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Cutaneous manifestations of the COVID-19 pandemic in schoolchildren and adolescents

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Abstract

This review article focuses on cutaneous manifestations in schoolchildren and adolescents 6 to 18 years old connected with various aspects of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, including personal protective equipment (PPE), SARS-CoV-2 infection, and the SARS-CoV-2 vaccine. The use of PPE has been associated with mask-related acne due to microbiome dysbiosis and disruption of skin homeostasis, leading to the emergence of new acne or exacerbation of preexisting acne. Chilblain-like lesions, erythema multiforme–like eruptions, and cutaneous manifestations of multisystem inflammatory syndrome related to SARS-CoV-2 are the most commonly described skin manifestations of SARS-CoV-2 infection. The proposed mechanisms involve either the direct interaction of the virus with the skin through cutaneous receptor angiotensin-converting enzyme 2 in the epidermal basal layer or hyperactive immune responses. The impact of SARS-CoV-2 infection has also been described on adnexa, including hair changes such as alopecia areata and telogen effluvium, as well as nail changes presenting as onychomadesis and periungual desquamation. Cutaneous adverse effects of the SARS-CoV-2 vaccine have been described in case reports and differ from those in adults. Therefore, there is a need for increased awareness regarding the most prevalent cutaneous manifestations associated with COVID-19 in children because they tend to be mild or nonspecific in nature.

Keywords: SARS-CoV-2 pandemic, COVID-19, cutaneous manifestations, adolescents, children

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Introduction

Following the onset of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, primarily in March 2020, several consequences caused by various aspects of the pandemic have been described. Concerning skin lesions, they vary from virus-induced skin symptoms to various conditions resulting from the use of protective measures such as disinfectants or face masks (Fig. 1) (1). The consequences of using personal protective equipment are presumed to have a greater impact on schoolchildren and adolescents than the infection itself. Thus, the aggravation of preexisting skin conditions and the emergence of mask-related acne have been described as COVID-19–related conditions (1, 2). In contrast to virus-induced skin manifestations, which resolve spontaneously in most cases, all these conditions usually require treatment.

The skin manifestations of COVID-19 infection in children differ from those in adults, as does the overall clinical presentation and outcome of the infection (3). Thus, skin conditions such as urticaria, maculopapular rash, and vesicular rash have been predominantly described in adult age groups, whereas chilblain-like lesions and erythema multiforme (EM) were more frequently seen in children and adolescents (Fig. 2). In addition, nail changes, including onychomadesis (4, 5), and hair disorders, such as telogen effluvium and androgenic alopecia, have also been observed in this age group (Fig. 3) (6, 7). Based on available data, the occurrence rate of COVID-19 infection in children and adolescents is estimated to account for 1% to 5% of confirmed (8) and 1% to 8% of all COVID-19 cases (9). In addition, the prevalence of cutaneous manifestations of COVID-19 in this age group is estimated to range between 0.25% and 3% (10).

Generally, the only sign of a COVID-19 infection for many children may be a rash known as "COVID toes." It manifests with red or purple toes (or fingers), swelling of the toes/fingers, and possibly atrophic centers that may ulcerate (11). However, this rash is temporary in children and without serious consequences (12).

Figure 1 | Acne patterns observed in the area where a mask is worn on a child's face.

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This review summarizes the current knowledge of cutaneous manifestations in schoolchildren and adolescents 6 to 18 years old within the scope of various aspects of the COVID-19 pandemic based on a thorough review of articles.

Figure 2 | Clinical presentation of erythema multiforme.

Figure 3 | Palmar keratoses (palmar filiform parakeratotic hyperkeratosis) in a patient infected by COVID-19 (courtesy of Prof. Rok Čivjak, University Hospital for Infectious Diseases, Zagreb, Croatia).

Methods

For this narrative non-systematic literature review, the PubMed, Google Scholar, and ScienceDirect databases were searched for the following keywords: "COVID-19 infection" OR "COVID-19 vaccine" OR "COVID-19 Pandemic" and "Skin", "Cutaneous manifestations", "Children", "Adolescents", "Mask related acne", "Facial dermatoses", "Pseudochilblains", "Erythema multiforme", "Nails", "Hair", "Multiinflammatory syndrome". We included data for children 6 to 11 years old and adolescents 12 to 18 years old. Thus, this article focuses on school-age children between ages six and 18. We excluded articles addressing children below age six and adults above age 19.

