

## Chilblain-like lesions during the COVID-19 pandemic: a serological study on a case series

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DEAR EDITOR, The outbreak of chilblain-like lesions (CLL) coincidentally to the COVID-19 pandemic is a topic of great concern.<sup>1–6</sup> SARS-CoV-2 has been hypothesized as the aetiological agent of CLL, on the basis of the temporal correlation between the ‘burst’ of skin manifestations and the viral pandemic. However, the relationship between CLL and COVID-19 remains unclear, as researchers have failed to confirm the SARS-CoV-2 infection in these patients using real-time reverse-transcription polymerase chain reaction (RT-PCR) from nasopharyngeal swabs, which seldom tested positive.<sup>1–5</sup> Indeed, the most recent articles on the prevalence of the SARS-CoV-2 infection in CLL reported a positive swab test in only about one-fifth of these patients.<sup>4,5</sup> In a few cases, serological tests were used, but these initially available tests were largely unreliable, as they had been rapidly developed and placed on the market with limited validation on clinical samples.

We collected data on 16 patients presenting with CLL, who were all negative to the nasopharyngeal swab. We then decided to recall our patients to perform a recently developed rapid chromatographic immunoassay (RCI) for the qualitative detection of specific antibodies to SARS-CoV-2, using the SD Biosensor COVID-19 IgM/IgG Duo assay (SD Biosensor Inc., Yeongtong-gu, South Korea). The SD Biosensor’s package insert claims a sensitivity of 99.10% and a specificity of 95.09%, established in a retrospective, multicentre, randomized, single-blinded study on 504 specimens, if used more than 14 days after the onset of symptoms. In total, 12 of our patients agreed to undergo the RCI test; their characteristics are summarized in Table 1. All of them were tested at least 14 days after presentation of skin disease (mean value  $51.3 \pm 25.8$ ), according to the manufacturer’s instructions. In 11 of 12 the presence of IgM or IgG was not detected. The sole patient with positive IgG was the only one with a history of exposure to a confirmed infected cohabitant. Four patients were also tested for other common viral infections, without significant results.

This is the first study in which patients with CLL have been investigated with both RT-PCR nasopharyngeal swab and serological RCI, after a sufficient time lapse to develop antibodies against SARS-CoV-2. Indeed, higher levels of IgM and IgG have been found in the second and third weeks of illness, then IgM begins to decline and almost disappears by week 7, while IgG persists. Their long-term persistence still remains unknown, although data suggest a serological profile similar to that of SARS-CoV, which shows detectable IgG for up to 24 months.<sup>7</sup>

Therefore, while swabs are known to be associated with an elevated number of false-negative results, serological tests may

represent a reliable instrument to identify past infections. We observed a high prevalence of negative serological results in CLL. These data, associated with the high prevalence of negative RT-PCR tests as seen in the literature,<sup>4,5</sup> raise two hypotheses.

Firstly, SARS-CoV-2 is not the aetiological agent of CLL. In this case, we should consider another viral agent, and the presence of SARS-CoV-2 may therefore be only a coincidental finding. However, a viral outbreak during another viral pandemic seems improbable. One of our cases presented with clinical onset of CLL some days before the first Italian recognized case of COVID-19. This could support the hypothesis of a different aetiological agent. On the other hand, the literature suggests that the SARS-CoV-2 virus had already appeared in northern Italy between the second half of January and early February 2020.<sup>8</sup> We also considered that these may be true chilblains, but this seems unlikely, as our patients had no personal history of chilblains or rheumatological diseases and were forced to stay home during lockdown, avoiding external cold weather. Furthermore, our regional meteorological station registered similar or higher temperatures during February, March and April 2020 compared with the mean temperatures of the past 13 years.

The second theory is that SARS-CoV-2 is the aetiological agent of CLL, but does not induce detectable IgM and IgG. In this case we can put forward two more hypotheses: (i) the viral load was not enough to induce antibody formation; and (ii) the host developed an early and robust interferon type I response, muting early viral replication and not permitting the development of detectable IgM and IgG.<sup>1</sup> However, this would be in contrast with the formerly proposed hypothesis of delayed immune-mediated reaction to the virus in genetically predisposed patients.<sup>1</sup>

The main limitation of our serological study is the lack of independent validation of the available tests on the market, despite excellent clinical performance in real life of the used assay (personal experience).



In conclusion, while our study confirms that acral skin lesions are not a specific marker of SARS-CoV-2 infection,<sup>4</sup> it is necessary not only to expand our observation by serologically testing a larger number of patients with CLL, but also to investigate aetiological agents other than SARS-CoV-2.

