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Evaluation of Chilblains as a Manifestation of the COVID-19 Pandemic

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IMPORTANCE During the coronavirus disease 2019 (COVID-19) pandemic, several cases of chilblains have been reported.

OBJECTIVE To determine if chilblains are associated with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS This monocentric case series was conducted at the Department of Dermatology at Cliniques universitaires Saint-Luc, a tertiary care hospital in Brussels, Belgium, between April 10 and April 17, 2020. We evaluated a total of 31 referred patients who had recently developed chilblains.

MAIN OUTCOMES AND MEASURES Real-time reverse transcriptase–polymerase chain reaction (RT-PCR) was used to detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA on nasopharyngeal swabs for all patients and in skin biopsy specimens for 22 patients. Blood samples from all patients were tested for specific anti–SARS-CoV-2 immunoglobulin (Ig) M and IgG antibodies. All patients had extended blood analyses. Histologic (22 patients) and immunofluorescence examinations (15 patients) were performed on the skin biopsy specimens.

RESULTS The 31 patients were generally in good health; most were teenagers or young adults, and 19 were women. Histopathologic analysis of skin biopsy specimens (22 patients) confirmed the diagnosis of chilblains and showed occasional lymphocytic or microthrombotic phenomena. Immunofluorescence analyses showed vasculitis of small-diameter vessels in 7 patients. In all patients, SARS-CoV-2 RNA remained undetected by RT-PCR on nasopharyngeal swabs and in biopsy samples of the skin lesions. The IgM and IgG antibody titers were negative for SARS-CoV-2 in all patients (<1.0 arbitrary unit/mL). No significant abnormalities in blood test results were suggestive of systemic disease. Antinuclear antibody titers were low in 7 patients and higher in 1 patient.

CONCLUSIONS AND RELEVANCE Chilblains appeared not to be directly associated with COVID-19 in this case series. Lifestyle changes associated with community containment and lockdown measures are a possible explanation for these lesions.

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Supplemental content

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Coronavirus disease 2019 (COVID-19) is mainly characterized by fever and respiratory symptoms.[1] During this pandemic, several cases of unusual purplish red lesions on the feet and/or hands, mimicking chilblains, have been reported in the literature and on social media. Some researchers have suspected that these lesions are associated with asymptomatic or mildly symptomatic COVID-19.[2-7] However, to our knowledge, no study has proved a pathologic link between these skin lesions and COVID-19. This observational prospective case series aimed to investigate the possible association between chilblains and COVID-19.

Methods

Between April 10 and April 17, 2020, we enrolled 31 patients who visited the Department of Dermatology at Cliniques universitaires Saint-Luc, Brussels, Belgium. All patients had purplish red chilblain lesions on toes and/or fingers, which had appeared between 1 and 30 days before consultation. The data from all study participants are summarized in the **Table**.

The study and data collection were approved by the institutional review boards of Cliniques universitaires Saint-Luc and Université Catholique de Louvain. Written informed consent was obtained from all study participants.

All patients underwent reverse transcriptase–polymerase chain reaction (RT-PCR) analysis by nasopharyngeal swab to detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA when they presented for chilblains. In all patients, blood analyses included the following: liver function and renal function; tests for antinuclear antibodies, rheumatoid factor, CH50, C3, C4, antineutrophil cytoplasmic autoantibody, antistreptolysin O antibody, and cold agglutinins; prothrombin time and activate partial thromboplastin time; levels of D-dimer, an-

ticardiolipin and anti-β_2-glycoprotein antibodies, cryoglobulins, and C-reactive protein; protein electrophoresis; and in a subgroup of patients, tests for factor VIII, von Willebrand factor, and lupus anticoagulant in addition to haptoglobin level, bilirubin level, reticulocyte count, and schizocyte count. Serologic testing for specific anti-SARS-CoV-2 IgM and IgG antibodies was performed in all patients. For some patients, skin biopsy specimens were obtained for histologic (22 patients) and immunofluorescence analyses (15 patients), as well as for the RT-PCR detection of SARS-CoV-2 RNA (22 patients).

Detailed methods of PCR, serologic, histologic, and immunofluorescence testing are available in the eAppendix in the Supplement.

Key Points

Question Is there an association between chilblains and coronavirus disease 2019 (COVID-19)?

Findings In this case series of 31 patients who had recently developed chilblains, none of the patients tested positive for COVID-19 on nasopharyngeal swabs, nor were blood immunoglobulin (Ig) M or IgG antibodies detected.