Common cutaneous manifestations associated with protective measures described in schoolchildren and adolescents

The exact prevalence of skin conditions related to personal protective equipment in schoolchildren and adolescents is unknown because they are rarely analyzed in this population. Most of the reported mask-related facial dermatoses have been described in healthcare workers initially and subsequently in the general population.

However, schoolchildren and adolescents may present with facial dermatoses such as acne caused by wearing protective face masks (Fig. 1). As is known, *Cutibacterium acnes* is the primary cause of acne, and at this age the percentage of *C. acnes* increases (13). Thus, the use of protective face masks is associated with microbiome dysbiosis and disruption of skin homeostasis (13). This, in turn, triggers skin inflammation mediated by the innate immune system (11, 13). In addition, another mechanism by which face masks contribute to the exacerbation of existing acne is elevated air temperature between the skin and the mask, leading to a 10% increase for every 1 °C rise (13).

Furthermore, the increased humidity may cause occlusion of pores, irritation, and skin swelling. Both sweat retention, especially in hyperhidrosis, and increased humidity may cause follicular obstruction and aggravation of acne (13). However, diagnosis of mask-related acne can be established based on the emergence of new acne (without a prior history of acne) or the worsening of existing acne (within 6 weeks from the onset of mask-wearing) (13). The presence of acne patterns along the facial "O-zone" (the perioral and perinasal areas) can also aid in diagnosis (14). Differential diagnoses of mask-related acne include impetigo (*Staphylococcus aureus* and *Streptococcus pyogenes*), perioral dermatitis (*Fusobacterium* sp.), seborrheic dermatitis (*Malassezia furfur*), pityrosporum folliculitis, and rosacea (*Demodex*), hence sometimes results obtained by analysis of swabs for bacterial cultures and skin lesion KOH exam may be very useful (11). Topical agents such as antibacterial cleansers and moisturizers are predominantly used in treatment (11).

Cutaneous manifestations of COVID-19 infection in children

Generally, according to the International League of Dermatological Societies (ILDS) and the American Academy of Dermatology (AAD), the skin manifestations most commonly recorded in patients with COVID-19 infection are exanthematous (morbilliform) rash (22%–40%), pernio-like acral lesions (19%–38%), urticaria (16%), varicella-like eruption (11%), papulosquamous rash

(9.9%), and retiform purpura (6.4%) (15). When it comes to data concerning COVID-19 infection–related skin manifestations specifically in children, various manifestations have been recorded, including chilblain-like lesions (67%), EM–like eruptions (31%), and cutaneous manifestations of pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS; 0.8%) (3, 8, 16). Varicella-like lesions (17) and vasculitis-associated lesions have also been described (0.8%) (18) as well as cases of toxic epidermal necrolysis (19). Thus, according to clinical data from two cases (19), in one patient that was positive for COVID-19 (PCR test), 3 days after the fever a vesiculopustular rash (toxic epidermal necrolysis) and worsening of skin symptoms occurred; in the second patient, 3 weeks before a vesiculopapular rash a positive family history of COVID-19 and positive antibody test were recorded.

Although urticaria is a relatively common cutaneous manifestation associated with COVID-19 in adults, its occurrence in children has only been described at the level of case reports (20). Sometimes some other skin manifestations may also occur, such as pityriasis rosea–like eruptions, eczema-like rashes, angiomatous lesions, palmoplantar keratoses, and so on (Fig. 3). Regarding manifestations of COVID-19 on skin adnexa, hair loss is a commonly described post-infectious cutaneous manifestation in adults. However, in children, COVID-19–associated hair loss has only been described in case reports, mostly as part of multisystem inflammatory syndrome in children (MIS-C) (21, 22).

It is observed that cutaneous COVID-19 manifestations can often precede other symptoms and vary in their presentation, with most cases exhibiting mild skin manifestations (1). Hence, they may be the only sign of the diagnosis, and it is therefore important for dermatologists to properly recognize them to prevent the further spread of COVID-19 whenever possible (1).

The proposed mechanisms for cutaneous manifestations involve either the direct interaction of the virus with skin through cutaneous receptor angiotensin-converting enzyme 2 (ACE2) in the epidermal basal layer (23) or hyperactive immune responses (including complement activation or microvascular injury) (24).

Figure 4 | Clinical presentation of alopecia areata.

