REVIEW ARTICLE

# Dermatological Manifestations of COVID-19 in Children

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**Context:** The clinical picture of pediatric severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection differs from adults as do the cutaneous manifestations. In this review, we summarize the varied morphological manifestations of SARS-CoV-2 infection in the pediatric population. **Evidence acquisition:** A comprehensive literature search was conducted (23 September, 2021) across multiple databases (PubMed, EMBASE, MEDLINE and Cochrane) with the relevant keywords. An additional filter of age group between 0-18 years was kept in each of the searches. **Results:** Chilblains constitute the most common cutaneous manifestation of pediatric coronavirus disease (COVID-19). Other commonly reported manifestations include maculopapular rash, urticaria, erythema multiforme, and papulovesicular eruptions. Majority of children with these manifestations are asymptomatic, highlighting the need to clinically suspect and appropriately manage such patients. A subset of pediatric patients develop severe multisystem involvement termed as multi-system inflammatory syndrome in children (MIS-C) that has varied mucocutaneous manifestations. **Conclusion:** A wide variety of dermatological manifestation of SARS-CoV-2 infection is reported, and both the pediatrician and dermatologist need to be aware of the same to suspect and diagnose COVID-19 infection in children.

**Key words:** *Chilblains, Erythema multiforme, MIS-C, SARS-CoV-2.*

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The mucocutaneous manifestations of corona-virus disease (COVID-19) in children are still evolving, with varied presentations, which are relatively milder [1]. Moreover, they can often go undiagnosed when presenting as a sole cutaneous manifestation of pediatric COVID-19.

The incidence of dermatological manifestations in pediatric COVID-19 is diverse, varying across ethnic groups and geographical regions. Chilblain like lesions, urticaria and confluent maculopapular rash are commonly observed in children in European countries [2]. Chinese literature suggests ischemic lesions and urticarial rash as common manifestations [3]; whereas, reports from Thai-land have observed dengue like rash in certain patients [4]. Multisystem inflammatory syndrome in children (MIS-C) is already an established entity, which has its own mucocutaneous manifestations. We, herein, summarize all relevant literature on the mucocutaneous manifestations of pediatric COVID-19.

## METHODS

A comprehensive literature search across multiple databases (PubMed, EMBASE, MEDLINE, and Cochrane) was carried out with keywords "COVID-19" OR "corona-virus" AND "rash", "skin rash", "cuta-neous", "chilblain", "chilblain-like", "pseudo-chilblain", "pernio like", "urticaria", "urticarial rash", "vesicular", "papulovesicular, "maculopapular", "morbilliform", "erythema multiforme", "varicella like", "vesicular rash", "dengue-like", "purpura", "hair", "nail", "mucosa", "Multisystem inflammatory syndrome in children", "MIS-C"," Multisystem inflammatory syndrome in neonate", and "MIS-N". An additional filter of age group between 0-18 years was kept in each of the searches.

## CUTANEOUS MANIFESTATIONS

### Chilblain

Chilblains represent the most common cutaneous manifestation reported among children affected with COVID-19. When the coronavirus pandemic began in March, 2020, a sudden surge in cases of chilblain-like lesions was noticed. A French study even revealed a rising trend regarding web searches of chilblains, fingers, toes and COVID-19 infection during the initial months of the pandemic [8]. The cases observed were not true chilblains, differing in terms of sex distribution (equal sex distribution), triggering factors (warm climate), and distribution of lesions (fingers and toes). Despite there being a temporal relation between the onset of chilblain-like lesions with the pandemic, there is still a debate regarding its association with SARS-CoV-2, as majority of patients test negative for infection both by reverse transcriptase - polymerase chain reaction (RT-PCR) or serology [9,10].

*Clinical features*: Multiple erythematous, violaceous and/or purpuric macules are observed predominantly over the

finger and toes (Covid toes). Majority of cases affect the toes with lesions not crossing the meta-tarsophalangeal joint. The reported mean age of patients is above 10 years [2]. Swelling of the surrounding skin may also be noted, with severe cases showing secondary vesiculation. They appear towards the end of COVID-19, and last for about 12 days on an average, but can last for up to 4-5 weeks. Unlike adults, where systemic association with chilblain-like lesions is common (up to 45%), children are commonly asymptomatic [11]. The chilblain lesions may; however, show local symptoms such as pain or itching. Co-existing erythema multiforme (EM) like lesions in pediatric patients with chilblains has also been noted [12]. A case of recurrent chilblain-like lesions in a patient with mild COVID-19 was also reported [13].

