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REVIEW ARTICLE

Rare and common manifestations of COVID-19 in children

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Abstract

Introduction: It has been almost 2 years since the first reports on cutaneous manifestations of COVID-19. Those reported in children are different and include macular, papular, lichenoid, vesicular, urticarial, and vascular morphologies, among others. The prognosis of isolated cutaneous involvement in COVID-19 in children is usually self-limiting but the extreme variety of clinical presentations complicates the clinical approach.

Methods: Numerous reviews have been systematically drafted and edited giving the clinicians a future direction for skin presentations during pandemics.

Results and Discussion: Hereby we report the rare and common manifestations of COVID-19 in children and question the recurrence phenomena and age-related distribution of the eruptions.

KEYWORDS
chilblain-like, chilblains, children, MIS-C, Sars-CoV-2

INTRODUCTION

SARS-CoV-2 infection has rapidly spread worldwide causing millions of COVID-19 cases in humans with a great variability of signs and symptoms. Children with COVID-19 are most often pauci-symptomatic with only mild respiratory symptoms. However, peculiar signs are sometimes found in this group of patients, including heterogeneous cutaneous signs. During the spring of 2020, a first perspective on the cutaneous manifestations observed was conducted in mainly adult patients with proven infection.[1,2] By that time, a striking number of children and adolescents were seen with acral cutaneous manifestations resembling chilblains. Their clinical features ranged from erythematous to violaceous macules to dusky, purpuric plaques on their feet and/or hands, often accompanied by itch and pain. Impressed by the unexpected repetitive clinical pattern observed in a very short period, we reported such chilblain-like lesions (CLLs) in four children, to warn for a possible association with SARS-CoV-2.[3] However, so far, despite thousands of similar cases described worldwide following the spread of the pandemic, the pathogenesis of CLLs and the definite causal relation between chilblains and COVID-19 remains uncertain.

Cutaneous manifestations have also been observed in children with a newly described inflammatory systemic condition leading to multiple organ failure and shock in multisystem inflammatory syndrome (MIS-C). Additionally, isolated skin phenomena have been described in children positive to SARS-CoV-2 with minimal or no systemic involvement, some of them resembling post-infective phenomena observed in other viral infections,

such as erythema multiforme (EM)-like lesions, and vesicular, maculopapular, urticarial, or papulosquamous rashes.

In this article, we review the frequent and the less common manifestations of COVID-19 in children reported in the medical literature.

CHILBLAIN-LIKE LESIONS (CLLS, COVID TOES)

Despite the existing variability in the definition of CLLs, common features are present in most cases. The population involved consists mainly of children, adolescents and young adults, with usually mild local symptoms (pain or itch). General symptoms are absent or represented by mild fever, cough, dyspnoea and anosmia–ageusia.[4] The lesions are morphologically identical to ordinary chilblains, mostly occurring on the feet and/or hands, showing acrocyanosis or cold toes, erythema and oedema, and sometimes bullous and purpuric necrotic areas (Figure 1).[5]

Ordinary chilblains are usually related to cold periods, but the outbreak of CLLs was unusual for appearing during springtime and in warm climate regions. Given the concomitant pandemic, a possible association with COVID-19 was considered. Due to difficulties caused by lockdown and the lack of validated tests for SARS-CoV-2, many patients were not tested. However, in most tested cases, real-time polymerase chain reaction (RT-PCR) and serum serologic analysis did not reveal any positivity.[6] An association with lifestyle changes and cold exposure during lockdown was hypothesized as the causative agent for the CLL outbreak.[7] Furthermore, larger studies revealed very low positivity for virologic testing, thus questioning a viral aetiology.[8] On the other hand, a strong temporal association with the circulation of COVID-19 in all countries was remarkable and warranted further research.[9] Histology and immunofluorescence confirmed close similarities with pernio, sometimes associated with vasculitis and/or microthromboses.[10,11] In detail, histopathology of chilblains and CLLs shared a superficial and deep lymphocytic inflammatory infiltrate in a lichenoid, perivascular and perieccrine distribution.[12] Immunohistochemical staining of lesional skin biopsies revealed positive marking of the vascular endothelium and eccrine epithelium with SARS-CoV/SARS-CoV-2 spike protein antibody.[13] However, these findings were not replicated in a case series of CLLs.[14] COVID-19-associated CLLs may be due to a direct effect of SARS-Cov-2 on endothelial cells leading to thrombosis or be the result of an enhanced type I interferon (IFN-I) response in the pathogenesis of CLLs; however, these potential mechanisms are not necessarily mutually exclusive and may be interdependent.[15,16] An association of CLLs with the cutaneous expression of IFN-I[10] was supported by activation of the IFN-I immune response in histopathological specimens of CLLs, with endothelial cells expressing the type I IFN-induced proteins MxA and pJAK1. In addition, lesional vessels showed complement and Ig deposition.[17] The authors' proposed pathogenesis was a local response to endothelial infection by SARS-CoV-2, driven by type I IFN immunity.[17] Furthermore, CLLs are mostly observed in

