

Review

Cutaneous manifestations in children with SARS-CoV-2 infection and/or COVID-19: what do we know after 10 months under this pandemic?Hongxin Li¹, MD,  Yong Zhao², PhD and Lin Zhou³,

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Introduction

Coronavirus disease 2019 (COVID-19) has become a global pandemic crisis that causes severe respiratory tract infection. As of October 6, more than 36 million confirmed patients have been reported across 214 countries and territories resulting in more than 1 million deaths. With significantly increased morbidity, transmission route, pathogenesis, clinical manifestations, and prognosis of COVID-19 infection (CI) have attracted more and more attention.

The clinical spectrum of CI is extremely variable, ranging from asymptomatic to severe pneumonia and multiple organ failures.¹ Common symptoms include fever, dry cough, sore throat, headache, fatigue, abdominal pain, nausea, vomiting, anosmia, myalgia, dyspnea, acute respiratory distress syndrome (ARDS), sputum production, hemoptysis, and diarrhea.^{2,3} COVID-19 could be transmitted by asymptomatic and

Abstract

Background Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global crisis. However, cutaneous manifestations in children with SARS-CoV-2 infection have received little attention.

Objective Our study was aimed to present clinical and cutaneous manifestations of children with SARS-CoV-2 and to provide the basis for early diagnosis.

Methods We analyzed the clinical data of COVID-19 infected (CI) children worldwide from December 2019 to October 6, 2020, by using search terms "COVID-19," "SARS-CoV-2," "Coronavirus" in combination with "cutaneous," "lesion," "rash," "skin," "dermatology," "epidermis," "dermis," "multisystem inflammatory syndrome." We collected and analyzed the general information, clinical symptoms, cutaneous manifestations, laboratory examination results, history of close contact with CI patients or suspected CI patients, and outcome in CI children.

Results Among 90 CI children, there were 46 boys (59%) and 32 girls (41%). Erythema was the most frequent lesion, followed by conjunctivitis, and edematous lesions. Face was the most commonly affected location including lips, conjunctivae, tongue, eyes, and eyelids. Sixty-three (73.3%) patients had multisystem inflammatory syndrome (MIS-C). As for clinical symptoms, 70 (81.4%) CI children suffered fever, and 34 (39.5%) patients had lung involvement. Meanwhile, 65.1% of patients had cardiac involvement, 4.7% of patients were asymptomatic, and 71.6% of patients received intravenous immunoglobulin, as well as 31.1% of CI children received systemic corticosteroids. Three children were dead. The most frequent route of infection was familial clustering. As silent virus carriers of CI children, it is important to find out the clinical and cutaneous manifestations in CI children to prevent and control COVID-19 transmission.

presymptomatic carriers.⁴ Presymptomatic transmission is considered to be very important in COVID-19 transmission, with a rate of 48–62% in presymptomatic patients.⁵

COVID-19 causes multisystemic infection including the skin. The prevalence of cutaneous lesions with CI ranged from 0.2% to 20.4% in different countries.^{6,7} Cutaneous manifestations are variable. Marzano divided the reported cutaneous lesions into six main clinical patterns: urticarial rash, confluent erythematous-maculopapular-morbilloform rash, papulovesicular exanthem, chilblain-like acral pattern, livedo reticularis-livedo racemosa-like pattern, and purpuric "vasculitic" pattern.⁸ Right now, cutaneous manifestations get more and more attention from dermatologists. Chilblain-like lesion was strongly associated with CI, especially in asymptomatic pediatric patients.⁹ Maculopapular eruptions, urticaria, or acral vasculopathic rashes (pseudo-chilblains, pernio-like lesions) considered as "COVID toe" are the most frequently

mucocutaneous manifestations of CI.¹⁰ COVID toes are very common in children as well as in adults in the range of 80-90 years old.¹¹ Chilblain-like lesion, ischemic lesion, and ecchymotic acral lesion could be found in asymptomatic or mildly symptomatic patients because of the coagulation disorder or hypersensitivity reaction, probably.¹² Rash occurred before other symptoms was in 77.9% CI patients.¹³

Pediatric population is less likely to be affected by COVID-19 than adults. There were less than 3% of reported cases in patients under 20 years.¹⁴ In USA, patients under 18 years old had made up 1.7% of the whole cases, of which was 2% in UK. Many CI children were from familial clusters identified through tracing adult cases.¹⁵

However, their clinical manifestations were quite different from that of the adults. CI children are usually asymptomatic, or even paucisymptomatic, and with a better prognosis. Dong presented 728 CI children patients' cases and found that more than 90% of patients were asymptomatic, mild, or moderate cases.¹⁶ They are milder symptomatic than adults which means they are silent carriers. Asymptomatic CI children and adolescents are difficult to identify, thus are threats to the health of communities.¹⁷ It is important to identify specific patterns of CI cutaneous manifestations associated with lesions in CI children.

