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# Multisystem inflammatory syndrome post-SARS-CoV-2 infection: A case series



To the Editor:

Multisystem inflammatory syndrome (MIS) is a hyper-inflammatory condition that can happen weeks after a severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection hallmarked by a hyperinflammatory state, cardiac injury, and/or shock. As cases of SARS-CoV-2 continue to persist it is imperative for clinicians to be aware of short- and long-term sequelae of these infections. MIS was first identified in children (MIS-C) in Spring of 2020 and adults (MIS-A) in early 2021. After this, the Centers for Disease Control (CDC) published a case series along with a way to report cases of MIS directly.<sup>1</sup> Our cases were not submitted to the CDC and thus have not been included in the current literature. Very little is known about the pathologic mechanism of this condition and literature regarding MIS-A remains sparse despite numerous studies on MIS-C. MIS-A shares many of the same characteristics as MIS-C, and if not recognized and treated promptly, it can lead to severe complications.

We identified four patients who were treated for MIS between December 2020 and March 2021 at two academic tertiary care hospitals. Three patients met the CDC Case Definition for MIS-A, and one met criterion for MIS-C.<sup>2, 3</sup> Analysis of each patient's hospitalization was conducted examining laboratory results, diagnostics, and clinical indicators of disease severity including vasopressor requirement and length of ICU stay.

The demographics, comorbidities, and clinical outcomes are described in Table 1. All patients were Black, aged between 20 – 42 years, three were male and two were obese. All patients presented with constitutional symptoms of fever, chills, and myalgias, three had gastrointestinal symptoms (abdominal pain, nausea, vomiting, or diarrhea) and two had cardiopulmonary manifestations (chest pain, shortness of breath, or cough). All patients met systemic inflammatory response syndrome (SIRS) criteria and required the intensive care unit (ICU) during their hospitalization. All had a negative SARS-CoV-2 RT-PCR but positive serology (IgG and IgM positive: n=2; IgG positive: n=3; IgM positive n=3). Of note, skin manifestations were not seen in our patients, which is one primary clinical criterion for MIS-A. However, all our patients exhibited severe cardiac dysfunction based on transthoracic echocardiogram (TTE), which would satisfy the primary clinical criterion based on the case definition for MIS-A.<sup>2</sup> TTE revealed reduced left ventricular ejection fraction (LVEF) in all patients. Two had left heart catheterization (LHC), and both demonstrated normal coronary

arteries. Laboratory findings showed marked elevation of C-reactive protein (CRP), procalcitonin, ferritin, d-dimer, troponin, and B-type natriuretic peptide (BNP). All patients were hypotensive but only two patients required vasopressors.

All patients were treated with intravenous (IV) methylprednisolone and IV immunoglobulins (IVIG). All patients required respiratory support; nasal cannula (NC) (n = 2), high flow nasal cannula (HFNC) (n = 1), non-invasive positive pressure ventilation (NIPPV) (n = 1). Two patients had a repeat TTE after treatment, and both demonstrated normalization of LVEF. Ultimately, all patients were discharged home.

This case series describes a hyperinflammatory state previously identified in recently published cases as MIS.<sup>1,4,5,6</sup> It remains unclear if there is a genetic or social predisposition to developing MIS. All patients in our case series were black. While this could represent local demographics of our area hospitals, where the black population represents 64.1% of Memphis and 54.3% of Shelby County<sup>7</sup>, it should be noted that a disproportionate amount of ethnic minority groups develops MIS<sup>1,6</sup>, which was again demonstrated in our case series. This concept could be explored further as more cases develop to adequately assess any genetic or social predispositions.

MIS is a unique condition, and more studies need to be done to further link or differentiate MIS-A and MIS-C. Fortunately, MIS appears to respond well to anti-inflammatory treatments and immune modulation resulting in a relatively low mortality rate highlighting the possibility of immune mediated injury as an underlying mechanism for MIS-A.<sup>3</sup> The American College of Rheumatology have published guidelines on the treatment of MIS-C, however no guidelines on the treatment of MIS-A have been established. Treatment focuses on immune modulation which includes IVIG, steroids, and anakinra.<sup>3</sup> All of our patients received medical therapy consistent with MIS-C treatment guidelines including steroids and intravenous immunoglobulins at the time of their illness and improved.