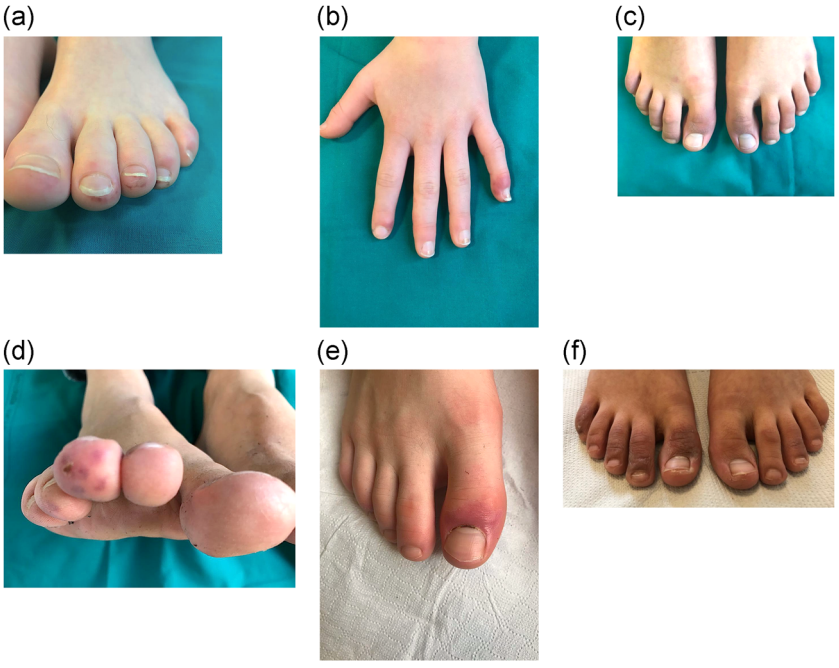

FIGURE 1 (a–f) Moderately painful chilblain-like lesions localized on the toes and fingers in male and female adolescents aged 12–17 years old

patients without severe COVID-19 organ manifestations, who express low rate of specific antibody positivity against SARS-CoV-2. The high levels of IFN-I could be associated with a precocious effective response against the virus leading to a milder course of the disease with suppressed antibody production.[18] The role of IFN-I pathway in the induction of CLLs is further supported by the observation that patients with chronic type I IFN activation in the setting of rare type I interferonopathies frequently develop chilblain-like lesions too.[17] Further studies are still required to definitely confirm the link between CLLs and COVID-19.

Clinical characteristics

CLLs have been mainly seen in children above 10 years of age and adolescents in good health with involvement of feet (75%–100% of the cases) and less frequently of the hands. The erythematous, violaceous or purpuric patches are usually multiple, round and vary from a few millimetres to centimetres in size. The periungual skin could be affected as well. There is a rare tendency to vesiculation and presentation with dark-purple or black crusts. The plantar region and the lateral margin of the feet and the heels may also be involved, with coarse, ecchymotic and infiltrated lesions.[19]

Unlike adults, children and adolescents are usually asymptomatic or present local pain and itch. Round or targeted lesions resembling erythema multiforme are seen in some cases of CLLs, involving mainly upper limbs and hands. Dermoscopy features of CLLs include a background area, described as varying from red-purple to grey-brown, globules and reticular network. Globules have been observed in most cases and range from red to purple. The grey-brown reticular network is usually located peripherally within the background area.[19] On capillaroscopy, anomalies in fingers and toes are reported, also in those cases in which skin lesions are mostly located on the feet only. These include slow capillary flow, enlarged loops, and major and minor tortuosity. A personal or familiar history of low-grade fever and systemic symptoms (cough, diffuse asthenia, gastrointestinal disorders) has been frequently reported before the appearance of CLLs, but even in these cases molecular or serologic SARS-CoV-2 tests are usually negative.[19,20] Despite an auto-resolving progression and a mean duration time of 40–60 days, some recent reports indicate the possibility of a prolonged course with reactivation phenomena before complete disappearance. Recurrence has been also reported in the same patient in consecutive disease waves suggesting a viral correlation.

