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.

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All that glisters is not COVID: Low prevalence of seroconversion against SARS-CoV-2 in a pediatric cohort of patients with chilblain-like lesions

To the Editor: On January 7, 2020, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was isolated in a patient affected by interstitial pneumonia. As SARS-CoV2 infection has spread worldwide, an increasing number of authors have reported chilblainlike lesions as possible manifestations of SARS-CoV-2 infection.[1,2]

To test this hypothesis, we performed serologic and stool/rectal polymerase chain reaction tests in a cohort of children who developed chilblainlike lesions during the SARS-CoV-2 outbreak in Italy, between March 8 and April 30, 2020.

Enrollment criteria are described in the Supplemental material (available via Mendeley at https://doi.org/10.17632/wzh2tyb46y.2).

During the enrollment period, 35 cases of chilblainlike lesions were eligible for the study. Twenty-four patients agreed to serologic testing (68.6%).

All patients were white, mean age was 13 years (range, 6-17 years), and the female to male ratio was 2:1. Twenty-two patients presented with chilblains on the toes (Fig 1) and 2 lesions were located on the heels, 6 patients developed blistering lesions, 83% of lesions lasted more than 14 days, and 8% lasted less than 1 week.

Two patients had known contact with SARS-CoV-2—positive individuals, defined by positive nasal swab result. Seven more patients had close contact with someone who presented symptoms that might be SARS-CoV-2 related such as asthenia, loss of smell (anosmia), cough, and prolonged fever. In 25% of cases, at least 1 parent was a health worker. Further details are available in the Supplemental Results.

Chemiluminescence assay (Liaison SARS-CoV-2 IgG, Diasorin) was performed for all patients; 7 patients were tested with In3diagnostic ERADIKIT COVID19, and the other 17 with EDI Novel Coronavirus COVID-19.

A total of 3 patients (12.5%) tested positive via both enzyme-linked immunosorbent assay and chemiluminescence. In 1 patient (4.1%), enzyme-linked immunosorbent assay test result was positive, whereas chemiluminescence result was negative. None of the 4 patients with positive results presented with fever, 50% had cough, and 25% presented with transient diarrhea up to 14 days before skin lesion appearance. All 4 patients had contact with a relative who had confirmed SARS-CoV-2 infection (2 patients) or anosmia (2 patients). Fecal polymerase chain reaction was tested in 4 patients (16.6%), and no result was positive; rectal swab was performed in 17 patients (70.8%) and was positive in 1, which also was positive at both serologic tests.

Finally, patients with chilblainlike lesions were compared with a cohort of 24 SARS-CoV-2—infected children. Table I shows the comparison between the 2 groups. Chilblain patients were significantly older (13 vs 4 year; $P < .001$); fever was present in a limited

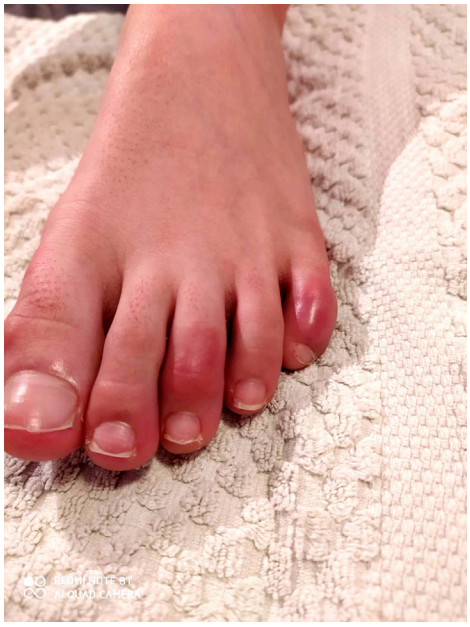

Fig 1. Typical chilblainlike lesions in a pediatric patient enrolled in the study.

Table I. Comparison between pediatric cohorts with chilblainlike lesions and severe acute respiratory syndrome coronavirus 2 infection

Epidemiological characteristics and symptoms	Chilblains	SARS-CoV-2 infection*	*P* value
No. of patients	24	25	NA
Age, y, (range)	13 (10.5–14)	3.8 (0.95–9)	<.001
Female patient, no. (%)	15 (62.5)	8 (32)	.04
Skin lesions, no. (%)	24 (100)	3 (12)	<.001
Fever, no. (%)	4 (16.7)	23 (92)	<.001
Cough, no. (%)	10 (41.7)	13 (52)	.5
Conjunctivitis, no. (%)	3 (12.5)	0	.1
GI symptoms, no. (%)	5 (20.8)	6 (24)	>.99
Certain exposure to SARS-CoV-2, no. (%)	2 (8.3)	14 (56)	<.001

The differences between groups were analyzed with Mann-Whitney *U* test for continuous data and Fisher's exact test for categoric data. All tests were 2 tailed, and the significance was set at $P < .05$.
GI, Gastrointestinal; *NA*, not available; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2.
*Twenty-two patients hospitalized and 3 evaluated in the emergency department at the Regina Margherita Children's Hospital.

number of cases (16.7% vs 92%; $P < .001$), and certainty of exposure to SARS-CoV-2 was limited (8% vs 56%; $P < .001$).

