

mixed infiltrate with a mainly perivascular and perieccrine distribution in the superficial and deep dermis and the hypodermis have been notified.²⁻⁴

However, our histological findings are reminiscent of the pauci-inflammatory thrombogenic vasculopathy that occurs seriously ill hospitalized COVID-19 patients with COVID-19. This thrombogenic vasculopathy is due to activation of the complement pathways and an associated procoagulant state.^{5,6} However, no cases of thrombotic vasculopathy have been reported to date in asymptomatic children or young adults with acral lesions.

In conclusion, the histological findings of purpura-erythema multiforme appearing on soles and heels reveal thrombogenic vasculopathy similar to that found in COVID-19 patients with severe forms of the disease, which suggests that these acral lesions may be related to SARS-CoV-2 or its etiopathogenesis.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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Are chilblain-like acral skin lesions really indicative of COVID-19? A prospective study and literature review

To the Editor

Recently, young COVID-19 patients have presented with erythematous and purpuric acral lesions similar to chilblains.¹⁻³ Despite the scarcity of published cases, this topic has attracted significant mass media attention.⁴ Dermatologists have noted that more people than would be expected at this time of year are seeking medical attention for these chilblain-like lesions. Some have suggested that people presenting with this manifestation should be tested and isolated.² Determining the accuracy of this association is, therefore, crucial.

To establish the real prevalence of COVID-19 in patients with acral skin lesions, we firstly evaluated all the cases of acral lesions presented in dermatology and paediatrics departments and family doctors' offices in an eastern Spanish region over a 3-week period. Then we prospectively performed a SARS-CoV-2 PCR on nasopharyngeal aspirates taken from all available patients to determine whether their cutaneous manifestations were predictive of a positive result.

To put our findings into context, we reviewed all the articles published before May 2020 concerning COVID-19 patients with cutaneous lesions.

We evaluated 58 patients, whose characteristics are summarized in Table 1. In most cases, lesions were chilblain-like. Fifteen patients had already been tested, and only one had a positive result: an 85-year-old man admitted for severe Covid-19 pneumonia. He had an ulcer on a toe that was finally determined to be vascular in nature.

We performed prospective PCR testing in 24 patients. All test results were negative. In total, then, PCR was negative in 38 patients and positive in a single patient whose lesion was very unlikely to be due to COVID-19.

Our bibliography search returned 97 articles and we found two more through cross-references. Nine of these articles dealt with acral lesions specifically. Their results are summarized in Table 2.

Table 1 Epidemiological characteristics and clinical features of 58 patients with acral lesions

Characteristic	Value†
Age	
Median (range)	14.0 years (3 months–85 years)
Sex	
Male	29 (50)
Female	29 (50)
History of thrombosis (N = 53)	
Yes	2 (3.8)
No	51 (96.2)
History of dermatologic conditions (N = 54)	
Yes	7 (13.0)
No	47 (87.0)
Dermatologic history	
Atopic dermatitis	3 (5.5)
Allergic contact dermatitis	1 (1.8)
Psoriasis	1 (1.8)
Recurrent herpes zoster	1 (1.8)
Perniosis	1 (1.8)
COVID-19 related symptoms (N = 52)	
Yes	11 (21.2)
No	41 (78.8)
Exposure or contact (N = 55)	
Contact with a confirmed case	12 (21.8)
Contact with a suspected case	7 (12.1)
No suspicious contacts	36 (65.5)
Location of lesions	
Hands	9 (15.5)
Feet	36 (62.1)
Hands and feet	13 (22.4)
Symptoms (N = 53)	
Pain	17 (32.1)
Pruritus	20 (37.7)
Pain and pruritus	5 (8.6)
Asymptomatic	11 (20.8)
Morphological features of the lesions	
Chilblain-like	42 (72.4)
Purpuric	3 (5.2)
Maculo-papular	3 (5.2)
Vesiculobullous	3 (5.2)
Eczematous	3 (5.3)
Paronychia	2 (3.4)
Ulcer	1 (1.7)
Desquamation	1 (1.7)
Time from development of lesions to PCR test	
Median (range)	12 days (1–28 days)
Time from COVID-19 symptoms to development of lesions (N = 11)	
Median (range)	7 days (0–42 days)
PCR result	
Positive	1 (1.7)
Negative	38 (65.5)
Not performed	19 (32.8)

†Unless otherwise indicated, all values are expressed in number (%) of patients.

