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SHORT PAPER

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No SARS-CoV-2 antibody response in 25 patients with pseudo-chilblains

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Abstract

Chilblain-like acral lesions have been identified in some coronavirus disease 2019 (COVID-19) patients. It has been suggested that these pseudo-chilblains could be a specific marker of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Most patients with these lesions have had negative polymerase chain reactions (PCRs), but some authors believe serology tests are likely to give positive results. We designed a prospective study including all patients with pseudo-chilblains treated in outpatient department in April and May 2020 and then performed SARS-CoV-2 PCR and serology tests on all available patients. We evaluated 59 patients, of whom 17 had undergone PCR before the study period, all with negative results. For the present study, we performed 20 additional PCRs, serology tests in 25 patients, and a parvovirus B19 antibody test in 15 patients. All results were negative. Our findings counter the hypothesis that serology is likely to reveal SARS-CoV-2 infection in patients with pseudo-chilblains. One hypothesis for our negative results is that the time period between symptom onset and antibody production is longer in these patients; another is that the lesions are caused by behavioral changes during lockdown rather than SARS-CoV-2 infection. We nevertheless maintain that COVID-19 should be ruled out in people presenting with chilblain-like lesions.

KEYWORDS

acral, chilblains, coronavirus, COVID-19, SARS-CoV-2

1 | INTRODUCTION

The rapid expansion of the coronavirus disease 2019 (COVID-19) pandemic has led physicians from various subspecialties to seek novel signs and symptoms of the disease. The role of dermatologists in the fight against this new virus ranges from directly attending affected patients to conducting exhaustive research on skin manifestations potentially associated with the infection.

Different cutaneous manifestations have been identified in COVID-19 patients, including acral lesions.[1-3] The first reports concerned critically ill patients with dusky acrocyanosis, probably caused by coagulopathy and leading to gangrene.[4] More recently, young COVID-19 patients have presented with erythematous and purpuric acral lesions similar to chilblains.[5,6] It has been suggested that these pseudo-chilblains could be a specific marker of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection[6]; however, most SARS-CoV-2 polymerase chain reaction (PCR) tests have resulted negative in these patients.[6-9] One explanation put forward for the negative results is that the lesions are a late manifestation of COVID-19, and PCR may have been positive if performed

earlier.[1,6] Some authors suggest that serology testing could detect the infection where PCR fails, but in the few published cases where serology testing has been employed, the results have mostly been negative.[8,10]

2 | METHODS

We designed a prospective study including all cases of pseudo-chilblains treated in our department in April and May 2020. We then performed SARS-CoV-2 PCR and serology tests on all available patients. For the serology tests, we used the VirClia system (Vircell Microbiologists, Granada, Spain), detecting immunoglobulin (Ig) G with the COVID-19 VIRCLIA IgG MONOTEST assay (sensitivity 92%, specificity 99%) and IgM + IgA with the COVID-19 VIRCLIA IgM + IgA MONOTEST assay (sensitivity 87%, specificity 99%). These are indirect chemiluminescent immunoassays to determine antibodies against SARS-CoV-2 in human serum.

This study was reviewed and approved by the Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL).

3 | RESULTS

We evaluated 59 patients with pseudo-chilblain lesions. Their epidemiological and clinical features are summarized in Table 1. Clinical pictures of two patients are shown in Figure 1. We had previously performed PCR on 17 patients, and all results had tested negative. These findings have already been published.[11] For the present study, we performed 20 additional PCR tests, serology testing on 25 patients, and a parvovirus B19 antibody test on 15 patients. All results were negative. No other viral tests were performed.

4 | CONCLUSIONS

Our findings counter the suggestion that patients with pseudo-chilblains will have negative PCRs but positive serology tests because their lesions are a late manifestation of SARS-CoV-2. It is very unlikely that in a sample of 25 patients all results were false negatives, and so other explanations must be considered.[12] One alternative hypothesis is that these negative results were due to lymphocyte exhaustion and viral-associated immunosuppression resulting in a lack of antibody production.[10] In our case series, the average time between the onset of lesions and performing the test was 26.5 days; it may take longer to generate detectable antibodies. Some studies have demonstrated that the vast majority of patients with COVID-19 generate antibodies within 2 weeks of developing symptoms,[12] but most patients in these studies had severe COVID-19 with respiratory symptoms, which are generally not present in patients with pseudo-chilblains. Another possible scenario is that these lesions are not directly produced by SARS-CoV-2 infection. The lockdown during the pandemic could have played a role, because at home people are more likely to walk barefoot on cold floors, increasing their risk of developing chilblains.[7] Nevertheless, some studies have reported serious pathology associated with pseudo-chilblains in SARS-CoV-2 children with positive

TABLE 1 Epidemiological and clinical features of 59 patients with chilblain-like lesions