Dermoscopy of chilblain-like lesions in children has revealed the following features viz., a red or purplish background area, with red to purple globules in majority of cases, and a grey brown reticular network on the periphery in 30% of cases [14]. In an Italian report studying nail videocapillaroscopy in children with chilblain, peri-capillary edema and microhemorrhage were striking features, especially in toe lesions, along with capillary dilation common to both finger and toe nails [15].

*Histopathology*: Chilblain-like lesions are characterized by lymphocytic vasculitis ranging from endothelial swelling to fibrinoid necrosis. Superficial and deep peri-vascular lymphocytic infiltrate along with peri-eccrine lymphocytic infiltrate is also seen, which is similar to idiopathic perniosis. SARS-CoV-2 virus has also been demonstrated on immunohistochemistry in the endothelial cells and epithelial cells of eccrine gland [2].

*Pathogenesis*: Various possible pathomechanisms have been put forth. They include:

*i*) Direct virus - induced endothelial damage: Association between direct endothelial damage and chilblain in COVID-19 was suggested by Colmereno, et al. [16] based on immunohistochemistry and electron micro-scopy findings of virus particles affecting endothelium and eccrine epidermal cells. However, this was later challenged by Brealey, et al. [17], who explained that the virus like structure was infact a clathrin-coated vesicle, a normal subcellular organelle [17]. Still, viral particles in endothelium along with evidence of vascular damage on histopathology support a causal association.

*ii*) Role of interferon type 1: Interferon type 1, a part of the innate immunity, is responsible for the first line of defense against viral infections. Compared to adults, the levels of INF-1 are higher in infants and children. Hubiche, et al. [18] found that there was a significantly higher IFN-á response in chilblains patients (associated with mild disease) compared to patients with moderate or severe COVID-19. In severe SARS-CoV-2 infections, there is impaired interferon response, explaining why chilblain-like lesions are seen infrequently [18]. Given the histopathological similarity of COVID-19 induced chilblain to type 1 interferonpathy induced chilblain, a causal association has also been suggested.

*iii*) Thrombotic or embolic hypothesis: COVID-19 infection is associated with raised D-dimer levels in moderate to severe cases and thus carry a high risk of thromboembolism. These fibrin micro-emboli may have tendency to block the smaller vessels leading to acral ischemia and subsequently chilblain-like lesions. In a study by Hachem, et al. [16], microthrombi were observed on histopathological analysis in three patients with chilblains. This supports the possibility of a thrombotic or embolic event precipitating chilblain-like lesions.

*Investigations*: Strikingly, majority of patients who develop chilblain-like lesions test negative for SARS-CoV-2 on a RT-PCR based test [19]. Given that chilblain develops during resolution of COVID-19 and in children having asymptomatic infection, a lower positivity can be explained. Antibody serology with IgM and IgG in children have also demonstrated lower positivity rates [20,21]. Interestingly, an Italian series has depicted 53.3% IgA-positivity against S1 spike protein, which establishes a causal-link between chilblain-like lesions and asymptomatic SARS-CoV-2 infection [9].

*Treatment*: In children, spontaneous resolution over days to weeks is the dictum. Symptomatic treatment with analgesics and antishistaminics usually suffices. More-over, chilblains, in children are associated with mild COVID-19, unlike adults. Counselling the patient regarding the benign nature of the condition is important.

### Urticaria

Acute urticaria is characterized by transient pruritic wheals not lasting for more than 24 hours, and for less than six weeks in duration. Among children presenting with acute urticaria, infections (mostly upper respiratory infections), drugs and food allergy are the most common precipitating factors [22]. During the ongoing pandemic, urticarial lesions have accounted for 13.5-26% of cutaneous manifestations arising due to SARS-CoV-2 infection in adults [23]. However, data in the pediatric age group is scarce and restricted to case reports (9 cases) (**Web Table I**). Majority of patients presented with urticaria as the sole symptom to the dermatologist or pediatrician; although, cases presenting with or after systemic symptoms have been reported. History regarding systemic symptoms and household contacts

gives a clue towards possible underlying etiology of SARS-CoV-2 infection. In the current pandemic, we feel that all children with acute urticaria must be subjected to SARS-CoV-2 testing (**Fig. 1**).

