

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

Miles Shen <sup>1\*</sup>, Aidan Milner <sup>1</sup>, Carlo Foppiano Palacios <sup>2</sup>, and Tariq Ahmad <sup>3</sup>

<sup>1</sup>Department of Internal Medicine, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA; <sup>2</sup>Section of Infectious Diseases, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA; and <sup>3</sup>Section of Cardiovascular Medicine, Yale School of Medicine, 333 Cedar Street, New Haven, CT, 06510, USA

Received 24 May 2021; first decision 26 July 2021; accepted 15 November 2021; online publish-ahead-of-print 19 November 2021

## 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.

\* Corresponding author. Tel: (650) 868-0428, Email: [miles.shen@yale.edu](mailto:miles.shen@yale.edu)

Handling Editor: Elizabeth Paratz

Peer-reviewers: Albert Galyavich; Giacomo Tini Melato; Diego Araiza-Garayordobil

Compliance Editor: Alexander Tindale

Supplementary Material Editor: Ross Thomson

© The Author(s) 2021. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com)

## 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.<sup>1</sup> A new multisystem inflammatory syndrome in adults (MIS-A) has also been identified.<sup>2</sup> 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.<sup>2–4</sup> We describe a case of a patient with MIS-A who presented with profound cardiac dysfunction likely due to delayed-onset myocarditis.

## Timeline

Pre-admission	Mildly symptomatic SARS-CoV-2 infection 7 weeks prior Fever and abdominal pain 3 days prior Computed tomography scan of abdomen with terminal ileitis and ascending colitis Negative repeat SARS-CoV-2 polymerase chain reaction, stool pathogen panel, <i>Clostridioides difficile</i> , hepatitis panel, blood cultures
Admission	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 Swan-Ganz catheter with elevated biventricular pressures Febrile to 40.3°C—started intravenous vancomycin and piperacillin/tazobactam Rising white count and worsening renal function
Day 2	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

