LETTER TO THE EDITOR

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Rash characteristics of paediatric patients with COVID-19 in Singapore

Dear Editor,

Children with COVID-19 infection can present with a variable spectrum of clinical manifestations, and sometimes mucocutaneous manifestations can be the only manifestation of COVID-19 infection in children.[1,2,3] We report 4 cases of paediatric patients who had COVID-19 with mucocutaneous involvement, admitted to a tertiary children's hospital in Singapore. The main objective is to describe the clinical characteristics of these patients, focusing on chilblains-like acute acral eruptions (AAE), and reactive infectious mucocutaneous eruption (RIME), with relevance to COVID-19 infection.

Case 1 was a 6-year-old Malay boy who presented acutely with painful skin lesions on his fingers with respiratory symptoms and fever. There were multiple shallow ulcers and erosions with violaceous plaques on his finger pulps (Fig. 1A). He was reviewed by the orthopaedic surgeon for initial concerns of felon progressing to septic arthritis or osteomyelitis. He was commenced on intravenous cefazolin. However, there was no clinical improvement so referral to the dermatology team was made. Blisters on his digital lesions were treated and topical cream (fusidic acid and betamethasone) was applied. Inflammatory markers were not raised. He was diagnosed to have COVID-19-related chilblains, and discharged after 4 days. There was almost full recovery of his digital lesions after another 2 weeks.

Case 2 was a previously well 10-year-old Indian boy who presented with 3 days of lower lip swelling and lip ulcers associated with mild cough and sore throat, which were complicated by poor feeding. Clinically, there were extensive erosions with crusting over the upper and lower lips, with blister formation (Fig. 1B). Coalescing ulcers were noted over the buccal mucosa, posterior pharynx and tongue. Examination by the ophthalmologist showed no keratoconjunctivitis. Results of SARS-CoV-2 polymerase chain reaction (PCR) and SARS-CoV-2 serology tests were positive. Inflammatory markers were mildly elevated (C-reactive protein 65.6mg/L, lactate dehydrogenase 326 U/L, ferritin 89.8µg/L and D-dimer 0.67mg/L). Microbiology investigations were negative for herpes simplex virus, mycoplasma and human herpesvirus 6. Antinuclear antibody was negative. He was diagnosed with RIME associated with COVID-19. He was started on intravenous fluid and analgaesia, lip treatment with mometasone cream and paraffin ointment, normal saline soaks and chlorhexidine mouthwash. He completed an empirical 5-day course of oral acyclovir, and a course of oral prednisolone (initial dose 1mg/kg/day) tapered over 12 days. He was discharged well after 1 week of inpatient hospital stay.

Case 3 was a previously well 3-year-old Chinese boy who presented acutely with fever, sore throat, hives and swelling of hands and feet. On examination, there were generalised scattered urticated papules and wheals. Both hands and feet were also slightly swollen (Fig. 1C). No other clinical features of Kawasaki disease were seen. He was diagnosed with acute urticaria related to COVID-19 infection. His symptoms improved on regular fexofenadine and he was discharged well on the second day of admission.

Case 4 was a 9-year-old Korean boy who presented with 3 days of sore throat and 5 days of itchy rash over the limbs and extremities. On examination, there were multiple urticated plaques, some with targetoid appearance, over the limbs and extremities (Fig. 1D). He was diagnosed with urticaria multiforme secondary to COVID-19 infection. He was given regular antihistamines, and topical corticosteroid twice a day with improvement.

The diagnosis of COVID-19-associated mucocutaneous manifestation in all above cases was based on morphology and distribution of the mucocutaneous lesions, temporal relationship with COVID-19 infection, clinical status of the child and laboratory confirmation by the SARS-CoV-2 PCR test. None of them had any predisposing autoimmune or vascular risk factors, drug exposure or systemic symptoms.

Compared with adults, young people demonstrate different antibody responses to SARS-CoV-2 infection and possess stronger antiviral innate and adaptive immunity (increased cytokines, interferons and T-cell response to new antigens), which likely aid in preventing serious respiratory sequelae. However, robust immune mechanisms might also contribute to alternate manifestations, including mucocutaneous eruptions.[4] Marzano et al. described 6 main clinical patterns: (1) confluent erythematous maculopapular or morbilliform rash, (2) urticarial rash, (3) papulovesicular exanthem, (4) chilblains-like acral pattern, (5) livedo reticularis and/or livedo racemosa-like pattern and (6) purpuric "vasculitic" pattern.[5] However, none of these are specific or diagnostic for the COVID-19 infection.