In our study, we analyzed worldwide reports of epidemiological and cutaneous manifestations in CI children between December 2019 and October 2020 to explore if CI children had especially cutaneous and histopathological manifestations.

Materials and methods

We analyzed studies published in the PubMed database and in Chinese medical journal search engines such as Wanfang Data (<http://www.wanfangdata.com.cn/>), Science China (<http://www.cnki.net/>) from December 2019 to October 6, 2020. Search MeSH terms "COVID-19," "SARS-Coronavirus-2," and "Coronavirus" were used in combination with "cutaneous," "lesion," "rash," "skin," "dermatology," "epidermis," and "dermis." Studies written in Chinese and in English on cutaneous manifestations of CI children were included. Studies that did not contain cutaneous manifestations with CI, did not include children's information, or were not written in English/Chinese were all excluded.

Gender, age, the onset of symptoms, clinical manifestations, comorbidities, cutaneous symptoms, type and location of rash, confirmed tests of CI (swabs, PCR, IgM, IgG), treatments, outcome, region, and previous history (allergy history, drugs intake, autoimmune-related diseases history) were analyzed. Children with autoimmune-related diseases, drug eruptions, or with the same eruptions history were excluded.

Results

Five-hundred ninety articles were evaluated. Fifty-seven studies including 90 children with confirmed CI from December 2019 to

October 6, 2020, were included in our study. CI children were confirmed with swabs, COVID-19 antibodies, COVID-19 virus PCR, or radiologic diagnosis, biopsy. Thirteen countries and regions including American, Italy, Spain, China, UK, Switzerland, Turkey, France, Iran, India, Russia, Morocco, and Israel, have reported cutaneous manifestations of CI children.

Clinical features of CI children are shown in Table 1. The median age was 9.01 years (ranged from 0.17 to 19). Forty-six patients were male, and 32 patients were female. Thirty patients presented lesions after other symptoms ranged from 1 day to 28 days. The median latency time from systemic symptoms to exanthema was 4.09 days (range, -17 to 28 days). Erythema was the most common lesion, which was in 62.1% of patients, followed by conjunctivitis in 59.8% of patients.

Sixty-three (73.3%) CI children presented with MIS-C. Kawasaki-like syndrome was found in 21 (33.3%) MIS-C patients, 10 of whom were with incomplete Kawasaki disease. Fever was reported in 70 patients. Thirty-four patients had lung involvement including pneumonia and abnormal chest radiological examinations. Fifty-nine patients had gastrointestinal symptoms, including diarrhea, abdominal pain, distended abdomen, vomiting, or abnormal abdominal radiologic examinations. A high level of the liver enzyme was reported in 19 patients. Cardiac involvement including pericardial effusions, myocarditis, aneurysms, abnormal ECG, elevated CK, and troponin were reported in 56 patients. High levels of cardiac troponin and B-type natriuretic peptide were found in 35 and 34 patients, respectively. Renal injury was found in 17 patients. Anemia was found in 15 patients. D-dimer level was increased in 32 patients.

Acral lesions were discovered in 43 patients. Face was the most commonly affected location, including lips, eyes, eyelids, conjunctiva, and tongue. Itching was reported in eight patients. Four patients were asymptomatic except for lesions, and three patients underwent skin "biopsy." Fifty-three patients were treated with intravenous immune globulin (IVIG), 23 patients received systemic corticosteroids, and 39 patients received antibiotic treatments, including ceftriaxone, ceftaroline, cefepime, clindamycin, cefotaxime, azithromycin, amoxicillin, and vancomycin. Tocilizumab and anakinra were prescribed in 10 and four patients, respectively. Twenty patients with MIS-C were admitted to the intensive care unit. The frequent rash in patients with MIS-C were edematous palms and feet, conjunctivitis, dry cracked lips, and oral mucosal changes. Rash improved or disappeared in 8.93 days and ranged from 2 days to 16 days. Death occurred in three patients (Table 2).

