Multisystem inflammatory syndrome in adults (MIS-A) associated with SARS-CoV-2 infection with delayed-onset myocarditis: case report

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Background
During the Coronavirus disease 2019 (COVID-19) pandemic, reports have emerged of a multisystem inflammatory syndrome in adults (MIS-A). Multisystem inflammatory syndrome in adults can affect various organ systems, including cardiovascular, gastrointestinal, and neurologic systems without significant respiratory involvement.

Case summary
A previously healthy 43-year-old man presented with fevers and abdominal pain then rapidly deteriorated into cardiogenic shock. His constellation of symptoms along with elevated inflammatory markers in the setting of a recent SARS-CoV-2 infection was consistent with the diagnosis of MIS-A. He also had a comprehensive infectious workup that was unremarkable, ruling out other potential infectious aetiologies for his presentation. He subsequently improved through supportive measures and after administration of intravenous immunoglobulin (IVIG). He later demonstrated recovery of cardiac function and cardiac magnetic resonance imaging (MRI) showed signs consistent with myocarditis.

Discussion
As the COVID-19 pandemic continues to be an ongoing issue, it is important to recognize MIS-A, a rare and potentially deadly clinical syndrome that can lead to profound cardiovascular complications. Non-invasive imaging modalities such as cardiac MRI can play a role in the identification of myocarditis. In addition to supportive management, adjunctive therapies such as IVIG may be efficacious in MIS-A and should be further investigated.

Keywords
COVID-19 • SARS-CoV-2 • Case report • Multisystem inflammatory syndrome • MIS-A • Myocarditis

ESC curriculum
6.2 Heart failure with reduced ejection fraction • 6.4 Acute heart failure • 2.3 Cardiac magnetic resonance • 6.5 Cardiomyopathy

Learning points
• Multisystem inflammatory syndrome in adults (MIS-A) is a potentially fatal syndrome that can involve various organ systems, including the cardiovascular system, and can be associated with delayed-onset myocarditis.
• Cases of MIS-A have been treated with intravenous immunoglobulin, corticosteroids, and IL-6 inhibition, but the efficacy of these treatments remains to be further validated.

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Introduction

Several months into the coronavirus disease 2019 (COVID-19) pandemic, cases of a new multisystem inflammatory syndrome in children (MIS-C) were reported, with clinical features including shock, cardiac dysfunction, and elevated inflammatory markers.1 A new multisystem inflammatory syndrome in adults (MIS-A) has also been identified.2 Patients with MIS-A have evidence of a recent COVID-19 illness and present with fevers, elevated inflammatory markers, and various cardiovascular, gastrointestinal, dermatologic, and neurologic manifestations without significant respiratory disease.2–4 We describe a case of a patient with MIS-A who presented with profound cardiac dysfunction likely due to delayed-onset myocarditis.

Timeline

| Day 1 | Intra-aortic balloon pump removed |
| Day 2 | Transthoracic echocardiogram showing left ventricular ejection fraction of 68% |
| Day 2 | Persistent leukocytosis despite lack of fevers and negative infectious workup |
| Day 3 | Multisystem inflammatory syndrome in adults suspected |
| Day 4 | Vancomycin discontinued |
| Day 5 | Doxycycline discontinued |
| Day 5 | Dopamine drip discontinued |
| Day 6 | Intravenous immunoglobulin administered |
| Day 6 | Piperacillin/tazobactam discontinued |
| Day 7 | Norepinephrine drip discontinued |
| Day 7 | Extubated to high-flow nasal cannula |
| Day 8 | Transitioned to intermittent haemodialysis |
| Day 10 | Cardiac magnetic resonance imaging with diffuse myocardial oedema and no delayed myocardial enhancement, consistent with myocarditis |
| Day 12 | Transferred to cardiac floor |
| Day 22 | Discharged from hospital |

