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COVID-19: Important Updates and Developments
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Cutaneous manifestations of COVID-19 in children (and adults): A virus that does not discriminate

Michael Joseph Lavery, MB, BCh, BAO, MRCP (UK) [a,c,*], **Charles Alexis Bouvier, MB, BCh, BAO, MRCPCH** [b], **Ben Thompson, MBChB, MRCPCH (Dermatology)** [a,c]

[a] *Department of Dermatology, Liverpool University Hospitals NHS Foundation Trust, Liverpool, United Kingdom*
[b] *Department of Pediatrics, Royal London Hospital, Barts Health NHS Trust, London, United Kingdom*
[c] *Department of Dermatology, Alder Hey Children's Hospital NHS Foundation Trust, Liverpool, United Kingdom*

Abstract Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a beta coronavirus with a characteristic S-glycoprotein spike on the cell surface. Initial reports did not include cutaneous manifestations as a feature of COVID-19; however, there is a growing repertoire of reports demonstrating an array of dermatologic manifestations on the skin in children and adults. Dermatologic afflictions have been summarized into different categories several times, with the most recent analysis identifying six clinical patterns: urticaria, maculopapular-morbilliform eruption, papulovesicular exanthem, chilblain-like acral pattern, livedo reticularis-livedo racemosa pattern, and purpuric vasculitic pattern. In children, the dermatologic features appear to occur before or concomitantly with other COVID-19 manifestations. Dermatologists play a key role in diagnosing patients with COVID-19 who may present for the first time unwittingly exhibiting early signs of COVID-19. We have reviewed the current evidence on the dermatologic impact of COVID-19 in both the adult and pediatric populations.

Pathophysiology of coronavirus disease 2019

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a beta-coronavirus of the Coronaviridae family,[1] is considered to have originated from bats at a food market in Wuhan, China; however, its main transmission since has been human to human.[2,3] Transmission is via respiratory droplets (and possibly aerosols), although there is recent evidence of fecal-oral transmission in children.[4,5] SARS-CoV-2 enters cells by attaching to angiotensin-converting enzyme-2 (ACE-2) receptors.[3,6,7] This receptor is found on numerous mucosal sites,[8,9] including the endothelium of dermal blood vessels and epithelial cells in eccrine glands, which may account for the cutaneous manifestations of coronavirus disease 2019 (COVID-19).[10,11]

Current evidence suggests that children are less likely to succumb to infection, accounting for 1% to 8% of all COVID-19 cases.[8,12,13] There is, however, an increased morbidity in infants and young children, compared with older children, as well as in children with a complex medical background.[12] Although neonatal cases have been reported, there is no sign of breast milk transmission,[3] but there are reports

* Corresponding author. Tel.: +44 151 282 6145.
E-mail address: michael.lavery@liverpoolft.nhs.uk (M.J. Lavery).

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Table 1 Cutaneous manifestations of COVID-19 in both the adult and pediatric population

	Adult patients	Pediatric patients
Macules and papules	√	√
Vesicles/varicelliform-like eruption	√	√
Urticarial eruption	√	√
Acral pseudo-chilblain	√	√
Acral macules and papules	√	√
Erythema multiforme		√
Multisystem inflammatory syndrome in children		√
Half-moon nail sign	√	

of possible vertical transmission.[12] There is also an increased risk among children of the black, Asian, and minority ethnic (BAME) community in the United Kingdom and globally of both COVID-19 and the multisystem inflammatory syndrome.[14–16] The latter has been called the pediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS),[17] or multisystem inflammatory syndrome in children (MIS-C).[8]

Cutaneous manifestations in adults

Initial reports did not include cutaneous manifestations as a feature of COVID-19.[18] Subsequent publications revealed that an eruption was present, although in very small numbers. A retrospective review of more than 1,000 patients throughout China revealed that two patients had developed an eruption (0.18%).[19] A growing body of evidence has since emerged showing an array of cutaneous afflictions in adults (Table 1). In Thailand, a patient presenting with a petechial eruption and thrombocytopenia was mistakenly diagnosed as having dengue fever, with a subsequent viral swab detecting SARS-CoV-2.[20] A later report revealed a purpuric eruption in the axillae and flank bilaterally in a patient with a positive polymerase chain reaction (PCR) to SARS-CoV-2. Although the patient had been given hydroxychloroquine and lopinavir/ritonavir, a viral exanthem was felt more likely, given the rarity of drug eruptions to these medications.[21]

