INTRODUCTION

Since the first reports of SARS-CoV-2-associated dermatosis, many cutaneous manifestations have been reported to date, ranging from urticaria and maculopapular rash, to perniosis.1 The pathogenetic mechanisms of such a plethora of polymorphic inflammatory skin diseases, often presenting a nasopharyngeal swab negativity particularly in children or young adults, still needs to be better defined.2,3

Papular exanthematous eruptions are common in children and are often interpreted as a pattern of skin reaction to various infectious agents; however, a clear-cut demonstration of such causative agents in the skin has often proved to be challenging.4 The clinical and histopathological characteristics of the lesions, as well as the number and frequency of cases observed over a relatively short pandemic period led us to investigate, among other causative agents, a possible association with SARS-CoV-2 as an infectious cause.

CLINICAL FEATURES

All clinical data and laboratory results of our series are summarized in Table 1.

We collected the clinical data of ten pediatric patients (identified as N1-N10) that presented diffuse papular eruption with purpuric characteristics during the period May to December 2020. The study includes eight males and two females (median age 10.2 years, range
TABLE 1 Characteristics of patients reported

| ID patient | Sex | Age (years) | Cutaneous lesions | Localization | Further symptoms | Complete regression |
|------------|-----|-------------|-------------------|--------------|------------------|-------------------|
| N1         | M   | 13          | Purpuric and hemorrhagic papules, some crusted | Trunk and limbs, facial sparing | Cough and fever | 10 d 9 wk |
| N2         | M   | 9           | Papular lesions with hemorrhagic appearance, some covered with blood crusts | Trunk and limbs, facial sparing | None | / 5 wk |
| N3         | F   | 14          | Erythematous and purpuric lesions with small crusts | Trunk and limbs, facial sparing | None | / 10 wk |
| N4         | F   | 7           | Erythematous purpuric papules, some covered with blood crusts | Trunk and limbs, facial sparing | Fever and asthenia | 20 days 9 wk |
| N5         | M   | 10          | Erythematous papules with necrotic-hemorrhagic, blood crust | Trunk, limbs, palms involvement facial sparing | None | / 12 wk |
| N6         | M   | 5           | Erythematous and purpuric papules | Groin and limbs, facial sparing | Fever | 8 d 8 wk |
| N7         | M   | 13          | Papular purpuric lesions associated with crusts | Trunk and limbs, facial sparing | Fever | 15 d 12 wk |
| N8         | M   | 14          | Papular purpuric lesions | Trunk | None | / 7 wk |
| N9         | M   | 11          | Erythematous papules with a purpuric appearance | Trunk and limbs, facial sparing | Fever, joint pain, headache, asthenia | 20 d 4 wk |
| N10        | M   | 6           | Papular purpuric lesions | Trunk and limbs, facial sparing | Fever | 5 d 12 wk |

FIGURE 1 Patient N3. On day 10 of the eruption, erythematous non-confluent papules on trunk and limbs, with a smooth, non-desquamating surface

6-14 years) that were attended to at either the Pediatric Dermatology Unit in Milan (IRCCS Ca’ Granda Ospedale Maggiore Polyclinico Milano) or the Department of Pediatric and Neonatal Pathology in Vicenza. Most cases were brought to our attention with an accompanying clinical diagnosis of pityriasis lichenoides et varioliformis acuta (PLEVA), also known as Mucha-Habermann disease.

All of the children displayed acute onset of symmetrical 2-6 mm, round purplish papules (Figure 1), that occurred in successive crops and evolved in crusty and necrotic lesions, sometimes coalescing into larger plaques (Figure 2). The purpuric characteristic of the lesions was clearly evident at dermoscopy (Figure 3). They presented trunk involvement with facial sparing that extended to the upper and lower limbs in nine patients. One patient showed relevant groin involvement.

Mild systemic symptoms were present in 6 out of 10 patients and were characterized by fever (five cases), asthenia (two cases), joint pain (one case), headache (one), and cough (one). These were present a few days before and during early skin eruption, with an average duration time of 13 days (range 5-20 days), subsiding with either no therapy or a short course of NSAIDs. Skin lesions spontaneously resolved without treatment, with a mean time of 8.8 weeks (range 4.0-12.0 weeks), leaving hypochromic lenticular lesions in five cases accompanied by atrophy and telangiectasias in two patients (Table 1).

