Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

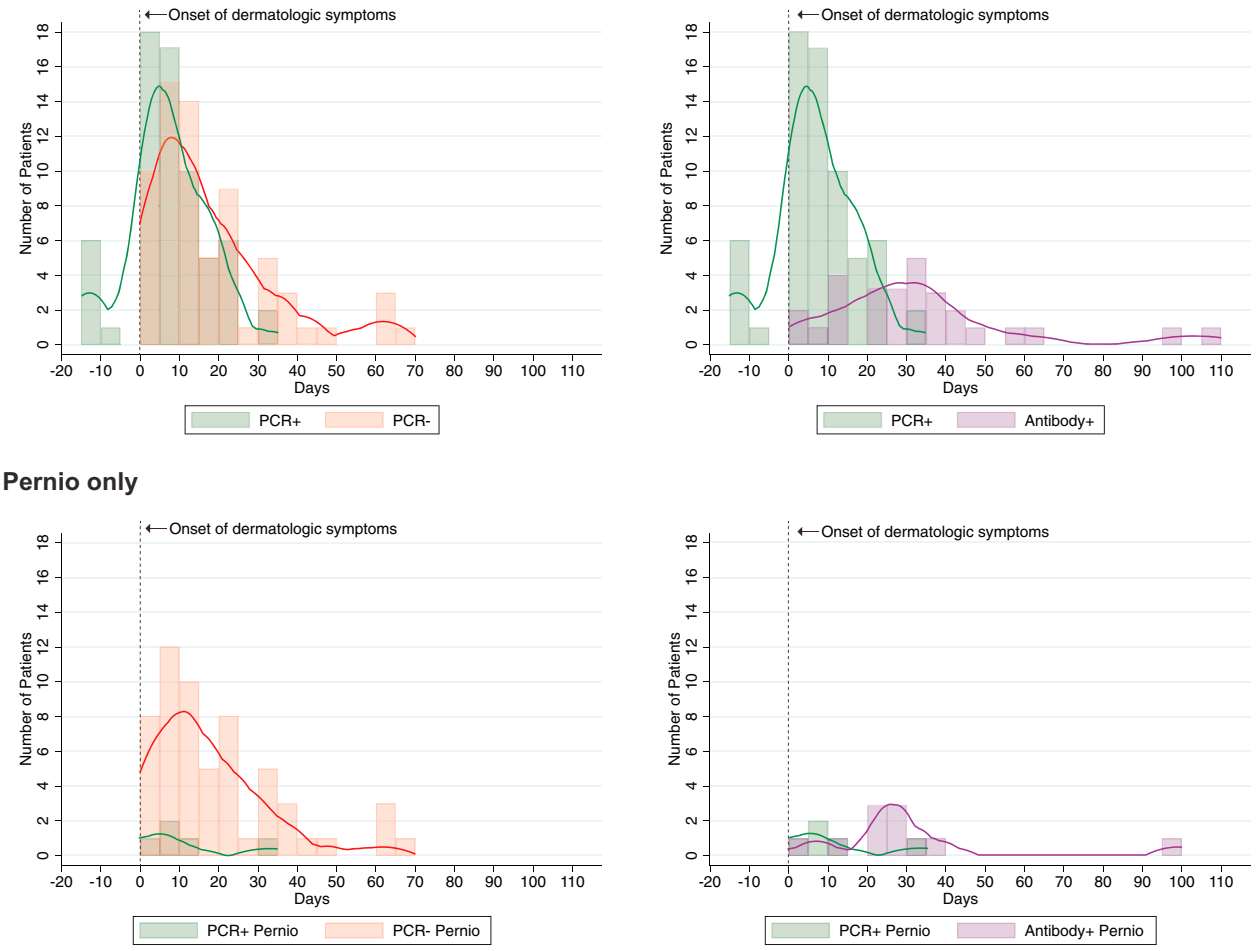

Fig 1. Distribution of positive and negative coronavirus disease 2019 test results in relation to onset of dermatologic symptoms, including polymerase chain reaction–positive/negative test results and polymerase chain reaction–positive/antibody-positive test results. Individual cases graphed as 5-day bins, defined by date of laboratory testing. *PCR*, Polymerase chain reaction.