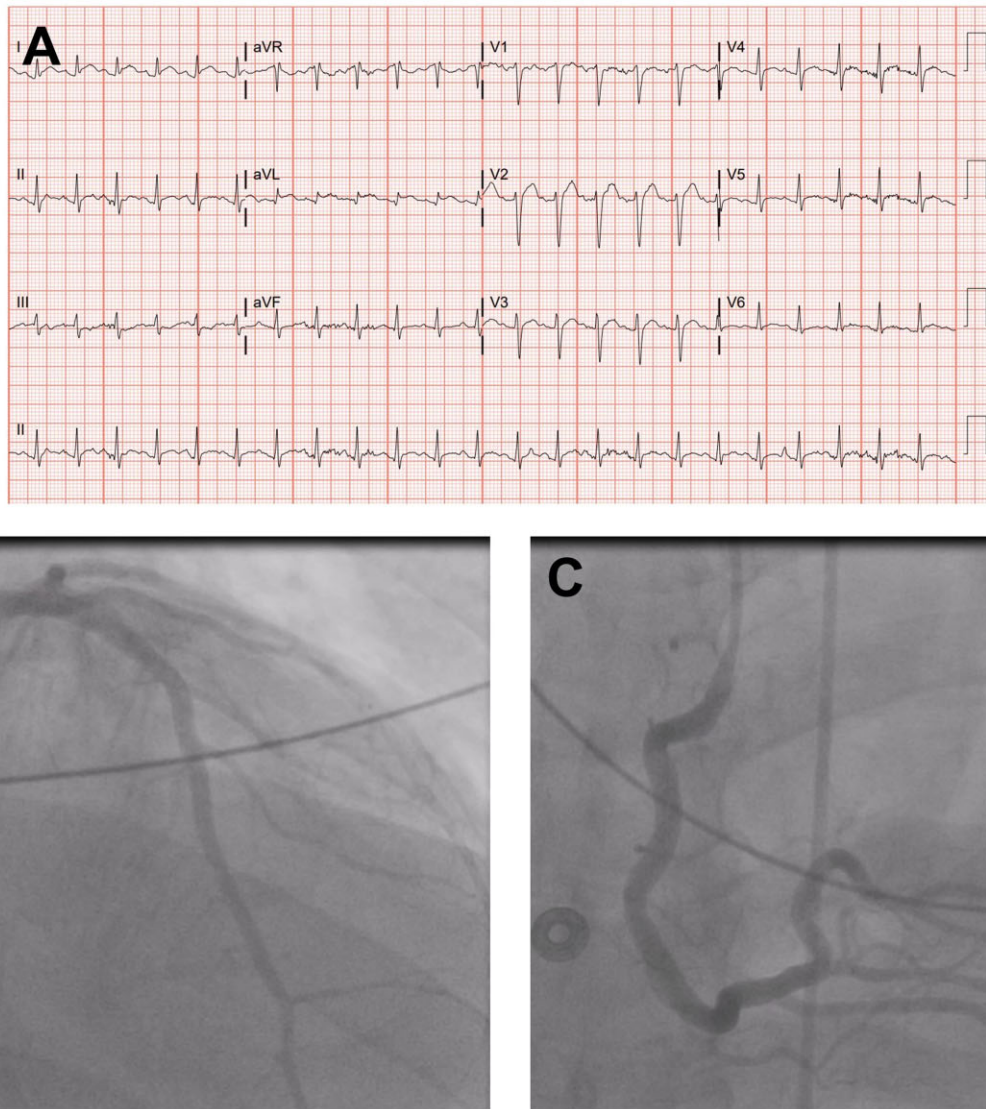
*Continued*

Day 4	Intra-aortic balloon pump removed Transthoracic echocardiogram showing left ventricular ejection fraction of 68% Persistent leucocytosis despite lack of fevers and negative infectious workup Multisystem inflammatory syndrome in adults suspected Vancomycin discontinued
Day 5	Doxycycline discontinued Dopamine drip discontinued Intravenous immunoglobulin administered
Day 6	Piperacillin/tazobactam discontinued Norepinephrine drip discontinued
Day 7	Extubated to high-flow nasal cannula
Day 8	Transitioned to intermittent haemodialysis
Day 11	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
11 days post-discharge	Continued on intermittent haemodialysis with improving renal function

## 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 new-onset dyspnoea and orthopnoea; he was found to be hypotensive to 89/48 mmHg with anterolateral ST-elevations on electrocardiogram (Figure 1A). Chest X-ray showed a small right pleural effusion. Labs were significant for alanine aminotransferase 347 U/L, aspartate aminotransferase 396 U/L, pro B-type natriuretic peptide (proBNP) 16,618 pg/mL (<125 pg/mL), troponin T 0.07 ng/mL (<0.01 ng/mL), CRP >300 mg/L, and ESR 112 mm/h. A limited point-of-care echocardiogram showed global hypokinesis with a grossly reduced left ventricular ejection fraction (LVEF). Aspirin 324 mg was administered and he underwent left heart catheterization (LHC) which showed non-obstructive coronaries (Figure 1B,C, Video 1). During LHC, he was intubated for rapidly worsening hypoxia and work of breathing; haemodynamic instability prompted the initiation of a norepinephrine infusion and placement of an intra-aortic balloon pump (IABP). A Swan-Ganz catheter displayed elevated biventricular pressures with mean right atrial pressure 15–20 mmHg, right

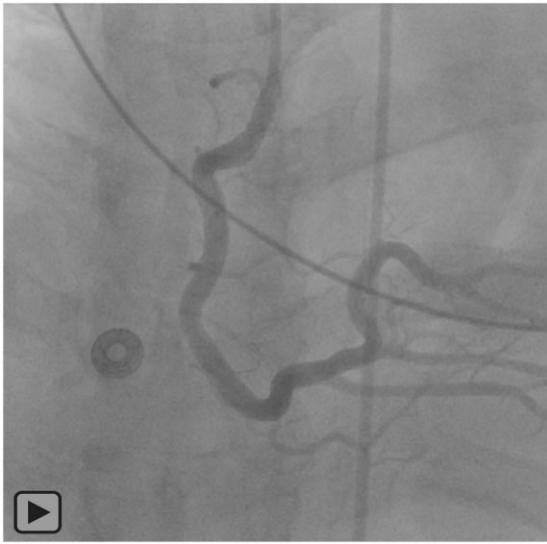


**Figure 1** (A) Electrocardiogram; left heart catheterization showing non-obstructive (B) left anterior descending artery and (C) right coronary artery.

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 hypokinesia 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  $14.5 \times 1000/\mu\text{L}$ , 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,  $\text{pCO}_2$  53 mmHg,  $\text{pO}_2$  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  $18.0 \times 1000/\mu\text{L}$ , D-dimer 2.74 mg/L FEU ( $\leq 0.5$  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- $\alpha$  (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

