

THE SKIN MANIFESTATIONS OF COVID-19 IN CHILDREN (PART II)

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Erythema multiforme

Erythema multiforme (EM) is an acute, self-limited hypersensitivity condition clinically characterized by a distinctive skin eruption with symmetrical erythematous lesions called iris or target lesions.

The most common cause of EM is systemic infection (up to 90%), while drug-associated EM is reported in less than 10% of cases (54). In paediatric age, the two pathogens most frequently involved are Herpes Simplex virus (HSV) and *Mycoplasma pneumoniae*(55).

An EM-like eruption has been observed associated with SARS-CoV-2 infection, both in adults and in children (10,56) (Figure 1). A 17-year-old patient (57) presented with discrete, acral papules and targetoid lesions. Four children (3 males and 1 female) with chilblain-like lesions also had associated EM, with both true targets and targetoid lesions; one of these patients had a positive PCR for SARS-CoV-2, and skin biopsies carried out in 2 cases demonstrated endothelial positive immunohistochemistry stain to SARS-CoV-2 spike protein (20). A 6-year-old boy with acral, target lesions of EM and severe, painful cheilitis, conjunctivitis was positive on PCR (58). Other cases of EM-like lesions on the heels of both feet in children can be better regarded as chilblains with central purpuric lesions and peripheral erythema (59).

Children with EM in the setting of COVID-19 have been otherwise asymptomatic or have had mild respiratory or gastrointestinal symptoms (20).

Urticaria

Urticaria presents with usually pruritic, circumscribed, raised wheals, which characteristically last less than 24 hours. Most common causes of urticaria are

allergens, food pseudoallergens, insect envenomation, drugs and infections. Viruses are a common cause of urticarial in children (60), including parvovirus, rhinovirus, rotavirus, Epstein-Barr virus, hepatitis A, B, and C viruses, and human immunodeficiency virus, among others. Bacterial infections (urinary tract infections, Streptococcus, Mycoplasma, Helicobacter pylori) and some parasites can also be associated with urticaria.

Urticaria represents about 10-20 % of the cutaneous manifestations in patients with COVID-19 (10,61-73) (Figure 2).

Most cases reported of urticaria in COVID-19 were adults and in the authors' experience, children with urticaria in the setting of COVID-19 appear mostly asymptomatic apart from the urticarial rash. Also, most patients were not tested, but had household contact with COVID-19 confirmed or suspected patients. Only a minority of patients were biopsied, all of them adults (62,63).

Viral infections may cause non-immunological urticaria by mast cell activation via complement or vasculitis as COVID-19 virus binds angiotensin-converting enzyme 2 (ACE2) receptors on blood vessels. Antibodies may therefore deposit at vascular walls with ensuing immune reaction. Thirdly, urticaria might be associated with bradykinin in the kinin-kallikrein system in conjunction with ACE2 (64).

Vesicular exanthem

There is no consensus regarding the definition of "COVID-19 vesicular rash"(74-76). The vesicular exanthem has been reported in 4% of 53 cases with dermatological symptoms and positive nasopharyngeal PCR for SARS-Cov2 in a prospective multicentre study in China and Italy (77), 9 % of confirmed or suspected COVID-19 cases with skin symptoms in Spain (10) and in 15% of suspected or confirmed cases in France (75).

Initially, the vesicular eruption reported in patients diagnosed with COVID-19 was referred to as varicella-like papulovesicular rash (77). This kind of rash may possibly be more frequent in middle-aged women (10,77) but adult males and children have also been reported. Vesicular lesions are thought to appear in early stages of COVID-19 disease, and occasionally even before the onset of other manifestations (10,78) compared to other skin manifestations occurring later (79).

The eruption is monomorphic (76) with disseminated vesicles, appearing after a median latency of 3 days after first respiratory symptoms (Figure 3) persisting for 8 days with no correlation with severity of infection (77,80-82). Vesicles predominate on the trunk, but limbs may also be affected (83) and papules, crust (83) or haemorrhagic lesions (9) are also associated. Itch is common, but usually is mild (77).

Most authors advise PCR on vesicle fluid for HSV-1 and VZV (HSV-3) to exclude herpes simplex and varicella and histology also differs (74,83-85).

The pathogenesis of the vesicular exanthema is unknown and other viruses have been simultaneously detected in some COVID-19 patients, such as HSV-1, HSV-2, HHV-6, HHV-7, VZV, parvovirus and EBV, (10,80).

Kawasaki disease-like inflammatory syndrome (Paediatric inflammatory multisystem syndrome, PIMS)

Kawasaki disease (KD) is the most common vasculitis in childhood (87) and its diagnosis is based on clinical and laboratory criteria (88,89). The role of an unspecific infection as a trigger factor including seasonal coronavirus is classically suggested (90-92).

Whereas COVID-19 affects children in a less severe way than adults (93), a temporo-spatial association between COVID-19 and a severe multisystemic condition has been observed in different countries in children (94-98). This has been named paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS) in Europe (99) and multisystem inflammatory syndrome in children (MIS-C) in the United States (100).

Around 40 articles have been published including case reports (USA and Italy) (101,102), and series (94), and two cohort studies (97).

