At the end of 2019, a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has recently been identified as the cause of a pandemic called coronavirus disease 2019 (COVID-19). In this context, some associated skin diseases have been described. Cutaneous lesions referred to as acute acro-ischemia have been reported as a possible sign of COVID-19 in adolescents and children.

The clinical, histologic, and laboratory test results were compatible with a diagnosis of perniosis, and no evidence was found to support the implication of SARS-CoV-2 infection.

Methods

A prospective case series was performed at La Fe University Hospital, Valencia, Spain, to assess the clinical and etiologic features of children and adolescents with acute acro-ischemia. Among 32 patients referred for acral lesions between April 9 and April 15, 2020, we included 20 who presented with new-onset acral inflammatory lesions without an obvious diagnosis of recognizable cause.

Each patient underwent a complete blood cell count; biochemistry tests for liver and kidney function, erythrocyte sedimentation rate, and levels of ferritin, lactate dehydrogenase, and C-reactive protein; coagulation tests, including levels of D-dimer, cryoglobulins, and proteins C and S; urine sediment examination; autoimmunity tests for antinuclear an-
tibodies (enzyme-linked immunosorbent assay [ELISA] and indirect immunofluorescence assay), antineutrophil cytoplasmic antibodies, antiphospholipid antibodies (lupus anticoagulant, anti-β2-glycoprotein, anticardiolipin antibody), C3, C4, and interleukin 6; serologic tests for enterovirus, Epstein-Barr virus, human herpesvirus 6, parvovirus B19, mycoplasma, rubella, and measles; tests for immunoglobulin (Ig) G, IgM, and IgA (COVID-19 ELISA Kit, Vircell; sensitivity and specificity for IgG and IgM + IgA joint detection of 70% and 98%); and reverse transcriptase–polymerase chain reaction (RT-PCR) by nasopharyngeal swab for SARS-CoV-2 (Viasure SARS-CoV-2 Real Time PCR Detection Kit, CerTest Biotech; detection limit ≥10 RNA copies per reaction for the ORF1ab and N genes).

This study was approved by the institutional review board of La Fe University Hospital, and written informed consent for each procedure and for publication was obtained from all patients or their families.

Results

Twenty patients were included in this study, 13 of whom were male. Main characteristics of the patients are depicted in the Table.

No patient had any clinical symptoms (fever, fatigue, dry cough, anorexia, myalgia, dyspnea, sputum, headache, sore throat, smell or taste disorders, or rhinorrhea) suspected to be COVID-19-related.

Similarly, no co-inhabitant showed any symptoms. Ten of 20 patients lived with relatives older than 50 years (6 of whom were older than 80 years). The mean (SD) age of the patients was 12.3 (4.3) years, and no patient was older than 18 years. Nine of them (45%) had a history of vascular re-active disease of the hands (Raynaud phenomenon or pernio-sis). Only patient 8 had a history of connective tissue disease (systemic lupus erythematosus). None of them reported previous drug intake except for patient 18, who had taken a single dose of 500 mg of acetaminophen 2 weeks before, and patient 10, who had started treatment for anemia with ferric sulfate 1 month before. Fifteen (75%) reported walking barefoot around the house during the quarantine. Of all patients, only 2 lived in a home equipped with a heating system. No abnormal test results were found in any patient except for patient 3 and patient 8, who had positive results for antinuclear antibodies (titers of 1/160 and 1/1280, respectively).

Dermatologic findings were classified into the following groups based on skin pattern: periungual erythema; inflammation of 1 or more fingers with occasional whitish areas, which we have called dactylitis; and purpuric maculopapules with occasional blisters. In some patients, we observed a mix of lesions. Acral erythema was found in 6 (30%) of the cases (Figure 1A), dactylitis in 4 (20%) (Figure 1B), purpuric maculo-papules in 7 (35%) (Figure 1C), and a mixed pattern in 3 (15%) (Figure 1D).

We obtained 6 skin biopsy specimens from 6 different patients. Results are presented in the Table and Figure 2. In all patients, results of serologic and viral testing were negative for SARS-CoV-2 as well as other viruses.

Key Points

Question What is the association between acute acral lesions and coronavirus disease 2019 (COVID-19) in children and adolescents?

Findings In this case series of 20 patients aged 1 to 18 years with new-onset acral inflammatory lesions, all lacked systemic manifestations of COVID-19. Both reverse transcriptase-polymerase chain reaction and serologic test results were negative for severe acute respiratory syndrome coronavirus 2.

Meaning An association between acral skin disease and COVID-19 has yet to be proved.

Discussion

On March 14, 2020, a state of emergency was declared in Spain, and strict stay-at-home rules were imposed. Citizens were alerted to a series of signs and symptoms to detect early SARS-CoV-2 infection. Reports of diverse cutaneous lesions as possible symptoms of COVID-19 have led to an increase in visits to our hospital for any of these manifestations. However, apart from temporal coexistence, the involvement of COVID-19 in the development of these lesions has not been proved so far.