Meaning These ischemic, acral cutaneous lesions appeared not to be directly associated with COVID-19.

Results

All demographic data and laboratory results are summarized in the Table as well as the eTable in the Supplement. Eleven patients were teenagers (<18 years), and 19 were female. Median (range) age was 22 (6-72) years. Median (range) body mass index (calculated as weight in kilograms divided by height in meters squared) was 19.13 (15.57-33.56), and 9 patients had a body mass index lower than 20.

Skin lesions were localized to the feet (29 patients) and/or hands (3 patients) and presented as erythematous or pur-

Table. Demographic Data of 31 Patients With Chilblains

Patient No./Age (decade of life)	BMI	Medical history	Chilblain localization	Time between chilblain onset and consultation, d	History of chilblains or Raynaud syndrome	Symptoms suggestive of COVID-19	Possible or confirmed family history of COVID-19 infection	Screen time during containment (before containment), h/d	Change in physical activity level during confinement	Regular wearing of shoes during lockdown
1/30s	23.2	No	Hand	18	No	No	No	8 (8)	Decrease	No
2/Teenager	21.4	No	Hand and foot	12	Chilblains	No	No	3 (1)	Decrease	No
3/40s	20.0	No	Hand and foot	9	Both	Dy; Di	No	6 (6)	Identical	No
4/30s	19.3	No	Foot	3	Chilblains	R; ST; Di	Yes	9 (3)	Decrease	No
5/40s	20.1	COPD	Foot	7	Chilblains	C; R; ST; Di	No	5 (3)	Decrease	No
6/20s	18.8	No	Foot	7	Both	Fe; T	No	8 (2)	Identical	No
7/Teenager	19.3	No	Foot	8	No	Dy; R;	No	4 (1)	Identical	No
8/50s	29.7	No	Foot	5	Both	C; Dy; T; R; ST	No	2 (2)	Identical	No
9/Teenager	15.6	Crohn disease	Foot	13	No	Di	No	5 (2)	Decrease	No
10/40s	22.1	High blood pressure	Foot	13	No	No	No	8 (8)	Identical	Yes
11/Child	16.0	No	Foot	4	No	No	No	3.30 (2)	Decrease	No
12/Teenager	21.8	No	Foot	10	No	R	No	8(2.30)	Decrease	No
13/40s	23.7	Depression	Foot	14	No	C; T; R; ST	No	8 (8)	Identical	No
14/20s	21.1	No	Foot	5	No	Di	No	6 (2)	Decrease	No
15/Teenager	19.4	No	Foot	11	No	R	No	5.30 (1)	Decrease	No
16/Teenager	20.0	No	Foot	20	No	No	No	8 (4)	Decrease	No
17/Teenager	32.0	No	Foot	7	No	R	No	8 (3)	Decrease	No
18/Teenager	21.5	No	Foot	14	Chilblains	Dy; R; Co; ST	No	4 (2)	Decrease	No
19/Teenager	23.4	Kawasaki disease	Foot	22	No	No	No	7 (3)	Decrease	No
20/50s	33.6	Breast cancer	Hand and foot	4	No	C; R	No	7 (5)	Identical	No
21/30s	19.0	No	Foot	5	No	C; ST	No	1 (1)	Identical	No
22/40s	23.0	Gastro-esophageal reflux	Foot	24	No	No	No	1 (1)	Increase	No
23/40s	16.0	No	Foot	12	Raynaud syndrome	C	No	5 (3.30)	Decrease	No
24/Teenager	21.8	Allergic rhinoconjunctivitis, headache	Foot	26	No	Di	No	8 (3.30)	Decrease	No