According to our data, the hypothesis of a direct etiologic link between SARS-CoV-2 and chilblain is not confirmed by serologic tests; it is difficult to assess whether in the 4 patients with positive serology SARS-CoV-2 was involved in the pathogenesis of chilblainlike lesions. A limit of our study is the absence of tissue biopsies, so our experimental approach could not rule out the presence of virus in patients' lesions that may induce an interferon-I response.[3] As confirmed by other studies,[4] the low prevalence (12.5%) of seropositive patients suggests that other pathologic hypotheses should be considered to explain the recent outbreaks of chilblainlike lesions worldwide.

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Evaluation of SARS-CoV-2 antibodies in 24 patients presenting with chilblains-like lesions during the COVID-19 pandemic

To the Editor: Chilblains-like lesions have been reported in primarily young, healthy patients with suspected or confirmed severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) infection[1,2] and are characterized histopathologically by chilblains-like changes, without necrosis.[3] Although SARS-CoV-2 viral particles have been identified within endothelial cells of patients with chilblains-like lesions,[4] negative results or absent SARS-CoV-2 laboratory testing in other patients has created uncertainty about the relationship between coronavirus disease 2019 (COVID-19) and chilblains-like lesions. We evaluated this relationship by performing multiple tests for SARS-CoV-2 antibodies on patients with chilblains-like lesions during a surge of SARS-CoV-2 infections.

Our dermatology service offered antibody testing to 26 consecutive patients with chilblains-like lesions evaluated during a surge of SARS-CoV-2-infections. Two patients declined participation. Testing was performed on the following platforms: Abbott Architect (IgA, immunoglobulin [Ig] M, IgG, repeat IgG; Abbott, Abbott Park, IL); DiaSorin Liaison (Saluggia, Italy) SARS-CoV-2 S1/S2 (IgG); and Euroimmun SARS CoV-2 enzyme-linked immunosorbent assay (IgG) (Euroimmun US, Mountain Lakes, NJ). Clinical information was obtained via medical record review.

All 24 patients (100%) tested negatively for SARS-CoV-2 IgG on 2 separate tests on the Abbott Architect platform, 21 (87.5%) tested negatively on the Euroimmun IgG platform, and 23 (95.8%) tested negatively on the Liaison Sars-Cov-2 platform (Table I).

All 24 patients (100%) tested negatively for IgA antibodies, 22 (91.7%) tested negatively for IgM, and 21 (91.67%) completed nasopharyngeal polymerase chain reaction testing for SARS-CoV2. Of these, 20 (95.2%) tested negatively. No patients reported a prior history of chilblains.

We observed minimal evidence of SARS-CoV-2 antibodies in patients identified with chilblains-like lesions because only 4 of 24 patients (16.7%) tested had any positive results and none had multiple positive results.

Despite our findings, an association between chilblains-like lesions and SARS-CoV-2 infections may exist. Our patients may have had SARS-Cov-2 infection but failed to mount a detectable antibody response. Chilblains-like lesions may be associated with mild infections in patients and who test negative on polymerase chain reaction,[1] and patients with mild clinical courses may mount weak antibody responses.[5] Problems with the timing or accuracy of antibody tests could produce negative results. Our patients were tested an average of 23.65 days from symptom onset, a timing thought to correlate with detectable IgG levels; however, 4 patients reported fewer than 14 days of cutaneous symptoms before testing, which may not have allowed sufficient time to produce antibodies. By testing patients on multiple platforms, we sought to reduce the likelihood of false-negative results. The observed discordance in IgG results in 4 patients suggests individual results may be unreliable.

Inappropriate patient selection through diagnostic error, anchoring bias, or selection bias could have occurred, although we attempted to minimize this by having multiple board-certified dermatologists review each patient's photographs. An epiphenomenon, whereby the COVID-19 pandemic leads to changes in behavior that may predispose patients to chilblains-like lesions without a causal link, is also possible.

In conclusion, we found a low frequency of SARS-CoV-2 antibodies in 24 patients presenting with chilblains-like lesions during a SARS-CoV-2 outbreak and discordance across different testing platforms. Patients presenting with chilblains-like lesions should not be presumed to have serologic immunity to SARS-CoV-2 as a result of recovery from prior infection, without confirmatory testing.

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