Multifactorial pathophysiological process has been put forth explaining the observation of urticaria in children. They include: affinity of SARS-CoV-2 with ACE2 receptor on endothelium may cause immune complex deposition leading to immune mediated urticaria; Cross-reactivity between viral IgM and IgG with mast cell IgE causing mast cell degranulation; Immune complexes stimulating basophils into producing vasoactive amines, which activates complement, leading to increased vascular permeability [32]; cytokine IL-6 (elevated in COVID-19 patients) directly stimulates mast cell degranulation, leading to urticaria [33]; and mediation via bradykinin due to activation of kinin-kallikerin system in conjunction with ACE2 receptor stimulation [34].

The diagnosis is primarily clinical. A possibility of drug-induced urticaria due to use of non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics in COVID-19 should be kept in mind. The treatment is symptomatic, with use of corticosteroids limited to resistant cases. The association of urticaria with COVID-19 infection in children has not been seen to be associated with any adverse effects.

### Erythema Multiforme-Like Eruption

Erythema multiforme is an acute onset hypersensitivity disorder characterized by a distinctive rash called target lesions. Among children, infections viz., herpes simplex virus and mycoplasma pneumonia, and drugs are frequently associated [35]. During the COVID-19 pandemic, three different types of EM or EM-like rash have been reported: juvenile-virus related EM like rash (age <30 years), older classical EM rash (age >55 years) and drug-induced EM [36].

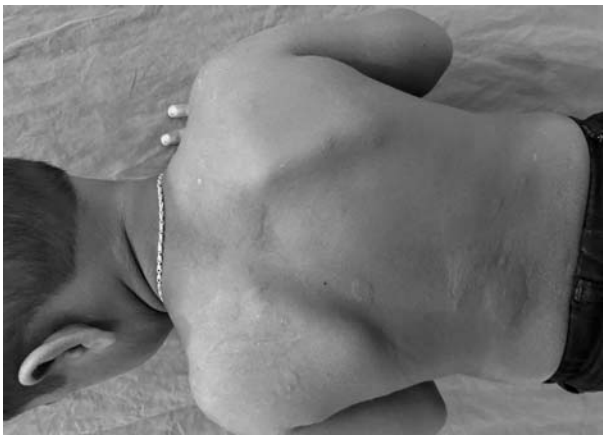

**Fig. 1** Acute urticaria in a 7-year-old boy as presenting feature of COVID-19 infection.

In children, the rash is an atypical target lesion restricted to the palms and soles in majority of the cases (**Web Table II**). The lesions are smaller, less widespread and may be itchy or painful. A latency of few days to three weeks between COVID-19 infection and EM-like rash is seen. In a retrospective analysis of 132 patients presen-ting with acral lesions during the pandemic in Italy [37], 28% patients had EM-like lesions ($n$=37) with only two patients having sites other than palms and soles involved. Torello, et al. [13] reported four patients with EM-like rash among 22 patients with chilblains.

Histopathologically, mild superficial perivascular and perieccrine lymphocytic infiltrate was observed without the characteristic findings of EM such as keratinocyte necrosis and eosinophils. The correlation with COVID-19 was confirmed in one case by a positive RT-PCR report while in two patients, immunohistochemistry revealed antibodies to SARS-CoV-2 spike glycoprotein in the vascular endothelium and eccrine epithelial cells [13]. Thus, it is fair to say that the lesions are not true EM lesions but EM-like or rather resembling chilblains clinically and histopathologically. Overall, EM or EM-like rash is not associated with a severe course of SARS-CoV-2 infection among children. Symptomatic therapy with topical or oral corticosteroids is enough in most of the cases.

### Papulovesicular Eruption

Papulovesicular eruption as a cutaneous manifestation of COVID-19 is well documented in adult literature. Average age of onset is 45-60 years with the eruption seen during early infection. The underlying pathogenesis is sus-pected to be the direct effect of SARS-CoV-2 virus on basal keratinocytes leading to acantholysis [41]. Two distinct morphological variants are described: localized monomorphic variant and diffuse polymorphic variant. In comparison to adults, wherein incidence rates of 7.2% have been reported [42], only a single case has been documented in pediatric literature. The case was that of an 8-year-old girl who presented with a three-day history of papulovesicular lesions along with six-day history of cough. A positive contact history led to suspicion of COVID-19 in this case which was confirmed by a RT-PCR test. The exanthema resolved in 7 days time without any need for intervention [43].