Demographics

The mean age of patients with PIMS was higher than that usually seen in classical KD, with a mean age ranging from 7.5 (SD 3-5) (96) to 7.9 (SD3.7-16.6) years (97). In the French cohort, the proportion of patients with at least one parent originating from sub-Saharan Africa or a Caribbean island was about 57% (97). This was also highlighted in patients with hyper-inflammatory shock syndrome (88), with a high frequency of African-Americans affected by more severe COVID-19 forms (103,104). Fourteen percent had at least one parent originating from Asia (97).

Whereas overweight is a well-known risk factor for complications of COVID-19 (94), overweight was not underlined as risk factor severe and fatal forms of COVID-19 in children (105).

Clinical features

According to the American Heart Association criteria of KD (82), a complete form of KD was found in 50-52% of cases (96,97), and an incomplete form of the disease, according to the American Heart Association criteria (89) was seen in 48-50% of cases (96,97). The diagnosis of incomplete types was based on fever for >_5 days plus 2 or 3 classical criteria, considering laboratory anomalies (Table 2) and/or abnormal echocardiography (coronary aneurysms, left ventricular depression, mitral valve regurgitation, pericardial effusion) as associated additional diagnostic criteria (96).

In general however, in comparison with KD, children with PIMS display an over-representation of gastrointestinal (GI) symptoms, myocarditis and shock syndrome.

GI symptoms were found in a large proportion of patients. 60 % in the Italian cohort and 100 % in the French cohort had diarrhoea (96,97) hence, the predominance of GI symptoms could lead to diagnostic and therapeutic delay as well as unnecessary surgical interventions.

Cardiovascular symptoms including hypotension or signs of hypoperfusion were present in 50-57% of cases (96,97) and myocarditis in 76% of patients in the French series (97). Hyperinflammatory shock, showing similar features to atypical KD (KD

shock syndrome) have been recently described (94), and were also described in a French study (106).

Kawasaki disease shock syndrome is a rare syndrome affecting 1.5 to 7% of patients with KD and is characterized by myocardial dysfunction associated with decreased peripheral vascular resistance, and a severe inflammatory syndrome (high levels of IgE, CRP, and procalcitonin) (106). A higher incidence has been found in Western countries compared to Asian countries (107).

Skin and mucosal manifestations

The cutaneous manifestations at the moment appear nonspecific to the pathogenesis, being similar to those usually described in KD or in viral infections (Figure 4).

Cutaneous and mucosal manifestations are common in PIMS (95-97). A non-exudative conjunctivitis was described in 50 % of Italian patients with complete form and 30% with incomplete form (96), and in 81 % of French patients (97). A 'polymorphic' rash was seen in 50 % of Italian patients with complete form and 30 % with incomplete form (96), and in 76 % of French patients with complete form, and 20 % with incomplete form (97). A perineal or face desquamation was observed in 19 % of French patients (97). Finally, hand and feet anomalies (erythema, firm induration or both) were described in 50% of Italian patients (96) and 48% of French patients (97). The semiology of the cutaneous lesions had no apparent specificity.

Laboratory studies

Inflammatory markers were elevated in almost all cases: CRP, ESR, neutrophil count and ferritin were elevated and pancytopenias have also been described along with other biochemical derangements (96-97). Median interleukin-6 (IL-6) level was elevated (97) and the 'cytokine-storm' has been seen (99,108,109).

Echocardiography

Sixty % of the Italian patients had abnormal heart ultrasound, showing aneurysms (20%), decreased ejection fraction (50%), mitral valve regurgitation anomalies (40%) and pericardial effusion (40%). In the French cohort, 38% of patients had coronary artery abnormalities including dilatations and increased coronary visibility, but no coronary aneurysms (97).

Evidence of SARS-CoV-2 infection

The incidence of KD in 2020 has been much higher than expected and the number of severe cases of KD has never been as high in the last 5 years (96). Other members of the coronavirus family (such as HCoV-NH, very similar to HCoV-NL63) have previously been suspected to trigger or cause KD (90-92,110-112)

In children with a diagnosis of KD during the COVID-19 pandemic RT-PCR was positive in only 20-38 % of PIMS cases (96,97), serologies were positive for IgG in 80-90 % of them (96,97). There are caveats of course with serology testing (113).

Treatment

More than 80 % of patients required admission to an intensive care unit (97) and received intravenous fluid resuscitation and/or vasoactive agents, plus systemic antibiotics (113,114).

All patients received aspirin (low or high dose) on admission and discharge, high-dose intravenous immunoglobulin infusion (2 g/kg) and over half required adjunctive steroids (methylprednisolone 2 mg/kg/day) (96,97).

Other manifestations

Several non-specific viral exanthems have however been putatively attributed to SARS-CoV-2. Vasculopathic rashes including purpuric thrombocytopenic purpura (115), Dengue-like exanthem (116,117), acro-ischemia (11) or livedoid eruptions (10,22) have been linked to COVID-19, occasionally in children as well (118, 119) (Figure 5). As in other viral exanthems, a tendency for flexural involvement has been advocated (117,120). Histological findings ranging from thrombotic vasculopathy (121) to perivascular lymphocytic infiltrate with abundant red cell extravasation and dermal edema without vascular occlusion (122) point to a paucisymptomatic inflammatory peripheral vasculopathy as the basic pathogenic mechanism.

