The data collected from published cases highlights a higher incidence of conjunctivitis, lymphadenopathy, and mucosal involvement in children with KD, 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.

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), 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. The localization of these manifestations is variable as well.

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

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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The guardians of the patients in this manuscript have given informed consent to publication of their case details.

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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### References
1 Lavery MJ, Bouvier CA, Thompson B. Cutaneous manifestations of COVID-19 in children (and adults): a virus that does not discriminate. *Clin Dermatol* 2021; 39: 323–328.
2 Larenas-Linnemann D, Luna-Pech J, Navarrete-Rodríguez EM et al. Cutaneous manifestations related to COVID-19 immune dysregulation in the pediatric age group. *Curr Allergy Asthma Rep* 2021; 21: 13.
3 Khalili M, Iramanesh B, Mohammadi S, Alfatoomian M. Cutaneous and histopathological features of coronavirus disease 2019 in pediatricians: a review article. *Dermatol Ther* 2021; 34: e14554.
4 Baradaran A, Malek A, Moazzen N, Abbasi SZ. COVID-19 associated multisystem inflammatory syndrome: a systematic review and meta-analysis. *Iran J Allergy Asthma Immunol* 2020; 19: 570–588.
5 Brunmfel CM, Di Lorenzo AM, Petronic-Rosic VM. Dermatologic manifestations of COVID-19-associated multisystem inflammatory syndrome in children. *Clin Dermatol* 2021; 39: 329–333.
6 Gupta A, Singh S. Kawasaki disease for dermatologists. *Indian Dermatol Online J* 2016; 7: 461–470.

### 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. 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).
The pathophysiology of MIS-A though debated symptoms, hypoxaemia or radiographic abnormalities in state in moderate-to-severe COVID-19 is generally accompanied postinfectious entities. Although multisystem inflammatory PCR and positive antibodies suggest that MIS-A/MIS-C are standing of the immunopathogenesis warrants further research. affected patients are yet to be understood, and better under-

term consequences in terms of morbidity and mortality in

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 under-
standing of the immunopathogenesis warrants further research.

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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˚C.38.0 C) for 2˚C.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*. | 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. 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. The pathophysiology of MIS-A though debated includes dysregulation of immune responses, dysfunction of renin-angiotensin-aldosterone axis, endothelial injury and thromboinflammation. 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, palmarplanar 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. 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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Informed written consent obtained from the patient to publish the case details.

Conflict of interest
None declared.

Data availability statement
Data sharing is not applicable to this article as no new data were created or analysed in this study.

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References
1 Genovese G, Moltrasio C, Berti E, Marzano A. V: Skin Manifestations Associated with COVID-19: Current Knowledge and Future Perspectives. Dermatology 2021; 237: 1–12. https://doi.org/10.1159/000512932.
2 Akca UK, Kesici S, Ozturekci Y et al. Kawasaki-like disease in children with COVID-19. Rheumatol Int 2020; 40 (12): 2105–2115. https://doi.org/10.1007/s00296-020-04701-6
3 Godfred-Cato S, Bryant B, Leung J et al. California MIS-C Response Team. COVID-19-associated multisystem inflammatory syndrome in children—United States, March–July 2020. MMWR Morb Mortal Wky Rep 2020; 69 (32): 1074–1080. https://doi.org/10.15585/mmwr.mm6932e2
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 × 10⁹/L) with a left shift. The platelet count was slightly elevated (359 × 10⁹/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-b2–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 haematoma 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 (original magnification × 100 [d] and × 200 [e]). (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

References

4. Gupta A, Madhavan MV, Sehgal K et al. Extrapolmonary manifestations of COVID-19. Nat Med 2020; 26: 1017–1032. https://doi.org/10.1038/s41591-020-0968-3.
5. Chow EJ. The multisystem inflammatory syndrome in adults with SARS-CoV-2 infection—another piece of an expanding puzzle. JAMA Netw Open 2021; 4(5): e2110344. https://doi.org/10.1001/jamanetworkopen.2021.10344.
6. Tenforde MW, Morris SB. Multisystem inflammatory syndrome in adults: coming into focus. Chest 2021; 159: 471–472. https://doi.org/10.1016/j.chest.2020.09.097

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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).