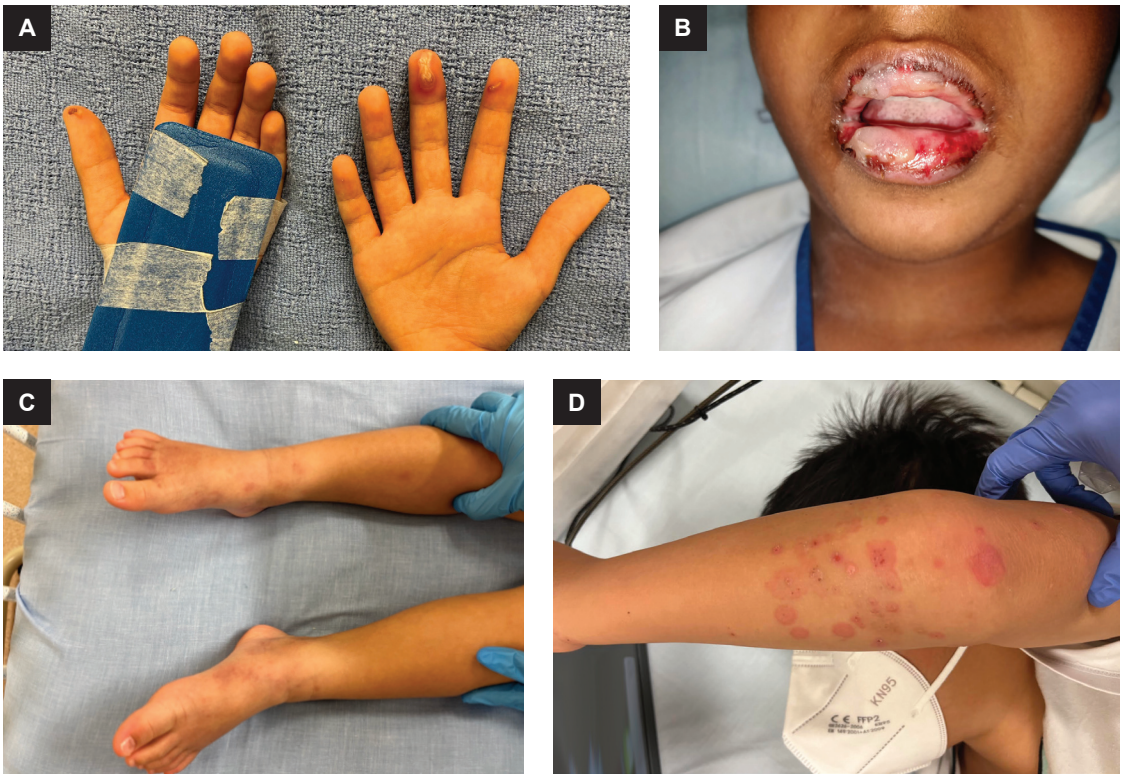


Fig. 1. (A) COVID-19-related chilblains. Multiple shallow ulcers and erosions with erythematous base and violaceous plaques were noted on finger pulps of the right second, third, fourth fingers; and left thumb. There was no lesion on his mucosal surfaces, toes or other parts of the body. (B) Reactive infectious mucocutaneous eruption in children diagnosed with COVID-19. Erosions and crusting were noted over upper and lower lips, with 1 blister over the right lower lip. There were no other rashes or eye and genital involvement. (C) Acute urticaria of hands and feet related to COVID-19 infection. He had scattered papules urticarial rashes over the extremities, thighs, trunk and back, with slightly swollen hands and feet. (D) Urticaria multiforme secondary to COVID-19 infection. He had urticated plaques, some with targetoid appearance over the elbows, hands, wrists, ankles and feet.

Traditional chilblains, also called pernio, is an inflammatory reaction of the superficial vasculature on acral surfaces (fingers, toes, nose, ears) characterised by erythrocyanotic skin lesions induced by non-freezing cold exposure. It is classified into 2 groups: idiopathic, often triggered by cool and/or damp temperatures (primary pernio); or less commonly, due to an underlying autoimmune or systemic inflammatory disease (secondary pernio).[4,7,12]

Chilblains-like AAE had gained attention during the COVID-19 pandemic. Based on observational studies across many countries,[2,3,7,12] COVID-19 chilblains (in contrast to traditional chilblains) was noted in the later course of the disease, often associated with less severe illness[1,8] in young patients having no cold exposure, pre-existing peripheral vascular disease or systemic inflammation, as observed in case 1 that occurred amid the warm and humid climate of Singapore.[2] This appearance is thought to be suggestive of acral ischaemia secondary to thrombosis in patients with severe COVID-19, which may be complicated by hypercoagulable state and often requires intensive care.[7] However, COVID-19 chilblains appear to be distinct from the ischaemic cutaneous presentations associated with severe COVID-19. It is thought that ischaemic lesions associated with severe COVID-19 may be caused by thrombotic microvascular insults induced by complement activation and a procoagulant state.[7] On the other hand, cases of multisystem inflammatory syndrome in children (MIS-C) showed greater laboratory inflammation and complications were more likely to involve the cardiac system.[4]