Additionally, all our patients exhibited cardiac dysfunction which has occurred in an estimated 60% of patients with MIS-A according to a recent systematic review.<sup>6</sup> This suggests that MIS-A may have a component of myocarditis and myocardial injury.<sup>4,5</sup> Furthermore, the CDC recently established a case definition for MIS-A where severe cardiac illness is listed as a primary clinical criterion which includes myocarditis, pericarditis, coronary artery dilatation/aneurysm, new onset right or

**TABLE 1.** Demographics, presentation, clinical findings, treatment, and outcomes of patients with MIS treated in adult hospitals.

	Average:	Patient 1	Patient 2	Patient 3	Patient 4
<b>Demographics</b>					
<b>Age (y), Sex</b>	30.5 (+/- 11.62)	21, Male	20, Male	39, Female	42, Male
<b>Race</b>		Black	Black	Black	Black
<b>BMI</b>	28.85 (+/- 5.61)	21.5	27.5	32.6	33.8
<b>Medical History</b>		No reported PMH	Gunshot wound w/ nephrectomy + small bowel resection.	Preeclampsia	HTN
<b>Clinical Presentation</b>					
<b>Presenting symptoms</b>		Headache, fever, anorexia due to nausea/vomiting, diarrhea, neck/back pain	Fever, abdominal pain, nausea/vomiting, diarrhea, muscle aches	Headache, fever, chills, abdominal pain, nausea/vomiting, body aches, sore throat, chest pain	Fever, chills, shortness of breath, cough, muscle aches, chest pain
<b>Admission Vitals</b>		T 39.4C, BP 140/81 mmHg, HR 123 bpm, 100% on RA	T 39.2C, BP 132/81 mmHg, HR 103 bpm, 99% on RA	T 39.5C, BP 97/60 mmHg, HR 139 bpm, 100% on RA	T 39.3, BP 131/75 mmHg, HR 110 bpm, 99% on RA
<b>Peak Temperature (C)</b>	39.55 (+/- 0.1)	39.5	39.7	39.5	39.5
<b>Lowest BP (mmHg)</b>	77.25/50	83/47	72/46	66/48	88/59
<b>Laboratory Results</b>					
<b>Peak Creatinine (mg/dL)</b>	1.76 (+/- 0.78)	1.1 Reference Range: 0.5-1.2 mg/dL	2.8 Reference Range: 0.5-1.2 mg/dL	1.23 Reference Range: 0.52-1.21 mg/dL	1.9 Reference Range: 0.52-1.21 mg/dL
<b>Peak CRP</b>	333.5 (+/- 84.59)	263 Reference Range: 0.00-0.50 mg/dL	379 Reference Range: 0.00-0.50 mg/dL	430 Reference Range: <3.00 mg/L	262 Reference Range: <3.00 mg/L
<b>Peak Procalcitonin (ng/ml)</b>	42.77 (+/- 44.53)	9.46 Reference Range: 0.00-0.50 ng/mL	47.91 Reference Range: 0.00-0.50 ng/mL	9.85 Reference Range: 0.5-2.0 ng/mL	103.84 Reference Range: 0.5-2.0 ng/mL
<b>Peak Ferritin (ng/mL)</b>	(1548.35 (+/- 914.60)	1853.1 Reference Range: 11.0-306.8 ng/mL	2103.1 Reference Range: 11.0-306.8 ng/mL	186 Reference Range: 8.0-252 ng/mL	2051.2 Reference Range: 8.0-252 ng/mL
<b>Peak D-Dimer</b>	8.09 (+/- 3.32)	11.87 Reference Range: 0.00-0.50 mcg/mL	9.24 Reference Range: 0.00-0.50 mcg/mL	4 Reference Range: 0.00-0.44 FEU/mL	7.25 Reference Range: 0.00-0.44 FEU/mL
<b>Peak Troponin (ng/mL)</b>	0.23 (+/- 0.16)	0.11 Reference Range: 0.00-0.034 ng/mL	0.19 Reference Range: 0.00-0.034 ng/mL	0.465 Reference Range: 0.00-0.045 ng/mL	0.173 Reference Range: 0.00-0.045 ng/mL
<b>Peak BNP (pg/mL)</b>	1463 (+/- 44.53)	1808 Reference Range: 0.0-100 pg/mL	940 Reference Range: 0.0-100 pg/mL	3600 Reference Range: <125 pg/mL	1641 Reference Range: <125 pg/mL
<b>Microbiology Results</b>					
<b>SARS-CoV-2 PCR</b>		Negative	Negative	Negative	Negative
<b>SARS-CoV-2 IgM</b>		Positive	Positive	Not tested	Positive
<b>SARS-CoV-2 IgG</b>		Positive	Not tested	Positive	Positive
<b>Blood Cultures</b>		No growth, 2 sets	No growth, 2 sets	No growth, 2 sets	No growth, 4 sets
<b>Imaging Results</b>					
<b>Initial CXR</b>		Normal	Scattered granulomatous changes; no acute CP findings	Normal	Normal
<b>Initial CT</b>		No PE and no abnormal lung findings.	Bilateral small pleural effusions with bilateral consolidations with adjacent GGOs.	Bibasilar atelectasis.	Medial left lung base opacity.
<b>Initial TTE</b>		LVEF 20-25% with stage II diastolic dysfunction; global hypokinesis; RVSP 35-40mmHg; mild tricuspid regurg	Severe global LV systolic dysfunction w/ LVEF 10-15%; unable to eval diastolic function; RVSP 30-35mmHg	LVEF 25-30% with global hypokinesis	LVEF 25-30% with global hypokinesis