In this article, we report a series of 20 cases of cutaneous lesions classifiable on the clinical spectrum of perniosis. Regarding histologic features, it is worth noting that there is bias because 5 of 6 biopsies were performed in patients with more severe lesions. Nevertheless, the histologic findings in all of them were characteristic of chilblains, confirming the clinical impression.

When evaluating the pathogenesis of these lesions, several possibilities emerge. Both our cases and others reported in the literature have developed in a short space of time, generally with an onset in the second to third week of the pandemic. Some of the cases that have been described occurred in patients with SARS-CoV-2 infection demonstrated by RT-PCR or in symptomatic patients, but there are also a large number of patients, similar to ours, in whom the presence of the virus could not be demonstrated by RT-PCR, the serologic test results were negative, or the patients were asymptomatic.

At least 3 different scenarios may be considered to explain the abrupt appearance, during the peak of the pandemic, of these characteristic lesions in a group of SARS-CoV-2–negative patients. One possibility is that the patients were in a very early stage of the disease, which would explain the negativity of PCR and serologic test results. This seems to us the least probable explanation, given that the mean (SD) duration of the disease before consultation in our series was 13.25 (8.11) days and we conducted follow-up in all patients for 4 additional weeks.

The second alternative is that acrocyanosis and perniosis were a subacute manifestation of the infection, in which patients no longer had detectable viral particles. Additionally, in situations in which the viral inoculum was small, it is conceivable that the RT-PCR results were negative, patients...
## Table. Main Characteristics of the Patients

| Patient No. | Sex | PAVR | Wears shoes at home | Heat in home | Co-inhabitants with similar symptoms | Disease duration before consultation, d | Location of skin lesions | Type of acral lesions | Histopathologic findings | Epidermal changes | Dermal changes | Infiltrate allocation |
|-------------|-----|------|---------------------|-------------|--------------------------------------|----------------------------------------|--------------------------|----------------------|------------------------|----------------|----------------|------------------|
| 1           | M   | Yes  | Yes                 | No          | No                                   | 7                                      | Feet                     | AE                   | Scattered NKA          | Endothelial swelling | Papillary dermis |                   |
|             |     |      |                     |             |                                      |                                        |                          | Spongiosis            |                         | PE             |                   |                   |
|             |     |      |                     |             |                                      |                                        |                          | Mild VC               |                         | PE             |                   |                   |
| 2           | F   | Yes  | No                  | No          | Yes                                  | 30                                     | Hands                    | D                    | NP                     | NP             | NP              | NP               |
| 3           | F   | Yes  | Yes                 | No          | No                                   | 9                                      | Hands and feet           | MP (D, PMP)           | NP                     | NP             | NP              | NP               |
| 4           | M   | Yes  | Yes                 | No          | No                                   | 26                                     | Hands and feet           | D                    | NP                     | NP             | NP              | NP               |
| 5           | M   | Yes  | Yes                 | No          | No                                   | 21                                     | Feet                     | PMP                  | Abundant NKA           | Endothelial swelling | Papillary dermis |                   |
|             |     |      |                     |             |                                      |                                        |                          | Spongiosis            |                         | PV             |                   |                   |
|             |     |      |                     |             |                                      |                                        |                          | Lymphocytic vasculitis |                         | PV             |                   |                   |
|             |     |      |                     |             |                                      |                                        |                          | Severe VC             |                         | PE             |                   |                   |
|             |     |      |                     |             |                                      |                                        |                          | Fibrin deposition      |                         | PE             |                   |                   |
|             |     |      |                     |             |                                      |                                        |                          | Moderate edema         |                         |                |                 |                   |
| 6           | F   | Yes  | Yes                 | No          | No                                   | 10                                     | Feet                     | D                    | NP                     | NP             | NP              | NP               |
| 7           | M   | No   | Yes                 | No          | No                                   | 10                                     | Feet                     | D                    | NP                     | NP             | NP              | NP               |
| 8           | F   | Yes  | Yes                 | No          | No                                   | 10                                     | Feet                     | PMP                  | Abundant NKA           | Endothelial swelling | Papillary dermis |                   |
|             |     |      |                     |             |                                      |                                        |                          | Spongiosis            |                         | PV             |                   |                   |
|             |     |      |                     |             |                                      |                                        |                          | Lymphocytic vasculitis |                         | PV             |                   |                   |
|             |     |      |                     |             |                                      |                                        |                          | Severe VC             |                         | PE             |                   |                   |
|             |     |      |                     |             |                                      |                                        |                          | Fibrin deposition      |                         | PE             |                   |                   |
|             |     |      |                     |             |                                      |                                        |                          | Moderate edema         |                         |                |                 |                   |
| 9           | M   | No   | Yes                 | No          | Yes                                  | 17                                     | Feet                     | PMP                  | NP                     | NP             | NP              | NP               |
| 10          | F   | No   | No                  | No          | Yes                                  | 7                                      | Feet                     | MP                   | NP                     | NP             | NP              | NP               |
| 11          | M   | No   | Yes                 | No          | No                                   | 10                                     | Feet                     | PMP                  | Mild NKA               | Endothelial swelling | Papillary dermis |                   |
|             |     |      |                     |             |                                      |                                        |                          | Spongiosis            |                         | PV             |                   |                   |
|             |     |      |                     |             |                                      |                                        |                          | Lymphocytic vasculitis |                         | PV             |                   |                   |
|             |     |      |                     |             |                                      |                                        |                          | Mild VC               |                         | PE             |                   |                   |
| 12          | M   | No   | Yes                 | No          | No                                   | 30                                     | Feet                     | PMP                  | NP                     | NP             | NP              | NP               |
| 13          | M   | No   | No                  | Yes         | No                                   | 10                                     | Hands and feet           | AE                   | NP                     | NP             | NP              | NP               |
| 14          | M   | No   | Yes                 | No          | No                                   | 3                                      | Feet                     | AE                   | NP                     | NP             | NP              | NP               |
| 15          | M   | No   | Yes                 | No          | No                                   | 7                                      | Feet                     | MP                   | NP                     | NP             | NP              | NP               |
| 16          | M   | No   | Yes                 | Yes         | No                                   | 7                                      | Feet                     | PMP                  | Mild NKA               | Endothelial swelling | Papillary dermis |                   |
|             |     |      |                     |             |                                      |                                        |                          | Spongiosis            |                         | PV             |                   |                   |
|             |     |      |                     |             |                                      |                                        |                          | Lymphocytic vasculitis |                         | PV             |                   |                   |
|             |     |      |                     |             |                                      |                                        |                          | Severe VC             |                         | PE             |                   |                   |
|             |     |      |                     |             |                                      |                                        |                          | Moderate edema         |                         |                |                 |                   |
| 17          | F   | Yes  | Yes                 | No          | No                                   | 4                                      | Hands and feet           | AE                   | NP                     | NP             | NP              | NP               |
| 18          | F   | No   | No                  | No          | Yes                                  | 14                                     | Hands and feet           | AE                   | NP                     | NP             | NP              | NP               |
| 19          | M   | Yes  | Yes                 | No          | Yes                                  | 14                                     | Hands and feet           | AE                   | NP                     | NP             | NP              | NP               |
| 20          | M   | No   | Yes                 | No          | No                                   | 19                                     | Feet                     | PMP                  | Abundant NKA           | Endothelial swelling | Papillary dermis |                   |
|             |     |      |                     |             |                                      |                                        |                          | Spongiosis            |                         | PV             |                   |                   |
|             |     |      |                     |             |                                      |                                        |                          | Fibrin deposition      |                         | PV             |                   |                   |
|             |     |      |                     |             |                                      |                                        |                          | Mild VC               |                         | PE             |                   |                   |

