LETTER TO THE EDITOR

Multisystem Inflammatory Syndrome in Adults and Adolescents Associated with COVID-19 Infection: A Single-center Experience

Rajalakshmi Arjun[1], Vettakkara KM Niyas[2], Sujith M Thomas[3], Muraleedharan Raman[4], Ajit Thomas[5], Wilson Aloysius[6], Bhuvanesh Mahendran[7]

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Post-COVID-19 infection multisystem inflammatory syndrome in adults (MIS-A) is now being recognized as an entity needing early diagnosis and appropriate therapy. Initial reports of MIS were noted in children (MIS-C), and since early 2020, several case series describing similar illness in adults have been published.[1–3] The case definition of MIS-A has evolved over time. Recently, the Centers for Disease Control and Prevention (CDC) released more stringent criteria to diagnose MIS-A, which are highlighted in Table 1.[4] In this case series, we retrospectively analyzed cases of MIS-A in our center who satisfied the CDC criteria. Though the CDC states patients >21 years and WHO >19 years as inclusion criteria for MIS-A, we included patients who are >16 years based on our institutional protocol, as adults. Patients were excluded if alternative diagnoses such as bacterial sepsis were identified.

From December 2020 to July 2021, there were six patients who fulfilled the criteria for MIS-A (Table 2). They ranged in age between 17 and 50 years and four were males. Two had type II diabetes mellitus, while others had no comorbidity. All of them had fever at presentation, four had diarrhea and abdominal pain, three had hypotension while only two had generalized erythematous rash, and two reported red-eye suggestive of nonpurulent conjunctivitis prior to admission. None had any respiratory symptoms. Four were diagnosed with COVID-19 by reverse transcriptase-polymerase chain reaction earlier and the time interval between COVID-19 diagnosis and MIS-A presentation ranged between 15 and 39 days. SARS-CoV-2 IgG antibody is positive in all patients. In one patient, who had received ChAdOx1 nCoV-19 vaccine, antibodies against both nucleocapsid (N) and spike (S) proteins of SARS-CoV-2 were present, suggesting a past infection. All patients had neutrophilia, elevated levels of C-reactive protein, procalcitonin, and troponin T, and five had thrombocytopenia. All except one had very high ferritin levels in serum. Blood cultures were negative in all. Echocardiography showed left ventricular dysfunction in four. Coronary angiogram was done for one patient and was normal. Three patients needed both vasopressor support and mechanical ventilation. Five patients received intravenous immune globulin (IVIG) followed by pulse methylprednisolone, while one received only IVIG. None of them received tocilizumab or anakinra. Five of them improved and were discharged in stable condition, while one succumbed to secondary sepsis.

The clinical presentation and laboratory findings in this series are similar to previously published studies.[1–3] In a review of 51 cases of MIS-A, the mean age of patients was 29.4 ± 10 years. Fever and gastrointestinal symptoms were prominent and cardiovascular abnormalities were the most frequent finding. Skin and eye involvement were reported in one-third only. Inflammatory markers were invariably raised. Most of the patients were treated successfully with IVIG and/or steroids.[5]

Several aspects of MIS-A are still unclear including pathophysiology, incidence, diagnostic criteria, and treatment strategies. Extrapulmonary inflammatory syndrome, occurring after a time interval of postacute COVID-19, and a positive SARS-CoV-2 IgG antibody test result should point to the diagnosis, as currently there is no confirmatory test for MIS-A. When history of previous COVID-19 infection is absent, epidemiological links to contact with confirmed COVID-19 cases may give a clue to the diagnosis.[6] Evidence for an optimal treatment strategy for MIS-A is lacking and extrapolated from the management strategies of Kawasaki disease and MIS-C. American College of Rheumatology recommends stepwise approach to immunomodulatory treatment in MIS-C with IVIG and/or glucocorticoids as first-tier agents for MIS-C. There are insufficient data available to compare the efficacy of IVIG and glucocorticoids in MIS-C or determine whether these treatments should be provided individually or as dual therapy.[7,8] Further research is needed to have evidence-based treatment recommendations for MIS-A.