Treatment and outcome

All children and adolescents published so far have had a favourable outcome with spontaneous regression of the lesions and no relevant complications. Reported resolution time ranged from 12 days to 12 weeks.[20] Oral analgesics, antihistamines and local pentoxifylline were administered in isolated cases, with poor results. The increased number of patients and the lack of therapeutical guidelines encouraged the use of heterogeneous therapies including nifedipine, pentoxifylline, tadalafil, topical glyceryl trinitrate, topical minoxidil, diltiazem, corticosteroids and vitamin D. A systematic review[21] showed moderate evidence to support the use of nifedipine and pentoxifylline in the treatment of severe or refractory cases of idiopathic chilblains, while other therapies had inadequate evidence or nonsignificant results compared with placebo. When preventive measures alone are inadequate, oral nifedipine is generally recommended as first-line pharmacologic therapy.

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C)

One of the most severe consequences of COVID-19 infection in children is MIS-C. It is defined as a hyperinflammatory response to SARS-CoV-2 infection that leads to multiorgan dysfunction. The Centers for Disease Control and Prevention (CDC) define an MIS-C case as an individual under 21 years old with current or recent SARS-CoV-2 infection (or exposure), a fever lasting greater than 24 h, laboratory inflammatory marker evidence and the presence of severe illness involving more than two organs (cardiac, respiratory, gastrointestinal, dermatologic, renal, haematologic or neurologic), requiring hospital admission that cannot be explained by other illness.[22] Cases have been reported from 1 month to 20 years old[23] with median age estimated between 5 and 11.5 years.[22] Although the exact mechanisms are not yet understood, MIS-C is described as the result of a cytokine storm in response to COVID-19 infection.[24] A great variety of cutaneous signs are associated with MIS-C. In 50%–83% of children with MIS-C, purpuric, erythematous, retiform, reticular, scarlatiniform, livedoid, urticarial, papular, macular, targetoid, maculopapular, desquamative, EM-like and morbilliform exanthems have been described.[25–28] The presence of CLLs in an MIS-C patient with severe cardiac involvement has also been noted (personal observation, Figure 2). MIS-C with multiorgan failure requires supportive or invasive care.[23,29] Mortality is estimated at 2% while the post-hospitalization sequelae of MIS-C are just beginning to

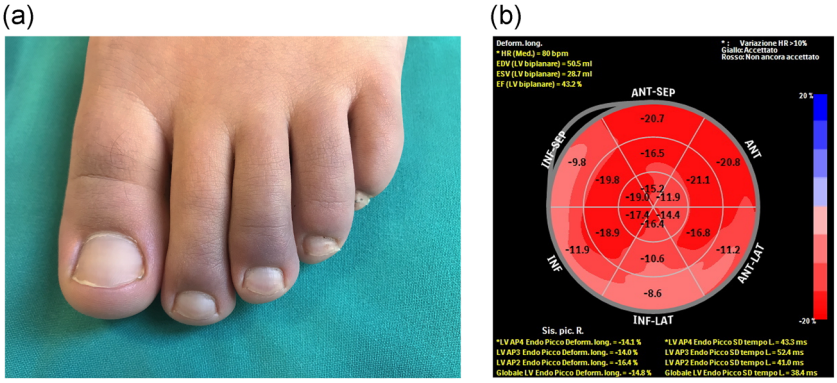

FIGURE 2 Chilblain-like lesions associated to MIS-C in a 13-year-old boy. Erythematous-violaceous and infiltrated lesions located on the dorsal toes. The extremities were cold to the touch (a). Global and regional systolic function of the left ventricle with the strain method at first evaluation. Global Longitudinal Strain −14.8% (normal value > −19% to 20%) with hypokinesia of inferior anterolateral and inferior septal wall. After 3 months, global Longitudinal Strain −19.9% with mild residual hypokinesia of the inferior wall (b). MIS-C, multisystem inflammatory syndrome

be appreciated. Reports of alopecia areata and telogen effluvium have been published which could be related directly to the infection, as well as postinfectious sequelae or associated stress.[30] Nonspecific and nondiagnostic skin findings may represent potential sequelae, and follow-up examination is necessary in children with past MIS-C who present new skin eruptions.