The first report to show cutaneous manifestations on a larger-scale was in a cohort of patients in the Lombardy region of northern Italy. Skin afflictions were noted in 20% of inpatients and described as an erythematous eruption, urticaria, or chickenpox-like vesicles, all predominantly affecting the trunk.[22] The Spanish Academy of Dermatology and Venereology published a review of 375 patients with suspected or confirmed SARS-CoV-2 who developed cutaneous eruptions. These cutaneous manifestations were divided into five presenting categories: pseudo-chilblain, other vesicular eruptions, urticarial lesions, maculopapular eruptions, and livedo or necrosis. Further analysis noted "other vesicular eruptions" as an early cutaneous sign (Fig. 1) and "pseudo-chilblains" as a late sign although the latter was associated with decreased disease severity. Livedo or necrosis was associated with increased disease severity.[23] Recently, nail changes have been identified in patients with COVID-19 manifesting as a convex half-moon shaped erythematous band at the distal margin of the lunula and coined "the red half-moon nail sign."[24,25]

Fig. 1 Vesicular eruption on the dorsal fingers in an adult female with SARS CoV-2 infection (image courtesy of Oliver Johnson MBChB; Liverpool, United Kingdom.

In the United Kingdom, researchers analyzed data from users of the COVID Symptom Study application and noted that 8.8% of 336,847 users, with a positive SARS-CoV-2 viral swab, reported a skin eruption. Similar results were noted in patients with no viral swab but one or more U.K.-government-listed COVID-19 findings (8.2%).[26] A subsequent online survey, by the same researchers, of 11,546 SARS-CoV-2-positive participants who reported having an eruption revealed that 17% had a skin eruption as the first clinical feature, with 21% of respondents who had such an eruption were without other clinical manifestations. The cutaneous signs were divided into three main categories: papular (erythemato-papular or erythemato-vesicular), urticaria, and acral lesions (chilblains).[26] Some authors have speculated that the pseudo-chilblains may be attributable to novel lifestyle changes due to COVID-19, such as decreased ac-

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tivity or walking barefoot in an unheated environment.[27,28] Despite these ideas, the constellation of papers reporting cutaneous manifestations of COVID-19 has led to calls of a skin eruption to be included in the list of clinical features suspicious of COVID-19 infection.[26]

Cutaneous manifestations in children

For reasons currently unknown, SARS-CoV-2 does not have as big an impact on children compared with adults. This appears counterintuitive, given the increased prevalence of other viral diseases in this patient population. Children with COVID-19 present in a similar fashion to adults, with pyrexia and cough the most common presenting features.[29] Gastrointestinal clinical manifestations and pharyngeal erythema may also be present. Cutaneous manifestations are similar to what is witnessed with other viral exanthems, including macular, papular, and vesicular eruptions.

A varicella-like eruption has been reported in an 8-year-old girl who presented to the clinic with a papulovesicular eruption on the trunk sparing other sites, along with a 6-day history of a cough. PCR testing was positive. Inflammatory markers were normal with only a mild thrombocytopenia noted on a routine blood panel.[30] Acral lesions have also been described in children.

In the United Kingdom, a teenage boy with a positive PCR swab presented with a skin eruption accompanied by headache and myalgia with no cough or dyspnea. Although the parents reported a subjective fever, vital signs were normal. On examination, there were tender plantar papules, macules, and petechiae on the legs and an annular patch developing a few days later. Papules were also noted in the axillae.[31]

An erythema-multiforme-like eruption has also been reported in a 12-month-old infant in Iran who presented with targetoid lesions on the trunk and extremities, along with acral erythema and pyrexia. SARS-CoV-2 PCR was positive. Subsequent clinical deterioration led to admission to the intensive care unit and improvement 5 days later.[32]

A case series from Spain has revealed four pediatric patients (11–17 years old) presenting with an erythema-multiforme-like eruption on the arms, legs, and ears, along with evidence of chilblain. Mild respiratory or gastrointestinal clinical manifestations were also reported with one patient otherwise asymptomatic. All but one had a negative PCR swab. Histopathologic analysis of the erythema-multiforme-like eruptions revealed a superficial and deep perivascular and perieccrine inflammatory infiltrate, with immunohistochemistry (IHC) demonstrating cytoplasmic granular positivity to the SARS-CoV/SARS-CoV-2 spike protein in endothelial and epithelial eccrine glands.[33]