Data published in the literature are heterogeneous, as are the methods employed to collect them. The first papers looked at cutaneous manifestations in patients with confirmed SARS-CoV-2 infection.^{5–8} This approach cannot reveal whether this dermatologic manifestation is a specific marker of SARS-CoV-2 infection, since patients without COVID-19 are not included. The other approach, which we have followed, is to analyse all patients with acral lesions. This can be done retrospectively, reporting on patients in the sample who have already been tested, or prospectively, performing the test on all available patients, regardless of whether they have symptoms. The retrospective method has a significant risk of confounding bias: due to the scarcity of COVID-19 tests,⁸ they are usually reserved for patients with COVID-19-related symptoms, who are obviously more likely to test positive.

All previous studies including only patients with cutaneous acral lesions (summarized in Table 2) have been retrospective, and only a minority of patients were tested. In total, 12 out of at least 49 tested patients were positive (24.5%). Combined with our results, they total 13 positives out of 88 tests (14.8%).

There are two possible explanations for the high proportion of negative results: (i) A high number of false negatives. (ii) The lesions are not related to SARS-CoV-2 infection. The low prevalence of an infected contact in our sample, after 3 weeks of strict confinement in Spain, makes the possibility of being infected in our cohort less likely. The diffusion of this entity by the mass media may have caused patients who would not normally consult to do so.⁹ Other possible explanations include a concomitant parvovirus B19 outbreak¹⁰ or trauma-induced lesions.

Our study suggests that acral skin lesions are not a specific marker of SARS-CoV-2 infection. Although larger prospective studies are needed, current evidence indicates that acral skin lesions should not be regarded as a sign of COVID-19 in otherwise asymptomatic patients.

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Table 2 Studies on patients with acral skin lesions

Study	No. of patients	Prospective/ retrospective	PCR (positive/total)	Serological test (positive/total)	Biopsy
Mazzotta and Troccoli T. Acute acro-ischæmia in the child at the time of COVID-19. <i>Eur J Pediatr Dermatol</i> 2020	1 ("few dozen" more through Whatsapp®)	Retrospective	2/unknown	0/0	No
Kolivras A, Dehavay F, Delplace D, <i>et al.</i> Coronavirus (COVID-19) infection-induced chilblains: a case report with histopathological findings. <i>JAAD Case Reports</i> 2020	1	Retrospective	1/1	0/0	Yes
Alramthan A, Aldaraji W. A case of COVID-19 presenting in clinical picture resembling chilblains disease. First report from the Middle East. <i>Clin Exp Dermatol</i> 2020	2	Retrospective	2/2	0/0	No
Estébanez A, Pérez-Santiago L, Silva E, Guillen-Climent S, García-Vázquez A, Ramón MD. Cutaneous manifestations in COVID-19: a new contribution. <i>J Eur Acad Dermatology Venereol</i> 2020	1	Retrospective	1/1†	1/1†	No
Romaní J, Baselga E, Mitjà O, <i>et al.</i> Lesions pernióticas y acrales en España durante el confinamiento por COVID: análisis retrospectivo de 12 casos. <i>Actas Dermosifilogr</i> 2020	12	Retrospective	0/12	0/5 (rapid tests)	Yes
Piccolo V, Neri I, Filippeschi C, <i>et al.</i> Chilblain-like lesions during COVID-19 epidemic: a preliminary study on 63 patients. <i>J Eur Acad Dermatology Venereol</i> 2020;:jdv.16526	63	Retrospective	2/11	2/6	No
Landa N, Mendieta-Eckert M, Fonda-Pascual P, Aguirre T. Chilblain-like lesions on feet and hands during the COVID-19 Pandemic. <i>Int J Dermatol</i> 2020. ijd.14937	6	Retrospective	3/4	0/1	No
Recalcati S, Barbagallo T, Frasin LA, <i>et al.</i> Acral cutaneous lesions in the Time of COVID-19. <i>J Eur Acad Dermatol Venereol</i> 2020	14	Not specified	0/5	0/0	Yes
Fernandez-Nieto D, Jimenez-Cauhe J, Suarez-Valle A, <i>et al.</i> Characterization of acute acro-ischæmic lesions in non-hospitalized patients: a case series of 132 patients during the COVID-19 outbreak. <i>J Am Acad Dermatol</i> 2020	132	Retrospective	2/11	0/0	No
Docampo <i>et al.</i>	58	Retrospective and prospective	Retrospective: 1/15 Prospective: 0/24	Retrospective 0/1 Prospective 0/1	No

†The authors do not specify whether PCR or serology were performed.

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