MACULOPAPULAR/PAPULAR-PURPURIC ERUPTIONS

Macules and papules are a manifestation of many different reaction patterns in the skin. In the setting of COVID-19, children with this type of rash are mainly pre-school and school age, but cases may also occur in adolescents and adults.[31] Prevalence of these lesions has varied among studies including a small number of cases. The anatomic distribution favours the trunk and diaper area, with a centrifugal pattern. The limbs are also frequently involved. We observed clinically acrosyringial involvement with a major distribution in perspiration areas (Figure 3).

URTICARIA

Urticaria is a common cutaneous manifestation described in association with SARS-CoV-2 infection in all ages, accounting for 10%−20% of all COVID-19-related rashes.[32] COVID-19 urticaria shares the characteristics of other urticarial reactions with transient duration (1−5 days) and association with itch. In consideration of the great variability of common causes of urticaria in children, including viruses, bacterial infection and parasites, the diagnosis of SARS-CoV-2 infection is challenging in a child with urticaria.[33,34] Children with urticaria and COVID-19 usually present mild general symptoms, especially below the age of 2 (Figure 4).

ERYTHEMA MULTIFORME (EM) AND EM-LIKE ERUPTION

EM is an acute, self-limiting hypersensitivity condition with a distinctive skin eruption with pink to red macules, papules, and plaques with a peculiar target arrangement.[35] Common locations include the forearms, thighs, knees, arms, especially around the elbows, and the dorsal aspect of the hands and feet. In children, the two pathogens most frequently involved in EM are herpes simplex virus (HSV) and *Mycoplasma pneumoniae*[36] but an association with SARS-CoV-2 infection has been observed, with typical EM lesions and EM-like atypical targets.[37] In COVID-19-associated EM, CLLs may coexist (Figure 5). EM in COVID-19 is reported to resolve after several days, even without any treatment. Adolescents and young adults seem to be the most frequently affected subgroup, as is the case in HSV and *Mycoplasma pneumoniae* infections. No or mild respiratory or gastrointestinal symptoms have been observed in COVID-19 EM.[38]

VESICULAR ERUPTION

SARS-CoV-2 causes a varicella-like papulovesicular rash, most frequently in adults, in particular middle-aged woman, but also in children.[39,40] Mildly pruritic vesicles with haemorrhagic crusts occur mainly on the trunk. These lesions appear in the earlier stages of COVID-19

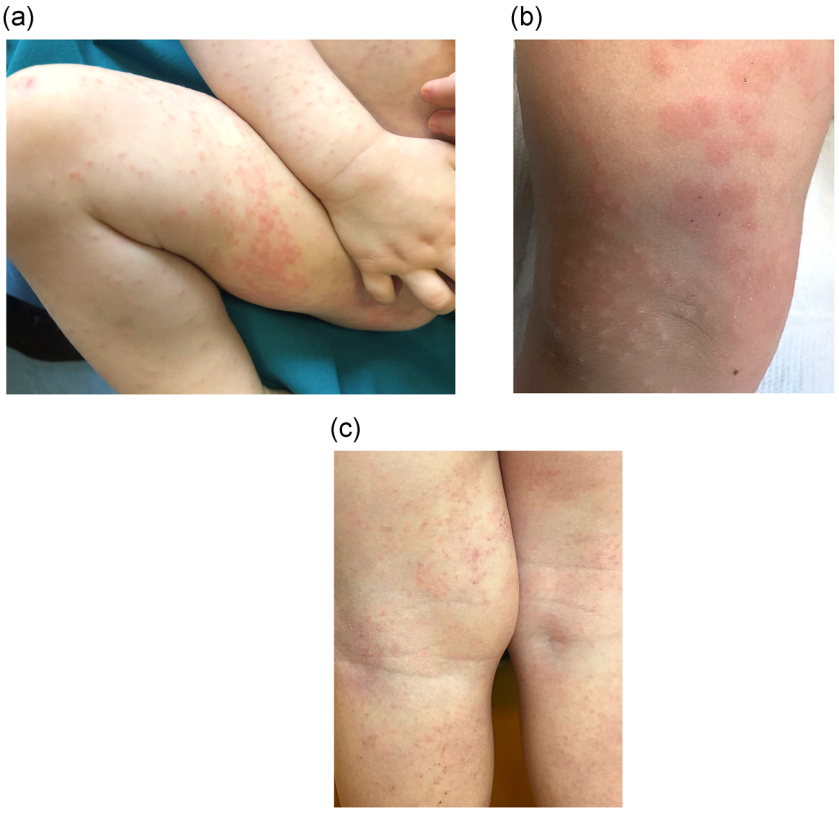

FIGURE 3 Maculopapular/papular-purpuric eruptions involving the diaper area, arms and limbs in a 2-year-old child (a), and the limbs in 4- and 8-year-old girls (b,c), confirmed or suspected for SARS-Cov-2 infection

