Table 1 *Continued*

	COVID-19 cases (*n* = 2)	Kawasaki on COVID-19 cases (*n* = 6)	MIS-C cases (*n* = 24)
Complete recovery	50%	100%	96%
Death	50%	0%	4%

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; PLT, platelets; WBC, white blood cells.

this finding is likely to have been influenced by the fact that way more cases of MIS-C were identified compared to the KD ones.

The data collected from published cases highlights a higher incidence of conjunctivitis, lymphadenopathy, and mucosal involvement in children with KD,[4,5] which is evident in our patients (Table 1).

The mechanism that leads to MIS-C is still under investigation, however many conjectures have been made: immune dysregulations and the ability of the novel coronavirus to halt interferon responses have been proposed as possible explanations for the appearance of this condition.[5]

Another matter that is still unsolved is the explanation behind the higher number of MIS-C cases seen in COVID-19 patient in Western countries compared to the ones reported in the East, given that KD is more prevalent in Asia.

The cutaneous manifestations of KD are well-known (polymorphous rash which is never vesicular that spreads from the trunk to the extremities and that disappears with fever resolution[6]), but the ones of COVID-19 and MIS-C are still being studied. Interestingly, MIS-C has been associated with nonspecific rashes, urticarial, petechial, purpuric, polymorphic, morbilliform, and maculopapular lesions, to name a few.[5] The localization of these manifestations is variable as well.[5]

Unfortunately, histopathological information regarding these lesions is not available yet because biopsies are generally not performed on children.[5]

We hope that our findings may provide further insight into the clinical and cutaneous characteristics of COVID-19 and MIS-C in children. However, we believe that further studies are needed to define the dermatological implications of COVID-19 and MIS-C as both are still being in the process of being unraveled.

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Conflict of interest

Nothing to declare.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Multisystem inflammatory syndrome in adults (MIS-A): a new addition to COVID-19 puzzle

Dear Editor,

The novel coronavirus (SARS-CoV-2) has crippled the world by its fatality and protean manifestations, of which multisystem inflammatory syndrome seems to be a relatively new trick under its sleeve. A myriad of dermatological manifestations with incompletely understood pathophysiology such as maculopapular rash, erythema multiforme-like lesions, vesicular and urticarial lesions, chilblains, livedo reticularis-like lesions have been reported in COVID-19.[1]

A 24-year-old male presented with a high-grade fever for 8 days accompanied by a subacute onset progressive holocranial headache, vomiting, malaise a day later followed by a generalized maculopapular rash, which appeared on the 5th day of fever, initially on his right arm and then gradually involved all the limbs

and trunk. Three weeks back, he had close contact with a confirmed case of COVID-19. On examination, the patient was febrile and pale with mild conjunctival congestion, suggestive of non-purulent conjunctivitis (Fig. 1; Panel a). Apart from meningism, his systemic examination was unremarkable. Dermatological examination revealed a non-pruritic, non-scaly, blanchable maculopapular rash which assumed a dusky, plaque-like morphology after 5 days. (Fig. 1; Panel b, c, d). Relevant laboratory investigations revealed normocytic, normochromic anaemia with transaminitis. Malaria, dengue, leptospirosis, scrub typhus were ruled out with supportive investigations; blood and urine culture did not reveal any growth. Reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2 was also negative. His coagulation profile was normal, and inflammatory markers were elevated. Chest, abdominal imaging, transthoracic echocardiography and brain imaging (contrast-enhanced MRI brain and MR venogram) were non-contributory. A guarded lumbar puncture revealed a mildly elevated opening pressure, lymphocytic pleocytosis and mildly elevated protein level and a negative neuroviral panel. Serum anti-SARS-CoV-2 S antibody was elevated with a value of 16 (reference range < 1.40). As per the clinical criteria of multisystem inflammatory syndrome in adults (MIS-A) formulated by the Centres for Disease Control and Prevention (CDC), the patient satisfied one primary and two secondary criteria, based on which he was diagnosed as a case of MIS-A. He was initiated on pulse intravenous methylprednisolone (1gram/day for 5 days) and relevant symptomatic management which led to dramatic improvement in his symptoms and an uneventful recovery. Multisystem inflammatory syndrome in children (MIS-C) predominantly manifesting as shock, cardiovascular abnormalities, pain abdomen with markedly elevated inflammatory markers is a relatively new entity reported worldwide in association with COVID-19. It tends to mimic Kawasaki disease as they present with polymorphic, erythematous rash, mucosal involvement in the form of conjunctivitis and mucositis, erythema and firm induration of limbs.[2] Several reports of a similar syndrome in adults with cardiovascular, gastrointestinal, dermatologic and neurologic symptoms without severe respiratory illness have concurrently received attention around the globe. These patients have either tested