Discussion

COVID-19 is a novel coronavirus that has spread fast all around the world, becoming a pandemic crisis. SARS-CoV-2 shares most of its gene identical with SARS-CoV, including S glycoprotein, RNA-dependent RNA polymerase, papain-like protease,

Table 1 Clinical symptoms and treatments during Coronavirus disease 2019 (COVID-19) until October 6, 2020, in children

	Number	Percent
Age (84)		
0-5	21	25
6-12	41	48.8
13-19	22	26.2
Gender (78)		
Male	46	59
Female	32	41
Other clinical syndromes (86)		
Fever	70	81.4
Cough	12	14
Headache	8	9.3
Nasal obstruction/congestion/ coryza/rhinorrhea/runny nose	5	5.8
Fatigue/weak	9	10.5
Myalgia	4	4.7
Chest pain	5	5.8
Nausea/vomiting/diarrhea/ abdominal pain	3/29/30/35	3.5/33.7/34.9/40.7
Lung involvement	34	39.5
Cardiac involvement	56	65.1
Kidney involvement	20	23.3
Nervous system involvement	1	1.2
Gastrointestinal involvement	59	68.6
MIS-C	63	73.3
Asymptomatic	4	4.7
Treatments (74)		
Hydroxychloroquine	3	4.1
Antibiotics	39	52.7
Lopinavir/ritonavir	2	2.7
Heparin/aspirin	1/27	1.4/36.5
Topical corticosteroids	2	2.7
Systemic corticosteroids	23	31.1
IVIG	53	71.6
Outcome (75)		
Recurrence	1	1.3
Resolved/disappeared/ subsided/recovered/regressed	40	53.3
Improved/remit	14	18.7
Alive	17	22.7
Death	3	4

and 3C-like protease.¹ Nearly 40-50% of CI patients exhibited an antibody response to SARS-CoV-2 infection after 7 days and mostly by 14 days.¹⁸

Angiotension-converting enzyme 2 (ACE2), mediated by RBD of S glycoprotein, has been confirmed as an important functional receptor of SARS-CoV-2 which is the entry of coronavirus into target cells.^{19,20} As the largest organ, skin plays a defensive and immune role. Skin can protect us from infection, such as bacteria, fungi, and viruses. Cutaneous manifestations of CI were up to 20.4%.⁷ Xue found high expression of ACE2 in keratinocytes, especially in differentiating keratinocytes and basal cells.²¹

Table 2 Cutaneous manifestations during Coronavirus disease 2019 (COVID-19) until September 8, 2020, in children

	Number	Percent
Cutaneous manifestations (87)		
Urticarial	3	3.4
Papulovesicular	2	2.3
Erythematous papules/plaques/macules/maculopapule	54	62.1
Edematous	25	28.7
Petechiae	6	6.9
Chilblain-like/perniosis-like/purpuric	5	5.7
Ulcer	3	3.4
Conjunctivitis	52	59.8
Cracked lips	22	25.3
Desquamation	5	5.7
Rash and symptom sequence (38)		
Before other symptoms	3	7.9
The same time as other symptoms	5	13.2
After other symptoms	30	78.9
Locations (86)		
Trunk	17	19.8
Extremities	28	32.6
Palms/finger/hands	33	38.4
Toes/soles/feet/heels	29	33.7
Face/lips/eyelids/conjunctivitis/eyes/tongue	62	72.1
Whole body/diffuse	3	3.5
Skin lesion sensations (11)		
Itching	8	72.7
Pain	5	45.5
Pain and itching	2	18.2

Calculated over 84 patients with known onset age.

Calculated over 78 patients with known gender.

Calculated over 86 patients with known location of lesions.

Calculated over 75 patients with known treatments.

Calculated over 75 patients with known outcomes.

The diagnosis of COVID-19 is based on clinical symptoms, vital parameters, radiological, laboratory findings, or histopathology examination. Isolation of virus is critical for CI, through nasopharyngeal and oropharyngeal swabs.²²

In viral infection, exanthems usually occur as an immune hypersensitivity response to viral DNA or RNA.²³ Coronavirus infections may own the same origin as the other virus lesions.²⁴ In our previous study, the most common lesion was erythema, followed by urticarial lesions in CI patients.¹³ Erythema was observed in 44.18% of patients, which was the most common skin lesion and located on patients' trunk, extremities, flexural regions, face, and mucous membranes by Qing.²⁵ In our study, lesions including erythema, urticarial lesions, petechiae, chilblain-like, and ulcer were displayed in CI children. We found the most frequent lesion was erythematous lesion in nearly 62.1% of CI patients, followed by conjunctivitis in 59.8%, and edematous lesions in 28.7%.

