Cutaneous Manifestations of COVID-19 in Children

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the ensuing disease coronavirus disease 2019 (COVID-19), has erupted as global pandemic. Clinical presentation, course and outcome of disease is different in children. Besides, respiratory symptoms, patients of COVID-19 can present with diverse cutaneous manifestations seen in 0.2% to 20% of patients, and 3.4% of children. Common dermatologic findings include pseudochilblain (COVID toes, maculopapular (morbilliform) exanthem, urticaria, vesicular rash, erythema multiforme and Kawasaki disease-like inflammatory multisystemic syndrome. Cutaneous involvement usually occurs concurrently with the systemic symptoms; nonetheless, these can follow or precede the systemic features. Any correlation between COVID-19 severity and cutaneous manifestations remains speculative. These cutaneous changes may guide to early diagnosis and treatment of COVID-19.

Key words
COVID-19, cutaneous manifestations, children, severe acute respiratory syndrome coronavirus 2, Covid toes, pseudochilblain, urticaria, vesicular eruption, maculopapular eruption, livedo reticularis

Introduction

According to the WHO statistics, the current pandemic of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected 53,766,728 patients in 220 countries with death toll of 1,308,975 (15th November, 2020).1 Pediatric age group accounts for 1-5% of patients.2 SARS-CoV-2 is a highly infectious and transmissible virus that spreads by respiratory droplets, close contact, aerosols, through the conjunctiva and gastrointestinal tract. It exhibits tropism for cells of respiratory system and immune system expressing angiotensin converting enzyme-2 (ACE-2) receptors. The virus also invades heart, vascular endothelial cells, liver, kidney and skin during viremic stage.2

Disease affects all age groups, both children and adults; but the disease shows fewer symptoms and less severity in children,2 whereas increasing age predisposes to serious complications like interstitial pneumonia, acute respiratory distress syndrome (ARDS), and sepsis.2 In a series of 2,143 children suffering from laboratory-verified or clinically diagnosed COVID-19, 4.4% were asymptomatic, 51.0% had mild, 38.7% moderate, 5.2% severe disease and 0.6% had critical disease.3 Zimmerman et al.4 reported 35% children to be asymptomatic. The most common symptoms in children are cough in 48% (19-100%), fever 42% (11-100%), mean duration 3-6 days, range 1-16 days) and pharyngitis in 30% (11-100%).4 Nasal congestion, rhinorrhea, tachypnoea, wheezing, diarrhea, vomiting, headache and fatigue are other less frequent features seen. Although respiratory system is the main target in COVID-19, extra pulmonary manifestations involving cardiac, gastrointestinal, hepatic, renal, neurological, olfactory and gustatory, ocular, cutaneous and hematological systems have been

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Figure 1: Reported frequencies of extrapulmonary manifestations of Coronavirus disease 2019 (COVID-19). [5]

reported in a significant number of patients (Figure 1).[5]

Like many other viral infections, COVID-19 is also associated with many cutaneous manifestations, which may precede, occur concurrently or follow the systemic symptoms. The first report from China showed a rash in 0.2% of 1,099 COVID-19 patients. [6] Subsequently, a series of 88 COVID-19 patients from Italy by Recalcati[7] showed that 18 patients (20.5%) developed cutaneous lesions. Subsequent studies, meta-analyses and reviews report varied frequencies of cutaneous changes. Most studies comprise of patients of all ages; however, in general cutaneous manifestations are less frequent in children. Pousa et al.[5] reported an incidence of 3.4% in children suffering from COVID-19. [5] These changes may correlate with severity of systemic symptoms, as well. Early diagnosis of dermatological manifestations may help in early diagnosis of patients and carriers, management and isolation of COVID-19 case to prevent spread of disease. [8]

Pathogenesis

Like other viruses, SARS-2 virus can target integument by many direct and indirect mechanisms (Figure 2). [5,9,10]

1. Virus particles reach endothelial cells of cutaneous blood vessels by hematogenous route directly or carried by inflammatory cells.
2. SARS-CoV-2, like other viral infections is supposed to induce autoimmunity by molecular mimicry, release of self-antigens and epitope spreading phenomenon. This leads to increased T cell (CD4+, Th1 type and CD8+), B cell activation and expansion, increased macrophage activation and release of cytokines e.g. interleukin (IL)-6, GM-CSF, IL-1beta, IL-18, TNF-α, IFN-γ etc. and
complement activation occurs.