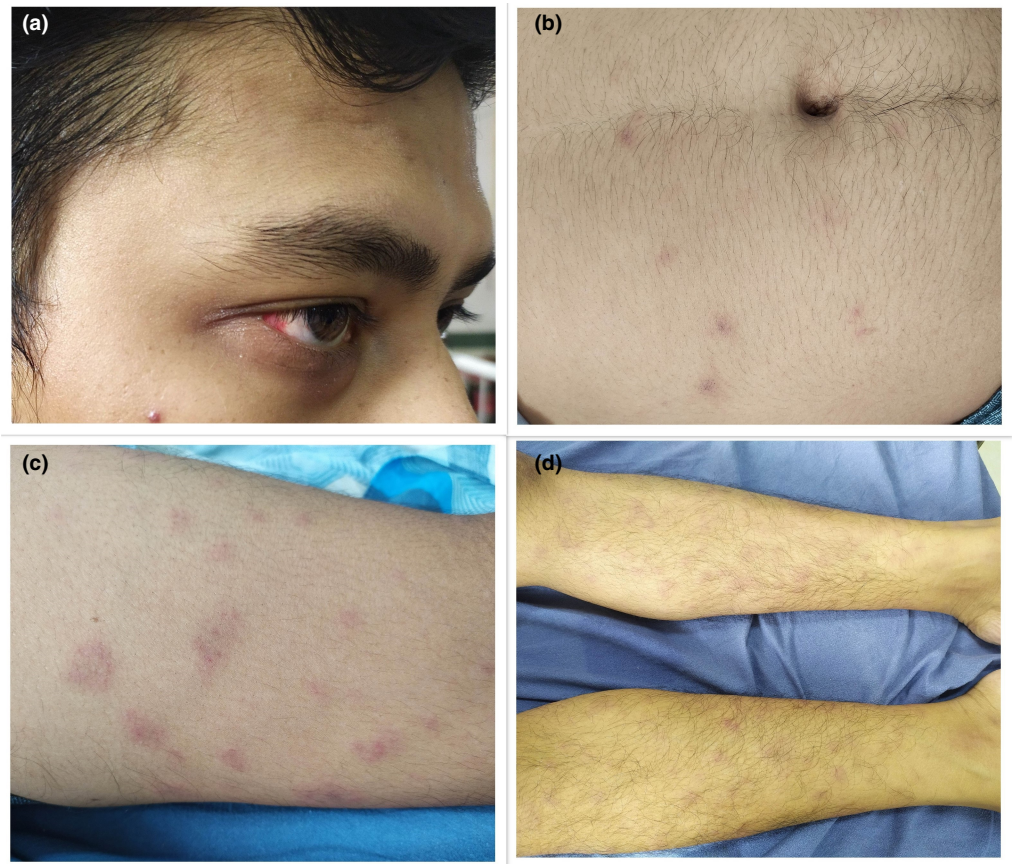

Fig. 1 Image of the patient showing conjunctival congestion suggestive of non-purulent conjunctivitis (a); non-scaly, blanchable maculopapular rash with plaque-like morphology in abdomen (b), arm (c) and both lower limbs (d).