Positive immunolocalization of SARS-CoV-2 has been observed in vascular endothelial cells and epithelial cells of eccrine glands (25). Thus, it is likely that SARS-CoV-2 uses transmembrane ACE2 as receptors to enter the vessels because they are widely expressed in these cells (23, 26, 27). Physiologically, there are two axes of the renin-angiotensin system: the classical ACE/angiotensin II/angiotensin II type 1 (AT1R) axis and the counter-regulatory ACE2/angiotensin 1-7/Mas1 receptor axis (28). Renin converts angiotensinogen to angiotensin I, which is cleaved by ACE to generate angiotensin II. Thus, ACE2 catalyzes the conversion of angiotensin II to angiotensin 1-7. The signaling pathway involving the ACE2/angiotensin 1-7/Mas1 receptor axis leads to vasoprotection due to the injury caused by ACE/angiotensin II/AT1R axis stimulation, mediating endothelium-dependent vasodilation via the production of nitric oxide (28). Moreover, nitric oxide further prevents inflammation by shifting macrophages to an anti-inflammatory state (18). When COVID-19 binds to and downregulates the cutaneous receptor ACE2, the balance changes in favor of angiotensin II, which causes a decrease in the production of nitric oxide, consequently leading to vasoconstriction, reduced blood flow, and ischemia in target tissues (18). These changes create a microenvironment susceptible to coagulation and inflammation.

In addition, observations have been made regarding EM–like and varicella-like manifestations, which are believed to involve a direct viral cytopathic effect on cutaneous cells, which leads to vacuolar degeneration and the induction of keratinocyte apoptosis (29).

Chilblain-like lesions (pseudochilblains, pseudoperniosis, COVID toes)

Chilblain or perniosis manifests as an acral skin lesion caused by poor blood circulation resulting from prolonged exposure to cold temperatures. The main differential diagnoses include vasculitis, Raynaud's phenomenon, acrocyanosis, and cryoglobulinemia (30). The term *chilblain-like lesions* or *pseudo-chilblains* is used to describe skin lesions in patients infected with SARS-CoV-2 infection that look similar to primary chilblains but have specific epidemiologic characteristics (a rapid surge in countries heavily affected by the virus) (31). The time interval between the onset of systemic COVID-19 symptoms and the later appearance of chilblain-like lesions ranges from a few days to a few weeks (11, 12). Furthermore, findings from clinical, capillaroscopic, and histopathological analyses and characteristics distinguish them from idiopathic perniosis (32). For instance, unlike primary chilblains that develop after exposure to low temperatures, many COVID-19–infected patients with chilblain-like lesions have reported no history of cold exposure or previous similar rash manifestations (3, 16, 33).

Clinically, chilblain-like lesions manifest predominantly as macules and patches (71.5%) (30). Specifically, chilblain-like lesions typically present as round macules and papules, with ill-defined borders and atrophic centers that may be ulcerated, with the occurrence of scale crust, usually affecting acral sites, including the dorsal and plantar surfaces of the feet, toes ("COVID toes"), ankles, and ears (11). The lesions may be unilateral or bilateral. They are usually asymptomatic; however, patients may experience symptoms such as tingling, itchiness, and a sensation of coldness.

In the literature, pseudo-chilblains have been rarely reported among individuals with moderate and severe forms of COVID-19 (34). A possible explanation for this, and one of the proposed mechanisms underlying these lesions, is the higher type I interferon (IFN-1) response observed in children and adolescents, which causes vascular microangiopathic damage and lowers viral concentration (35). Indeed, severe cases of COVID-19 in the younger population have been associated with loss-of-function variants that affect IFN-1 response (36). Because the exaggerated IFN-1 response can attenuate viral replication, it possibly leads to a lower frequency of COVID-19–associated respiratory and systemic symptoms (30). It is also possible for SARS-CoV-2 infection to be cleared before the development of humoral immunity, which may explain the relatively low rate of seropositivity observed in patients with pseudo-chilblains (34). In addition, in the pathogenesis of chilblain-like lesions, aside from the IFN-1 response, another proposed mechanism involves endothelial damage, leading to thrombosis, coagulopathy, and vasculitis. This is supported by the presence of microthrombi and obliterative microangiopathy consisting of endothelial and intensive myointimal growth with complement activation (27, 35).

