Review article

CED
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CPD

Mucocutaneous manifestations of COVID-19-related multisystem inflammatory syndrome in adults: an update

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Abstract

Multisystem inflammatory syndrome in adults (MIS-A) is an inflammatory condition that affects multiple extrapulmonary organ systems (cardiac, gastrointestinal tract, dermatological and/or neurological), attributed to a postinfectious and atypical complication occurring weeks to months after infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The diagnosis is primarily based on findings encompassing persistent fever, elevated inflammatory markers, multiorgan involvement and a temporal relationship with COVID-19 infection. The existing literature on MIS-A, although growing, is limited to case reports and small case series. It is imperative that dermatologists be aware of this entity and aid the critical care team to ensure timely diagnosis and early therapeutic intervention. In this review, we concisely highlight the varied presentations, pathogenesis and treatment options in MIS-A.

Introduction

In March 2020, WHO declared severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced novel coronavirus 2019 (COVID-19) infection a pandemic. Over the past 2 years, healthcare providers across the globe have described a gamut of mucocutaneous manifestations that precede, appear simultaneously with or follow typical COVID-19 symptoms.[1] In June 2020, multisystem inflammatory syndrome in adults (MIS-A) received attention when the US Centers for Disease Control and Prevention (CDC) began receiving initial reports of patients presenting with delayed and multisystem involvement of the disease, with a clinical course resembling MIS in children (MIS-C). Initially, two terminologies were used: 'multisystem inflammatory syndrome in adults' (MIS-A) and adult-onset 'paediatric multisystem inflammatory syndrome' (PIMS). Over time, the former has become the preferred nomenclature.[2] This post-acute COVID-19 multisystem inflammatory syndrome has been recognized as a rare, yet severe complication of SARS-CoV-2 infection. To date, the true incidence of MIS-A is unknown, but it appears to be rare. There is a dearth of literature on the mucocutaneous manifestations of MIS-A, which prompted the current study, In this review, we attempted to succinctly summarize the current understanding of its pathomechanisms of MIS-A, briefly highlight its clinical presentation, elaborate the associated mucocutaneous manifestations and discuss treatment options.

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Search strategy

A comprehensive English literature search was conducted across the PubMed, MEDLINE, EMBASE, Google Scholar and Cochrane databases using Medical subject headings (MeSH) and non-MeSH keywords: OR 'SARS-CoV-2' AND 'MIS-A' OR 'multisystem inflammatory

syndrome' OR 'adult-onset paediatric multisystem inflammatory syndrome' OR 'kawasaki' OR 'kawasaki-like' AND 'covid-19 vaccine'. The references from all the encountered articles were further scanned to obtain relevant data. The information retrieved was reviewed and analysed.

Features of multisystem inflammatory syndrome in adults

Immunopathogenesis

Despite the rapid strides in our understanding of this virus and its implications on host immunology, the immunopathogenesis of MIS-A is not yet fully established. In adults, COVID-19 is typically characterized by hyperactivation of the inflammatory cascade. MIS usually occurs 2–6 weeks after SARS-CoV-2 infection. Elevation of inflammatory biomarkers in blood serves as an initial indication. The delay in presentation after COVID-19 infection favours the presumption of activation of the adaptive immune response.[3] The childhood equivalent, MIS-C, is attributed to a dysregulated immune response with persistent low-grade extrapulmonary infection of SARS-CoV-2 and an increase in autoreactive antibodies. Macrophage hyperactivation, autoantibody formation and antigen–antibody complex deposition are thought to be the underlying pathomechanism of MIS.[4] A study on immunological profile of patients with MIS-C identified autoantibodies that targeted endothelial, gastrointestinal and immune-cell antigens in the plasma, thereby providing a tangible explanation for the tissue-specific responses in MIS.[5] The stark similarities between the clinical presentations of Kawasaki disease (KD) and MIS-C have promoted studies comparing the immunological status of these two diseases. Similar to KD, the inflammatory response in MIS-C is autoimmune in nature, with autoantibodies to endothelial cells, immune cells and structural proteins in multiple tissues being detected. However, the two disorders can be differentiated immunologically. In KD, activation of the interleukin (IL)-17A-mediated pathway and relatively infrequent involvement of endothelial cells is observed.[6] Similar mechanistic reasoning may be extrapolated in MIS-A. With age, the host's antiviral and proinflammatory systemic responses may be adversely affected.[7] The mucocutaneous features are also thought to be autoimmune in nature.

