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Papulo-purpuric dermatitis of childhood: a distinct PLEVA-like eruption associated to SARS-CoV-2 infection. Clinical, histopathological and immunohistochemical study of 10 cases

Raffaele Gianotti MD[1] | Lucia Restano MD[2] | Mario Cutrone MD[3] | Cristiana Colonna MD[2] | Giovanni Fellegara MD[4] | Isacco Debernardi BSc[4] | Francesca Boggio MD[5] | Alessandro Del Gobbo MD[5] | Nicola Adriano Monzani MD[6] | Claudio Tripodo MD[7] | Carlo Gelmetti MD[2] | Emilio Berti MD[1]

[1]Department of Pathophysiology and Transplantation, Dermatology Unit, Università degli Studi di Milano, Foundation IRCCS, Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

[2]Department of Clinical Sciences and Community Health, Pediatric Dermatology Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[3]Dipartimento Materno Infantile Unità Operativa di Pediatria e Patologia Neonatale, Vicenza, Italy

[4]Pathology Unit C.D.I. Centro Diagnostico Italiano S.p.A. Milan, Milan, Italy

[5]Division of Pathology, Università degli Studi di Milano, Foundation IRCCS, Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

[6]Department of Clinical Sciences and Community Health, Neonatal Intensive Care Unit, IRCCS Foundation Cà Granda, Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy

[7]Tumor Immunology Unit. Department of Health Sciences, Istituto di Patologia Generale, University of Palermo School of Medicine, Palermo, Italy

Correspondence
Lucia Restano MD, Department of Clinical Sciences and Community Health, Pediatric Dermatology Unit, IRCCS Ca' Granda, Ospedale Maggiore Policlinico di Milano, Via Pace 9, 20122, Milan, Italy.
Email: lucia.restanocassulini@policlinico.mi.it

Abstract

We observed ten children with a papular eruption with purpuric features during the SARS-CoV-2 pandemic in Northern Italy (May-December 2020). Histological examination showed signs of SARS-CoV-2-related dermatosis. Evidence of nucleocapsid viral proteins using SARS-CoV-2 (2019-nCoV) nucleocapsid antibody revealed cuticular staining of the deep portion of the eccrine glands in all cases.

KEYWORDS

dermatopathology, pediatric, PLEVA, SARS-CoV-2, skin histopathology

1 | 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.

2 | 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, valuated 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	
						Further symptoms (d)	Skin manifestations (wk)
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

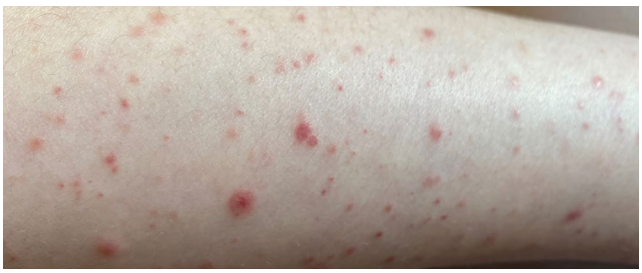

FIGURE 1 Patient N3. On day 10 of the eruption, erythematous non-confluent papules on trunk and limbs, with a smooth, non-desquamating surface

6-14 years) that were attended to at either the Pediatric Dermatology Unit in Milan (IRCCS Ca' Granda Ospedale Maggiore Policlinico 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 CFX96TMDx platform, Bio-Rad Laboratories, Inc) tested positive. IgG serology for SARS-CoV-2 (LIAISON® SARS-CoV-2 S1/S2 IgG test

Residual lesions	Histopathological pattern	Blood tests, bacterial and viral serology	SARS-CoV-2 nasopharyngeal swab	SARS-CoV-2 serology	
				IgM	IgG
None	No biopsy performed	No contributory, no recent infection	Positive	Not performed	Not performed
None	Perivascular and periadnexal infiltrate	No contributory, no recent infection	Not performed	Negative	Negative
None	PLEVA-like	No contributory, no recent infection	Negative	Negative	Negative
Hypochromic lenticular lesions	PLEVA-like	No contributory, no recent infection	Negative	Negative	Negative
Hypochromic and slightly atrophic lesions	PLEVA-like	No contributory, no recent infection	Negative	Negative	Negative
Hypochromic lenticular lesions	No biopsy performed	No contributory, no recent infection	Positive	Not performed	Not performed
None	Perivascular and periadnexal infiltrate	No contributory, no recent infection	Negative	Negative	Negative
None	PLEVA-like	No contributory, no recent infection	Not performed	Negative	Positive
Hypochromic and slightly atrophic lenticular lesions' teleangiectasias	Perivascular and periadnexal infiltrate	No contributory, no recent infection	Negative	Negative	Negative
Hypochromic lenticular lesions	PLEVA-like	No contributory, no recent infection	Positive	Negative	Positive

kit automated on LIAISON®) 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.