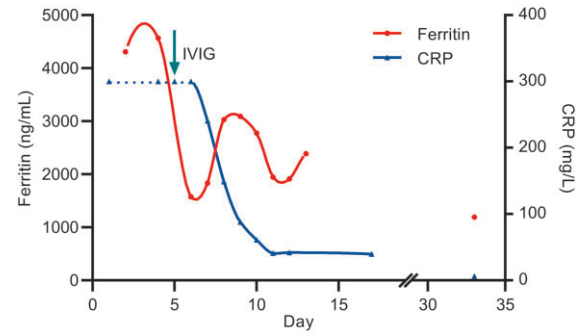


**Video 1** Left heart catheterization.



**Video 2** Transthoracic echocardiogram (initial).

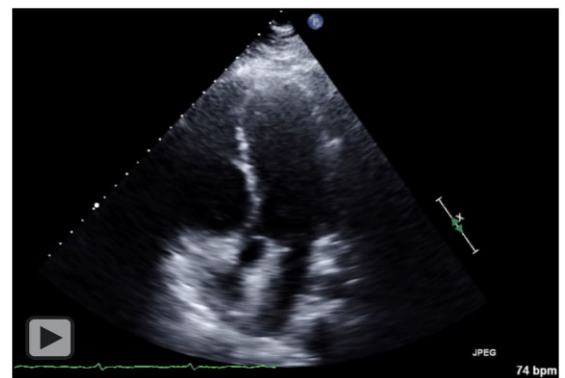
haemodynamics. IABP was removed on hospital Day 4 and TTE showed recovered LVEF 68% (Video 3). Despite haemodynamic improvement and defervescence, leucocytosis progressed with absolute neutrophilia and lymphopenia. Infectious disease was consulted, and repeat infectious workup, including tracheal aspirate 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



**Figure 2** Trend of C-reactive protein and ferritin.

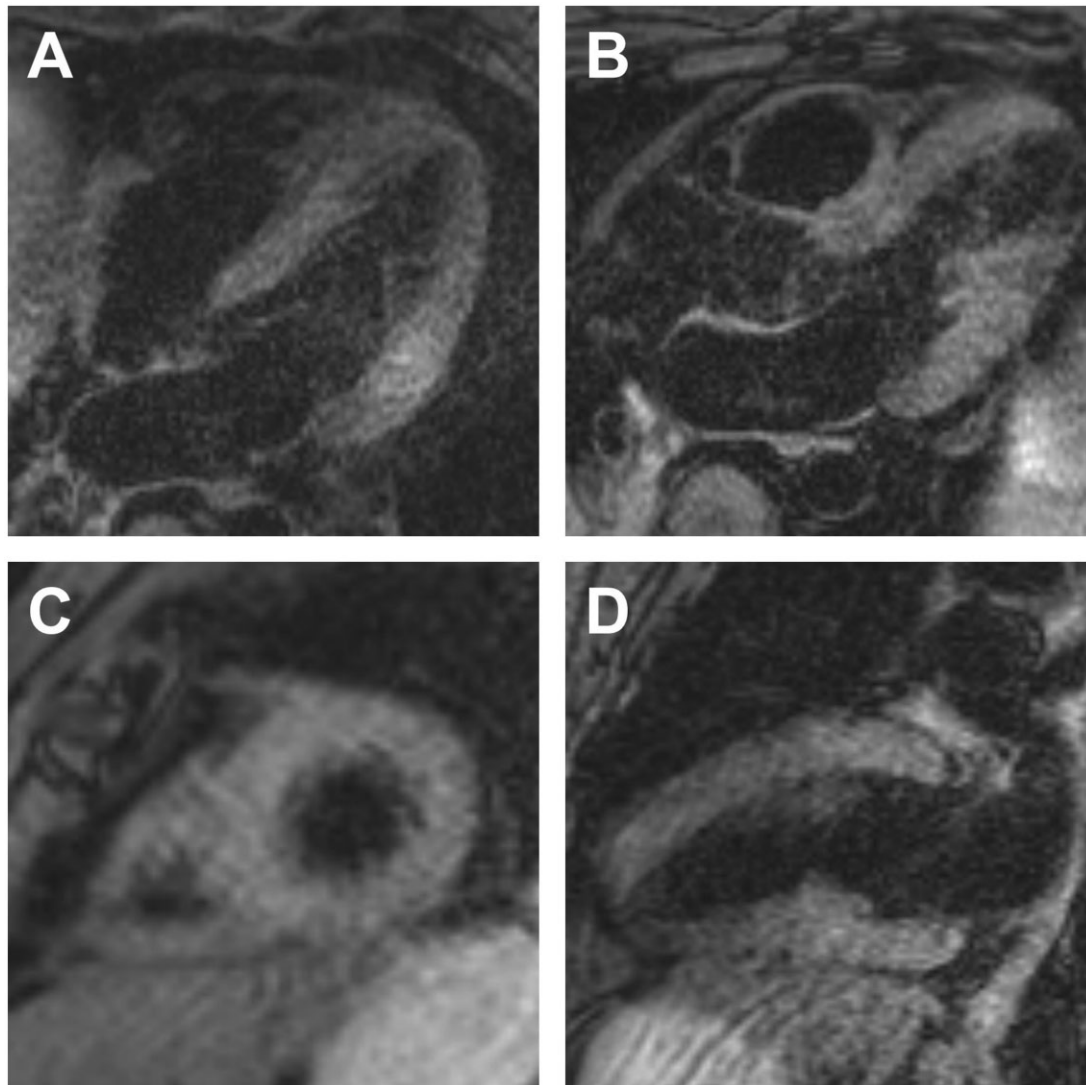
**Table 1.** Cytokine panel

Cytokine	pg/mL (reference range)
IL-1 $\beta$	<1.0 (0.0–1.0)
IL-10	4.2 (0.0–5.0)
IL-2	<1.0 (0.0–1.0)
sIL-2R	21 489.0 (435.0–2347.0)
IFN- $\gamma$	1.2 (0.0–4.0)
TNF- $\alpha$	40.3 (0.0–13.0)
IL-8	24.0 (0.0–14.0)
IL-6	48.4 (<5.0)