However, some children patients exhibited similar lesions with CI children, with a history of contact with CI patients or

suspected CI patients whose CI tests were negative. In a PCR-negative COVID-19 chilblain-like patient, SARS-CoV-2 spike protein was shown depositing in the cytoplasm of cutaneous dermal vessels and eccrine cells. The negative test might be a swift response from the innate immune system or to an antibody response different from that of patients without this cutaneous presentation,²⁶ or because of the lower sensitivity of PCR for COVID-19 in mild cases or low viral load.²⁷ Locatelli presented a 10-year-old patient with a long-lasting chilblain-like lesion who went to the hospital and tested positive for COVID-19.²⁸ We suggest that suspected patients with negative initial test should be followed up for a long time, and pathological examination should be performed if necessary.

CI in children is commonly mild, possibly because of young age and lack of additional pathologies.²⁹ In our previous study, the trunk was the most affected location in CI patients.¹³ In CI children, the face was the most affected location, including lips, eyelids, conjunctivitis, eyes, and tongue. Interestingly, we found only 9% of CI adult patients with facial lesions. COVID-19 toes presented microthrombotic presentations, which meant patients were in good health condition in CI children and adolescents. Vesicular and perniosis-like lesions were related to milder diseases. Cutaneous mottling in infants and chilblain-like lesions were associated with a good prognosis. Limb ischemia was linked to a poor prognosis. Livedo-like and necrotic lesions were associated with severe diseases.³⁰ Seventy-eight percent of CI patients with pernio-like lesions were outpatient only, while 8.7% of hospitalized adult CI patients with pernio-like lesions died.³¹ A series of purpuric and petechial lesions were linked with CI, typically in adult patients, which could be associated with a burning feeling.³²

Chilblain-like lesions were investigated in CI negative children and young adults during COVID-19 by Anna and Neri, analyzing risk factors: physical (cold, wet extremities, low BMI), cold and wet indoor and outdoor environment, behaviors, habits and lifestyles, and histological, immunohistochemical examinations. However, they found some chilblain-like lesions during the COVID-19 pandemic might be because of cold exposure, lifestyle changes, and lockdown measures.^{33,34}

In our study, the youngest CI child was 2 months old. Most CI children were ranged from age 6 to 12 years old. It is believed that COVID-19 is a low risk for vertical transmission. Some researchers found better neonatal outcomes and no maternal deaths when mother were infected in the third trimester of pregnancy.^{35,36} However, SARS-CoV-2 RNA was also found on the fetal side of the placenta in CI mothers, and neonates were positive for virus at birth.³⁷ Baud presented placental and amniotic membranes which tested positive for SARS-CoV-2 in a miscarriage CI woman during the second trimester.³⁸

"Kawasaki-like" syndrome was first published in April 2020 and then reported in Spain, Italy, and the USA.³⁹ On May 14, 2020, this syndrome was named "Multisystem Inflammatory Syndrome in Children (MIS-C)," which probably affected

children beyond infancy. CI children with multisystem inflammatory syndrome share many similarities with Kawasaki disease (KD),⁴⁰ presenting with persistent fever, asthenia, rash, conjunctivitis, oral mucosa changes, redness of oropharynx, hands or feet edema, cardiac involvement, gastrointestinal symptoms, symptoms of shock, and even death.⁴¹ However, MIS-C differentiates from KD,⁴¹ which has a similar clinical presentation to Kawasaki disease, toxic shock syndrome, and severe sepsis.⁴² The morbidity of MIS-C was 0.6% in CI children.⁴³ There was a 30-fold increase in Kawasaki-like disease after COVID-19 epidemics. We found many countries reported MIS-C, including USA, UK, Spain, Italy, France, Switzerland, Iran, China, Korea, and India. Cytokine storm and antibody-mediated immune system likely play an important role in MIS-C,^{44,45} especially IL-6.² Afro-Caribbean descent may have a genetic susceptibility in MIS-C. KD-like syndrome usually affects children aged 5 to 14 years. However, there were few reports on KD-like syndrome in COVID-19 patients in East Asia and Southeast Asia, which might be a genetic factor.⁴⁶

Marie found CI children who presented with severe KD-like syndrome had a high risk of poor outcome for patients more than 5 years old and had a high level of ferritin.⁴⁷ Cutaneous involvement included diffuse skin rash, rash/edema of hands and feet, redness at palms and soles, conjunctivitis, red and dry cracked lips, and cervical lymphadenopathy. Liver enzymes were abnormal in 19 CI patients. Ferritin was abnormal in 41 CI patients. In our study, 95.2% of MIS-C CI children had high levels of D-dimer, ferritin, ESR, and CRP.