In skin lesional biopsies from patients presenting with pseudo-chilblains, the presence of viral particles within endothelial cells has been described, along with positive immunohistochemistry (26). However, this has recently been challenged by the use of electron microscopy. It revealed the presence of clathrin coat vesicles, which at first sight resemble the spikes of a coronavirus but are actually false-positive coronaviral particles (37). The aforementioned indicates that pseudo-chilblains are more likely caused by immune responses secondary to viral infection rather than the direct cytopathic effect. However, chilblain-like lesions typically resolve spontaneously within 2 to 8 weeks, and so specific treatment is usually unnecessary (16). Table 1 provides an overview of studies demonstrating a link between COVID-19 and chilblain-like lesions.

Erythema multiforme–like lesions

EM is a skin disease characterized by the appearance of reddish, annular macules that may progress into papules and occasionally coalesce to form plaques. It typically exhibits a target-like appearance and predominantly appears on the extremities, although it can also occur in other skin areas (Fig. 2) (44). Petechiae and purpura often co-occur with the target lesions (11). Conversely, the term *EM-like eruption* describes an atypical clinical pattern of EM showing unusual distribution or a lack of the target appearance (44). However, EM-like lesions are usually rare in children and adolescents.

The outbreak of these EM-like lesions coincided with the peak incidence of COVID-19. The lesions may appear together with pseudo-chilblains (45). According to data from one article (based on patients' medical histories), contact with COVID-19 occurred some days before the appearance of the skin lesions of erythema multiforme (45). According to another article, the contact with symptomatic COVID-19 infection occurred 3 weeks prior to developing EM-like lesions (and hospital admission), when MIS-C was diagnosed (even though PCR for SARS-CoV-2 was negative some days before admission) (46). However, positivity for SARS-CoV-2 spike protein by immunohistochemistry has been observed, which strongly suggests a link between EM-like eruptions and SARS-CoV-2 (45).

A possible pathophysiological cause of EM-like lesions may be a hypersensitivity reaction targeting SARS-CoV-2 antigens in the skin, mediated by lymphocytes (44). It is similar to the mechanism of EM induced by other infections such as *Mycoplasma pneumoniae*, herpes simplex virus, Epstein–Barr virus, adenovirus, and parvovirus B19 (46). Furthermore, the acral involvement could be indicative of a cutaneous hypersensitivity reaction of type III and/or IV (in small cutaneous vessels), thus being responsible for dermal and perivascular lymphoid infiltration (44). In the literature, one case was described (46) in which EM was one of the first signs of PIMS-TS temporally related to COVID-19. In this case, the outcome was the spontaneous resolution of skin lesions and the improvement of overall symptoms (46). In summary, EM and EM-like eruptions were not related to a severe course of COVID-19.

Dermatologic conditions associated with multisystem inflammatory syndrome in children and Kawasaki-like disease

MIS-C is a pediatric hyperinflammatory disorder caused by SARS-CoV-2 (47). Some of the clinical manifestations of MIS-C mimic Kawasaki disease, a medium vessel vasculitis of undetermined etiology typically affecting children below 5 years of age.

According to the literature, MIS-C develops 2 to 6 weeks following SARS-CoV-2 infection and is presumably triggered by an adaptive immune response (47). Even though its cardiovascular manifestations are more prominent, skin manifestations have been described as well (47, 48).

In children, among the cutaneous manifestations associated with severe COVID-19, periorbital erythema and edema were frequently described (16, 35, 49). According to data from one article (on a school-age child) (49), skin lesions (periorbital erythema) developed 1 day before fever (in the context of MIS-C), whereas according to another article (which included four school-age children with MIS-C) (35) in three children skin findings were followed by the onset of COVID-19.

Other commonly described cutaneous manifestations in children that met diagnostic criteria for MIS-C included rashes on the lips, hands, and feet, perineal or facial desquamation, erythemas, and exanthems (11, 21, 46, 49). However, the cutaneous manifestations described may also be a symptom of other inflammatory and toxin-mediated disorders such as Kawasaki disease or toxic shock syndrome, as well as infectious diseases such as rickettsial infections, which need to be considered as a differential diagnosis (11).

Adnexal changes

Changes of skin adnexa related to COVID-19 infection primarily include changes of the hair and nails. Hair changes include alopecia areata and telogen effluvium, and nail changes particularly include onychomadesis and periungual desquamation. These conditions have been described separately (4, 7) and as part of MIS-C syndrome (5, 22).