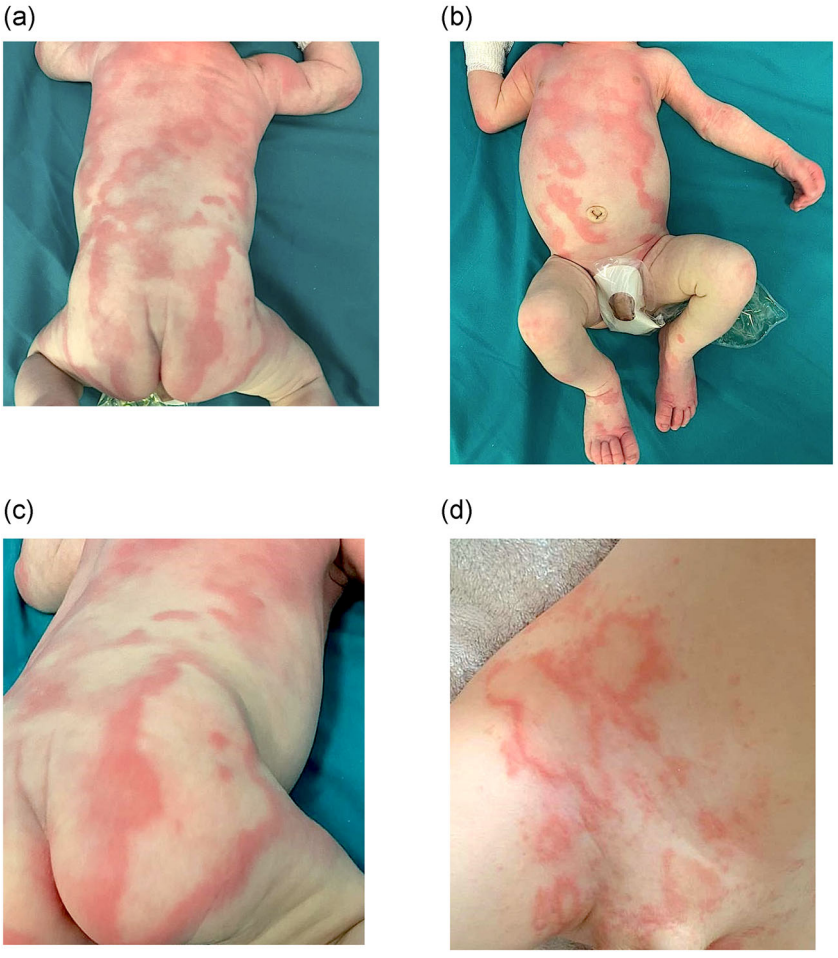

FIGURE 4 Diffuse oedematous and itchy urticarial lesions in a 12-month-old, SARS-Cov-2-positive baby (a–c). Urticarial lesions in a 2-year-old boy (d)