(continued)

TABLE 1. (continued)

	Average:	Patient 1	Patient 2	Patient 3	Patient 4
<b>Follow up TTE</b>		None	Normal LV systolic function with LVEF 55-60%	LVEF 50-55% with normal regional wall motion	None
<b>LHC</b>		None	None	Normal coronary arteries, nonischemic cardiomyopathy	Normal coronary arteries, LVEF 35-40%, global hypokinesis
<b>Treatment</b>					
<b>IV Steroid</b>		Methylprednisolone	Methylprednisolone	Methylprednisolone	Methylprednisolone
<b>IVIG</b>		Yes	Yes	Yes	Yes
<b>Pressor requirement?</b>		None	Norepinephrine	Norepinephrine	None
<b>Length of time on Pressors (days)</b>	1.75 (+/- 2.06)	0	3	4	0
<b>Respiratory Support</b>		NIPPV	HFNC	NC	NC
<b>Length of stay in ICU (days)</b>	3.75 (+/- 0.96)	3	4	5	3
<b>Outcome</b>		Discharged home	Discharged home	Discharged home with home health	Discharged against medical advice
<b>Length of stay in hospital (days)</b>	11.25 (+/- 1.71)	9	11	12	13

left ventricular dysfunction, 2nd/3rd degree heart block, and ventricular tachycardia.<sup>2</sup>

It is also important to note that MIS-A can be difficult to differentiate from primary SARS-CoV-2 as evidenced by the fact that both conditions usually produce a hyper-inflammatory state. However, MIS-A typically involves extrapulmonary symptoms and is heralded by a past SARS-CoV-2 infection with MIS-A symptoms starting around four weeks after the initial infection.<sup>6</sup>

We also recognize that the number of cases of MIS that we observed were disproportionately high considering the rarity of the condition. This could be attributed to the high number of SARS-CoV-2 cases we saw in our region and the subsequent surge in cases during that time. Our hospital also has a high proportion of physicians who concurrently care for hospitalized children, so familiarity with MIS-C may have contributed to earlier recognition. In response to this, we did develop hospital guidelines for recognition, diagnosis, and treatment in April 2021 which were approved by hospital administration and disseminated to the medical staff.

These cases emphasize the need for recognition and diagnosis of MIS-A, especially in the absence of alternative diagnoses. All patients had negative blood cultures, no source for their severe sepsis, and progressive clinical deterioration. This study demonstrates that more work needs to be done to further examine MIS-A/C, develop treatment algorithms for adult hospitals, and explore its short- and long-term effects in all patient outcomes.

Link to CDC reporting page: <https://www.cdc.gov/mis-c/pdfs/hcp/mis-c-form-fillable.pdf>

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We declare no competing interests.

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