In patients who develop MIS-A following COVID-19 vaccination, a cascade of immune reactions has been speculated to have a significant impact. In antigen-presenting cells, the innate immune pathway, involving Toll-like receptor (TLR)7 and TLR8, detects viral mRNA, resulting in activation of the descending cascade and secretion of proinflammatory cytokines and Type I interferons.[8] Notably, MIS-A has not been reported among adult participants in COVID-19 vaccine trials.[9]

Clinical presentation

According to the CDC,[10] the working case definition for a typical MIS-A presentation includes the presence of a severe illness requiring hospitalization in patients aged ≥ 21 years, positive test results (PCR, antigen or antibody), for recent SARS-CoV-2 infection severe dysfunction of ≥ 1 extrapulmonary organ systems and marked elevation acute inflammatory markers, all in the absence of severe respiratory illness to exclude the subset of the patients in whom organ dysfunction might be the result of tissue hypoxia (Table 1). Patients with MIS-A are usually young (< 40 years) but are often severely ill and require hospitalization or intensive care management; some may even succumb to the disease. A systematic review by Patel *et al.*[7] summarized the descriptive epidemiology and clinical characteristics of MIS-A, the pertinent findings of which are summarized in Table 2.

Differences between MIS-C and MIS-A. Comparison with MIS-C showed that patients with MIS-A were more likely to have documented previous COVID-19 infection, and to present with myocarditis, cardiac dysfunction, arterial thrombosis, pulmonary embolism and/or deep vein thrombosis.[11–13] By contrast, patients with MIS-C were found to be more likely to have mucocutaneous manifestations and to receive intravenous immunoglobulin as treatment. With respect to outcomes, MIS-A was associated with longer hospital stay, a higher proportion needing mechanical ventilation and a higher number of deaths (Table 3).

Mucocutaneous manifestations

The CED case definition of MIS-A does not include cutaneous features as a mandatory criterion; however, this can serve as a helpful indicator towards the diagnosis. Mucocutaneous manifestations are encountered in approximately half (46%) of patients with MIS-A, and include rash (38%), conjunctival injection (26%) and mucocutaneous lesions (16%).[7] Overlapping clinical manifestations are seen in MIS-A and MIS-C, although patients with MIS-A are more likely to have

Table 1 Case definition for multisystem inflammatory syndrome in adults.

Case definition
A patient aged ≥ 21 years hospitalized for ≥ 24 h 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 (e.g. bacterial sepsis, exacerbation of a chronic medical condition)
Clinical criteria
Subjective fever or documented fever (≥ 38.0 °C) for ≥ 24 h prior to hospitalization or within the first 3 days of hospitalization[a] and at least three of the following clinical criteria occurring prior to hospitalization or within the first 3 days of hospitalization.[a] At least one criterion must be a primary clinical criterion
(a) Primary clinical criteria
Severe cardiac illness includes myocarditis, pericarditis, coronary artery dilatation/aneurysm or new-onset right or left ventricular dysfunction (LVEF < 50%), second/third degree AV block or ventricular tachycardia[b]
Rash and nonpurulent conjunctivitis
(b) Secondary clinical criteria
New-onset neurological signs and symptoms: includes encephalopathy in a patient without prior cognitive impairment, seizures, meningeal signs or peripheral neuropathy (including Guillain–Barré syndrome)
Shock or hypotension not attributable to medical therapy (e.g. sedation, renal replacement therapy)
Abdominal pain, vomiting or diarrhoea
Thrombocytopenia (platelet count < 150 × 10^3/μL)
Laboratory evidence
Presence of laboratory evidence of inflammation AND SARS-CoV-2 infection
(a) Elevated levels of at least two of the following: CRP, ESR, ferritin, IL-6, procalcitonin
(b) A positive SARS-CoV-2 test for current or recent infection by RT-PCR, serology or antigen detection

AV, atrioventricular; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukin; LVEF, left ventricular ejection fraction; RT, reverse transcription; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. [a]These criteria must be met by the end of hospital Day 3, where the date of hospital admission is hospital Day 0. [b]#cardiac arrest alone does not meet this criterion.