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Chilblain-like lesions and COVID-19 infection: A prospective observational study at Spain's ground zero

To the Editor: Chilblain-like lesions (CBLL) have been related to severe acute respiratory coronavirus 2 (SARS-CoV-2) infection,[1] although solid microbiological confirmation is still lacking.

We present a prospective cohort study of 37 patients (median age, 14 years) presenting new-onset CBLL during the COVID-19 outbreak in Spain that included (1) SARS-CoV-2 testing (nasopharyngeal polymerase chain reaction [PCR] and serologies) and immunologic profiles for all patients, (2) custom recall antigen experiments and

intracellular cytokine production evaluation in selected cases, and (3) skin biopsy for histopathology and immunochemistry (11 samples) and SARS-CoV-2 PCR and electron microscopy (3 cases) (Supplemental Tables I-IV; available via Mendeley at https://doi.org/10.17632/vgvxtcb82c.1).

CBLL mainly affected the toes (Table I), with other features including dusky erythematoedematous changes on the dorsal surfaces of the toes and fingers (24.32%), purpuric macules (37.83%), and blisters (10.81%). Two patients presented with more obvious signs of distal skin ischemia (Supplemental Figs 1-3; available via Mendeley at https://doi.org/10.17632/vgvxtcb82c.1). In most cases, the lesions fully/partially remitted with topical therapy or no therapy. Only 1 patient presented with signs of retinal vasculitis. Vascular pulses and Doppler ultrasonography showed normal blood flows in the entire series. All biopsy specimens were consistent with pernio, and 54.5% showed complement C3d and C4d deposition around small vessels (Supplemental Fig 4; available via Mendeley at https://doi.org/10.17632/vgvxtcb82c.1). Nasopharyngeal PCR had positive results in 8.1%, and SARS-CoV-2 serology results were positive in just 8.1% of patients. Recall antigen assays showed positive responses in the 3 patients who underwent them (2 with negative SARS-CoV-2 serologies). Five of the 37 patients presented mild anticardiolipin titer elevation. Interferon (IFN) alfa levels were increased in only 1 of 24 tested patients, whereas the rest of the cytokines remained within normal or undetectable levels. No virus was detected on electron microscopy or PCR testing in skin samples.

Our patients presented with CBLL in striking parallel to the rise and fall of the COVID-19 pandemic in Madrid, but approximately 2 weeks later (Fig 1). The low proportion of positive SARS-CoV-2 serology test results would argue against the idea of a causal relationship between CBLL and SARS-CoV-2 infection. Lack of serologic test accuracy and a more prominent innate immune response might explain this discrepancy.[2] However, our preliminary results with SARS-CoV-2 assays suggest that patients could have been exposed to SARS-CoV-2 despite negative routine serologic test results. These patients might have had mild SARS-CoV-2 infection, although the upregulation of the type I IFN pathway could have resulted in the onset of CBLL in genetically predisposed patients. The lower rate of measured IFN alfa could be due to the fact that we measured it in a late phase of infection, according to PCR test results.

Table I. Summary of demographic and clinical features of the patients presenting chilblain-like lesions (N = 37)

