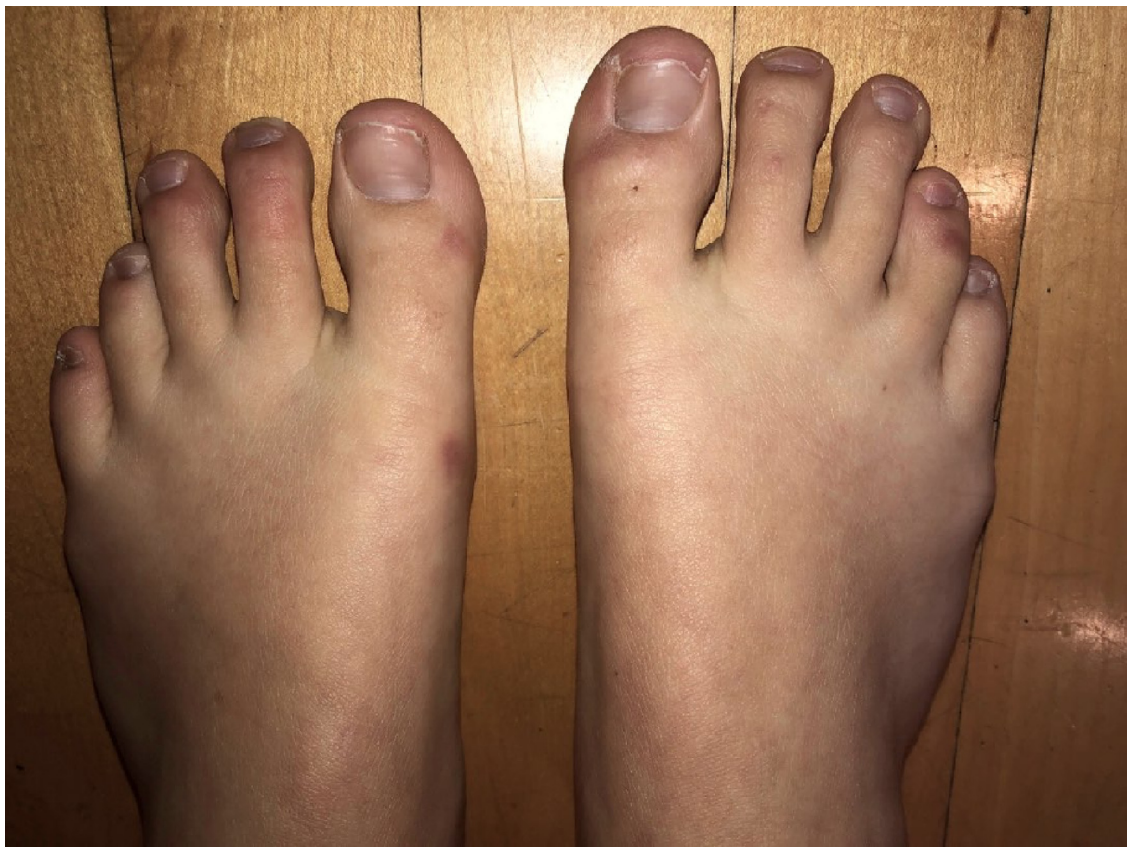

Fig. 2 Dusky papules and incipient vesicles on the dorsal toes.

with either polymerase chain reaction (PCR) or antibody testing.[3]

T-cell immunity

The lack of reactive PCR and serology data in these cohorts raises questions about the pathophysiology and immunologic mechanism behind "COVID toes" and those affected. Aside from monitoring antibody titers and viral PCRs, recent studies have investigated the role of T-cells in COVID-19 disease and immunity. T-cells have been found in unexposed and asymptomatic individuals who exhibit cross-reactivity between SARS-CoV-2 proteins and proteins in the common cold coronaviruses. We hypothesized that variegated T-cell memory to other coronaviruses may help to

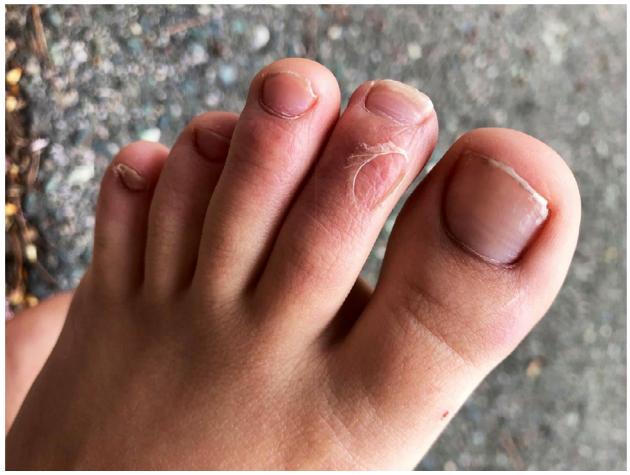

Fig. 3 Postinflammatory desquamation at site of prior vesicle.