In COVID-19 chilblains, however, coagulation, haematological and biochemical studies; D-dimer; and autoantibodies were reportedly normal for most patients.[2,4] This is supported by findings from skin biopsies performed in a small percentage of patients with initial diagnostic dilemma involving superficial and deep lymphocytic perivascular dermal infiltration consistent with chilblains, though neither thrombosis

nor vasculitis were identified.[2,7] Thus, in the absence of symptoms and signs of secondary causes in an otherwise well child, the complete work-up of chilblains is not routinely required in suspected COVID-19 patients.[7]

Avoidance of cold, damp conditions is the cornerstone of chilblains management. Ladha et al. proposed a systematic and practical approach to COVID-19 chilblains.[7] Potent topical corticosteroids (e.g. clobetasol propionate 0.05% ointment) are often recommended, as the anti-inflammatory effect via inhibition of interferon production provides relief of the inflammatory lesions. Oral analgaesia and antihistamines also provide symptomatic relief. Gentle debridement or normal saline soaks to remove crusts can also be instituted. The second-line therapy for chilblains includes a calcium channel blocker such as oral nifedipine (0.25–0.5mg/kg/day thrice a day).[7] Additional reported treatments for chilblains include topical nitroglycerin, topical tacrolimus, oral prednisone (0.5 mg/kg once daily).[7] Our patient with chilblains-like AAE (case 1) achieved almost complete remission of his wounds within two weeks of illness. COVID-19 chilblains is mildly symptomatic, usually requiring no therapy, with excellent prognosis and full recovery.[6]

Case 2 presented with only mucosal involvement without significant cutaneous manifestation. RIME was recently proposed to replace the term, "*Mycoplasma pneumoniae* (MP)-induced rash and mucositis" to account for the fact that non-MP pathogens may also cause rash and mucositis.[9] Proposed mechanisms of pathogenesis include immune complex deposition, complement activation and molecular mimicry.[9]

To make the diagnosis of RIME, evidence of an infectious trigger is required: (1) history, clinical examination or investigations supporting a respiratory infection; (2) confirmation by ≥2 of the following criteria: non-contributory medication history, erosive mucositis affecting ≥2 sites, or vesiculobullous lesions/atypical targets affecting <10% BSA; and (3) support by prodromal symptoms and histology excluding other diagnoses.[10] Erythema multiforme has been reported in children with COVID-19, but most cases described targetoid cutaneous lesions without mucositis, similar to case 4.

Case 3 presented with acute urticaria and case 4 with urticaria multiforme, both related to COVID-19 infection. They appear morphologically different but represent the same disease spectrum, which can be caused by many other viral infections. Urticaria is commonly seen in COVID-19 infections, accounting for 10–20% of all COVID-19-related rashes. Based on previous international registry for COVID-19 dermatological manifestations, urticarial reactions typically last 4 days (interquartile range 2–10), and for a maximum of 28 days.[12] Urticarial multiforme presents with targetoid lesions, usually distributed over the thighs, knees, arms (especially around the elbows), and dorsal aspects of hands and feet. These lesions improve within 1–3 weeks with topical or oral corticosteroids, or without treatment in some cases.

In the context of COVID-19 infection with mucocutaneous involvement in children, MIS-C is a consideration and must be ruled out for the diagnosis of RIME. Screening for MIS-C based on previous case reports were unremarkable except for elevated C-reactive protein levels in some RIME cases.[11] The management of RIME is largely supportive (analgaesia, eye drops, hydration and parenteral nutrition). The role of antimicrobial agents and immunomodulatory agents including corticosteroid is unclear. In terms of prognosis, RIME is considered self-limiting with excellent prognosis.

Outcome was favorable in all our patients. No specific treatment was indicated apart from symptomatic management except for our patient with RIME (case 2) who was started on a course of oral corticosteroid in view of significant symptoms.

In conclusion, it is important for physicians to recognise self-limiting mucocutaneous involvement in children with COVID-19, and differentiate it from similar-looking severe diseases such as a thrombotic phenomenon, vasculitis or MIS-C. These lesions may become more common as the prevalence of mild infection increases with easing of safety measures and reopening of borders. Having this knowledge can prevent unnecessary investigations in otherwise well patients, and aid physicians in rendering appropriate treatment plans and counselling.

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