Table 1 Case definition of MIS-A as per CDC. Source: https://www.cdc.gov/mis/mis-a/hcp.html

Case definition for MIS-A:	Clinical criteria	Laboratory evidence
A patient aged ≥21 years hospitalized for ≥24 hours or with an illness resulting in death, who meets the following clinical and laboratory criteria. The patient should not have a more likely alternative diagnosis for the illness (eg, bacterial sepsis, exacerbation of a chronic medical condition).	Subjective fever or documented fever (2':38.0 C) for 2':24 h prior to hospitalization or within the first THREE days of hospitalization* and at least THREE of the following clinical criteria occurring prior to hospitalization or within the first THREE days of hospitalization*. **Primary clinical criteria** 1. Severe cardiac illness includes myocarditis, pericarditis, coronary artery dilatation/aneurysm or new-onset right or left ventricular dysfunction (LVEF < 50%), 2nd/3rd degree A-V block or ventricular tachycardia. (Note: cardiac arrest alone does not meet this criterion) 2. Rash and non-purulent conjunctivitis **Secondary clinical criteria** 1. New-onset neurologic signs and symptoms Includes encephalopathy in a patient without prior cognitive impairment, seizures, meningeal signs or peripheral neuropathy (including Guillain-Barre syndrome) 2. Shock or hypotension not attributable to medical therapy (eg, sedation, renal replacement therapy) 3. Abdominal pain, vomiting or diarrhea 4. Thrombocytopenia (platelet count < 150 000/ microliter)	The presence of laboratory evidence of inflammation and SARS-CoV-2 infection. A. Elevated levels of at least TWO of the following: C-reactive protein, ferritin, IL-6, erythrocyte sedimentation rate, procalcitonin B. A positive SARS-CoV-2 test during the current illness by RT-PCR, serology, antigen detection

*These criteria must be met by the end of hospital day 3, where the date of hospital admission is hospital day 0.

positive for SARS-CoV-2 by polymerase chain reaction (PCR) or they had positive antibody assays indicating recent infection. Considering the heterogeneity of presenting symptoms, CDC has formulated the case definition for MIS-A (Table 1). Negative PCR and positive antibodies suggest that MIS-A/MIS-C are postinfectious entities.[3] Although multisystem inflammatory state in moderate-to-severe COVID-19 is generally accompanied by respiratory failure, there has been a paucity of respiratory symptoms, hypoxaemia or radiographic abnormalities in MIS-A.[4] The pathophysiology of MIS-A though debated includes dysregulation of immune responses, dysfunction of renin-angiotensin-aldosterone axis, endothelial injury and thromboinflammation.[5] The distribution of rash was generalized in majority of MIS-C, although only palm and sole erythema were present along with desquamation of the digits in some. Conjunctivitis and cheilitis with variable pruritic and painful rash have also been reported. Dermatological manifestations of MIS-A are grossly underreported with reports of mucositis, polymorphic rash, acral or facial swelling, erythema multiforme-like lesions, palmoplantar desquamation, erythroderma in the literature. The optimal treatment of MIS-A is unclear, although intravenous immunoglobulin, steroids and other immunomodulatory agents have been used with clinical improvement in some instances.[6] Moreover, the chronic sequelae and the long-term consequences in terms of morbidity and mortality in affected patients are yet to be understood, and better understanding of the immunopathogenesis warrants further research.

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Conflict of interest

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Data availability statement

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Genital necrosis with cutaneous thrombosis after COVID-19 mRNA vaccination

Editor

Thrombosis is a rare complication of COVID-19 vaccines that typically affects cerebral and visceral vessels.[1–4] However, skin involvement is largely unknown.[5,6] Here, we describe a case of genital necrosis associated with cutaneous thrombosis following COVID-19 vaccination.

An 84-year-old Japanese woman presented to our department with a three-day history of genital necrosis. She had received her first dose of Pfizer–BioNTech (New York, NY, USA; Mainz, Germany) BNT162b2 mRNA COVID-19 vaccine 26 days before admission. Nine days after the vaccination, she developed increasing pain in her genital region. She denied any trauma or precipitating event. Her medical history was significant for deep vein thrombosis after orthopaedic surgery, for which she had been receiving edoxaban over the past three years. She had no other risk factors for thrombosis.