An emerging theme from these publications is that cutaneous manifestations, alongside cough and fever, appear to be one of the early clinical features of COVID-19 in the pediatric population. This has also been noted in the adult literature, where an urticarial eruption was the first manifestation of COVID-19 in an internal medicine resident in France, with pyrexia and other clinical manifestations developing 2 days later.[34] This further exemplifies the importance of a full skin examination when evaluating patients, both pediatric and adult, with suspected COVID-19 infection. Pediatric patients presenting with cutaneous manifestations of COVID-19 may also have a false-negative PCR nasopharyngeal/oropharyngeal swab, yet are harboring COVID-19.

Table 2 Diagnostic criteria for Kawasaki disease

Fever for ≥5 days and ≥4 of the following features:	
Bilateral bulbar conjunctival injection	Nonsuppurative conjunctivitis
Oral mucosal changes	Red +/or cracked lips Red throat "Strawberry" tongue
Peripheral extremity changes	Palmar/plantar erythema (Painful) acral edema/swelling Desquamation
Cutaneous signs	Diffuse Polymorphic
Cervical lymphadenopathy	>1.5 cm diameter Often solitary/unilateral Usually anterior cervical triangle

Systemic involvement of COVID-19 in children

Another reported manifestation of COVID-19 in children is the development of the pediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS), also termed "multisystem inflammatory syndrome in children" (MIS-C). This syndrome has similarities to Kawasaki disease (KD). KD, first described by Tomisaku Kawasaki (1925-2020) in 1967,[35] is an acute vasculitis with a global incidence ranging between 8 and 67 cases per 100,000.[36] KD commonly affects children less than 5 years of age with a 1.5:1 male-to-female ratio.[37] The underlying pathophysiology is complex but postulated to be secondary to an overactive innate and adaptive immune system in genetically predisposed individuals.[8,15]

The diagnosis of KD requires the presence of fever for ≥5 days, and ≥4 "other features" (Table 2). The diagnosis of KD may also be confirmed with only three "other features" when there is evidence of cardiac involvement (eg, coronary aneurysm, myo/pericarditis, pericardial effusion).[38] Dermatologic features are common in KD and represent the majority of these other features. Manifestations include acral erythema, edema, and desquamation, along with oral mu-

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cosal pathology that includes a "strawberry tongue." A diffuse polymorphic eruption may be noted including macules, papules, micropustules, and an erythema-multiforme-like eruption, distributed on the trunk, groin, and perineal sites.[39]

A pustular eruption in febrile children can be mistaken for other pathologies, such as acute generalized exanthematous pustulosis or pustular psoriasis.[40] The eruption appears early in the illness and may last days to weeks. Nail changes, reported in patients with COVID-19, include transverse erythematous bands and Beau's lines.[41] In addition, transverse red bands have been reported in KD occurring on the mid-distal portion of the nail plate during the active inflammatory phase of the disease.[41] Although the pathogenesis of these red lines is unclear, nail bed hyperemia or localized vasculitis has been hypothesized. It is plausible that the transverse erythronychia at the mid-distal nail plate may be observed in children presenting with KD in the context of COVID-19. The pathophysiologic process may be similar to the observed half-moon sign, and it is plausible that these two nail findings could occur in tandem.

Although the features of MIS-C are similar to those observed in KD, the two conditions are considered two distinct entities, with less than 25% of patients with MIS-C fulfilling the diagnostic criteria for KD.[42] Although cutaneous manifestations are an important diagnostic criteria for KD, just over half of patients report an eruption as part of their clinical presentation in MIS-C.[42]

Multiorgan involvement can occur in pediatric patients with COVID-19 (Table 3). The pulmonary system is the most commonly affected organ in COVID-19. Children may suffer from pneumonia, which can progress to acute respiratory distress syndrome (ARDS).[6] Other organ systems involved include cardiac, renal, hematologic, neurologic, ophthalmologic, and the gastrointestinal tract (Table 3). The World Health Organization (WHO) does not include respiratory clinical manifestations or signs within their case definition for the MIS-C, instead focusing on signs of septic shock along with dermatologic, cardiac, hematologic, and gastrointestinal features.[43] Similarly, the U.K. Royal College of Pediatrics and Child Health (RCPCH) case definition for PIMS-TS includes single or multiorgan dysfunction, substituting renal and neurologic presentations with dermatologic and hematologic disorders.[17] The Centers for Disease Control and Prevention (CDC) case definition includes all of the above organ involvements.[44] Despite these disparities, the WHO, CDC, and RCPCH case definition for MIS-C all include children with features suggestive of KD, with which it bears similarities.