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**Table 1** Age, sex, disease, onset of symptoms, details of tests and history of exposure in the described population

Pt	Age (years)/sex	Areas of involvement		Date of onset	Interval (days) <sup>a</sup>	SSR	Serology	History of exposure	Other viruses tested
		Hands	Feet						
1	19/F	No	Yes	11 March	70	Neg	Neg	—	—
2	15/F	No	Yes	8 March	72	Neg	Neg	Schoolmate with COVID-19 confirmed by swab	CMV Neg, EBV latent infection
3	16/M	Yes	No	1 April	55	Neg	Neg	Son of a nurse	—
4	14/F	No	Yes	27 March	48	Neg	Neg	Nurse's daughter (nurse tested negative)	CMV Neg, PB19 Neg, EBV latent infection, enterovirus Neg
5	12/F	Yes	Yes	8 April	15	Neg	Neg	Police officer's daughter	CMV Neg, PB19 Neg, EBV latent infection; enterovirus: IgG Neg, IgM undefined results
6	15/M	No	Yes	15 April	36	Neg	Neg	Public health employee's son	Enterovirus Neg
7	15/M	No	Yes	27 March	14	Neg	IgM (Neg), IgG (Pos)	Sister with COVID-19 confirmed by swab	—
8	12/F	No	Yes	27 February	81	Neg	Neg	—	—
9	12/M	No	Yes	10 February	90	Neg	Neg	—	—
10	9/F	Yes	No	4 May	18	Neg	Neg	Both parents are nurses (tested negative)	—
11	11/F	No	Yes	3 April	55	Neg	Neg	Sister of patient 12	—
12	12/F	No	Yes	28 March	61	Neg	Neg	Sister of patient 11	—

CMV, cytomegalovirus; EBV, Epstein-Barr virus; Neg, negative; PB19, Parvovirus B-19; Pos, positive; Pt, patient; SSR, SARS-CoV-2 swab result (polymerase chain reaction). <sup>a</sup>Interval between onset of disease and serological test.

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## No evidence of SARS-CoV-2 infection by polymerase chain reaction or serology in children with pseudo-chilblain

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DEAR EDITOR, Despite its aggressive clinical course, leading to a 6.4% fatality rate as of 25 May 2020,<sup>1</sup> COVID-19 has been only marginally aggressive in children.<sup>2,3</sup> In a report from Lombardy, 18 of 88 adults (20%) hospitalized with COVID-19 had developed cutaneous manifestations: erythematous rash, widespread urticaria and chickenpox-like vesicles. The trunk was the main involved region. Itching was mild or absent and usually lesions healed in a few days.<sup>4</sup>

An unexpected outbreak of acute pseudo-chilblain skin lesions is being reported from different countries and is related to COVID-19.<sup>5–7</sup> Unfortunately, information about COVID-19 status was available in only a minority of cases. In their study of 63 patients, Piccolo et al. reported that swab was performed in only 11 patients (17%) and resulted positive in two cases (3%).<sup>7</sup> Serology was available in six cases (9%) and was positive in the two patients with positive swab. Nevertheless, the authors stated that ‘children presenting even with only skin manifestations potentially imputable to COVID-19 should be considered contagious until otherwise proven’.<sup>7</sup>

In a prospective nationwide consensus study in Spain with 375 cases, Galván Casas et al. reported 71 cases of this type of lesion, of which 41% (29 patients) were positive by polymerase chain reaction (PCR). The remaining 59% had clinical criteria for COVID-19 (European Centre for Disease Prevention and Control). The sensitivity analysis comparing those who were PCR positive and those with only clinical criteria showed no difference between groups. As that study included only patients confirmed positive by PCR or with suspected COVID-19, the percentage is not comparable with that of other studies that include cases with acral lesions, with or without COVID-19 diagnosis.<sup>5</sup>

To clarify this assumed association, we examined 38 consecutive children (median age 13.5 years) referred to our tertiary-care, university hospital who had acute pseudo-chilblain skin lesions. These were defined as multifocal and asymmetric purpuric–ecchymotic patches and/or ‘pernio-like’ lesions or ecchymotic lesions on the sole, heel and/or plantar aspect of a single toe or dorsal aspect of the hands.

SARS-CoV-2 virus was detected by a real-time PCR assay targeting the E, RdRP and N genes. All of the collected samples were subjected to real-time PCR analysis for the molecular detection of other viral (influenza A; influenza B; parainfluenza 1/2/3/4; human rhinovirus; adenovirus; metapneumovirus; respiratory syncytial virus A/B; human coronaviruses OC43, NL63 and 229E; enterovirus and bocavirus) and bacterial pathogens (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Bordetella pertussis* and *Bordetella parapertussis*). A commercial real-time PCR kit was used (Allplex™ Respiratory Full Panel Assay; Seegene, Seoul, South Korea). Detection of IgM and IgG anti-SARS-CoV-2 was performed with the VivaDiag COVID-19 IgM/IgG Rapid Test (VivaChek Laboratories, Wilmington, DE, USA) and also by an enzyme-linked immunosorbent assay for IgA and IgG antibody detection (Anti-SARS-CoV-2 ELISA IgA Test and Anti-SARS-CoV-2 ELISA IgG Test; Euroimmun, Lübeck, Germany).

The study was approved by our paediatric institutional review board. Informed consent for the study was obtained from the patient (if aged ≥ 7 years) and the parents in all cases. Thirty-eight patients were enrolled, all evaluable, with 22 (58%) male and 16 (42%) female. Their age ranged between 7 and 18 years (median 13.5); three had an associated condition (one each with X-linked and coeliac disease, diabetes mellitus and coeliac disease, and nephrotic syndrome).

Upon specific request, associated symptoms were recorded (but never concurrent) in eight patients (21%): six had fever