In four patients, SARS-CoV-2 positivity was detected with laboratory methods. Three out of 8 patients that performed nasopharyngeal swab (NPS, Seegene AllplexTM2019-nCoV Assay), automated RNA extraction and PCR setup were carried out using Seenege NIMBUS, a liquid handling workstation. Real-time PCR on a CFX96TMDS platform, Bio-Rad Laboratories, Inc) tested positive. IgG serology for SARS-CoV-2 (LIAISON® SARS-CoV-2 S1/S2 IgG test
TABLE 1

| ID patient | Sex | Cutaneous lesions | Localization | Further symptoms (d) | Complete regression (wk) | SARS-CoV-2 serology | Histopathological features | Blood tests, bacterial and viral serology | SARS-CoV-2 nasopharyngeal swab | \( \text{IgM} \) | \( \text{IgG} \) |
|-----------|-----|-------------------|--------------|----------------------|-------------------------|----------------------|--------------------------|-----------------------------------|-------------------------------------|--------|--------|
| N9        | M   | Erythematous papules with    | Trunk        | None / 7 wk          |                         | Positive             | No biopsy performed | No contributory, no recent infection | Positive                             | Not performed | Not performed |
| N8        | M   | Papular purpuric lesions    | Trunk        | None / 7 wk          |                         | Positive             | No biopsy performed | No contributory, no recent infection | Positive                             | Negative | Negative |
| N7        | M   | Papular purpuric lesions    | Trunk and limbs, facial | None / 12 wk         |                         |                  | PLEVA-like             | No contributory, no recent infection | Negative                             | Negative | Negative |
| N6        | M   | Erythematous and purpuric   | Trunk and limbs, facial | None / 12 wk         |                         |                  | PLEVA-like             | No contributory, no recent infection | Negative                             | Negative | Negative |
| N5        | F   | Erythematous purpuric       | Trunk, limbs, palms | None / 10 wk         |                         |                  | PLEVA-like             | No contributory, no recent infection | Positive                             | Negative | Negative |
| N4        | F   | Erythematous and purpuric   | Trunk and limbs, facial | None / 9 wk          |                         |                  | PLEVA-like             | No contributory, no recent infection | Positive                             | Negative | Negative |
| N3        | F   | Erythematous and purpuric   | Trunk and limbs, facial | None / 5 wk          |                         |                  | PLEVA-like             | No contributory, no recent infection | Positive                             | Negative | Negative |
| N2        | M   | Papular lesions with        | Trunk and limbs, facial | None / 5 wk          |                         |                  | PLEVA-like             | No contributory, no recent infection | Positive                             | Negative | Negative |
| N1        | M   | Purpuric and hemorrhagic    | Trunk and limbs, facial | None / 20 d          |                         |                  | PLEVA-like             | No contributory, no recent infection | Positive                             | Negative | Negative |

 kit automated on LIAISON\textsuperscript{4} was positive in 2 out of 8 tested patient. IgM for SARS-CoV-2 were negative in all patients tested.

All patients underwent laboratory testing for complete blood count (CBC), liver and kidney function tests, C-reactive protein (CRP), coagulation profile, ferritin, fibrinogen, ANA, C3, C4, and CH50 with no relevant abnormal findings. Serology evaluation with IgM and IgG for coxsackievirus, cytomegalovirus (CMV), Epstein-Barr virus (EBV), Mycoplasma pneumoniae, parvovirus B19 did not show any signs of recent infection; throat swab for group A beta-hemolytic Streptococcus (GABS) was negative. A 4 mm skin punch biopsy was performed in 8 out of 10 patients for histological and immunohistochemical study.

3 | HISTOPATHOLOGICAL FEATURES

All the skin biopsies were characterized by dermal lymphocytic infiltrate.

In five cases (N 3, 4, 5, 8, and 10), histopathology revealed a diffuse interface dermatitis, consisting of CD4+ and CD8+ lymphocytes that diffusely infiltrated the epithelium inducing scattered necrosis of keratinocytes. Lymphocyte cuffs were particularly evident surrounding the acrosyringeal ducts, dermal eccrine ducts, and deep eccrine glands. In addition to these features, one case (N5) also showed diffuse thrombosis of the superficial dermal small vessels in absence of leukocytoclastic vasculitis. (Figure 4).

In the remaining three cases (N 2, 7, and 9), the fully developed lesion had a dense coat or sleeve-like perivascular lymphoid infiltrate and many interstitial eosinophils. Capillaries were conspicuously dilated and engorged with red blood cells. Extravasated erythrocytes were frequently observed in papillary dermis. A massive lymphoid infiltration was present surrounding dermal ducts and deep eccrine glands. (Figure 5).