explain the mixed clinical presentations of COVID-19 disease.[5] Young children and adults with more frequent social contacts and exposure to common cold coronaviruses may harbor some protective immunity against SARS-CoV-2.[6] In such patients, there is possibly a robust T-cell response to the virus that may allow for rapid immunity development before antibodies are produced in large numbers. Additional large-scale studies are needed to validate these hypotheses, but this may offer insight into why young patients with "COVID toes" exhibit a nonreactive antibody serology.

Inteferon

In addition to a heterogeneous T-cell response, further studies have investigated the variation in interferon (IFN)-I levels in patients infected with SARS-CoV-2. COVID-19 is known to trigger the expression of IFN-inducible genes that help augment the host's antiviral behavior. Early IFN-I activation is beneficial to the host by inhibiting viral replication leading to a more muted or mild clinical course. Late activation of IFN-I may be deleterious and exacerbate hypercytokinemia (C-reactive protein, IL-6), which leads to poorer clinical outcomes in those infected.[7]

The role of interferons and how they pertain to the development of pernio-like lesions has been previously described in familial chilblain lupus (FCL), an interferonopathy syndrome. The clinical lesions seen in "COVID toes" are clinically and histologically similar to those seen in FCL. FCL is caused by a mutation in TREX1 and is characterized by excessive type I IFN production.[8] The type I IFN response plays a vital role in antiviral immunity, but when elevated to an inappropriate activation, can drive autoimmunity. It can even induce thrombotic microangiopathy in some patients through direct effects on the microvasculature.[9] The clinical and histologic manifestations observed in "COVID toes" and TREX1-FCL are similar, and thus, the eruption may represent a manifestation of a systemically elevated type I IFN response. It has been proposed that the early IFN antiviral response to COVID-19 in young healthy patients may explain the low rates of positive PCR testing and mild clinical courses.

Histopathologic findings

Despite an increased number of cases during the COVID-19 pandemic, there have been little data to support a definite causative role for the SARS-CoV-2 virus in the development of perniosis. Skin biopsies have been examined from 7 pediatric patients presenting with perniosis during the COVID-19 pandemic. None of the patients had a history of rheumatic disease, lupus erythematosus, Raynaud phenomenon, or previous chilblains lesions. Nasopharyngeal and oropharyngeal SARS-CoV-2 PCR samples were collected and were negative in all cases. Despite negative PCR studies, cytoplasmic granular positivity for SARS-CoV-2 spike protein was directly identified in the endothelial cells within capillaries of all specimens examined. The findings were confirmed in one sample with electron microscopy.[10] This study strongly supported a pathogenic role for the virus in the development of chilblains. The histopathologic features identified in their cohort were similar to the features seen in chilblains of other etiologies, which include interface dermatitis with vacuolar degeneration of the basal epidermal layer and indirect features of vascular damage, like red cell extravasation and dermal edema. This suggests that widespread endothelial infection by the virus plays a role in the pathogenesis of mild and severe forms of the disease. Why some patients present with mild disease limited to the skin and others with extensive multiorgan dysfunction remains unclear.

Epiphenomenon?

Additional case series altogether question the direct association between COVID-19 and this pernio eruption. There have been two studies that examined 31 and 20 patients with acral pernio lesions during the time of the pandemic; none of the patients in either study tested positive for SARS-CoV-2 PCR, and positive COVID-19–specific antibodies were not detected in a single patient.[11,12] Some of the patients in each cohort reported a history of Raynaud or a prior history of chilblains. Both authors proposed that lifestyle modifications that were a result of quarantine could explain their findings, such as walking barefoot in unheated homes, inactivity, and time spent in sedentary positions. In the first study cohort, some patients even reported consumption of recreational drugs, herbal medicines, and/or energy drinks. Ultimately, the investigators from both studies could find no direct causative role that the virus played in the development of

perniosis. This suggests that the increased rates of pernio are an indirect result of changes in lifestyle behaviors created by various quarantine measures.

Conclusions

Do "COVID toes" represent a dermatologic marker of an active viral infection, a delayed immune response to the virus during the convalescent phase, or an epiphenomenon indirectly related to COVID-19? As the pandemic continues to evolve, there should be ongoing public and physician awareness of "COVID toes," even if our understanding of the etiology remains uncertain.

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