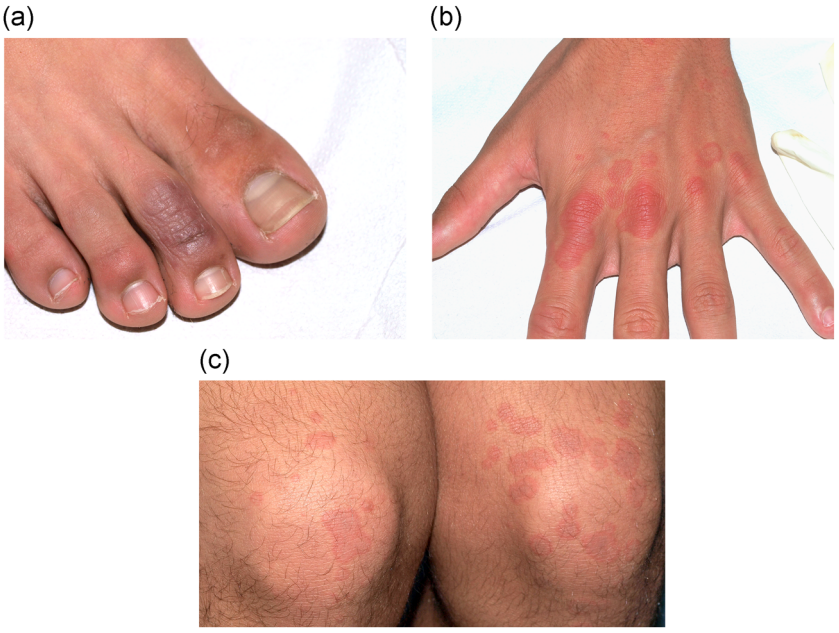

FIGURE 5 CLLs (a) and EM-like lesions (b,c) appearing in a 14-year-old, SARS-Cov-2-positive boy. CLL, chilblain-like lesion; EM, erythema multiforme

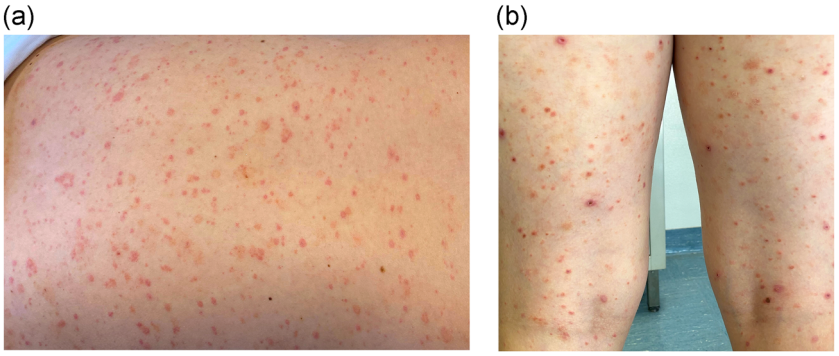

FIGURE 6 Diffuse, slightly elevated, purpuric papules on the trunk in an adolescent with PLEVA-like exanthem (a). Widespread, red-purple papules on the limbs in the same patient (b). PLEVA-like, papular-purpuric dermatitis of childhood

than other skin manifestations.[41] The eruption is monomorphic[42] with disseminated vesicles, appearing after a short median latency of around 3 days from the first respiratory symptoms and lasting 8 days. The correlation with the severity of infection is low. A possible coinfection with herpes simplex virus (HSV-1 and HSV-2) or human herpesvirus virus (HHV) 6 and 7 may occur in some patients.[43]

PAPULOSQUAMOUS RASHES AND PAPULO-PURPURIC DERMATITIS OF CHILDHOOD (PLEVA-LIKE ERUPTION)

Papulosquamous rashes in COVID-19 consist of scaly macules and papules that may be localized or confluent. Characteristic papules are perifollicular and itchy. Some patients develop purpura and pseudo-vesicles. A frequent presentation in this group mimics pityriasis rosea.[44] In other patients, the rash features punctate purpura or pseudo-vesicular papules on the extremities. Mean duration of papulosquamous eruptions is around 20 days, but they may last up to 70 days in some patients.[45]

Acute PLEVA-like dermatitis was observed in scholar children and adolescents with symmetrical round purplish papules that occurred in successive crops and evolved into crusted and necrotic lesions, sometimes coalescing into larger plaques (Figure 6). The purpuric characteristic of the lesions is notorious on dermoscopy (Figure 7). There is a predominant trunk involvement with facial sparing and extension to the upper and lower limbs. Histologically, this eruption is characterized by a massive lymphocytic infiltration of the acrosyringia and eccrine glands.[46]

OTHER MANIFESTATIONS

A number of cutaneous nonspecific exanthems have been attributed to SARS-CoV-2. These include purpuric thrombocytopenic purpura, dengue-like exanthem,[47]