4 | IMMUNOHISTOCHEMICAL FEATURES

Immunohistochemical analysis with the SARS-CoV-2 (2019-nCoV) nucleocapsid antibody, rabbit monoclonal antibody (MAB) was performed on all of the biopsies.

Immunohistochemical staining was performed on Ventana Automatic Stainer—Ventana Benchmark Ultra (Ventana Medical Systems). SARS-CoV-2 (2019-nCoV) nucleocapsid antibody, rabbit MAB (Cat No 40143- R019; Sino Biological) was used at 1:1500 dilution for 32 minutes.
As positive controls, skin biopsies from three SARS-CoV-2-positive patients that presented skin lesions during intensive care unit hospitalization were used. In all three control cases, the

**FIGURE 2** Patient N5. 4 wks from onset with widespread red-purple papules on trunk and limbs. Some lesions were in the necrotic-hemorrhagic phase and were covered with blood crust

**FIGURE 3** Patient N3. The purpuric feature of the lesion evident on dermoscopy

**FIGURE 4** Patient N9. Superficial and deep dermatitis with dense perivascular and periductal lymphocytic cuff (black arrows)

**FIGURE 5** Diffusely necrotic epidermis. Superficial and deep periductal and periglandular lymphocytic infiltration
immunohistochemical staining was limited to the cuticular region of the eccrine glands; however, in one case it was also present at the acrosyringium. As a reliability check of the monoclonal antibody, we used five pediatric cases of PLEVA (year 2018) as negative control. No immunohistochemical staining was detected in all control cases. All cases reported herein showed clear and strong cuticular staining of the deep portion of the eccrine glands (Figure 6).

5 | DISCUSSION

All cases were observed in the Pediatric Dermatology Units of Milan and Vicenza during a relatively short period of time during which Northern Italy was the region with the highest number of registered SARS-CoV-2 cases during the pandemic. Children were either in good general condition or had mild systemic symptoms, and displayed acute onset of symmetrical papular lesions with striking purpuric features, that evolved in crops and subsided in 4-12 weeks.

The morphology, distribution, and sudden onset of multiple subsequent lesions were very similar to those observed in PLEVA, a condition that also has been viewed as an altered immune response to a viral antigenic trigger. However, our cases were distinct due to the intensely red-purple color of the lesions as opposed to the red-brown color of acute pyrtiriasis lichenoides and the evident prevalence of the purpuric component seen with dermoscopy; moreover, in our cases even smaller lesions tended to develop early hemorrhagic crusts rather than resolve with desquamation. Laboratory testing ruled out coagulation disorders, vasculitis, and other known infectious causes of papulo-purpuric eruptions.

In all cases, histopathological examination showed highly suspected clues for COVID-19 related dermatosis. Features observed in patients N 3,4,5,8, and 10 could be histologically classified as PLEVA due to band-like infiltration with scattered necrotic keratinocytes and diffuse lymphocytes exocytosis. However, the massive infiltration of acrosyringeal and the dense deep periglandular lymphocytic infiltration are not a typical feature of Mucha-Habermann disease, but have been consistently described in COVID-19-related dermatosis. The histological features observed in patients N 2,7, and 9 that may represent a different stage of the same spectrum also do not fit completely with the standard histopathological description of PLEVA. Superficial and deep perivascular dermatitis with perivascular, periductal, and periglandular lymphocytic sleeves associated with focal blood extravasation has not been frequently described in inflammatory skin diseases prior to SARS-CoV-2 infection. A case with the same histopathological and immunological features in which mRNA-FISH detected the spike glycoprotein of SARS-CoV-2 in eccrine glands, however, was recently described in a young woman.

The immunohistochemical positivity in eccrine glands has already been described by several authors and our findings confirm that this epithelial component could also play a role in modulating the autoimmune cross-reactivity, maybe also leading to IL-1, IFN-γ, and TNF-α release and recruiting cytotoxic and NK cells that target the keratinocytes, as has been already shown in HSV related to erythema multiforme.

The peculiar clinical and histopathological aspect of the lesions in our patients and the number and frequency of cases, over a relatively short pandemic period, pointed to an association with SARS-CoV-2 as etiologic agent. Furthermore, as already stated, PLEVA eruptions has been already described as paraviral exanthema, making our assumption reasonable also since it was supported by the immunohistochemical analysis performed.