Table 2 Salient features of clinical presentation in multisystem inflammatory syndrome in adults (adapted and modified from Patel *et al.*[7]).

Patient characteristics	Result
Sex (*N* = 219), *n* (%)	
Male	154 (70)
Female	65 (30)
Age	
Median, years	21
IQR, days	19–34
Ethnicity (*N* = 169), *n* (%)	
Asian	12 (7)
Hispanic	50 (30)
Black	60 (36)
White	41 (24)
Prior SARS-CoV-2 infection	
Symptomatic COVID-19-like illness (*N* = 149)	102 (68)
SARS-CoV-2 infection[a] (*N* = 175), *n* (%)	139 (79)
Time since onset of symptoms, days; median (IQR)	28 (20–36)
Positive SARS-CoV-2 laboratory result (*N* = 211)	207 (98)
Clinical characteristics, *n* (%)	
Fever (N = 205)	197 (96)
Pre-existing comorbidities/underlying medical conditions (*N* = 209)	158 (76)
Number of organ systems involved (*N* = 221), *n* (%)	
2–5	162 (73)
> 6	55 (25)
Organ system involved, *n* (%)	
Cardiovascular (*N* = 221)	193 (87)
Haematological (*N* = 200)	184 (92)
Gastrointestinal tract (*N* = 218)	182 (83)
Mucocutaneous (*N* = 218)	100 (46)
Respiratory (*N* = 215)	159 (74)
Neurological (*N* = 218)	102 (47)
Renal (*N* = 85)	79 (43)
Laboratory findings, *n* (%)	
Elevations in:	
Fibrinogen (*N* = 102)	93 (91)
D-dimer (*N* = 151)	138 (91)
Troponin (*N* = 163)	127 (78)
BNP (*N* = 76)	56 (74)
NT-proBNP (*N* = 59)	53 (90)
CRP (*N* = 95)	176 (90)
Ferritin (*N* = 165)	150 (91)
IL-6 (*N* = 62)	61 (98)
Thrombocytopenia (*N* = 109)	53 (49)
Lymphopenia (*N* = 109)	94 (86)
Outcomes	
Duration of hospital stay, days; median (IQR)	8 (5–12)
Admission to ICU (*N* = 201), *n* (%)	115 (57)
Death (*N* = 220), *n* (%)	15 (7)

BNP, brain natriuretic peptide; CRP, C-reactive protein; IL-6, interleukin 6; ICU, intensive care unit; IQR, interquartile range; NT-proBNP, N-terminal pro-brain natriuretic peptide; ICU, intensive care unit. [a]By symptoms and/or testing results.

underlying comorbidities and respiratory problems. The common skin features include rash, erythema of the oropharynx and lips (including lip cracking), bilateral nonexudative conjunctivitis, and erythema/oedema of the hands and feet.[9]

During the early part of the pandemic, when MIS was not a defined condition, post-COVID cases were diagnosed with KD-like syndrome. Afra *et al.*[14] described a case of a middle-aged Indian woman (initially suspected to have a drug reaction) with MIS-A having prominent KD-like mucocutaneous features: morbilliform rash on the limbs and trunk (appeared within a day of fever development, associated with unilateral cervical lymphadenopathy), strawberry tongue, crusting of the lips, palmoplantar erythema and conjunctivitis, all of which resolved with steroids. An

Table 3 Pertinent differences between multisystem inflammatory syndrome in adults and children.

