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Funding sources: none.

Conflicts of interest: The authors declare they have no conflicts of interest.

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

DOI: 10.1111/bjd.19349

Dear Editor, Despite its aggressive clinical course, leading to a 6.4% fatality rate as of 25 May 2020,[1] COVID-19 has been only marginally aggressive in children.[2,3] 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.[4]

An unexpected outbreak of acute pseudo-chilblain skin lesions is being reported from different countries and is related to COVID-19.[5–7] 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%).[7] 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'.[7]

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.[5]

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

about 1 month before, and two had diarrhoea. History of autoimmune disorders was found in only six patients (one with antinuclear antibody positivity), while familial or personal history of coagulation defects was seen in four cases.

The skin lesions were localized on the feet, and in only a few cases they were also seen on the hands. The lesions were characterized by multifocal and asymmetric purpuric–ecchymotic patches and/or 'pernio-like' lesions. Ecchymotic lesions were observed on the sole, heel and/or plantar aspect of a single toe or the dorsal aspect of the hands. A 'pernio-like' pattern with red-bluish erythematous patches was observed on the dorsal aspect of the toes and fingers, sometimes with superficial skin vesicular–bullous swelling and erosion. The time between the onset of skin lesions and evaluation of SARS-CoV-2 infection status ranged between 3 and 88 days (median 25).

In none of the study patients could we document SARS-CoV-2 infection by real-time PCR or serological tests for SARS-CoV-2 antibodies, IgM, IgG or IgA. No other pathogens potentially causing the lesions were identified by molecular tests, except for the detection of *Mycoplasma pneumoniae* in one patient.

In conclusion, despite the systematic use of both molecular and serological assays, we have not found data to support the relationship of the outbreak of pseudo-chilblain, frequently observed in children and adolescents during the COVID-19 pandemic, with SARS-CoV-2 infection. Our data do not allow us to say that there is no association due to the absence of PCR (which is only positive in the early stages of the disease) or detectable immunoglobulins (with inconsistent sensitivity and reliability of tests). It would only be possible to reach this conclusion if we were able to assess the duration of the positive serology and the percentage of affected persons who acquire antibodies, in relation to their age and the intensity of the COVID-19 symptoms, and the percentage of positives in the general population. Serology was used to explore the hypothesis that skin alterations appear as a late manifestation of COVID in children and adolescents, when nasopharyngeal swab may test negative. Yet, based on the current knowledge, seronegativity cannot be taken as an absolute marker of noninfection.

Clustering of skin lesions during the peak of the pandemic in our region and their quick decline in the last few weeks suggest some nonrandom association, which someway parallels that suggested for Kawasaki disease.[8] Understanding such inflammatory phenomena in children might provide vital information about immune responses to SARS-CoV-2, relevant for both adults and children, and could possibly help clarify why children are usually mildly or not affected by COVID-19.

Acknowledgments: We would like to thank Dr W. Amorosi, M. Carone, A. Giannini, R. Grandolfo, D. Larovere, P. Massagli, V. Santoiemma, F. Transella and D. Tricarico (Paediatric Infectious Diseases, Giovanni XXIII Children Hospital, Azienda Ospedaliero Universitaria Consorziale Policlinico, Bari) and D. Ferri (Paediatric Practitioner, Bari) for their support in patient care.

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Funding sources: none.

Conflicts of interest: The authors declare they have no conflicts of interest.

Treatment of severe cutaneous adverse reaction with tocilizumab

DOI: 10.1111/bjd.19129

Linked Article: Thompson and Chen. *Br J Dermatol* 2020; **183**:613.

Dear Editor, A 29-year-old Chinese man with recurrent alveolar soft part sarcoma of the tongue metastatic to lung presented with fever and rash (Figure 1a). He underwent glossectomy and adjuvant radiotherapy, complicated by