A positive result with throat swab or serology for SARS-CoV-2, however, was obtained only in four out of ten patients. Findings of nucleocapsid viral proteins using the SARS-CoV-2 antibody through immunohistochemical analysis still needs to be largely validated in the skin, but seems to be promising to detect SARS-CoV-2 in COVID-19-related dermatosis, especially in pauci-symptomatic children and young adults with PCR swab negativity. In infancy and young adulthood, it was hypothesized that a high type I interferon response, crucial in the early response to viral infections, might explain the relatively low rate of seropositivity in patients with chilblains because such patients could clear SARS-CoV-2 infection before humoral immunity can occur. A similar mechanism may have occurred in our cases.

All these facts lead us to believe that these distinctive clinicopathological pediatric features could represent a peculiar COVID-19 associated dermatosis of childhood.

Our study, however, exhibits limitation such as the unavailability of confirmation of SARS-CoV-2 infection performed with other methods and the low number of cases presented, and further observation is needed to confirm and validate our hypothesis.

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CONFLICTS OF INTEREST
No conflicts of interest to declare.

DATA AVAILABILITY STATEMENT
Data available upon request to the corresponding author.

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REFERENCES
1. Marzano AV, Cassano N, Genovese G, Moltrasio C, Vena GA. Cutaneous manifestations in patients with COVID-19: a preliminary review of an emerging issue. Br J Dermatol. 2020;183(3):431-442. 10.1111/bjd.19264
2. Bessis D. Impaired type I interferon response in SARS-CoV-2 infection: looking through the cutaneous window. Br J Dermatol. 2021;184(1):11-12. 10.1111/bjd.19596
3. Hubiche T, Cardot-Leccia N, Le Duff F, et al. Clinical, laboratory, and interferon-alpha response characteristics of patients with chilblain-like lesions during the COVID-19 pandemic. JAMA Dermatol. 2020;25:e204324. 10.1001/jamadermatol.2020.4324
4. Chuh A, Zawar V, Law M, Sciallis G. Gianotti-Crosti syndrome, pityriasis rosea, asymmetrical periflexural exanthem, unilateral mediastinal and purpuric gloves and socks syndrome: a brief review and arguments for diagnostic criteria. Infect Dis Rep. 2012;4(1):e12. 10.4081/idr.2012.e12
5. Tomasini D, Tomasini CF, Cerri A, et al. Pityriasis lichenoides: a cytotoxic T-cell-mediated skin disorder. Evidence of human parvovirus B19 DNA in nine cases. J Cutan Pathol. 2004;31(8):531-538. 10.1111/j.0303-6987.2004.00186.x
6. Gianotti R, Coggi A, Boggio F, Fellegara G. Similarities in cutaneous histopathological patterns between COVID-19-positive and COVID-19 high-risk patients with skin dermatosis. Acta Derm Venereol. 2020;100(15):adv00249–10.2340/00015555-3612
7. Gianotti R, Recalcati S, Fantini F, et al. Histopathological study of a broad spectrum of skin dermatoses in patients affected or highly suspected of infection by COVID-19 in the northern part of Italy: analysis of the many faces of the viral-induced skin diseases in previous and new reported cases. Am J Dermatopathol. 2020;42(8):564-570. 10.1097/DAD.0000000000001707
8. Gianotti R, Barberis M, Fellegara G, Galván-Casas C, Gianotti E. COVID-19-related dermatosis in November 2019: could this case be Italy’s patient zero? Br J Dermatol. 2021;184(5):970-971. 10.1111/bjd.19804
9. Liu J, Li Y, Liu L, et al. Infection of human sweat glands by SARS-CoV-2. Cell Discov. 2020;6(1):84.
10. Santonja C, Heras F, Núñez L, Requena L. COVID-19 chilblain-like lesion: immunohistochemical demonstration of SARS-CoV-2 spike protein in blood vessel endothelium and sweat gland epithelium in a polymerase chain reaction-negative patient. Br J Dermatol. 2020;183(4):778-780.
11. Lucchese A. From HSV infection to erythema multiforme through autoimmune crossreactivity. Autoimmun Rev. 2018;17(6):576-581. 10.1016/j.autrev.2017.12.009
12. Le Cleach L, Doussel L, Assier H, et al. Most chilblains observed during the COVID-19 outbreak occur in patients who are negative for COVID-19 on polymerase chain reaction and serology testing. Br J Dermatol. 2020;183(5):866-874. 10.1111/bjd.19377
13. Colonna C, Monzani NA, Rocchi A, Gianotti R, Boggio F, Gelmetti C. Chilblain-like lesions in children following suspected COVID-19 infection. Pediatr Dermatol. 2020;37(3):437-440. 10.1111/pde.14210

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