**Video 3** Transthoracic echocardiogram (hospital Day 4).

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



**Figure 3** 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.

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  $\geq 21$  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.<sup>2</sup> Reported cardiac manifestations from the CDC case series included shock-requiring vasopressors, arrhythmias, elevated troponin levels, and ventricular dysfunction.<sup>2</sup> 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.<sup>5</sup> In another case series, common characteristics included high-grade fever, abdominal pain, hypotension—all present in our patient; some also had COVID-19 one month prior, supportive of a delayed manifestation.<sup>6</sup> Furthermore, cardiac MRIs consistently demonstrated findings of diffuse myocardial oedema, as was observed in our patient.<sup>6</sup> 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.<sup>7–15</sup> Given that our patient

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.<sup>2,5,7</sup> 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.

**Funding:** None declared.

**Conflict of interest:** None declared.

## References

- Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J, et al.; California MIS-C Response Team. COVID-19-associated multisystem inflammatory syndrome in children—United States, March–July 2020. *MMWR Morb Mortal Wkly Rep* 2020;**69**:1074–1080.
- Morris SB, Schwartz NG, Patel P, Abbo L, Beauchamps L, Balan S et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 Infection — United Kingdom and United States, March–August 2020. *MMWR Morb Mortal Wkly Rep* 2020;**69**:1450–1456.
- Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med* 2020;**382**:e60.
- Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. *Transl Res* 2020;**220**:1–13.
- Chau VQ, Giustino G, Mahmood K, Oliveros E, Neibart E, Oloomi M et al. Cardiogenic shock and hyperinflammatory syndrome in young males with COVID-19. *Circ Heart Failure* 2020;**13**.
- Hékimian G, Kerneis M, Zeitouni M, Cohen-Aubart F, Chommeloux J, Bréchet N et al. Coronavirus disease 2019 acute myocarditis and multisystem inflammatory syndrome in adult intensive and cardiac care units. *Chest* 2021;**159**:657–662.
- Veysseh M, Webster P, Blanco I. COVID-19-associated inflammatory syndrome in an adult woman with unexplained multiple organ failure: staying vigilant for COVID-19 complications as the pandemic surges. *BMJ Case Rep* 2021;**14**:e242034.
- Newton-Cheh C, Zlotoff DA, Hung J, Rupasov A, Crowley JC, Funamoto M. Case 24-2020: a 44-year-old woman with chest pain, dyspnea, and shock. *N Engl J Med* 2020;**383**:475–484.
- Shaigany S, Gnirke M, Guttman A, Chong H, Meehan S, Raabe V et al. An adult with Kawasaki-like multisystem inflammatory syndrome associated with COVID-19. *The Lancet* 2020;**396**:e8–e10.
- Vujaklija Brajković A, Zlopaša O, Gubarev Vrdoljak N, Goran T, Lovrić D, Radonić R. Acute liver and cardiac failure in multisystem inflammatory syndrome in adults after COVID-19. *Clin Res Hepatol Gastroenterol* 2021;**45**:101678.
- Yamada Y, Fujinami K, Eguchi T, Takefuji H, Mori N. Multisystem inflammatory syndrome in adults after Mild SARS-CoV-2 infection, Japan. *Emerg Infect Dis* 2021;**27**:1740–1742.
- Tung-Chen Y, Algora-Martín A, Rodríguez-Roca S, Díaz de Santiago A. COVID-19 multisystemic inflammatory syndrome in adults: a not to be missed diagnosis. *BMJ Case Rep* 2021;**14**:e241696.
- Mieczkowska K, Zhu TH, Hoffman L, Blasiak RC, Shulman KJ, Birnbaum M et al. Two adult cases of multisystem inflammatory syndrome associated with SARS-CoV-2. *JAAD Case Rep* 2021;**10**:113–115.
- Bajaj R, Sinclair HC, Patel K, Low B, Pericao A, Manisty C et al. Delayed-onset myocarditis following COVID-19. *Lancet Respir Med* 2021;**9**:e32–e34.
- Gulersen M, Staszewski C, Grayver E, Tam Tam H, Gottesman E, Isseroff D et al. Coronavirus disease 2019 (COVID-19)-related multisystem inflammatory syndrome in a pregnant woman. *Obstet Gynecol* 2021;**137**:418–422.