[1,2]Department of Infectious Diseases, KIMSHEALTH, Thiruvananthapuram, Kerala, India
[3,4]Department of Critical Care Medicine, KIMSHEALTH, Thiruvananthapuram, Kerala, India
[5,6]Department of Internal Medicine, KIMSHEALTH, Thiruvananthapuram, Kerala, India
[7]Department of Rheumatology, KIMSHEALTH, Thiruvananthapuram, Kerala, India
Corresponding Author: Rajalakshmi Arjun, Department of Infectious Diseases, KIMSHEALTH, Thiruvananthapuram, Kerala, India, Phone: +91 9447151920, e-mail: dr.a.rajalakshmi@gmail.com

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Table 1: CDC criteria to diagnose MIS-A

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 (e.g., bacterial sepsis, exacerbation of a chronic medical condition).

I. Clinical criteria

Subjective fever or documented fever (≥38.0°C) for ≥24 hours prior to hospitalization or within the first 3 days of hospitalization* and at least three of the following clinical criteria occurring prior to hospitalization or within the first 3 days of hospitalization.* At least one must be a primary clinical criterion.

A. Primary clinical criteria

- Severe cardiac illness [myocarditis, pericarditis, coronary artery dilatation/aneurysm, or new-onset right or left ventricular dysfunction (LVEF <50%), second/third degree A-V block, or ventricular tachycardia (Note: cardiac arrest alone does not meet this criterion)]
- Rash and nonpurulent conjunctivitis

B. Secondary clinical criteria

- New-onset neurologic signs and symptoms [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 diarrhea
- Thrombocytopenia (platelet count <150,000/μL)

II. Laboratory

The presence of laboratory evidence of inflammation and SARS-CoV-2 infection.

- Elevated levels of at least two of the following: C-reactive protein, ferritin, IL-6, erythrocyte sedimentation rate, procalcitonin
- A positive SARS-CoV-2 test during the current illness by RT-PCR, serology, or antigen detection

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

Table 2: Clinical details of six adult and adolescent patients with multisystem inflammatory syndrome (MIS-A) associated with COVID-19 infection

Patient	*Age, sex*	*Underlying medical conditions*	*Symptoms and signs at presentation*	*Tested positive for SARS-CoV-2 by RT-PCR previously?*	*Time interval in days between COVID-19 infection and current symptoms*	*SARS-CoV-2 testing at the time of admission RT-PCR/IgG Ab*	*Laboratory parameters*	*Echocardiography/ lung imaging by CT*	*Treatment*	*Outcome*
1	27, F	DM	Fever, rash, **diarrhea,** abdominal pain, **hypotension**	Yes	28	RT-PCR: ND **Ab:** (+)	TLC: 19700 cells/μL PMN: 83% Platelets:188 thou/mm^3 **CRP: 308 mg/L** **PCT: 20.83 ng/mL** **Ferritin: 2140 ng/mL** D-dimer: 2816 ng/mL **Trop-T: 928 pg/mL** Bil: 1.9 mg/dL, AST: 59 U/L, ALT: 34 U/L, Cr: 0.5 mg/dL, Blood culture: negative	**Echo: LV hypokinesia** CT: atelectasis lower lobes	IVIG, followed by MP, later tapering dose of oral predniso-lone Vasopressors Mechanical ventilation	Dis-charged in stable condition