3. Virus binds to ACE2 receptors, expressed on surface of keratinocytes and other cells in cutaneous tissues, to enter the host cells, followed by downregulation of ACE2 receptors. Keratinocyte structural modification and apoptosis occur due to direct virus cytopathic effect or cytotoxic lymphocytes. ACE-2 is a negative regulator of the renin-angiotensin system (RAS). Interference of ACE2-RAS underlies different vascular pathologies.

4. Hypoxic injury to skin augments the anaerobic metabolism, followed by lactic acid accumulation which further reduces cutaneous blood flow.

5. Hypercoagulable state is a hallmark of severe COVID-19 infection. Different underlying mechanisms may be activation of coagulation pathway and suppression of fibrinolytic pathways by IL-6 and other cytokines; direct activation of coagulation system by virus particles; and production of antiphospholipid antibodies. The end result is low-grade disseminated intravascular coagulation. Different dermatological manifestations may involve more than one of these mechanisms.

**Cutaneous manifestations in children**

As clinical presentation, course and outcome of COVID-19 in children differ from those in adults, likewise, the cutaneous manifestations of COVID-19 also differ from those of adults as shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1 Comparison of COVID-19-related cutaneous manifestations in adult and pediatric patients.[11]</th>
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</thead>
<tbody>
<tr>
<td><strong>Cutaneous manifestation</strong></td>
</tr>
<tr>
<td>Morbilliform/maculopapular eruption</td>
</tr>
<tr>
<td>Urticaria</td>
</tr>
<tr>
<td>Vesicular eruption</td>
</tr>
<tr>
<td>Pseudochilblain</td>
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<tr>
<td>Erythema multiforme</td>
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<tr>
<td>Multisystem inflammatory syndrome in children</td>
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<tr>
<td>Half-moon nail sign</td>
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</table>
While manifestations such as urticaria, maculopapular rash or vesicular rash can occur in patients of all ages, certain such as chilblains, erythema multiforme (EM) and cutaneous rash of pediatric inflammatory multisystem syndrome associated with SARS-CoV-2 (PIMS-TS) are more frequently seen in pediatric patients.\textsuperscript{11}

COVID-19-related cutaneous manifestations can be classified on the basis of their, etiology, morphology and histopathology (Table 2).\textsuperscript{10,12-14} Heterogeneous cutaneous manifestations of COVID-19 can be broadly grouped as six dermatological patterns as 1-chilblain like (pseudochilblain, covid toes), 2- maculopapular/ morbilliform, 3-urticarial, 4-vesicular, 5-petechiae/ purpura and 6-livedoid. These clinical findings can be further classified as either inflammatory (maculopapular/ morbilliform, urticarial, and vesicular) or vascular lesions (chilblain-like, petechiae/ purpura, and livedoid). Multisystem inflammatory syndrome in children (MIS-C), a new disease entity related to COVID-19 in children, presenting with dermatological eruption. Based on etiology, cutaneous manifestation may be part of disease itself, caused by the antiviral drugs and others treatment modalities, or may result from personal protective equipment. While interpreting these cutaneous eruptions, non-COVID-19 causes should also be ruled out (Table 3). These dermatologic manifestations undergo self-resolution, 98% in adults and 100% in children, with mean duration of 5.8 days in children (1 to 14 days) and 8.5 days in adults (1 to 21 days).\textsuperscript{1}

**Chilblain-like lesions (COVID toes)**

Chilblain lesions, also known as pernio, are characterized by pruritic or painful erythematous-violaceous papules, macules, or nodules on acral areas of the extremities, usually toes and fingers which last for more than one day. Lesions in children are asymptomatic as compared to adults. Pernio-like or chilblain-like lesions associated with systemic symptoms, have been named as pseudochilblain or ‘COVID toes’(Figure 2).\textsuperscript{12}