Parameters	MIS-A	MIS-C
History		
Documented COVID-19 infection	More likely	Less likely
Clinical presentation		
Mucocutaneous	Less common	More common
Extracutaneous	More common[a]	Less common
Treatment with IVIG	Not uniformly prescribed	Commonly given
Outcome		
Hospital stay	Longer	Not as long
Requirement for MV	More frequent	Not as frequent
Fatality	More reported deaths	Lower fatality rates

IVIG, intravenous immunoglobulin; MIS-A, multisystem inflammatory syndrome in adults; MIS-C, multisystem inflammatory syndrome in children; MV, mechanical ventilation. [a]Usually in association with myocarditis, cardiac dysfunction, arterial thrombosis, pulmonary embolism and/or deep vein thrombosis.

interesting KD-like presentation was reported in which blanchable erythematous rash on the hands, feet and buttocks were the only skin features; the condition resolved with supportive treatment.[15] An Italian study reported that the most common signs in their cohort were polymorphic rash, bilateral nonexudative conjunctivitis, and erythema of the hands and feet.[16] Dabas *et al*. reported a 22-year-old Indian man with raised SARS-CoV-2 antibody level (but negative results on reverse transcription PCR), who presented with bilateral nonexudative conjunctival erythema, hyperpigmented fissured lips, generalized erythema with well-defined hyperpigmented macules on the face, trunk and extremities, and oedema of the hands and feet.[17]

Apart from a nonpruritic and nonscaly maculopapular rash, which seems to be the most common symptom, palmoplantar erythema and desquamation, cheilitis (with or without pain/pruritus), and conjunctivitis are often seen (Fig. 1). Additionally, mucositis, erythroderma, erythema multiforme-like lesions, targetoid papules and plaques, periorbital oedema with overlying erythema, and even solely facial or acral swelling have been demonstrated in MIS-A.[18–20]

Based on the existing literature, there has been little histopathological characterization of MIS-A-related skin manifestations. Skin biopsies in two patients reported by So *et al*.[21] demonstrated nonspecific histological findings of perivascular dermatitis with negative *in situ* hybridization for SARS-CoV-2 spike protein. Lesional direct immunofluorescence was also negative, which is consistent with patterns commonly observed in viral exanthems.

Recently, some case reports of MIS-A have also been described to occur 2–6 weeks after a variety of vaccines against SARS-CoV-2.[22–25] Nune *et al*.[23] reported a 44-year-old woman who developed an erythematous rash on her chest with subcutaneous oedema (subsequently diagnosed with MIS-A) only a few days after receiving the Pfizer-BioNTech mRNA vaccine. A faint erythematous rash over the torso was described in a young man with history of symptomatic COVID-19 infection 6 weeks previously, in whom the onset coincided with the second dose of an inactivated SARS-CoV-2 vaccine (BBIBP-CorV; Sinopharm). The aluminium hydroxide adjuvant adopted for this vaccine have raised a potential concern.[24] In South Korea, a maculopapular rash was observed 6 days after the first vaccination (ChAdOx1 nCoV-19; Oxford AstraZeneca).[25] Grome *et al*.[26] describe a fatal case of MIS-A with onset 22 days after a second dose of mRNA coronavirus disease vaccine (BNT162b2; Pfizer/BioNTech). The pertinent findings on physical examination included right-sided cervical lymphadenopathy, marked bilateral conjunctival erythema, and a faint papular rash on the pelvis and left flank. Clinical history and seroanalysis was compatible

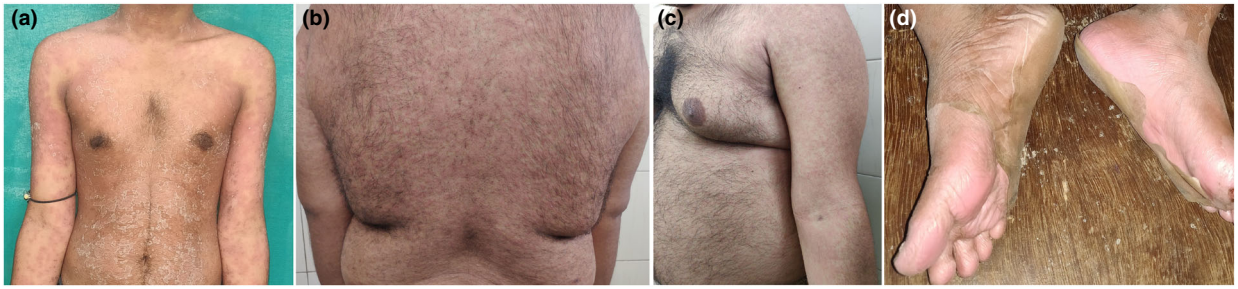

Figure 1 Clinical photographs of patients with multisystem inflammatory syndrome in adults, showing (a) maculopapular rash and desquamation on the chest; (b) maculopapular rash over back; (c) urticarial eruption and (d) desquamation of the feet.

with natural infection beginning 6 days before the first mRNA vaccine dose and consistent with negative SARS-CoV-2 nucleocapsid IgM (the most sensitive target for serological diagnosis for natural infection) on testing during hospitalization.