Table 3 Systemic organ involvement in children with COVID-19 and MIS-C

Cardiac	Raised troponin/BNP Myocarditis/pericarditis Valvulitis Pericardial effusion Coronary artery dilation/aneurysm Shock (requiring inotropic support)
Respiratory	Pneumonia ARDS Pleural effusion
Gastrointestinal	Diarrhea ± vomiting Abdominal pain Transaminitis Ascites Hepatosplenomegaly Colitis/ileitis
Dermatologic	Kawasaki-like eruption
Neurologic	Encephalopathy Seizures Stroke Brain imaging sequelae
Ophthalmologic	Conjunctival injection Nonsuppurative/nonpurulent conjunctivitis
Renal	Acute kidney injury Proteinuria ± hematuria
Hematologic	Coagulopathy (including thrombosis) Leukocytosis Raised inflammatory markers (eg, ferritin)

ARDS, acute respiratory distress syndrome; BNP, brain natriuretic peptide; MIS-C, multisystem inflammatory syndrome in children.

Histopathologic findings of COVID-19

Patients presenting with clinical manifestations of COVID-19 undergo investigation with a routine blood panel along with a nasopharyngeal and oropharyngeal swab for PCR testing to SARS-CoV-2. Serum antibody testing to SARS-CoV-2 immunoglobulin G (IgG) is performed several weeks after presentation of clinical manifestations. False negatives have been reported due to low-test sensitivity, and novel investigational methods have been sought.[45] This was exemplified in an 81-year-old woman in Switzerland who presented with fever and an acral eruption, along with a generalized macular and vasculitic-like eruption. Although COVID-19 was clinically suspected, the SARS-CoV-2 PCR swab was negative. A skin biopsy was performed revealing a lichenoid interface dermatitis along with a scant perivascular lymphohistiocytic infiltrate. PCR testing of the skin tissue detected SARS-CoV-2, although at low levels. A serology antibody test, performed 6 weeks later, was negative.[46]

The histopathologic, immunohistochemical (IHC), and electron microscopic analyses have been performed in a cohort of seven pediatric patients presenting with features of chilblain and COVID-19 clinical manifestations and having negative SARS-CoV-2 PCR nasopharyngeal and oropharyngeal swabs.[47] All patients showed the presence of the SARS-CoV-2 protein, which was present in the endothelial cells of capillaries or the epithelial cells of the eccrine ducts.

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This correlates with the presence of the ACE-2 receptor in the vascular endothelium and eccrine glands.[10,11] Common histopathologic features observed included an interface dermatitis with lymphocytic exocytosis, a superficial and deep dermal perivascular lymphocytic inflammation with lymphocytic vasculitis, and a perieccrine lymphocytic infiltrate. A lobular panniculitis was also noted in all samples that included representation of the subcutaneous fat in the biopsy specimen. On IHC there was a predominance of CD4 T-helper lymphocytes over CD8 cytotoxic T-lymphocytes, with CD61 positivity on IHC highlighting intravascular platelet thrombi in four cases.

Conclusions

The COVID-19 pandemic has placed unprecedented burdens on the economy and health care services. It has also had a detrimental effect increasing morbidity and mortality through systemic organ involvement. Although the cutaneous manifestations were not initially reported, a dearth of data has shown that the largest organ in the body may yield clues for the diagnosis as well as provide useful clinical information on disease severity. Although children are less commonly affected, skin manifestations can still occur in this population, including macules, papules, vesicles, erythema multiforme, and chilblain. Patients may be otherwise asymptomatic and the cutaneous features may be the first sign of infection, with some reports of subsequent clinical deterioration. False-negative SARS-CoV-2 PCR tests may also be misleading and prompt inappropriate investigations and premature cessation of strict infection control procedures. Physicians should remain cognizant when reviewing pediatric (and adult) patients, who may present for the first time in the dermatology office or emergency room with COVID-19 manifesting as an eruption.

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Conflict of interest

The authors declare no conflict of interest.

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