Case presentation

A 43-year-old previously healthy man with mildly symptomatic SARS-CoV-2 infection 7 weeks prior presented with abdominal pain, nausea, and fever to 39.4°C; he was otherwise haemodynamically stable and had an elevated erythrocyte sedimentation rate (ESR) 90 mm/h (0–20 mm/h) and C-reactive protein (CRP) 275.1 mg/L (<1 mg/L). Abdominal computed tomography (CT) scan showed terminal ileitis and ascending colitis. Repeat SARS-CoV-2 polymerase chain reaction (PCR), multiplex stool pathogen panel, viral hepatitis panel, Clostridioides difficile assay, and blood cultures were negative. Given the improvement in pain, he left against medical advice.

The patient subsequently returned to the emergency department with dyspnoea and hypotension. Electrocardiogram with anterolateral ST-elevations—cath lab activated. Elevated pro B-type natriuretic peptide, troponin T, erythrocyte sedimentation rate, C-reactive protein. Echocardiogram with global hypokinesis and severely depressed left ventricular ejection fraction. Left heart catheterization with non-obstructive coronaries. Intubated, started on norepinephrine drip, intra-aortic balloon pump inserted.

Febrile to 40.3°C—started intravenous vancomycin and piperacillin/tazobactam.

Rising white count and worsening renal function.

Transferred to our hospital’s cardiac intensive care unit.

 Started on dopamine drip

Intravenous doxycycline added

Oliguric despite high dose bumetanide challenge

Started on continuous veno-venous haemofiltration

Continued
ventricular pressure 40/20 mmHg, pulmonary artery pressure 40/28 mmHg (mean 32 mmHg), mean pulmonary capillary wedge pressure 25–28 mmHg. A post-procedural transthoracic echocardiogram (TTE) confirmed global hypokinesis and a severely depressed LVEF 20-25% (Video 2). He later became febrile to 40.3°C requiring active external cooling and broadening of antibiotics. Labs displayed a rising white blood cell (WBC) count of 14.5×10⁶/µL, creatinine 1.95 mg/dL (prior 1.01 mg/dL) accompanied by oligoanuria despite diuretics, and arterial blood gas with mixed metabolic and respiratory acidoses with pH 7.21, pCO₂ 53 mmHg, pO₂ 83 mmHg on 60% fraction of inspired oxygen. Given suspicion for myocarditis, tests for adenovirus, parainfluenza viruses 1–4, rhinovirus, influenza A & B, human metapneumovirus, respiratory syncytial virus A & B, coxsackie B, and enterovirus were sent—all ultimately unremarkable. As vasopressor requirements increased, the decision was made to transfer the patient to our institution for consideration of advanced mechanical support and possible heart transplant evaluation. Upon arrival at our cardiac intensive care unit, he was started on a dopamine infusion and was given a diuretic challenge which did not yield any urine output. Labs were notable for worsening creatinine 3.08 mg/dL, proBNP >70 000 pg/mL, ferritin 4311 ng/mL (30–400 ng/mL), WBC 18.0×10⁶/µL, D-dimer 2.74 mg/L FEU (<0.5 mg/L FEU). C-reactive protein and ferritin levels were trended throughout his course (Figure 2), and the cytokine panel showed elevated soluble IL-2 receptor (sIL-2R), IL-6, IL8, and TNF-α (Table 1). HIV antibody and toxoplasma gondii IgG were negative. Given persistent hypoxaemia and anuric renal failure, continuous veno-venous haemofiltration was initiated with improvements in oxygenation and
haemodynamics. IABP was removed on hospital Day 4 and TTE showed recovered LVEF 68% (Video 3). Despite haemodynamic improvement and defervescence, leucocytosis progressed with absolute neutrophilia and lymphopenia. Infectious disease was consulted, and repeat infectious workup, including tracheal aspirate SARS-CoV-2 PCR, was unrevealing; CT abdomen was unchanged and CT chest displayed bilateral infiltrates, but these were not felt to represent infectious processes. Given the constellation of rapid deterioration with profound cardiac dysfunction, gastrointestinal symptoms with signs of enteritis, increased inflammatory markers with absolute neutrophilia and lymphopenia, all in the context of a recent SARS-CoV-2 infection, his presentation was consistent with MIS-A. A joint decision was made to halt antibiotics and proceed with a single dose of 1 mg/kg intravenous immunoglobulin (IVIG) on hospital Day 5. Dopamine and norepinephrine were weaned off by Day 6, and he was extubated on Day 7. He was subsequently transitioned to intermittent haemodialysis (HD) on Day 8. Cardiac magnetic resonance imaging (MRI) on Day 11 showed diffuse myocardial oedema without delayed myocardial enhancement, findings compatible with non-ischaemic cardiomyopathy including myocarditis (Figure 3). Since the patient recovered through supportive therapies alone, an endomyocardial biopsy was deferred. He was transferred to the floor on Day 12 and discharged.
on Day 22 on intermittent HD. During a follow-up visit 11 days post-discharge, he reported continued weakness and shortness of breath but was gradually recovering.