Alopecia areata is a non-scarring hair loss condition characterized by the acute onset of well-defined oval-to-round patches of complete hair loss (Fig. 4) (7). It usually occurs in the first two decades of life (48%), with a prevalence of 0.1% to 0.2% (7). The proposed mechanism of alopecia areata pathogenesis is organ-specific autoimmunity directed against the hair follicles. It also involves genetic factors and major histocompatibility complex class

I (MHC-I), which leads to oxidative stress-related pathogenetic pathways, with consequent destruction of hair follicle cells, mediated by the release of perifollicular IFN (IFN-γ) and tumor necrosis factor alpha (TNF-α) from T cell activation (7).

According to literature data, alopecic patches (alopecia areata) appear 3 to 7 weeks after symptomatic COVID-19 infection (7). A heightened inflammatory response has been shown in patients with confirmed COVID-19, in which substantially elevated plasma concentrations of these proinflammatory cytokines and other cytokines, such as interleukins (IL)-6, IL-1β, IL-2, and IL-17A, have been reported (50).

Telogen effluvium is a common condition characterized by diffuse hair shedding caused by premature termination of the anagen phase and entry of hair follicles into the catagen phase (6). It is usually triggered by various factors, including acute illnesses accompanied by fever, systemic diseases, or severe stress reactions (emotional or physical) (22). Therefore, acute telogen effluvium mostly appears within 2 to 3 months following the triggering event, and it usually resolves spontaneously or after the elimination of the trigger. Telogen effluvium may also occur as a late complication of MIS-C (22). According to one article, about 7 to 8 weeks after the diagnosis of MIS-C, a patient's hair loss began and telogen effluvium appeared (22), whereas, according data from another case of a patient with MISC, telogen effluvium appeared a month after SARS-CoV-2 infection (21). However, regarding telogen effluvium that develops after COVID-19 infection, the possible pathogenesis involves a cytokine storm and the formation of microthrombi, leading to obstruction of blood supply to the hair follicles (6).

Nail involvement has been described as part of other conditions mentioned earlier, such as pseudo-chilblains (4) and MIS-C (5). Prominent clinical findings include nail changes that are otherwise typically associated with lichen striatus: nail thinning, onychodystrophy, onycholysis, and longitudinal ridging (51). Lichen striatus, a skin condition characterized by lichenoid, erythematous, flat-topped papules in a linear distribution on the lower extremities, has also been described in case reports following COVID-19 infection in children (51). The occurrence of lichen striatus has been reported after viral stimuli such as influenza and varicella. Although its pathogenesis is not fully known, it is proposed to involve the loss of immunotolerance triggered by the virus toward mosaic keratinocyte clones, which are attacked by cytotoxic T cells (51). Histological analysis reveals the presence of lymphocytes surrounding subpapillary vessels, as well as hyperkeratosis and parakeratosis, a few necrotic keratinocytes, intercellular edema, and spongiosis (51).

In addition, periungual desquamation has been described in MIS-C (5), and periungual erythematous edema and onychomadesis have been observed in chilblain-like lesions (4). Furthermore, nailfold videocapillaroscopy of patients with MIS-C has revealed significantly lower capillary density and capillary length, and higher intercapillary distance (5, 52). Thus, the findings include microhemorrhage, pericapillary edema, capillary meandering, capillary branching and ramification, bushy capillary, enlarged capillaries, and neoangiogenesis.

Other nail changes potentially related to COVID-19 include Beau's lines, which are transverse grooves of the nails. They result from suppressed growth of the nail matrix and may precede onychomadesis, the separation of the nail plate from the nail matrix (5).

COVID-19 vaccine–related cutaneous manifestations in schoolchildren and adolescents

A crucial public measure that limits the spread of infection is COVID-19 vaccination. It is estimated that over 3.2 billion doses of vaccines have been administered. The most commonly reported skin adverse effects were in adults with underlying comorbidities and included erythema, erythromelalgia, urticaria, chilblains, pityriasis rosea–like reaction, and chilblain-like lesions (53).

However, skin adverse effects of the COVID-19 vaccine in children have been described in the literature, such as vitiligo (Fig. 5), toxic epidermolysis, and alopecia areata. Thus, there are case reports that include a case of vitiligo (54), a case of toxic epidermolysis (55), and a case of alopecia areata (56) that occurred as skin adverse effects of the COVID-19 vaccine in children, summarized in Table 2.