<table>
<thead>
<tr>
<th>Table 2 Classification of reported cutaneous manifestations.</th>
</tr>
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<tbody>
<tr>
<td><strong>Basis of classification</strong></td>
</tr>
</tbody>
</table>
| Etiology | 1. Primary dermatoses related to SARS-CoV-2  
2. Virus treatment-related  
3. Personal protective equipment-related |
| Histopathology\textsuperscript{[10]} | Lesions showing features of vasculitis only  
1. Covid toes  
2. Acute urticarial lesions  
Lesions showing features of vasculitis, coagulopathy and complementopathy  
1. Levidoid lesions  
2. Necrotic lesions  
3. Haemorrhagic lesions |
| Morphology | Lesions showing non-specific features similar to those in any other viral diseases  
1. Morbilliform lesions  
2. Papular lesions  
3. Pityriasis like lesions  
4. Vesicular lesions (varicella-like lesions)  
Lesions mimicking other specific diseases  
1. Dengue-like lesions  
2. Kawasaki-like lesions  
3. Lesions seen as a part of pediatric multisystemic inflammatory syndrome |

SARS-CoV-2 Severe acute respiratory symptoms coronavirus 2.
Table 3 Differential diagnosis of cutaneous manifestations in children suffering from COVID-19. [16,17]

<table>
<thead>
<tr>
<th>Morphological type of rash</th>
<th>Non-COVID-19 causes</th>
</tr>
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<tbody>
<tr>
<td>Chilblains</td>
<td>Raynaud’s phenomenon, systemic lupus erythematosus, systemic sclerosis, Buerger’s disease</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>Viral exanthem, Scarlet fever, measles, rubella, medication reaction, secondary syphilis, heat rash, leukemia, graft-versus-host disease</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Allergic reaction to drugs, infections, insects, foods, anaphylaxis</td>
</tr>
<tr>
<td>Vesicular</td>
<td>Varicella (chicken pox), herpes zoster, herpes simplex, rhus dermatitis (e.g. poison ivy, poison oak, and poison sumac)</td>
</tr>
<tr>
<td>Petechiae/purpura</td>
<td>Thrombocytopenia, meningococcemia, systemic lupus erythematosus, leukemia, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, vasculitis, vitamin C deficiency</td>
</tr>
<tr>
<td>Livedo reticularis/livedo racemosa</td>
<td>Antiphospholipid antibody syndrome, Sneddon syndrome, cryoglobulinemia, multiple myeloma, disseminated intravascular coagulation, hemolytic uremic syndrome, deep venous thrombosis, systemic lupus erythematosus, rheumatoid arthritis, polyarteritis nodosa, Sjogren’s syndrome, multiple sclerosis, Parkinson’s disease, cancer (e.g., renal cell cancer, breast cancer, lymphoma, and leukemia)</td>
</tr>
<tr>
<td>Digital ischemia</td>
<td>Arterial ischemia, disseminated intravascular coagulation, Buerger’s disease</td>
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In certain cases, COVID toes have been associated with typical target lesions of erythema multiforme (EM), affecting hands, feet, forearms, elbows, arms, ankles, thighs, legs and ears. Few case reports also describe nail splinter hemorrhages and dilated nail fold capillaries. COVID-associated chilblain affected both genders equally in absence of any triggering factor in contrast to the classic perniosis.11

Frequency varies from 14.3% to 72% and adolescents and young adults are commonly affected.12 Lesions follow the onset of COVID-19’s systemic symptoms and spontaneously resolve in children in a period of two to four weeks.11 These rashes were typically associated with relatively mild COVID-19 infection, representing a good prognosis in contrast to the acral ischemic lesions in adults. Most of the patients tested negative for PCR for SARS-CoV-2, the reason being that COVID toes are late manifestation of disease when viral RNA is not detectable in nasopharynx; however, family history of COVID-19 positive symptomatic adult family members has been reported in half of patients in one series.11 Histopathological examination showed a diffuse dense lymphoid infiltrate of the superficial and deep dermis and hypodermis, with a prevalent perivascular neutrophilic infiltrate and signs of endothelial activation.15 The exact pathogenesis of lesions is not fully known as its presentation is unrelated to cold exposure. Immune dysregulation, vasculitis, vessel thrombosis, or neoangiogenesis are suggested as underlying mechanism.11,12