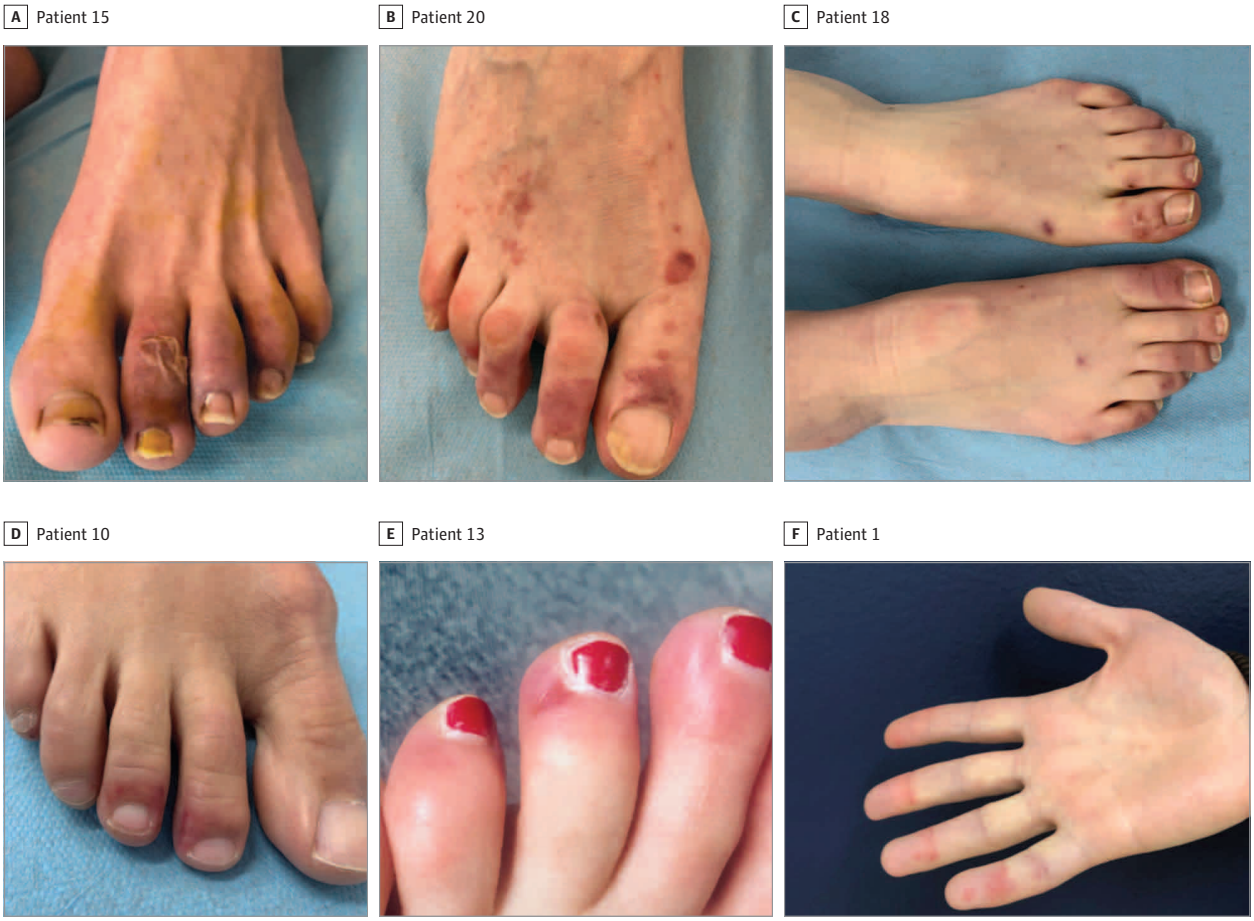
(continued)

Table. Demographic Data of 31 Patients With Chilblains (continued)

Patient No./Age (decade of life)	BMI	Medical history	Chilblain localization	Time between chilblain onset and consultation, d	History of chilblains or Raynaud syndrome	Symptoms suggestive of COVID-19	Possible or confirmed family history of COVID-19 infection	Screen time during containment (before containment), h/d	Change in physical activity level during confinement	Regular wearing of shoes during lockdown
25/60s	24.8	No	Foot	14	Chilblains	No	No	4 (4)	Identical	Yes
26/30s	24.1	No	Foot	6	No	Dy; T; Di	Yes	3 (2.30)	Identical	No
27/30s	20.8	No	Foot	25	No	C; Dy; T	No	5 (2)	Decrease	No
28/Teenager	18.8	No	Foot	18	No	No	No	8 (2)	Decrease	Yes
29/Teenager	23.0	No	Foot	30	No	R	No	5 (2)	Decrease	No
30/70s	27.3	Cardiovascular disease	Foot	28	Chilblains	No	No	0 (0)	Identical	Yes
31/Teenager	20.8	No	Foot	14	No	R; ST	Yes	2.30 (1)	Decrease	No

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); C, cough; Co, conjunctivitis; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; Di, diarrhea; Dy, dyspnea; Fe, fever; R, rhinitis; ST, sore throat; T, tiredness.