Characteristic	Value[a]
Age (y)	
Median (range)	14.0 (0-50)
Sex	
Male	34 (57.1)
Female	25 (42.9)
History of thrombosis (N = 51)	
Yes	1 (2.0)
No	47 (98.0)
History of dermatologic conditions (N = 54)	
Yes	6 (11.1)
No	45 (88.9)
Dermatologic history	
Atopic dermatitis	4 (6.8)
Psoriasis	1 (1.7)
Herpes zoster	1 (1.7)
COVID-19-related symptoms (N = 54)	
Yes	9 (16.7)
No	45 (83.3)
Exposure or contact (N = 57)	
Contact with a confirmed case	5 (8.8)
Contact with a suspected case	12(21.1)
No confirmed or suspected contact	40 (70.2)
Location of lesions	
Hands	6 (10.2)
Feet	43 (72.9)
Hands and feet	10 (16.9)
Symptoms (N = 55)	
Pain	12 (21.8)
Pruritus	25 (45.5)
Pain and pruritus	6 (10.9)
Asymptomatic	12 (21.8)
Time from COVID-19 symptoms to development of skin lesions (N = 7) (d)	
Median (range)	3 (0-18)
Time from development of lesions to serology test (d)	
Median (range)	26.5 (9-40)
PCR test (N = 37)	
Prospective	22 (59.5)
Retrospective	15 (40.5)

Abbreviations: COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction.

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

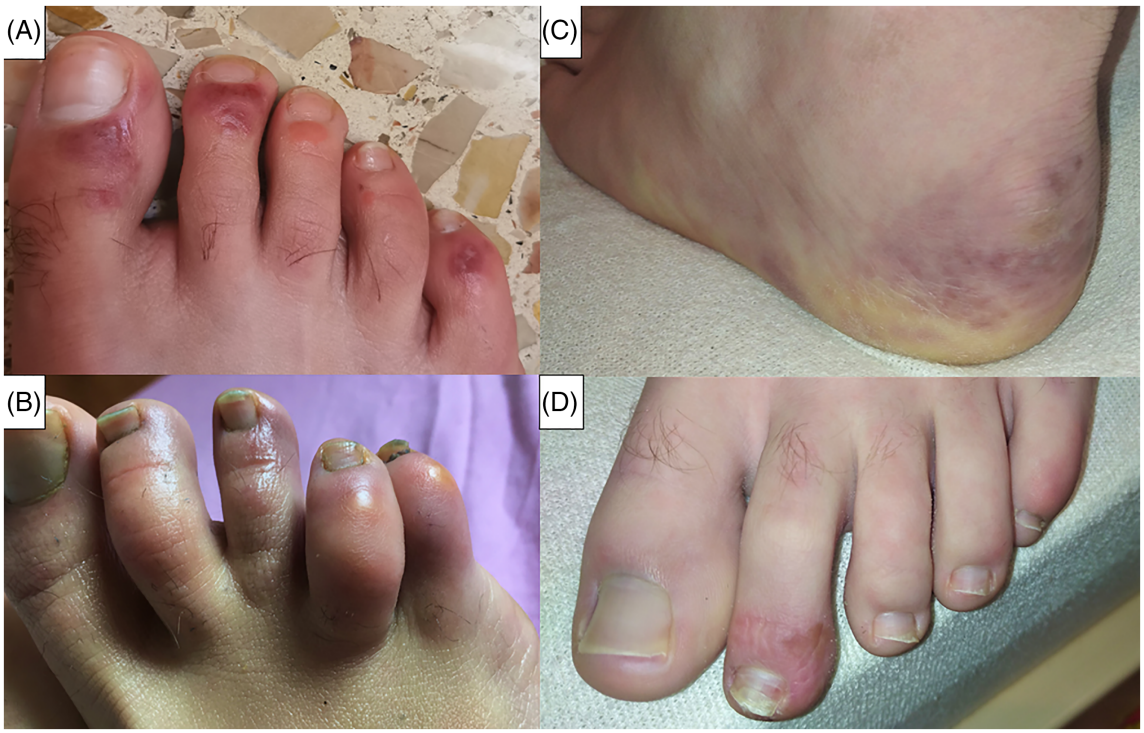

FIGURE 1 A, Pseudo-perniotic lesions on the toes of a 22-year-old man. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) and serology were negative. B, Pseudo-perniotic lesions on the toes of a 22 year-old-woman. SARS-CoV-2 PCR and serology were negative. C and D, Pseudo-perniotic lesion on the ankle and toes of a 14-year-old boy. SARS-CoV-2 PCR and serology were negative

serology test results, which highlights the importance of ruling out SARS-CoV-2 infection in these patients.[13]

The limitations of our study include the relatively small number of patients tested and the absence of skin biopsies. Until further studies are conducted, our results appear to indicate that pseudo-chilblains should be considered a possible but not definitive marker of COVID-19.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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