Other aspects of the COVID-19 pandemic and skin in children and adolescents

The impact of COVID-19 on the skin of patients with preexisting skin diseases has also been recorded. For instance, patients with psoriasis experienced more deterioration of their condition under the influence of COVID-19 (57). Moreover, staying in quarantine may negatively affect patients with chronic diseases such as atopic dermatitis (3). Furthermore, an interplay between the COVID-19 pandemic, skin, and psychological aspects has been recorded, although less attention has been given to the topic in literature concerning children.

Figure 5 | Clinical presentation of vitiligo.

Conclusions

There is a need for increased awareness regarding the most prevalent cutaneous manifestations associated with COVID-19, particularly in children, where they tend to be mild or nonspecific in nature. When evaluating skin rashes and disseminated lesions, there is a wide range of differential diagnoses to include, such as seasonal flu, drug hypersensitivity, various allergic reactions, manifestations of herpes infections (zoster or simplex), and dengue fever, but also COVID-19–associated manifestations. The recognition and management of COVID-19–associated skin manifestations is important not only to dermatologists, but to the entire medical community, in order to ensure optimal clinical outcomes for both adults and children affected by the disease.

Table 1 | Summary of evidence on the association between COVID-19 and chilblain-like lesions.

Research	Subjects	Materials and methods	Results
Fernandez Lazaro D, et al. (2021) (24)	Patients with cutaneous manifestations of COVID-19 (data from various studies and review articles)	Review article	Chilblains occur as a cutaneous manifestation in younger age groups, a possible sign of COVID-19 in patients with scarce or poorly expressive symptomatology.
Koschitzky M, et al. (2021) (31)	Adolescents and children presenting with chilblain-like lesions, possible association with COVID-19	Review article	Detection of pernio may be a useful tool for the early diagnosis of COVID-19 in otherwise asymptomatic carriers and should be considered in contact tracing, thereby having an important public health implication for preventing disease spread.
Galván Casas C, et al. (2020) (38)	Patients with an eruption of recent onset and no clear explanation, and suspected or confirmed COVID-19	Rapid prospective nationwide consensus study in Spain, case collection survey of images and clinical data	Pseudo-chilblain lesions affected younger patients, lasted longer, took place later in the course of COVID-19 disease, and were associated with less severe disease; lesions could cause pain (32%) or itch (30%).
Colmenero I, et al. (2020) (26)	Pediatric patients (n = 7) presenting with chilblains during the COVID-19 pandemic	Histopathological immunohisto-chemical and ultrastructural study	The presence of viral particles in the endothelium and the histological evidence of vascular damage support a causal relation of the lesions with SARS-CoV-2.
Pasquini Neto R, et al. (2022) (8)	Pediatric patients (n = 369) with cutaneous manifestations of COVID-19	Systematic review	The most common COVID-19 cutaneous manifestations in children and adolescents were chilblain-like lesions, (67.5% of the cases), followed by erythema multiforme–like (31.7%) and varicella-like lesions (0.8%).
Andina D, et al. (2020.) (3)	Children and adolescents (n = 22, 6–17 years old) presenting with chilblain-like lesions during the peak incidence of the COVID-19 pandemic	Retrospective review	Acute chilblains were observed during the COVID-19 pandemic in children and teenagers. It is a mildly symptomatic condition with an excellent prognosis, usually requiring no therapy.
El Hachem M, et al. (2020) (32)	Adolescent patients (n = 19) with chilblain-like lesions, among which most of them and/or their cohabitants reported flu-like symptoms 1 to 2 months prior to skin manifestation onset	Case-control study; clinical, capillaroscopic, histopathological, ultrastructural, and laboratory findings	Chilblain-like lesions during the COVID-19 pandemic have specific epidemiologic, clinical, capillaroscopic, and histopathological characteristics that distinguish them from idiopathic perniosis. History data and the detection of anti-SARS-CoV-2 immunoglobulin A strongly suggest a relationship between skin lesions and COVID-19.
Piccolo V, et al. (2020) (39)	Patients (n = 63) with chilblain-like lesions during the COVID-19 epidemic	Cohort study	Possible delayed immune-mediated reaction to the virus in genetically predisposed patients.
Cordoro K, et al. (2020) (40)	Healthy adolescents (n = 6) with acral perniosis-like lesions that had mild symptoms of viral upper respiratory infection or contact with symptomatic persons 1 to 2 weeks preceding the rash	Clustered cases	The temporal relationship to the pandemic indicates that perniosis could be a cutaneous sign of SARS-CoV-2 infection and may represent a response to subclinical infection or a convalescent-phase reaction.
Carazo Gallego B, et al. (2021) (41)	Children (n = 62) presenting with cutaneous manifestations during the first wave of the pandemic, of whom nine had positive antibodies to SARS-CoV-2	Observational, cross-sectional, multicenter study	The presence of chilblain-like lesions was significantly related to SARS-CoV-2 contact.
Garcia-Lara G, et al. (2020) (42)	Children under age 16 that consulted for acral lesions in the context of the pandemic	Retrospective cross-sectional study	Acute self-healing acro-ischemic lesions are different from other chronic conditions such as acrocyanosis, perniosis, or vasculitis.
Rodriguez Pastor SO, et al. (2021) (43)	Children (n = 62) seeking medical attention at the emergency department for skin lesions, 34 with chilblains	Prospective observational study	The number of emergency department visits for chilblains significantly increased during the first peak of the COVID-19 pandemic.