The authors also encountered of papulovesicular eruption in an 11-year-boy who was asymptomatic; however, he and his parents later tested positive for SARS-CoV-2 infection.

### Multisystem Inflammatory Syndrome in Children

Multisystem inflammatory syndrome in children (MIS-C) is a relatively common complication of COVID-19 that presents clinically resembling incomplete Kawasaki disease and toxic

shock syndrome. Majority of children have positive serology for COVID-19 and negative polymerase chain reaction, supporting the hypothesis that this condition is related to immune dysregulation after acute infection has subsided.

In a large series of MIS-C patients across the United States, mucocutaneous findings were identified in 74% of children, out of which 59% had nonspecific eruption, 55% bilateral conjunctivitis, 42% oral mucosal changes, and 37% peripheral extremity changes. [52]. Commonly reported cutaneous features include diffuse non-specific eruptions, palmoplantar erythema, hyperemia of lips, strawberry tongue, periorbital and malar erythema [53]. EM has also been reported in a child with MIS-C [54]. The skin findings associated with MIS-C are more common in younger children and decrease with age (**Fig. 2**).

*Pathogenesis*: No literature with regards to pathogenesis of mucocutaneous manifestations in MIS-C is available.

*Differential diagnosis*: At the beginning of the COVID-19 pandemic, MIS-C was confused with Kawasaki disease, toxic shock syndrome and secondary hemophagocytic lymphohistiocyosis as the clinical features were overlapping. However, differences exist in the geographic distribution, pathogenesis, cardiac and gastrointestinal manifestations and hematological parameters. Moreover, majority of MIS-C patients are seropositive for SARS-CoV-2 antibodies.

*Treatment*: The mainstay of MIS-C treatment is intravenous immune globulin (IVIG), and adjunctive high-dose corticosteroids. The cutaneous manifestations are transient and resolve with treatment of MIS-C.

### Non-Specific Cutaneous Lesions

Maculopapular or morbilliform rash has been reported in nearly 47% of adult patients with cutaneous mani-festations; however, in children, they are infrequently documented [61] (**Fig. 3**). Other nonspecific cutaneous manifestation reported in children include retiform purpura [62], cutaneous vasculitis (**Fig. 4**), dengue-like exanthem [4] (**Fig. 5**), livedoid lesions [63], acral ischemia [64] and petechial rash [65].

**Fig. 2** Cutaneous manifestations of multisystem inflammatory syndrome in childhood (MIS-C) (strawberry tongue, periungual desquamation, and desquamation around buttocks) occurring in a 6-year-old boy four weeks after COVID-19, associated with IgG SARS-CoV-2 antibody positivity.

### Hair and Nail Changes

Post-COVID hair changes have been commonly reported in adults; however, there is paucity of literature for hair changes after COVID-19 in children. Hayran, et al. [66] presented two children with different hair loss patterns post-MIS-C. The first patient was a 10-year-old boy who developed telogen effluvium. The second patient who was a 13-year-old boy who developed alopecia areata. The duration in both the cases was nearly four weeks after COVID-19-associated MIS-C [66]. The cause of hair loss in COVID-19 patients is unknown but stress and anxiety were the proposed precipitating factors. In a series of five patients, fluorescence of hair and nails was observed under Wood lamp in patients of COVID-19, who were treated with favipiravir [67].

Nail changes have been observed in patients with SARS-CoV-2 infection in the form of red half-moon nails, transverse orange nails, Mee lines and Beau lines. In a study by Thuangton, et al. [68], two patients had nail changes in the form of brittle nails and chromonychia. No documented reports are available for nail changes after SARS-CoV-2 infection in the pediatric population. However, clinicians should keep an eye out for these nail changes in children too, as these are also commonly seen in other viral infections.

## INFERENCE IN SKIN OF COLOR

A lack of representation in skin of color have been well documented in COVID-19 cutaneous manifestations. The ethnic and racial disparities pose a problem in clinical imaging of the dermatological manifestation, and may impact the health outcomes as well as create a gap in the educational resources.