Urticaria

Acute urticarial lesions have been described in 7% to 40% of patients. It mainly affects adult patients of COVID-19. Children with urticaria and COVID-19 are usually asymptomatic otherwise; however, they often have history of exposure to confirmed or suspected, symptomatic adult patients. Pruritic wheals of variable sizes, lasting for <24 hours, are seen on trunk usually.
Table 4 Major cutaneous drug eruptions due to virus treatments used in COVID-19. [14,19]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reported cutaneous drug eruption</th>
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| Hydroxychloroquine    | **Common**: itching, hair loss.  
|                        | **Less common**: morbilliform rash, erythroderma, exfoliative dermatitis, urticaria, eczematous eruption, erythema annulare centrifugum, photosensitivity, pigmentation.  
|                        | **Rare**: Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis. |
| Azithromycin          | **Rare**: morbilliform eruption, angioedema, blisters, skin peeling, burning sensation in eyes or painful skin. |
| Oseltamivir           | **Rare**: SJS/TEN, angioedema.                                                                 |
| Ribavirin             | **Rare**: Alopecia; acneiform eruptions; maculopapular and eczematous lesions; localized scleroderma, skin dryness. |
| Lopinavir and ritanavir| **Rare**: Maculopapular drug eruptions, injection site reactions, exfoliative erythroderma, SJS/TEN. |
| Corticosteroids       | **Common**: skin atrophy, acneiform eruption, telangiectasia, petechiae, ecchymosis, striae, hirsutism. |
| Tocilizumab           | **Less common**: anaphylaxis.  
|                        | **Rare**: morbilliform rash, erythroderma, leukocytoclastic vasculitis. |
| Convalescent serum    | **Less common**: morbilliform rash, itching, evanescent red spot.                                |

Figure 3 Dusky erythematous plaques on toes (A) and fingers (B) of a 15-year-old girl suspected of COVID-19.[12]

Disease can be generalized or localized. Rash occurs at the same time as other systemic symptoms of COVID-19 with an average duration of 6.8 days; however, eruption can precede or follow systemic symptoms. Urticarial lesions are associated with a more severe COVID-19 disease with 2% mortality in one study. SARS-CoV-2 may directly cause mast cell degranulation or complement activation and vasculitis may precipitate urticarial. Bradykinin-kinin-kallikrein system in association with ACE2 receptors and drugs can be the other possible triggers. Microscopically, urticarial lesions show perivascular infiltrate of lymphocytes, some eosinophils and upper dermal edema whereas lesions of urticarial vasculitis exhibit erythrocyte extravasation and neutrophilic perivascular inflammation with prominent karyorrhexis, endothelial swelling, and fibrin deposition.
**Vesicular lesions**

Vesicular lesions occur in 4% to 15% of patients. Pruritic maculopapular (morbilliform, measles-like) lesions are the most prevalent cutaneous manifestations seen in 5% to 70% of COVID-19 patients. Usually middle-aged or elderly patients are affected than young adults. Eruption is characterized by erythematous macules, small papules or large plaques (Figure 5). Lesions can be perifollicular and scaly. Larger lesions may mimic pityriasis rosea. Rash is usually diffuse located on the trunk mainly and may show a centrifugal spread to limbs and face.

Frequently, the eruption occurs simultaneously but may follow the systemic symptoms of COVID. Mean duration of the rash varies from 8.6 to 11.6 days. One study suggested that maculopapular rashes are associated with greater severity of COVID-19 infections; this was supported by a 2% mortality rate reported in patients with these lesions. These lesions can result from viremia, adverse drug reactions, cytokine storm or combination of more than one mechanisms. Histopathological findings depend on the time of onset; early lesions show epidermal spongiosis and dermal perivascular lymphohistiocytic infiltrate with eosinophils. Lesions heal without any postinflammatory sequelae.

Vesicular lesions occur in 4% to 15% of patients. Vesicular lesions, occasionally hemorrhagic, papular, crusted typically appear in middle-aged patients but children are less frequently affected, as well. They can be polymorphic (varicella-like) or monomorphic, scattered or diffuse and usually are located on trunk (Figure 4) and extremities. Mild itching is commonly seen. Lesions appear after median latency of 3 days of disease and the time of onset of cutaneous eruption coincides with the early systemic symptoms, but occasionally can follow or precede COVID-19 symptoms. The rash disappears after 8-10 days. Vesicular lesions are associated with intermediate severity of COVID-19. Histopathological examination shows intraepidermal cleft, mild acantholysis and ballooning degeneration, multinucleate, hyperchromatic keratinocytes and dyskeratotic cells and vacuolar degeneration of the basal layer. Vesicular eruption results from overactivity of immune system, or a direct cytopathic effect of virus on endothelial cells. Some authors advise PCR for herpes viruses and parvovirus. Vesicular lesions have been described as “specific cutaneous manifestations” of COVID-19.