Table 2 | **Summary and causes of skin conditions influenced by various aspects of the COVID-19 pandemic.**

Skin condition	COVID-19 infection	COVID-19 vaccine	COVID-19 protective measures
Chilblain-like lesions	– Usually mildly symptomatic, mostly affected toes, resolved spontaneously. Possibly a delayed immune response to the – infection. Details are described in Table 1 (3, 4, 10, 20, 26, 29–32, 34, 35, 38, 41–43).	No studies confirmed a causal relationship between the COVID vaccine and chilblain-like lesions in the age group 6–18 years.	—
Erythema multiforme–like eruptions	– Four children (age 11–17) with chilblain-like lesions presenting with targetoid lesions affecting the hands, feet, forearms, elbows, arms, ankles, legs, thighs, and ears, clinically consistent with erythema multiforme and histopathological features not specific or typical for erythema multiforme (45). – One child (age 13) affected by multisystem inflammatory syndrome in children presented with four isolated round papular lesions compatible with the target lesions of erythema multiforme (46).	—	—
Periorbital erythema	– Seven of 25 children that met the criteria for MIS-C developed periorbital erythema and edema (49). – Eleven out of 46 (23.9%) children hospitalized for COVID-19 developed periorbital erythema and edema (35).	—	—
Telogen effluvium	– A 10-year-old boy with diffuse hair loss, hospitalized due to COVID-19 infection, developed MIS-C, diagnosed with telogen effluvium (21). – A 7-year-old girl that developed hair loss 73 days after the diagnosis of MIS-C, diagnosed with telogen effluvium after the dermatologic examination (22). – One of 46 children hospitalized for COVID-19 developed telogen effluvium (35).	—	—
Alopecia areata	– A 13-year-old patient earlier diagnosed with COVID-19–associated MIS-C developed an alopecic patch (21). – Three school-aged children, 8 and 9 years old, presented with alopecic patches 3 to 7 weeks after symptomatic COVID-19 infection (7).	A 7-year-old girl presented with a nonscarring alopecic patch in the occipital region 20 days after the second dose of Pfizer-BioNTech (BNT162b2) vaccine (56).	—
Acne	—	—	Wearing protective face masks is related to microbiome dysbiosis and disruption of skin homeostasis, which leads to skin inflammation triggered by the innate immune system (11, 13).
Vitiligo	—	A 13-year-old girl with light-colored skin patches spreading across her body that started 2 weeks after the first dose of Pfizer-BioNTech (BNT162b2) vaccine (54).	—
Toxic epidermal necrolysis	– A 6-year-old boy (SARS-CoV-2 antibody positive) and a 6-year- old girl (SARS-CoV.2 PCR positive) with widespread erythematous, vesiculopustular lesions on the face and body; punch biopsy result was consistent with toxic epidermal necrolysis; it is suspected that COVID-19 infection may have a role in the etiology due to poor response to conventional therapies (19).	Six days after the first dose of Pfizer-BioNTech (BNT162b2) vaccine, a 12-year-old girl with no previous medical history presented with erythematous, painful patches, and plaques on the chest wall and trunk, which subsequently spread to the face, palms, and soles; the rash rapidly coalesced and developed into tense bullae, diagnosed with TEN, improvement 2nd day after IVIG administration (55).	—

MIS-C = multisystem inflammatory syndrome in children, IVIG = intravenous imunoglobulin, TEN = toxic epidermal necrolysis.

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