Sex, n (%)	
Female	20 (54.05)
Male	17 (45.95)
Mean age, y, mean ± SD	22.08 ± 15.46
Median age, y	14
Latency between systemic symptoms and skin lesions, days	21.76 ± 23.01
Affected areas, n (%)	
Toes only	15 (40.55)
Fingers only	10 (27.03)
Toes and sides of feet	7 (18.92)
Toes and heels	2 (5.40)
Toes and fingers	2 (5.40)
Toes, fingers, and sides of feet	1 (2.70)
Associated signs and symptoms, n (%)	
Purpuric macules	14 (37.83)
Erythema	6 (16.21)
Pruritus	5 (13.51)
Cold skin	5 (13.51)
Blisters	4 (10.81)
Pain	3 (8.10)
Edema	3 (8.10)
Ulceration and/or necrosis	2 (5.40)
History of systemic symptoms, n (%)	17 (45.95)
Evolution of the lesions (+2 weeks), n (%)	
Complete resolution	16 (43.24)
Partial resolution	14 (37.84)
Persistence	4 (10.81)
Worsening	3 (8.11)
Prescribed therapy, n (%)	
None	24 (64.86)
Topical corticosteroids	8 (21.63)
Oral corticosteroids	1 (2.70)
Pentoxifylline	4 (10.81)

SD, Standard deviation.

The exact role of SARS-CoV-2 in the development of CBLL, if any, remains unclear.[3] We were unable to detect the virus in skin samples; however, the SARS-CoV-2 spike protein has been shown in the endothelial and epithelial cells of eccrine glands.[4] Additionally, immune complex deposition can lead to tissue injury through various mechanisms, including complement activation, which could contribute to their pathogenesis.[5]

In conclusion, if CBLL were secondary to SARS-CoV-2, absence of a more evident humoral response would be highlighted. Recall antigen assays could help clarify this association.

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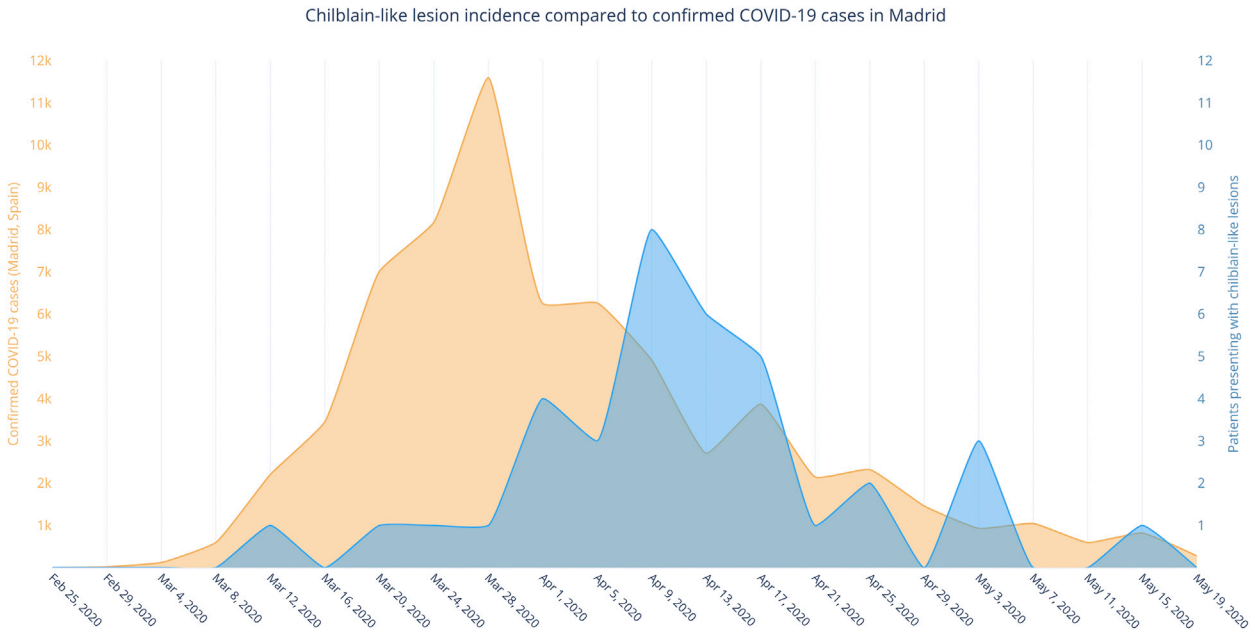

Fig 1. Chilblain-like lesions: the incidence at our center compared with confirmed COVID-19 cases over time in Madrid.

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