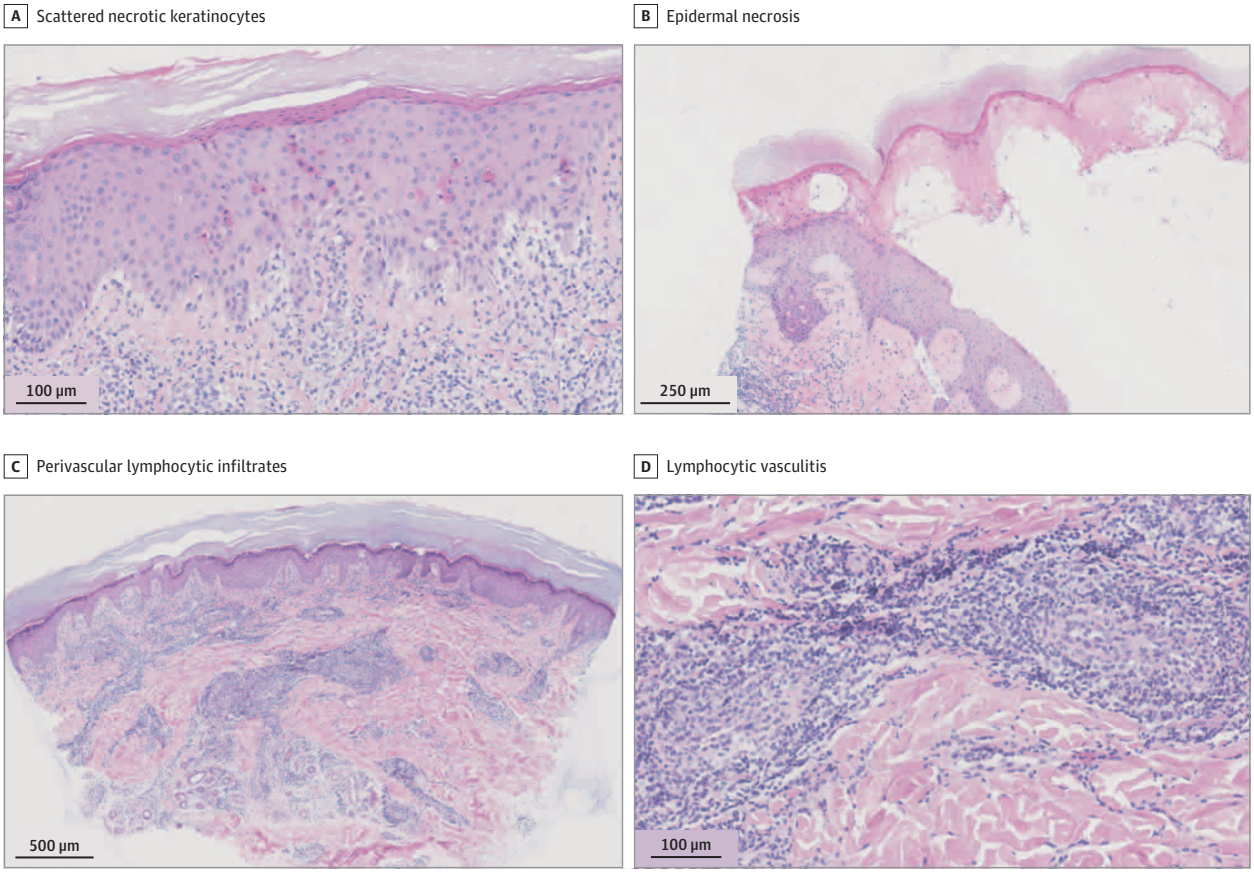
Figure 1. Clinical Aspects of Chilblains Observed



A, Patient 15 had erythematous macules as well as bullous lesions on the second and fourth toes of the left foot. B, Patient 20 had purplish erythematous macules located in the periungual area of all toes and some erythematous macules on the backs of the feet, at the root of some toes. C, Patient 18 had purplish erythematous macules on all toes, vesicular in places, with some additional lesions on the backs of the feet. D, Patient 10 had discrete periungual, annular erythematous lesions, vesicular at the center, on the second and third toes. E, Patient 13 had purplish erythematous macular periungual lesions. F, Patient 1 had annular erythematous macules on the fourth and fifth fingers.