**Maculopapular/morbilliform lesions**

![Figure 4](image1.png) Diffuse monomorphic papulovesicular eruption on 16-year-old in a PCR-conformed case of COVID-19.

![Figure 5](image2.png) Erythematous maculopapular (morbilliform) eruption in confirmed case of COVID-19.[12]
Multisystem inflammatory syndrome in children

Severe multisystemic condition has been observed in children suffering from COVID in US (named as multisystem inflammatory syndrome in children [MIS-C]) and Europe (pediatric inflammatory multi-system syndrome [PIMS]) in various countries.\(^\text{17,18}\) MIS-C shows overlapping features of Kawasaki disease and toxic shock syndrome. About 50% of patients show complete criteria of Kawasaki disease whereas an incomplete form of the disease is seen in the rest. Mucocutaneous manifestations included nonpurulent conjunctivitis, polymorphic rash, perineal or face desquamation, and erythema and induration of hands and feet.

As compared to Kawasaki disease, there is predominance of older children and adolescents, gastrointestinal and cardiac involvement. PCR for SARS-CoV-2 was positive in only 20-38% of patients, and positive IgG serology in 80-90%.\(^\text{17}\)

Petechiae/ purpura lesions

Petechiae, nonblanching erythematous spots 2mm or more in diameter, are relatively less common cutaneous manifestations of COVID-19 seen in around 3% of patients.\(^\text{12}\) Lesions can be macular or palpable are located on distal extremities or other areas of body (Figure 6).

Rash can precede or follow COVID-19 symptoms and associated with severe infection.\(^\text{13,14}\) Histopathological examination in retiform purpura showed significant interstitial and perivascular neutrophilia along with prominent leukocytoclasia. Some lesions showed pauci-inflammatory thrombogenic vasculopathy.\(^\text{9,10}\) COVID-19 patients with petechial rash may be misdiagnosed as dengue fever.\(^\text{13}\)

Livedoid eruption lesions

Livedo reticularis is characterized by a reticular (net-like) pattern of reddish-blue to purple mottled discolorations, with occasional areas of necrosis (Figure 7).\(^\text{11-13}\)

Livedoid eruption appears to be one of the least common cutaneous manifestations of COVID-19 infection. It was noticed in only 6% of patients.\(^\text{11-13}\) Trunk, flexor surface of forearms, dorsal hand, and dorsal foot are usual affected sites. Cutaneous eruption occurs concurrently with other Covid-19 symptoms and represents more severe systemic infections. The average duration of this eruption is 9.4 days.\(^\text{13}\) Livedo reticularis is attributed to hypercoaguable state and disseminated intravascular secondary to Covid-19-induced inflammatory cytokine storm. Laboratory investigations may reveal high D-dimer and fibrin degradation product levels, and prolonged prothrombin time.\(^\text{12}\)

Less frequent conditions

Distal ischemia leading to finger and toe cyanosis, red and purple papules, skin bullae and
Skin problems related to personal protective equipment and personal hygiene measures

Prolonged use of personal protective equipment (PPE) can give rise to a number of dermatologic manifestations. Nasal bridge, cheeks, forehead, and hands are the usual sites. Hyperhydration effect, friction, pressure, epidermal barrier breakdown, and contact reactions due to PPE give rise to burning, itching, and stinging, erythema, papules, maceration, and scaling. Similarly, an existing dermatosis like seborrheic dermatitis, contact dermatitis, urticaria, folliculitis, may get aggravated.

Occlusion and a hyperhydration subsequent to use of protective gloves clinically may manifest as maceration and erosions and contact dermatitis. Similarly, frequent hand washing with detergents/disinfectants can impair barrier function of the skin and may manifest as contact dermatitis.

Cutaneous manifestations due to treatment

Several drug regimens e.g. hydroxychloroquine, azithromycin, antivirals, IL-6 inhibitor, dexamethasone etc. have been used for treatment of COVID-19 patients, which can result in cutaneous drug eruptions (Table 3), precipitation of a new dermatosis or aggravation and flare of a preexisting cutaneous disorder.

Conclusion

Multiorgan involvement can occur in COVID-19, with diverse cutaneous manifestations among children. Common dermatologic findings may include morbilliform eruption, urticaria, vesicular rash, petechia, purpura, chilblains and livedo reticularis. During clinical practice, diagnosis of these eruptions may help to identify potential COVID-19 pediatric patients, start early treatment and prevent dreadful
complications.

References