On admission, she was well but febrile to 37.5°C. Dermatological examination revealed extensive necrosis with surrounding purpura that involved the mons pubis, labia majora and perineum (Fig. 1a). Laboratory investigations showed a leukocytosis (15.9×10^9/L) with a left shift. The platelet count was slightly elevated (359×10^9/L). The coagulation profile was unremarkable. Biochemical parameters were within the normal range except for an elevated C-reactive protein (11.6 mg/dL, normal <0.3 mg/dL). A thrombophilia screen—including antithrombin, protein C, protein S, lupus anticoagulant, anti-cardiolipin antibodies and anti-β-2-glycoprotein-1 antibodies—was unremarkable. Serological tests for rheumatoid factor, anti-nuclear antibody and anti-neutrophil cytoplasmic antibodies were all negative. Pelvic CT was performed to show subcutaneous fat stranding without fascial thickening. No haemorrhage or hematoma was noted. CT angiography detected no evidence of thrombosis. Skin biopsy showed epidermal necrosis, scattered neutrophils and lymphocytes in the dermis, and thrombotic occlusion of dermal vessels with mild perivascular infiltration (Fig. 1b,c). Immunohistochemistry revealed that the thrombi were positive for CD61, a platelet-specific marker (Fig. 1d,e). Based on the clinical and histopathological findings, a diagnosis of cutaneous necrosis with platelet thrombi formation and secondary infection was made. Treatment was started with ampicillin/sulbactam along with local wound care. Her fever, leukocytosis and genital pain resolved within the first week. The skin lesions also improved: more than 80% of the eschar had fallen off when she was discharged after one month of admission (Fig. 2a), and epithelization was almost completed another month later (Fig. 2b).

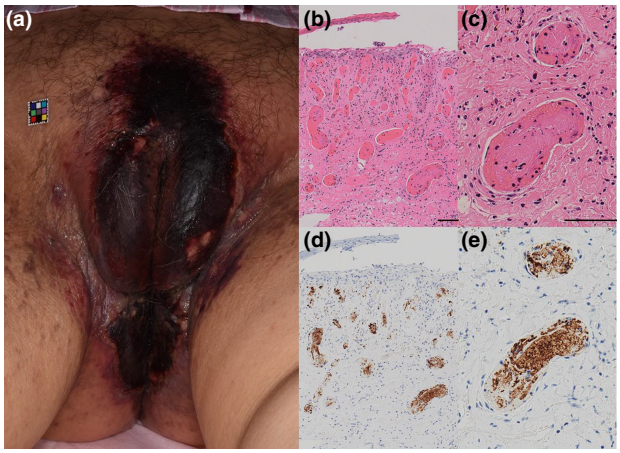

Figure 1 Skin lesions and histopathological findings at the time of admission. (a) Extensive necrosis with purpura in the genital region. (b,c) Histopathology showing epidermal necrosis and thrombotic occlusion of dermal vessels (haematoxylin-eosin stain, original magnification × 100 [b] and × 200 [c]). (d,e) Immunohistochemistry showing that the thrombi were positive for CD61 (original magnification × 100 [d] and × 200 [e]). Scale bar = 50 μm (b,c).

A small but increasing number of thrombotic events have been reported since the launch of mass vaccination campaigns against COVID-19. Adenovirus vector-based vaccines from AstraZeneca (Cambridge, UK) and Johnson & Johnson (Titusville, NJ, USA) are associated with severe thrombosis with thrombocytopenia, while mRNA-based vaccines from Pfizer–BioNTech and Moderna (Cambridge, MA, USA) are also associated with some thrombotic events, which do not always accompany thrombocytopenia.[1–4] The exact pathogenesis remains unknown, but platelet activation is thought to be a key feature underlying these events.[7] For both types of vaccines, thrombosis typically occurs in unusual locations such as cerebral and portal veins. However, only two cases of skin involvement have been reported, both of which manifested as local skin necrosis at injection sites.[5,6] To the best of our knowledge, this is