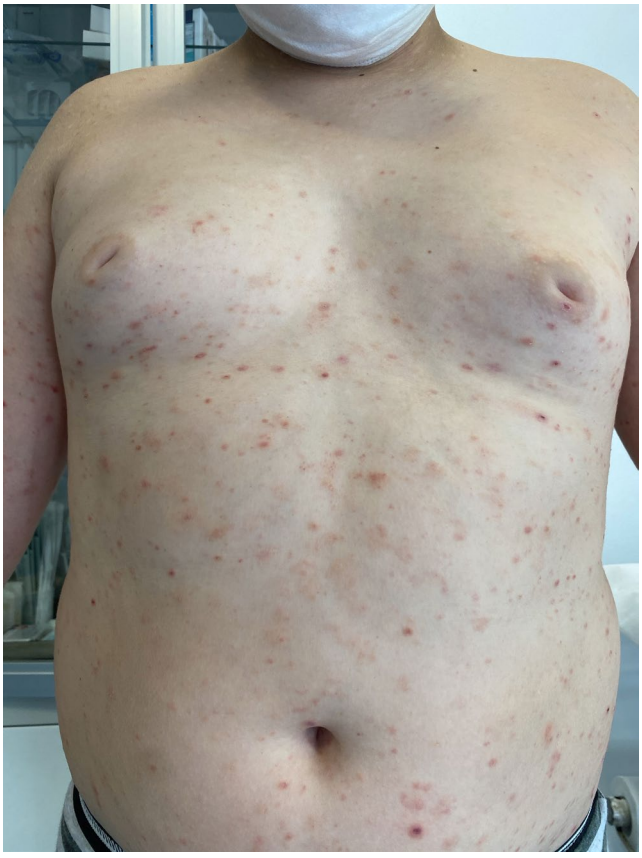

FIGURE 2 Patient N5. 4 wks from onset with widespread red-purple papules on trunk and limbs. Some lesions were in the necrotic-hemorrhagic phase and were covered with blood crust