plish erythematous macules, sometimes with central vesicular or bullous lesions or with necrotic areas (**Figure 1**). Patients complained of pain, burning, and/or itching. Of the 31 patients, 20 (64%) reported mild symptoms possibly corre-

Figure 2. Histopathologic Images of Skin Biopsy Specimens



A. The epidermis shows scattered necrotic keratinocytes and focal vacuolar alteration of the basal layer (hematoxylin-eosin, original magnification ×20). B, In some samples, full-thickness epidermal necrosis is seen with subepidermal cleavage (hematoxylin-eosin, original magnification ×10). C, All biopsy specimens reveal heavy perivascular lymphocytic infiltrates in the superficial and deep dermis; eccrine extension of the infiltrates is often present (hematoxylin-eosin, original magnification ×5). D, Some specimens show lymphocytic vasculitis (mural and perivascular infiltrates of lymphocytes) (hematoxylin-eosin, original magnification ×20).

lated with COVID-19. Only 3 patients (10%) reported contact with a person considered COVID-19 positive.

Nine patients (29%) had a history of chilblains (perniosis) and 4 (13%) of Raynaud syndrome. In addition, 3 patients were receiving β-blocker treatment, 1 smoked, and some occasionally consumed recreational drugs, herbal teas, herbal medicines, alcohol, or energy drinks.

Histopathologic analysis of skin biopsy specimens (22 patients) confirmed the diagnosis of chilblains (**Figure 2**). Occasional signs of lymphocytic or microthrombotic phenomena were observed. Results of immunofluorescence analyses were negative in 7 cases and noncontributory for 1 patient. In 7 others, results showed vasculitis of small-diameter vessels: 1 patient with IgM, IgA, and C3 deposits, 3 with IgM and C3, and 3 with only C3; test results were negative for IgG and C1q.

The RT-PCR analysis failed to detect SARS-CoV-2 RNA on nasopharyngeal swabs from all patients and in the 22 biopsy samples from the skin lesions. Tests for IgM and IgG antibody titerswere negative for SARS-CoV-2 all patients (<1.0 arbitrary unit/mL). No significant biochemical, autoimmune, hematologic, or hemostatic abnormalities were found on blood test results. Eosinopenia, lymphopenia, and hyperferritinemia, often reported in patients with COVID-19, were not observed in this series. Low titers of antinuclear antibodies were detected in 7 patients, and higher titers were detected in 1 patient with a history of perniosis. The most relevant laboratory findings are reported in the eTable in the Supplement.

Discussion

Since the beginning of the current pandemic, ischemic acral lesions have been observed both in adults with severe forms of COVID-19[8] and in younger, otherwise healthy patients. In patients with severe COVID-19, these lesions present as peripheral cyanotic lesions and appear to be secondary to systemic consequences of the disease, particularly thrombotic vasculopathy.[9] However, chilblains observed in patients with no, or possibly mild, symptoms of COVID-19 have raised the possibility of a link between this type of lesion and COVID-19.[2-7]

Histopathologic examination of skin biopsy specimens revealed patterns consistent with typical chilblain lesions with, in some cases, vasculitic and microthrombotic phenomena.[10] Results of some immunofluorescence analyses showed

microvascular deposits of IgM and/or C3 consistent with vasculitis of small-diameter vessels.

In this series, patients were predominantly teenagers or young adults with unremarkable medical histories and no known autoimmune diseases. No significant abnormalities were found in blood test results, including antiphospholipid antibodies or hypercoagulability status, as has been reported in patients with critical COVID-19 pneumonia with acro-ischemia.[11]

We did not detect SARS-CoV-2 RNA in the nasopharyngeal swabs of any patient, nor in the 21 skin biopsy samples analyzed. Negative RT-PCR findings could suggest that chilblains are a late manifestation of COVID-19, occurring outside the time frame of viral shedding in the nasopharynx.[12] Therefore, serologic tests were carried out to detect IgM and IgG anti–SARS-CoV-2 antibodies; unexpectedly, these results were negative for all patients. The sensitivity and specificity of the serologic tests used[13] was estimated to be 100% 15 days after the beginning of symptoms. Because some patients had experienced chilblains for more than 15 days (≤30 days) at the time of inclusion, we can reasonably exclude the possibility that serologic testing was done too soon. Given the negativity of RT-PCR and serologic test results in all patients, we can assume that these patients had not been infected with SARS-CoV-2.