Management

Therapeutic strategies in MIS-A are primarily based on guidelines published by the American College of Rheumatology for treatment of MIS-C.[27] Randomized controlled trials in adults with MIS-A are yet to be documented. From the dermatological point of view, supportive management with topical emollients, corticosteroids and oral antihistaminics form the mainstay of therapy. For patients with shock or multiorgan failure, dramatic improvement has been observed with moderate-dose steroids. Critically ill patients may require inotrope or vasopressor support, intubation or mechanical ventilation, anticoagulants, or even convalescent plasma therapy. Some studies have also highlighted the role of intravenous immunoglobulin and IL-1 and IL-6 receptor antagonists (anakinra and tocilizumab, respectively) in the management of MIS-A.[28]

Conclusion

Owing to a myriad of possible manifestations and lack of previous history of symptomatic COVID-19, MIS-A cases are often frequently misdiagnosed and under-reported. Dermatological manifestations may not be a hallmark but rather serve as pertinent clues in reaching the diagnosis of MIS-A. Dermatologists and physicians alike should be aware of this under-recognized entity and actively consider its possibility, especially when encountering patients presenting with fever and rash.

Learning points

- MIS-A is a recently emerging condition that occurs as a delayed complication of COVID-19 infection.
- It usually occurs 2 weeks after initial SARS-CoV-2 infection (including asymptomatic cases).
- It involves inflammation of multiple extrapulmonary organs, with frequent involvement of the cardiovascular, haematological and gastrointestinal systems.
- Mucocutaneous manifestations are usually seen in about half of cases.
- Unlike MIS-C, MIS-A is associated with longer hospital stay, a higher proportion of patients needing mechanical ventilation and higher fatality rates.
- Systemic corticosteroids, IVIG, anakinra and tocilizumab have been used in management of MIS-A.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethics statement

Ethics approval and informed consent not applicable.

Data availability

Data are available on request from the corresponding author.

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CPD questions

Learning objective

To gain up-to-date knowledge on the features of multisystem inflammatory syndrome in adults.

Question 1

According to the US Centers for Disease control criteria, what is the minimum patient age required to qualify for multisystem inflammatory syndrome in adults?

(a) 12.
(b) 18.
(c) 21.
(a) 25.
(e) 30.

Question 2

Multisystem inflammatory syndrome in adults usually occurs after how many weeks post SARS-CoV-2 infection?

(a) < 1.
(b) 2–6.
(c) 7–12.
(d) 13–20.
(e) > 20.

Question 3

According to the US Centers for Disease control criteria, which of the following is a secondary clinical criterion required to substantiate the diagnosis of multisystem inflammatory syndrome in adults?

(a) Gastrointestinal symptoms.
(b) Myocarditis.
(c) Pericarditis.
(d) Rash and conjunctivitis.
(e) Fever.

Question 4

Which of the following is the most likely histopathological finding on skin biopsy specimen of rash in a patient with multisystem inflammatory syndrome in adults?

(a) Granulomatous inflammation.
(b) Vasculitis.
(c) Epidermal necrosis.
(d) Perivascular inflammatory aggregates.
(e) Panniculitis.

Question 5

Which of the following inflammatory marker(s) is/are raised in multisystem inflammatory syndrome in adults?

(a) Interleukin (IL)-10.
(b) IL-12.
(c) IL-36.
(d) IL-6.
(e) IL-5.

Instructions for answering questions

This learning activity is freely available online at http://www.wileyhealthlearning.com/ced

Users are encouraged to

- Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures.
- Reflect on the article.
- Register or login online at http://www.wileyhealthlearning.com/ced and answer the CPD questions.
- Complete the required evaluation component of the activity.

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