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Case Report

Multisystem inflammatory syndrome in adults: A rare sequela of SARS-CoV-2 infection

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ABSTRACT

Multisystem inflammatory syndrome in adults (MIS-A) came to attention back in June 2020, when the United States Center for Disease Control and Prevention (CDC) received initial reports regarding patients who had presented delayed and multisystem involvement of the disease, with clinical course resembling multisystem inflammatory syndrome in children (MIS-C). This study introduces a case of MIS-A, where the patient presented 3 weeks after initial COVID-19 exposure. His clinical course was consistent with the working definition of MIS-A as specified by the CDC. Aggressive supportive care in the intensive care unit, utilization of advanced heart failure devices, and immunomodulatory therapeutics (high-dose steroids, anakinra, intravenous immunoglobulin) led to clinical recovery. Management of MIS-A is a topic of ongoing research and needs more studies to elaborate on treatment modalities and clinical predictors.

Introduction

Most of our understanding of MIS-A is based on various case reports and case series shared by the CDC and published in the medical literature (Bastug et al., 2021; Morris et al., 2020). Here we describe a case of MIS-A in a patient admitted to the Creighton University Medical Center —Bergan Mercy campus in Omaha, Nebraska with clinical presentation and diagnostics suggestive of MIS-A.

Case

A 26-year-old Caucasian male nonsmoker presented to the emergency room with 5 days of diffuse abdominal pain, constant in nature, described as 5 out of 10 in intensity, and associated with fever, nausea, loose stool, and decreased urine output. He additionally noted a rash on his hands and feet that started 3 days prior to the presentation. His roommate had COVID-19 three weeks ago. The patient self-quarantined for 10 days and his reverse transcriptase-polymerase chain reaction (RT-PCR) test for SARS-CoV-2 was reported negative at the end of quarantine. He was afebrile, had a blood pressure of 98/48 mmHg, a respiratory rate of 35/minute, and 94% saturation on room air. On chest auscultation, the lungs were clear bilaterally. His abdomen was soft and non-distended, with generalized tenderness to deep palpation. Initial abnormal laboratory results included BUN 38 mg/dl, creatinine 4.66 mg/dl, CRP 246 mg/l, ferritin 1657 ng/ml, LDH 236 U/L, procalcitonin 105.12 ng/ml, D-dimer 2.03, venous lactate 9.7 mg/dl, and WBC count 21 700/U/L with 71% bands (Table 1). At this point he tested positive for SARS-CoV-2 by nasopharyngeal PCR test, with SARS-CoV-2 antibody testing also positive. A duplex venous scan of the lower extremities revealed an acute left peroneal deep vein thrombosis. His initial chest X-ray revealed mild peribronchial

Abbreviations: AF, atrial fibrillation; CDC, Center for Disease Control and Prevention; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; ICU, intensive care unit; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; LHC, left heart catheterization; LVEF, left ventricular ejection fraction; MIS, multisystem inflammatory syndrome; MIS-A, multisystem inflammatory syndrome in adults; MMWR, Morbidity and Mortality Weekly Report; RT-PCR, reverse transcriptase-polymerase chain reaction; SCAD, spontaneous coronary artery dissection; TTE, transthoracic echocardiogram; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VF, ventricular fibrillation.

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Table 1
Clinical features and laboratory results of the patient with MIS-A.