The concomitant increase in reports of chilblains during spring, in conjunction with the COVID-19 pandemic, suggests that there may be an indirect link between these events. One hypothesis points to an indirect consequence of the COVID-19 pandemic due to imposed community containment and lockdown measures leading to lifestyle changes that are considered risk factors for developing chilblains.[14] When subsequently questioned about their lifestyles, all patients reported that they had either been working from home or were home schooled since the beginning of containment measures in Belgium (March 11, 2020). Most of them (20/31 [64%]) reported decreased physical activity and considerably more time spent in sedentary positions. Some patients also reported a consumption of recreational drugs, herbal medicines, and/or energy drinks. Finally, most patients declared that they remained barefoot or in socks most of the day.

Median (range) body mass index of the patients was relatively low (19.13 [range, 15.57-33.56]), suggesting that thin people may be more at risk for developing chilblains. A few patients reported a history of Raynaud phenomenon or chilblains in winter, and some blood analyses revealed an isolated positive result for antinuclear antibodies.

Limitations

Limitations of this study include a small sample size and a population that may not be representative. There was also no control group and no long-term follow-up.

Conclusions

We report several cases of chilblains occurring mainly in young people during the COVID-19 pandemic. The RT-PCR and serologic test results showed no signs of COVID-19 in all 31 patients. Other important risk factors for chilblains were also excluded. We hypothesize that these skin lesions may be caused by lifestyle changes brought on by containment and lockdown measures. Dermatologic lesions, even if increasingly observed during the current pandemic, should be carefully interpreted.

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Concept and design: Herman, Peeters, Tennstedt, Baeck.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Herman, Peeters, Tennstedt, Hermans, Baeck.
Critical revision of the manuscript for important intellectual content: Peeters, Verroken, Tromme, Marot, Dachelet, Gruson, Baeck.
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Editor's Note

Focus on "COVID Toes"

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Worldwide case collections of cutaneous manifestations of coronavirus disease 2019 (COVID-19) are ongoing, with acral lesions (similar to classic chilblains) being one of the reported patterns. Also known as *pernio-like, pseudo-chilblain, acute acro-ischemia,* and "COVID toes," the pattern of acral lesions is described as erythematous to purple purpuric macules, papules, and/or vesicles. Its close temporal appearance with the COVID-19 pandemic suggests that the two are associated. Galván Casas et al[1] confirmed that 29 of 71 cases of pseudo-chilblains were associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), noting that this pattern is less commonly associated with virologic confirmation. Fernandez-Nieto et al[2] reported that 95 of 132 patients with acro-ischemic changes had a chilblains pattern. Acral lesions often occurred later during the course of COVID-19, and late-stage disease testing was believed to partly account for low positive rates of SARS-CoV-2 infection (2 of 11 patients).

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Two case series in this issue question a direct association between COVID-19 and acral lesions. Herman et al[3] examined 31 patients with acral lesions and found a relatively low mean body mass index (22, calculated as weight in kilograms divided by height in meters squared), a known predisposing factor for perniosis. None of the patients tested positive for COVID-19 by nasopharyngeal swab and reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2, nor were SARS-CoV-2–specific immunoglobulin (Ig) M or IgG antibodies detected. Roca-Ginés et al[4] evaluated 20 children and adolescents with acral purpuric changes. No patient had COVID-19 symptoms or evidence of infection according to results of nasopharyngeal swab and RT-PCR or viral serologic testing. In both studies, extensive testing failed to identify other risk factors for these acral lesions, and a subset of patients had biopsy results consistent with perniosis. Both author groups propose that lifestyle changes imposed by the quarantine, such as walking barefoot in unheated homes, inactivity, and time spent in sedentary positions, could explain these findings.

It is still unclear whether a viral cytopathic process vs a viral reaction pattern or other mechanism is responsible for "COVID toes." Further complicating matters is the lack of confirmatory SARS-CoV-2 testing in some cases, which instead rely on indirect evidence such as systemic symptoms consistent with possible infection, cohabitation with an individual with COVID-19, or serologic test results pointing to the convalescent phase of infection. Conflicting evidence highlights that testing needs to occur in larger numbers and also at different stages of the disease to determine if a low viral load, undetectable with current methods, or the inability to mount an adequate immune response accounts for the negative SARS-CoV-2 test results. Dermatologists must be aware of the protean cutaneous findings that are possibly associated with COVID-19, even if our understanding of their origins remains incomplete.

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