Maculopapular exanthems have been reported in 47% of Spanish adult patients (but 78% were on one or more drug) (10) and in 14 out of 18 Italian cases (1) (Figure 6).

Pathology findings (see Part III of this series) (123,124) do not differ from other viral infections and drug eruptions. Despite thousands of patients with COVID-19 receiving therapy, available data on the prevalence of drug eruptions are lacking and only anecdotal reports suggesting such a possibility have been published to date (117,125). Similarly, pityriasis rosea-like eruptions have been widely reported (10,126), but whether this is a specific COVID-19 eruption or it is due to a reactivation of HHV6 (127) is not known (Figure 7).

Oral mucosa findings have received little attention in all age groups. In a recent study performed in a field hospital in Spain, up to 25 % of patients showed oral mucosa abnormalities, 18 % of which had macroglossia and anterior papillitis (Nuño-Gonzalez A, personal communication). A 12-year-old girl with tongue swelling and prominent papillae showing PCR positive testing has been reported (118), further supporting the potential involvement of the oral cavity in COVID-19 patients.

Some of these rashes may not be directly related to SARS-CoV-2 (128), and other etiologies of cutaneous rashes should be kept in mind (129) even in the setting of COVID-19 pandemic.

Learning points

- Lesions indistinguishable from erythema multiforme may occur in association with chilblains in children suspected of COVID-19.
- Urticaria occurs in 10-20 % of patients with COVID-19, and its incidence may be underestimated in children.
- A monomorphic vesicular or papulovesicular, disseminated exanthema has been described both in patients with PCR-proven and suspected COVID-19, mostly in adults.
- The Paediatric inflammatory multisystem syndrome (PIMS) is a rare, but most severe form of COVID-19 in children, and resembled severe Kawasaki disease (KD) with shock. It presents with skin lesions that may mimic KD
- Other forms of exanthems, whose relation with COVID-19 is unknown, have been reported during COVID-19 outbreak; these include purpuric rashes, maculopapular exanthems, pityriasis rosea-like eruptions, and oral findings, among others

Questions and answers

1. One of the following facts is true about erythema multiforme in the setting of COVID-19

- A. Lesions are mostly located on the face and trunk
- B. They sometimes appear in association with chilblains
- C. A positive PCR to SARS-CoV-2 has been reported in a majority of these cases
- D. All patients reported so far had systemic symptoms of COVID-19
- E. A severe and prolonged course has been mostly reported

Answers to question 1

- A. Incorrect. Lesions predominate on the hands, feet, elbow and knees
- B. Correct.
- C. Incorrect. Most cases are PCR-negative
- D. Incorrect. Most cases are asymptomatic or mildly symptomatic
- E. Incorrect. A benign course with good response to oral corticosteroids has been reported

2. What is the most common skin manifestation in COVID-19 patients?

- A. Chilblains
- B. Urticaria
- C. Vesicular exanthem
- D. Maculoapapular eruption
- E. Purpuric exanthem

Answers to question 2

- A. Incorrect.
- B. Incorrect.
- C. Incorrect.
- D. Correct. A maculopapular exanthem was seen in 176 (47 %) of 375 cases of COVID-19, and 122 of them were positive for PCR
- E. Incorrect.

3. One of the following skin signs is not characteristic of Paediatric inflammatory multisystem syndrome

- A. Non-exudative conjunctivitis
- B. Erythematous rash
- C. Splinter haemorrhage of the fingernails
- D. Perineal desquamation
- E. Hand erythema and induration

Answers to question 3

- A. Incorrect.
- B. Incorrect.
- C. Correct.
- D. Incorrect.
- E. Incorrect.

4. Which of the following signs is more frequent in Paediatric inflammatory multisystem syndrome than in Kawasaki disease?

- A. Prominent gastrointestinal symptoms
- B. Myocarditis
- C. Shock
- D. All of the above
- E. None of the above

Answers to question 4

- A. Incorrect.
- B. Incorrect.
- C. Incorrect.
- D. Correct.
- E. Incorrect.

5. Which of the following skin manifestations has not been reported linked to COVID-19

- A. Lichen planus
- B. Livedoid eruptions
- C. Pityriasis rosea
- D. Macroglossia
- E. Retiform purpura

Answers to question 5

- A. Correct.
- B. Incorrect.
- C. Incorrect.
- D. Incorrect.
- E. Incorrect.

Figures

Figure 1. A, B. Typical targets and targetoid lesions in COVID-19-related erythema multiforme

Figure 2. Urticaria in a child with COVID-19

Figure 3. Vesicular exanthem of COVID-19

Figure 4. A, B. Erythematous exanthem in PIMS

Figure 5. Purpuric rash in a child with suspected COVID-19

Figure 6. Maculopapular exanthema in COVID-19

Figure 7. A, B. Pityriasis rosea-like eruption in a child with suspected COVID-19

References

See complete list of references at the end of Part III