Francesco considered CI might trigger a severe inflammatory syndrome after seroconversion when COVID-19 might not be found in upper airways.⁴⁸ Symptoms of these patients were more severe including more signs of cardiac involvement and macrophage activation syndrome features. Patients were older than before.⁴⁹ These patients had lower white blood cell counts, lymphocyte and platelet counts, higher ferritin level, and elevated cardiac markers.⁴⁹ In our study, MIS-C patients were all hospitalized and had pulmonary and cardiac involvement. Anti-inflammatory drugs including IVIG and steroids are commonly prescribed in MIS-C patients. In our study, 71.6% of patients received IVIG therapy and aspirin, and 31.1% of patients had systemic steroid therapy, which was similar to Elizabeth's study.⁴³ Three patients were dead. Tocilizumab as an IL-6 receptor antagonist is used in cytokine release syndrome and severe CI pneumonia. In our review, 11 patients had tocilizumab treatment. The pathophysiology of SARS-CoV-2-related Kawasaki-like MIS-C is still unknown, which may be because CI induces abundant inflammation and children with Kawasaki-like multisystem inflammatory syndrome demonstrate a storm of inflammation.⁵⁰ Respiratory, gastrointestinal, and neurological symptoms and cardiovascular involvement commonly present in MIS-C patients.⁴⁴ In our study, 68.6% of patients had diarrhea, vomiting, and abdominal pain. Acute renal injury was found in 11.9% of children.⁵¹ We also found

11.2% of adult CI patients presented nausea, vomiting, diarrhea, or abdominal discomfort.¹³

Histopathological examinations were performed on three CI patients. Cutaneous manifestations were erythematous-edematous macules, plaques, and erythema multiforme. In erythematous-edematous macules and plaque lesions, histopathological examination presented dermal papillary edema, perivascular lymphocytic infiltration, and a strong perieccrine pattern.⁵² In erythema multiforme lesions, histopathological examinations presented normal epidermis, mild vacuolar interface damage and exocytosis of lymphocytes; lymphocytic infiltration from superficial and deep perivascular and perieccrine to adipose tissue; vascular ectasia and mild features of lymphocytic vasculitis. Immunohistochemistry for SARS-CoV/SARS-CoV-2 spike protein showed granular positivity in endothelial cells and epithelial cells of eccrine glands.⁵³

CI children are silent carriers of virus, which are important for containment strategies.⁵² COVID-19 viral spike protein deposited in the cytoplasm of cutaneous dermal vessels and eccrine cells.²⁶ Children could be viral transmission promoters in the early stage, before skin involvement. Yung found CI infants contaminated (with COVID-19) the surfaces which could transmit virus to caregivers.⁵⁴ CI children increased the possibility of fecal-oral transmission through persistent shedding of COVID-19 in stools.⁵⁵

Cutaneous lesions vary at different times in the disease course and associate with different duration, severity, and prognosis.⁵⁶ In our study, 78.9% of patients had other symptoms before cutaneous lesions.

In our review, 4.7% of CI children were asymptomatic. Esther found 22% of adult CI patients with pernio-like lesions were asymptomatic. The asymptomatic or paucisymptomatic COVID-19 children may not go to the hospital or take examinations. We also found that many suspected children had negative tests. It may be because of lower sensitivity of PCR for COVID-19 in mild cases or low viral load.²⁷ In order to reduce the spread of COVID-19 virus, rashes and clinical manifestations of suspected children should also be of great concern to doctors.

Our review has many limitations. First, because of the few number of CI children, the sample size may result in bias. Second, CI had a mild influence in children. Most parents refused to take biopsy examination. We still have unclear cutaneous histopathology manifestations of CI children.

Conclusions

In summary, the contribution of children to the asymptomatic transmission of COVID-19 should be emphasized because of the impact on control measures for identification, isolation of children, and for tracing close contacts as well. Cutaneous manifestations on CI children are still concerning. Whether CI has a long-term or short-term impact on children is still unknown.

Cutaneous manifestations and pathological studies in CI children can be a useful clue to diagnose and predict disease

outcomes in CI children. We suggest more attention should be paid to asymptomatic or mild symptoms in children, who could help us with early detection of silent carriers. COVID-19 virus has mutated globally. CI rashes are of great significance for early diagnosis.

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