Age	26
Sex	Male
Ethnicity	Not Hispanic or Latino
Race	White
BMI	31.39
Comorbidities	Obesity, generalized anxiety disorder
Maximum body temperature	39.8 °C (103.6 °F)
Evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement	
Cardiac (e.g., shock, elevated troponin, BNP, abnormal echocardiogram, arrhythmia)	Yes
Renal (e.g., acute kidney injury or renal failure)	Yes
Respiratory (e.g., pneumonia, ARDS, pulmonary embolism)	Yes[a]
Hematological (e.g., elevated D-dimers, thrombophilia, or thrombocytopenia)	Yes
Gastrointestinal (e.g., elevated bilirubin, elevated liver enzymes, or diarrhea)	Yes
Dermatological (e.g., rash, mucocutaneous lesions)	Yes
Neurological (e.g., CVA, aseptic meningitis, encephalopathy)	No
No alternative plausible diagnosis	Yes
COVID-19 exposure within the 4 weeks prior to the onset of MIS-A symptoms	Yes
SARS-COV-2 serology, PCR, and other abnormal laboratory results for current admission (with normal reference range)	
RT-PCR	Positive (Ct value: 34.1)
SARS-CoV-2 total antibody	Positive
Initial and peak WBC (k/ul)	21.7 and 76.5 (4–12)
Initial and peak CRP (mg/l)	246[b] (<9.0)
Initial and peak creatinine (mg/dl)	4.66 and 6.79 (0.6–1.3)
Initial and peak procalcitonin (ng/ml)	105.12[c] (<0.05)
Initial and peak LDH (units/L)	236 and >6000 (84–246)
Initial and peak ferritin (ng/ml)	1657 and >20 000 (22–388)
Echocardiogram and cardiac catheterization	
Initial	Mild mitral regurgitation; severe global hypokinesis of the left ventricle; LVEF 10–15%
Prior to discharge	LVEF 60–65%
Coronary artery evaluation	RHC and LHC — no evidence of coronary artery aneurysm, severe cardiomyopathy with cardiogenic shock
Imaging studies	
Abdominal imaging	CT abdomen/pelvis with contrast: mesenteric lymphadenopathy, bilateral perinephric edema extending to the adrenal glands
Chest imaging	Chest X-ray: peribronchial thickening without focal consolidation
Management	
Supplemental O_2 requirements	Yes
Mechanical ventilation	Yes
ECMO	No
Hemodialysis	Yes
Vasoactive medications	Norepinephrine, vasopressin, epinephrine, dobutamine
Steroids	Yes
IVIG	Two doses
Immune modulators	Anakinra
Antiplatelets	Aspirin
Anticoagulation	Heparin drip, rivaroxaban
Total length of hospital stay (days)	24
Number of days admitted in ICU	21
Outcome	Discharged to the skilled nursing facility

[a] Peribronchial thickening on chest X-ray in the absence of focal consolidation or diffuse multifocal infiltrates on presentation.
[b] Initial values were the peak values.
[c] Peak values on the initial test.

thickening and a non-contrast CT scan of the abdomen illustrated lymphadenopathy in the ileocolic mesentery and bilateral peri-nephric edema. Over the course of the next 12 h, his mean arterial pressure dropped to less than 60 mmHg, requiring initiation of vasopressor support. A transthoracic echocardiogram (TTE) revealed a new, markedly reduced left ventricular ejection fraction (LVEF) of 15–20% and severe right ventricular dysfunction. He eventually required endotracheal intubation for rapidly progressive cardiogenic shock, along with commencement of mechanical ventilation prior to requiring Impella placement and continuous renal replacement therapy (CRRT). He received intravenous immunoglobulin (IVIG) at a dose of 1 mg/kg once followed by IV methyl-prednisolone 250 mg every 6 h, subcutaneous anakinra 100 mg every 6 h, and aspirin 325 mg daily. The anakinra dose was tapered over the course of 2 weeks. After 10 days in the intensive care unit, his LVEF recovered to 60%. His presentation and clinical course were consistent with the working definition of MIS-A.

Discussion

According to the CDC, the working case definition for a typical MIS-A presentation includes the presence of a severe illness requiring hospitalization in persons aged 21 or older, positive test results for recent SARS-CoV-2 infection (PCR, antigen, or antibody), severe dysfunction of one or more extrapulmonary organ systems, as well as markedly elevated acute inflammatory markers, all in the absence of severe respiratory illness to exclude the subset of the patients in which organ dysfunction might be the result of tissue hypoxia (Morris et al., 2020).