Abbreviations: AE, acral erythema; D, dactylitis; MP, mixed pattern; NKA, necrotic keratinocytes; NP, not performed; PAVR, previous acral vascular reactivity; PE, perieccrine; PMP, purpuric maculopapules; PV, perivascular; VC, vacuolar changes.

* Ages ranged from 1 to 18 years.
did not develop other symptoms, and the serologic response was of low intensity and not detectable with the tests currently available. Serologic responses have been shown to be lower in young individuals than in older ones. In this scenario, the only manifestations of COVID-19 could be endotheliitis and a facility for thrombosis in the distal small vessels of the extremities. Entotheliitis and thrombosis have been described in patients with severe COVID-19 with previous endothelial damage and cardiovascular comorbidity (eg, diabetes, hypertension, obesity). However, the absence of those risk factors and the unaltered results of the coagulation tests performed in our patients do not support this explanation.
Finally, a third possibility, which is not supported by the results of all of the complementary examinations carried out in our patients, is that these skin lesions are not induced by the virus but by the quarantine state itself. Accordingly, this quarantine perniosis appeared mainly in children isolated in houses that were not well suited for individuals who spent long periods barefoot or only wearing socks and with very little physical activity.

Limitations
This study was carried out in a short period and with patients from a single center. Furthermore, there is still limited knowledge regarding the clinical manifestations of and detection methods for SARS-CoV-2.

Conclusions
In this case series of 20 children and adolescents, a relationship between acute acral skin changes and COVID-19 could not be demonstrated. Other studies with improved microbiologic tests or molecular techniques aimed at demonstrating the presence of SARS-CoV-2 in the skin may help to clarify this problem.

Figure 2. Main Histologic Features

A. Acral skin with moderate edema in the papillary dermis, perivascular/perieccrine lymphohistiocytic infiltrate, and lymphocytic vasculitis (hematoxylin-eosin). B. Severe perieccrine and deep perivascular infiltrate. Notice the presence of lymphocytic vasculitis as well as fibrin deposition in the vessel walls (hematoxylin-eosin).

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