Discussion

This case illustrates a characteristic presentation of MIS-A in a young man with a recent SARS-CoV-2 infection who developed profound cardiogenic shock likely due to delayed-onset myocarditis. The Centers for Disease Control and Prevention (CDC) defines MIS-A through 5 criteria: (i) presence of a severe illness requiring hospitalization in adults >21 years old; (ii) a positive SARS-CoV-2 test within the last 12 weeks; (iii) severe organ dysfunction (apart from lungs); (iv) elevated inflammatory markers (including CRP, ferritin, D-dimer, IL-6); and (v) absence of severe respiratory disease, all of which our patient satisfied. Reported cardiac manifestations from the CDC case series included shock-requiring vasopressors, arrhythmias, elevated troponin levels, and ventricular dysfunction. In another case series of seven patients, all had initially decreased ventricular function requiring inotropes or vasopressors and three required IABP support; all had improvements in LVEF on repeat echocardiogram. Furthermore, cardiac MRIs consistently demonstrated findings of diffuse myocardial oedema, as was observed in our patient. A handful of other cases of COVID-19-associated myocardial dysfunction in adults have been described in the literature, including several cases of delayed-onset myocarditis. Given that our patient

![Figure 3](https://example.com/figure3.png) Cardiac magnetic resonance imaging, T2-weighted sequence (A) four-chamber view; (B) left ventricular outflow tract view; (C) short-axis stack view; (D) vertical long-axis view.
had a prolonged time period from initial diagnosis of COVID-19 to his subsequent admission for cardiogenic shock, as well as the lack of endomyocardial biopsy results, we cannot definitively establish a causal relation between COVID-19 infection and myocarditis. However, our patient did meet the criteria for COVID-19-associated MIS-A and his clinical course was consistent with prior reported cases of COVID-19-associated myocarditis. Furthermore, we had performed a comprehensive workup, which did not reveal an alternate aetiology of myocarditis.

Patients with MIS-A have been treated with a combination of IVIG, corticosteroids, and the IL-6 inhibitor tocilizumab.2,5,7 Our patient received a single dose of IVIG, with a sustained reduction in CRP (Figure 2) along with clinical improvement; however, the efficacy of such therapies remains to be further elucidated. As COVID-19 continues to be globally prevalent, clinicians should consider MIS-A as a diagnosis in similar clinical syndromes.

### Lead author biography

Miles Shen is an Internal Medicine resident at Yale New Haven Hospital. He graduated from Princeton University in 2014 with a BA in Molecular Biology then earned his medical degree at Rutgers New Jersey Medical School in 2020. His particular interests lie in cardiovascular diseases and critical care.

### Supplementary material

**Supplementary material** is available at European Heart Journal—Case Reports online.

**Slide sets:** A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

**Consent:** The authors confirm that written consent for the submission and publication of this case, including images, has been obtained from the patient in line with COPE guidance.

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### Conflict of interest

None declared.

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