In October 2020, the CDC published an initial review of 27 cases with a clinical course consistent with MIS-A (Chau et al., 2020;

Magro et al., 2020; Oxley et al., 2020). Those cases had heterogeneous involvement of cardiac, gastrointestinal, dermatological, and neurological symptoms without severe respiratory system involvement at presentation. The first reported case series of CDC Morbidity and Mortality Weekly Reports (MMWR) included 11 MIS-A patients based on data collected from March to August, 2020, seven of whom underwent cardiogenic shock on presentation (Morris et al., 2020). Similarly, a recent review of 51 cases with MIS-A highlighted that cardiovascular involvement has been the most frequently reported finding (82.4%), followed by gastrointestinal manifestations (72.5%) (Bastug et al., 2021). Importantly, in MIS-A, initial COVID-19 infection can be asymptomatic too (Morris et al., 2020). This has been further illustrated in a case-based review of 51 MIS-A cases, in which only 14 patients had previous symptomatic COVID-19 illness, while in the remaining cases the initial COVID-19 infection was either asymptomatic or there were no data available (Bastug et al., 2021). Elevated CRP, neutrophil count, ESR, and fibrinogen have been reported in more than 75% of MIS cases in adolescents (Feldstein et al., 2020).

The proposed COVID-19 infectious process includes three progressive clinical phases (Siddiqi and Mehra, 2020):

Stage I: Early infection phase, with clinical manifestations driven by actively replicating virus.

Stage II: Pulmonary phase, with an overlap of viral replication effects and host inflammatory response.

Stage III: Hyperinflammation phase, with the pathophysiological process driven by the host inflammatory response.

MIS-A is proposed to be a post-infectious phase driven by dysregulated immune complex activation, causing direct endothelial damage and associated thrombo-inflammation (Morris et al., 2020). Notably, as compared with severe COVID-19, patients with MIS are more likely to demonstrate cardiorespiratory involvement (56.0% vs 8.8%) and cardiovascular without respiratory involvement (10.6% vs 2.9%) on presentation (Feldstein et al., 2021).

It should be noted that while serology consistent with prior COVID-19 infection is required to fulfill the case definition of MIS-A, it has a minimal prognostic or diagnostic role due to various limiting factors, including persistent PCR detection of non-replicable SARS-CoV-2 RNA and persistent antibody positivity due to remote previous exposure (Bastug et al., 2021; Hékimian et al., 2021). The American College of Rheumatology has recently published its initial recommendations for the management of hyperimmune response in the post-infectious phase of COVID-19, with particular focus on MIS-C and the role of immunomodulatory therapies, i.e., intravenous immunoglobulin (IVIG) and anakinra (Henderson et al., 2020).

IVIG influences the number and function of regulatory T cells (T_{regs}), which help control inflammation (Lo and Newburger, 2018). Based on its mechanism of action, IVIG is considered a first-tier therapy, and steroids can be used as adjunctive therapy in cases of distributive shock. The proposed starting dose of IVIG is 2 g/kg (Jiang et al., 2020).

Anakinra, a recombinant IL-1 receptor antagonist, is a well-known drug due to its role in the management of various autoimmune conditions. It has been shown to have a quick onset of action, short half-life (4 h), and a large therapeutic window. Moreover, anakinra is rather preferred over tocilizumab, given its safety profile and lesser myelosuppressive and hepatotoxic effects (Mehta et al., 2020). Interestingly, so far there has been no randomized controlled trial to elaborate on the role of anakinra in adults with MIS-A. Our case shows that, following a similar protocol to that carried out in children with MIS-C, anakinra is likely to be effective. In its recommendations regarding MIS-A, the American College of Rheumatology has mentioned that anakinra can be considered as an additional therapy in patients refractory to IVIG and glucocorticoids (Siddiqi and Mehra, 2020). The proposed starting dose is over 4 mg/kg/day IV, with an eventual plan to taper the dose based on clinical recovery and resolution of the markers of inflammation.

Overall, we are still in the early stages of understanding MIS-A. More research is needed to further delineate diagnostic and prognostic markers of MIS-A, as well as to elaborate on disease management in critically ill patients.

Conflicts of interest

All authors declare:

- no financial relationships with any organizations that might have an interest in the submitted work.
- no other relationships or activities that could appear to have influenced the submitted work.

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Ethical approval

Not required. The individual case report submission was exempt from Institutional Review Board approval.

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