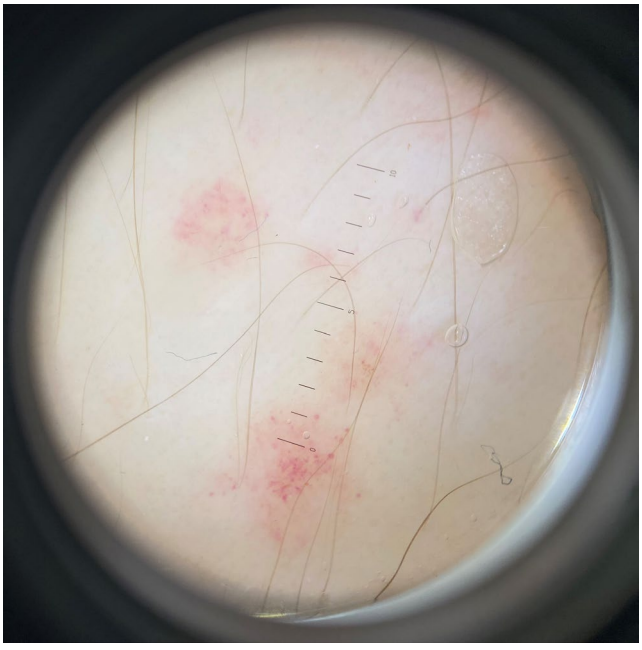

FIGURE 3 Patient N3. The purpuric feature of the lesion evident on dermatoscopy

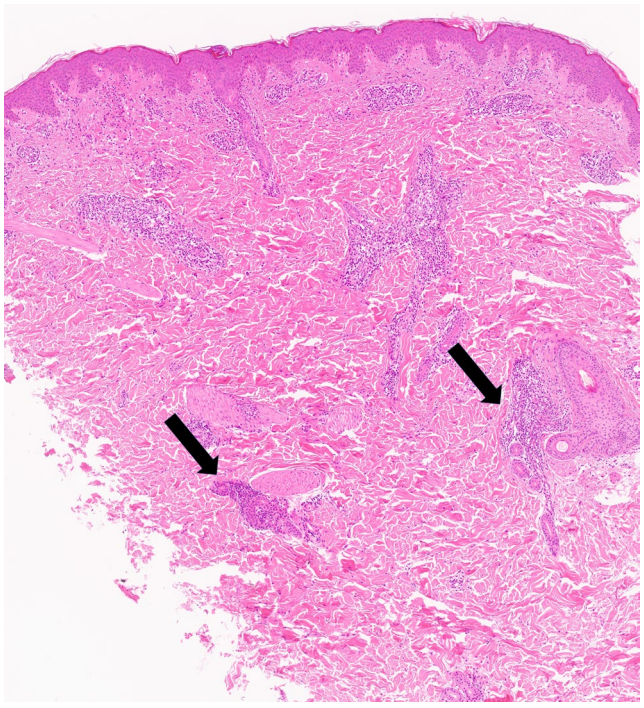

FIGURE 4 Patient N9. Superficial and deep dermatitis with dense perivascular and periductal lymphocytic cuff (black arrows)

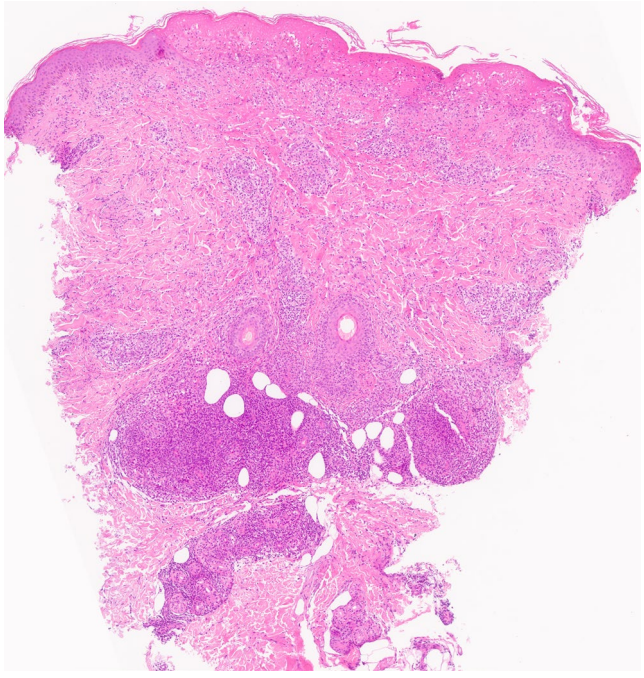

FIGURE 5 Diffusely necrotic epidermis. Superficial and deep periductal and periglandular lymphocytic infiltration

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

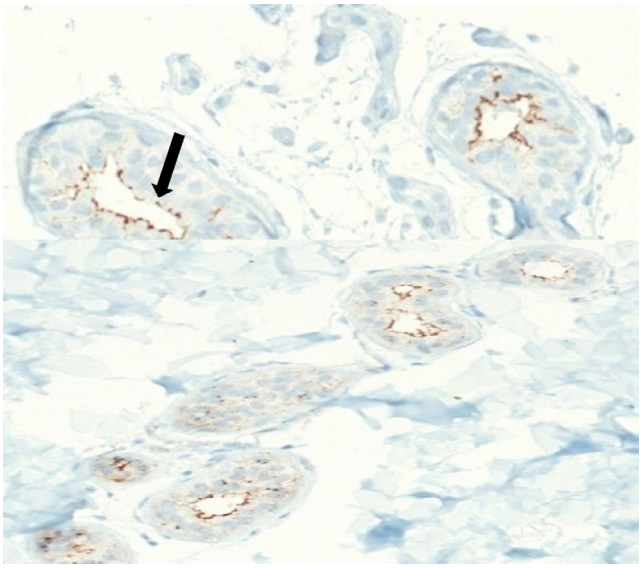

FIGURE 6 Patient N9. Cuticular positivity of the eccrine glands using the SARS-CoV-2 (2019-nCoV) nucleocapsid antibody

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.[5] However, our cases were distinct due to the intensely red-purple color of the lesions as opposed to the red-brown color of acute pytiriasis 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.[5]

In all cases, histopathological examination showed highly suspected clues for COVID-19 related dermatosis.[6,7] 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.[6,7] 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.[6] 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.[8]

The immunohistochemical positivity in eccrine glands has already been described by several authors[9,10] 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.[11]

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,[5] 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.[12,13] 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.[2,3] A similar mechanism may have occurred in our cases.

All these facts lead us to believe that these distinctive clinicpathological 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.

ORCID

Lucia Restano https://orcid.org/0000-0002-5569-8237
Nicola Adriano Monzani https://orcid.org/0000-0001-7332-3888

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