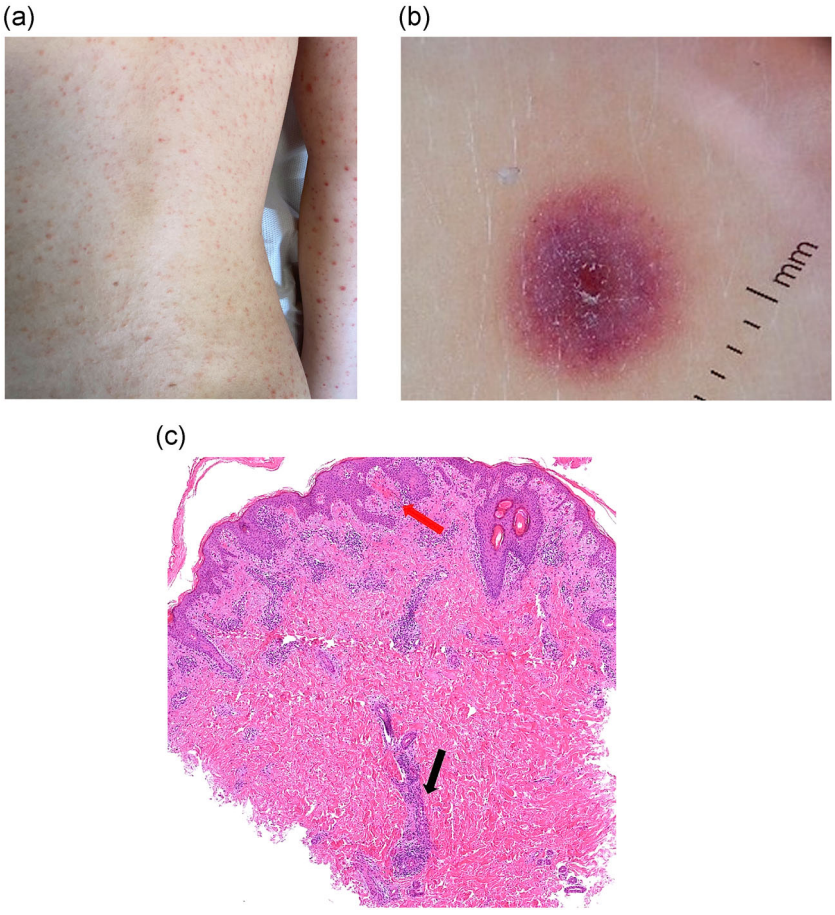

FIGURE 7 Non-confluent, erythematous papules on the trunk and limbs on the 10th of a PLEVA-like eruption (a). Purpuric and haemorrhagic aspect on dermoscopy (b). Histopathology in this patient shows superficial and deep perivascular dermatitis, extravasated red blood cells in the papillary dermis (red arrow) and dermal eccrine ducts surrounded by heavy lymphocytic infiltration (black arrow), Hematoxylin and eosin stain, original magnification ×40 (c). PLEVA-like, papular-purpuric dermatitis of childhood

livedoid eruptions, vasculopathic rashes, and have been reported in adults and occasionally in children as well.[48] Finally, various dermatological lesions are being reported possibly associated with SARS-CoV-2 vaccination.

DISCUSSION AND OPEN ISSUES

To date, the difficulties in identifying a clear correlation between cutaneous symptoms, especially CLLs, and SARS-CoV-2 represent an unsolved challenge. For more than 1 year, the main limitation was the lack of positive testing. As previously highlighted, a temporal correlation with the spread of the pandemic seems to support a causal link. Reappearance of skin phenomena during subsequent pandemic waves could strengthen a causative association. During the second SARS-CoV-2 spread, we observed a new call for dermatological evaluation. As previously detected, CLLs played the main role in the same asymptomatic or pauci-symptomatic cohort of children and adolescents. Clinical features and time to resolution were consistent with the data collected during the first COVID-19 wave (unpublished data). Again, a very low percentage of positive viral tests has been detected again. Isolated cases[3] and case series have reported recurrence of CLLs. A small number of children admitted for chilblains during the first pandemic wave and dismissed to follow-up because of a complete resolution without complications, presented again with CLLs in the same locations, months apart. Lack of positive testing was also constant.[4]

We investigated retrospectively the possible relation of the multiple varieties of cutaneous manifestations observed with age. One hundred and ninety-eight patients presenting all the clinical presentations discussed in this paper followed a particular age distribution (Figure 8). Seventy percent of all the lesions reported were CLLs, mainly present in adolescents. EM-like lesions showed a similar age correlated distribution. PLEVA-like lesions mainly involved 8- to 13-year-old children, while vesicular and papular-purpuric eruptions affected pre-school and school children (2–8 years old), with a relevant variability range. Interestingly, we observed in our patients relevant urticarial manifestations, specifically in infants and toddlers, with no cases observed beyond the age of 2. MIS-C involves patients between 5 and 11 years of age. Further studies are