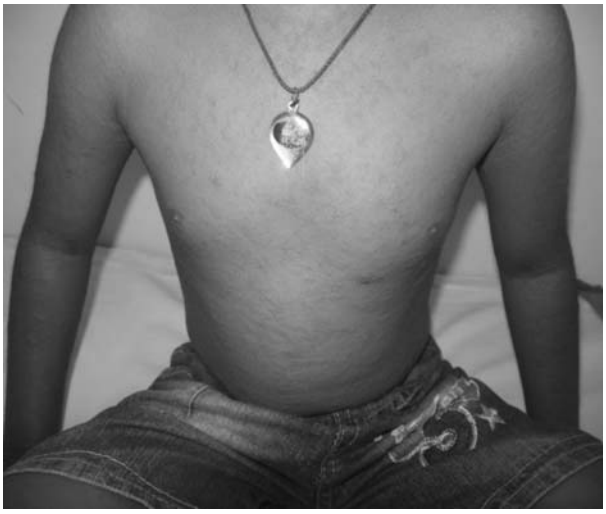

**Fig. 3** Maculopapular rash appearing 3 days after diagnoses of COVID-19 infection in an 8-year-old boy.

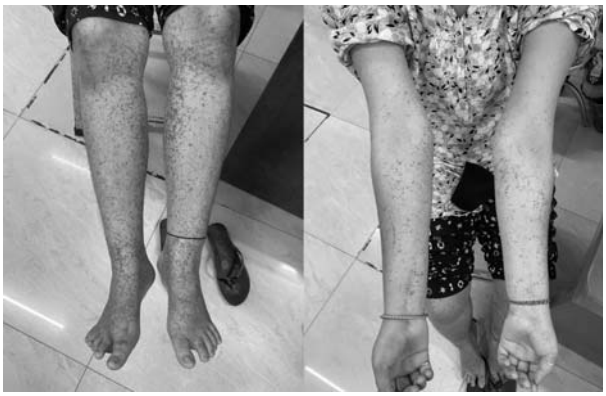

**Fig. 4** Palpable purpura on all four limbs as presenting feature in a 13-year-old girl later diagnosed with COVID-19 infection. The biopsy was suggestive of leucocytoclastic vasculitis.

**Fig. 5** Dengue-like rash with classical islands of sparing in a 6 year old girl diagnosed with COVID-19 infection.

Some authors have emphasizd the under represen-tation of skin manifestations of COVID-19 and paucity of images in Fitpatricks IV, V or VI types [69,70]. A study by Dalal, et al. [71] described the dermatological mani-festation in 12.7% of COVID-19 cases from Northern India, in which 7.8% had pruritus without cutaneous findings, 2.9% had maculopapular rash and 1.9% had urticarial rash. The largest series from Southern India consisting of 1065 SARS-CoV-2 positive patients had cutaneous manifestations in only 4.5% cases [72]. Urticaira and itching were the commonest, followed by maculopapular rash, vesicular rash, acral erythema, apthous ulcer, herpes zoster and others. Another cases series from India [73] had similar manifestations of urticaria, maculopapular rash and herpes zoster. However, none of these series reported any pediatric cases.

## CONCLUSION

Cutaneous manifestation may present before, at or after the diagnosis of COVID-19 among children. Chilblains, the most common cutaneous manifestation, is associated with mild SARS-CoV-2 infection, unlike the adult population. Literature on urticaria, erythema multiforme like, papulovesicular eruptions and maculopapular rash is limited compared to adults, probably due to under-reporting and the fact that these manifestations are often associated with asymptomatic or mild infection. A subset of pediatric patients develop varied muco-cutaneous manifestations along with as MIS-C, which has not been observed in adults. We feel that acute urticaria and maculopapular rash in a child should prompt testing for SARS-CoV-2 infection in the current pandemic.

Given the relaxations on COVID-19 norms worldwide and vaccination status among children particularly, a surge in the cases of paediatric COVID-19 may be on the horizon. An in-depth knowledge regarding cutaneous manifestations of COVID-19 is necessary for both the pediatrician and dermatologist to suspect and diagnose COVID-19 infection in children early. Data regarding such manifestations is still evolving and further information is needed to diversify our understanding regarding the subject.

*Contributors*: MP: contributed to initial conceptualization and prepared the initial draft of the manuscript; AA,TH: contributed to literature review and drafting of final manuscript. All authors prepared and approved the final manuscript.
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