2	19, F	Nil	Fever, **rash, diarrhea** **h/o red-eye 2 days prior to admission**	Yes	15	RT-PCR: ND **Ab:** (+)	TLC: 4900 cells/µL PMN: 84% **Platelets: 124 thou**/mm^3 **CRP: 233 mg/L** **PCT: 34.7 ng/mL** **Ferritin: 122 ng/mL** D-dimer: 2817 ng/mL **Trop-T: 110 pg/mL** Bil: 1.6 mg/dL, AST: 61 U/L, ALT:45 U/L, Cr: 0.8 mg/dL, Blood culture: negative	Echo: Normal CT: bilateral mild pleural effusions with air space densities in bilateral lower lobes	IVIG, followed by MP, later tapering dose of oral prednisolone	Discharged in stable condition
3	25, M	Nil	Fever, **diarrhea, abdominal pain, hypotension**	No	-	RT-PCR: (+) **Ab:** (+)	TLC: 23000 cells/µL PMN: 94% **Platelets: 120 thou**/mm^3 **CRP: 230 mg/L** **PCT: 16.76 ng/mL** **Ferritin: 3086 ng/mL** D-dimer: 9935 ng/mL **Trop-T: 81.7 pg/mL** Bil: 1.3 mg/dL, AST: 944 U/L, ALT: 723 U/L, Cr: 1 mg/dL, Blood culture: negative	**Echo: LV hypokinesia** CT: Bilateral pleural effusion	IVIG Vasopressors Mechanical ventilation	Discharged in stable condition
4	17, M	Nil	Fever, **diarrhea, abdominal pain, hypotension** h/o **rash and red-eye** a day prior to admission	Yes	21	RT-PCR: ND **Ab:** (+)	TLC: 11800 cells/µL PMN: 90% **Platelet: 86 thou**/mm^3 **CRP: 288 mg/L** **Procalcitonin: 24.8 ng/mL** **Ferritin: 810 ng/mL** D-dimer: 2019 ng/mL **Trop-T: 54 pg/mL** Bili: 1.6 mg/dL, AST: 34 U/L, ALT: 53 U/L, Cr: 1.1 mg/dL, Blood culture: negative	ECHO: Normal CT: not done	IVIG, followed by MP, later tapering dose of oral prednisolone	Discharged in stable condition
5	50, M	DM	Fever, **hypotension**	No	-	RT-PCR: ND **Ab:** (+) (had received ChAdOx1 nCoV-19 vaccine. However, antibodies against both S and N antigen positive, suggestive previous infection)	TLC: 11700 cells/µL PMN: 90.2% **Platelet: 41 thou**/mm^3 **CRP: 410 mg/L** **PCT: 94.2 ng/mL** **Ferritin: 46665 ng/mL** D-dimer: ND **Trop-T: 381 pg/mL** Bil: 2.4 mg/dL, AST: 2425 U/L, ALT: 500 U/L, Cr: 3.2 mg/dL, Blood culture: negative	**ECHO: LV hypokinesia** CT: not done	IVIG, followed by MP, later tapering dose of oral prednisolone Vasopressors Mechanical ventilation	Expired

(*Contd...*)

Table 2: (*Contd...*)

Patient	Age, sex	Underlying medical conditions	Symptoms and signs at presentation	Tested positive for SARS-CoV-2 by RT-PCR previously?	Time interval in days between COVID-19 infection and current symptoms	SARS-CoV-2 testing at the time of admission RT-PCR/IgG Ab	Laboratory parameters	Echocardiography/ lung imaging by CT	Treatment	Outcome
6	38, M	Nil	Fever, **abdominal pain**	Yes	39	RT-PCR: ND **Ab: (+)**	TLC: 8800 cells/µL PMN: 92% **Platelet: 121 thou/**mm^3 **CRP: 252 mg/mL** **Procalcitonin: 4.24 ng/mL** **Ferritin: 3550 ng/mL** D-dimer: 3240 ng/mL **Trop-T: 74 pg/mL** Bil: 3.5 mg/dL, AST: 45 U/L, ALT: 52 U/L, Cr: 0.9 mg/dL Blood culture: negative	**Echo: LV hypokinesia** CT: post COVID-19 changes.	IVIG, followed by MP, later tapering dose of oral prednisolone	Discharged in stable condition

Those highlighted in bold are the clinical and laboratory criteria fulfilled to diagnose MIS-A in each patient; DM, type II diabetes mellitus; RT-PCR, reverse transcriptase–polymerase chain reaction; ND, not done; Ab, antibody; TLC, total leukocyte count; PMN, polymorphonuclear leukocytes (%); CRP, C-reactive protein; PCT, procalcitonin; Bil, bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Cr, creatinine; LV, left ventricle; IVIG, intravenous immune globulin; MP, methylprednisolone

Orcid

Rajalakshmi Arjun https://orcid.org/0000-0002-4838-183X
Vettakkara KM Niyas https://orcid.org/0000-0002-7255-6257
Sujith M Thomas https://orcid.org/0000-0002-2758-5702
Muraleedharan Raman https://orcid.org/0000-0001-6534-5307
Ajit Thomas https://orcid.org/0000-0003-0309-6485
Wilson Aloysius https://orcid.org/0000-0002-9752-3072
Bhuvanesh Mahendran https://orcid.org/0000-0002-5415-0296

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