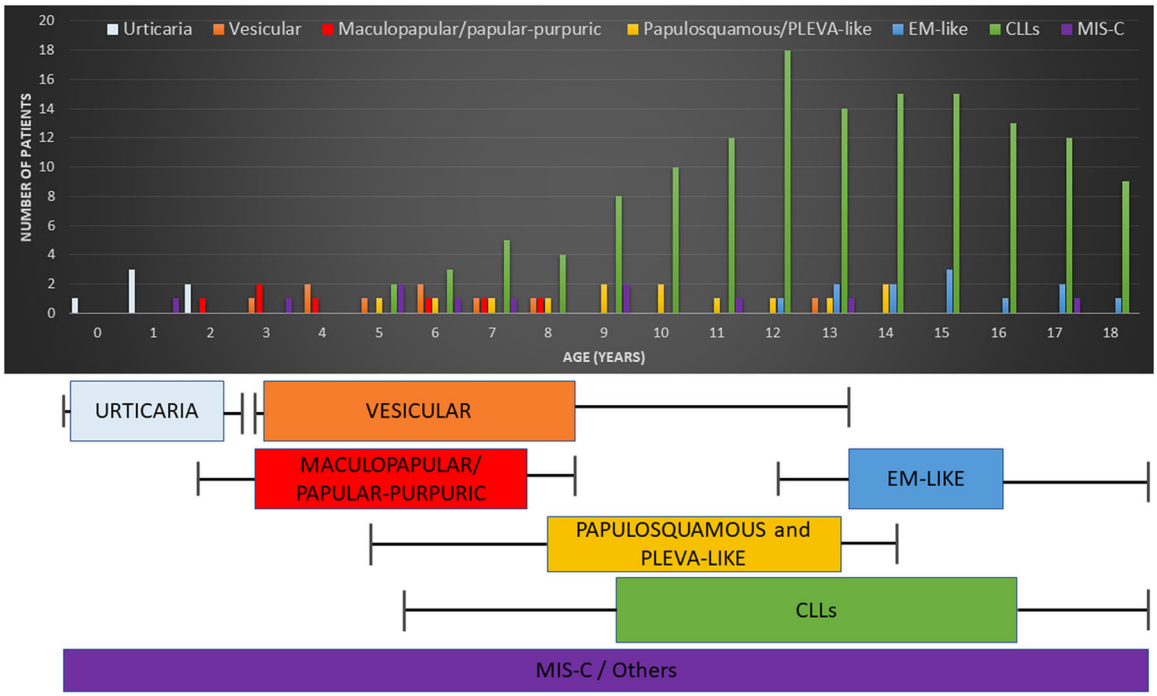

FIGURE 8 Age distribution of SARS-Cov-2-positive or suspected paediatric patients (0–18 years) observed in our centre during the first pandemic spread categorized by cutaneous manifestations. In the lower part of the figure, boxes correspond to the highest frequency rate of patients with the clinical characteristics mentioned. Lateral strings include all the sample span. CLLs, chilblain-like lesions (COVID toes); EM-like, erythema multiforme-like; MIS-C, multisystem inflammatory syndrome; PLEVA-like, papular-purpuric dermatitis of childhood

warranted to identify a definitive correlation between age and infection or reinfection with SARS-CoV-2.

CONCLUSIONS

Almost 2 years passed since the first clinical reports on chilblain-like lesions during COVID-19 pandemic. A lot has been found out, clinical features and new pathogenetic mechanisms have been detailed, and more sensitive tests have been developed and widely applied. A more comprehensive general view of COVID-19 cutaneous manifestations has been obtained. Larger studies will lead to a greater understanding of these worldwide diffuse clinical aspects, including recurrence phenomena and age-related distribution.

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The patients or their caregivers in this manuscript have given written informed consent to the publication of their case details. The funding information is not available.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

This material is the authors' own original work, which has not been previously published elsewhere. The paper is not currently being considered for publication elsewhere. The paper reflects the authors' own research and analysis in a truthful and complete manner. The paper properly credits the meaningful contributions of co-authors and co-researchers. The results are appropriately placed in the context of prior and existing research. All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference. All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content. Consent for publication has been obtained from the patient caregiver. All the authors have consented to publication.

AUTHOR CONTRIBUTIONS

Conception or design of the work: Christiana Colonna, Lucia Restano, Riccardo Cavalli. *Data collection*: Nicola A. Monzani, Martina Zussino and Alessandra Ponziani. *Data analysis and interpretation*: Martina Zussino and Alessandra Ponziani. *Drafting the article*: Nicola A. Monzani. *Critical revision of the article*: Stefano

Cambiaghi, Christiana Colonna and Riccardo Cavalli. All authors discussed the results and contributed to the final manuscript.

DATA AVAILABILITY STATEMENT

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

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