A case report of multi-system inflammatory syndrome in adults (MIS-A) associated with heart failure

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Background
Multi-system inflammatory syndrome in children (MIS-C) is a systemic inflammatory condition where various body organs, such as the heart, kidney, gastrointestinal organs, become inflamed. Several cases have been reported in children linking MIS-C with novel corona virus disease-2019 (COVID-19); however, few cases have been reported in adults [multi-system inflammatory syndrome in adults (MIS-A)].

Case summary
A case of a 20-year-old male patient with a history of COVID-19 infection 2 months before presentation who presented with fever and acute right lower quadrant pain. Workup revealed right-sided mesenteric lymphadenopathy and mild colitis that was non-responsive to antibiotics. The patient was found to have significantly elevated inflammatory markers. He also developed myocarditis resulting in acute systolic heart failure with reduced ejection fraction. The diagnosis of MIS-A was made by exclusion. The patient showed improvement with intravenous immunoglobulin and pulse steroids. Based on the available literature, MIS-C was defined till the age of 21; however, we think it is a misnomer for adults more than 18. Hence, we prefer to use MIS-A for our patient.

Conclusion
It is essential to diagnose and treat patients with the multi-system inflammatory syndrome at an early stage; the management of these patients, especially with heart disease, should include immune-modulatory therapy as well as guideline-directed therapy.

Keywords
Case report • Multi-system inflammatory syndrome • MIS-A • MIS-C • COVID-19 • Heart failure

Learning points
• Multi-system inflammatory syndrome in children presents with broad range of symptoms, including gastrointestinal symptoms (abdominal pain, vomiting, diarrhoea), myocarditis, respiratory symptoms (shortness of breath, cough), headache, fever, conjunctivitis, rash, and fatigue.
• Similar syndrome in adults, multi-system inflammatory syndrome in adults, have more severe symptoms: cardiovascular (shock and left ventricular systolic dysfunction), mucocutaneous, haematologic, gastrointestinal, and respiratory systems.
• Our aim is to stress on the importance of early diagnosis and treatment in this patient population; the management of these patients, especially with heart disease, should include immune-modulatory therapy as well as guideline-directed therapy.

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Introduction

SARS-CoV-2, the causative agent of Corona Virus Disease-2019 (COVID-19), continues to cause a worldwide pandemic. The most common symptoms are fever, cough, headache, dyspnoea, sore throat, vomiting, and diarrhoea. Some patients may present with end-organ failure. Acute respiratory distress syndrome (ARDS), shock, acute kidney injury, or even death.\(^2\,\(^1\)\) In children, the symptoms are likely milder; however, children can have more severe symptoms in rare cases. In April 2020, the first cases of an atypical Kawasaki disease or toxic shock-like syndrome had been reported, and since then, more cases have been reported.\(^3\) The condition has been termed multi-system inflammatory syndrome in children (MIS-C), which is a systemic inflammatory condition affecting various body organs.\(^4\,\(^5\)\) This syndrome usually presents 2–4 weeks after COVID-19 infection. The prevalence is rare, with the incidence reported 2/100 000. There are very few case reports of a similar condition in adults, termed multi-system inflammatory syndrome in adults (MIS-A).\(^6\,\(^7\)\) It has been suggested that this syndrome results from an abnormal immune response to the virus. As time elapses, more cases will be studied to explain the link of MIS-C/MIS-A with COVID-19.

Timeline

| Emergency Department | Transfer to MICU | MICU Stay | Back to Floor/Discharge |
|----------------------|-----------------|-----------|-------------------------|
| Symptoms: Abdominal pain, watery diarrhoea, high grade fever cough, shortness of breath, nausea, vomiting, tachycardic. | Patient remained tachycardic, fever, hypotension, signs of shock, so transferred to MICU. | With no improvement on current therapy along with constellation of acute colitis, myocarditis, conjunctival injection, lymphadenopathy, negative infectious work-up = MIS-A was diagnosed. | After 5 days, IV methyl-prednisone was switched to oral prednisone 60 mg/day and tapered over 3 weeks. |
| Hx of COVID-19 infection 8 weeks ago. | Patient started on IV Norepinephrine. | Developed mild respiratory distress with SpO2 in mid 80s. | For heart failure, started IV furosemide along with oral B-Blockers and ACE-inhibitors. |
| Physical Exam: Significant scleral injection with mild conjunctivitis bilaterally. Before transfer to our facility, the patient had a negative SARS-CoV-2 Polymerase chain reaction (PCR) by nasopharyngeal swab and a negative rapid antigen test in our ED. Lab work showed leukocytosis with lymphopenia, thrombocytopenia, elevated C-reactive protein (CRP) at 27.4 mg/dL, low fibrinogen level 133 mg/dL, and D-Dimer at 2270 ng/mL FEU. Infectious workup was negative, including blood and urine cultures, stool enteric panel by PCR, and a respiratory viral panel. Computed tomography of the abdomen and pelvis indicated right-sided colitis, right mesenteric lymphadenopathy, and mild hepato-splenomegaly (see Figure 2A). His chest X-ray (CXR) was normal. On admission, the patient was started on piperacillin–tazobactam for suspected colitis. Over the next 24 h, the patient remained tachycardic with intermittent fevers >102°F with the development of hypotension that was initially responsive to intravenous (IV) fluid boluses. He was subsequently transferred to the medical intensive care unit (MICU) for possible septic shock and was started on IV norepinephrine. The patient developed mild respiratory distress with a drop in oxygen saturation to 85%, requiring nasal cannula. A repeat CXR revealed bilateral pulmonary oedema, raising concern for cardiac dysfunction (see Figure 2B). Pro-brain natriuretic peptide (BNP) was |
| Labs: ↑ CRP, D-Dimer, WBCs, ↓ fibrinogen. | Pan-negative infectious work-up. | CXR: bilateral pulmonary edema; TTE = reduced EF 40–44% with mild global hypokinesis of left ventricle. | Patient was discharged on lisinopril, carvedilol and furosemide for heart failure. |
| CT Abdomen/Pelvis: Right-sided colitis and mesenteric lymphadenopathy. | | Over next 24 h, weaned off norepinephrine, BP stabilized and was transferred out of MICU. | After 3 months, follow-up → complete resolution of symptoms. |

Case presentation

A 20-year-old previously healthy Caucasian male presented to the emergency department (ED) as a transfer from an outside hospital for further evaluation of abdominal pain, watery diarrhoea, nausea, vomiting, fever, chills, cough, and shortness of breath. Six days before admission, the patient was evaluated at an outside ED, where he was prescribed oral ciprofloxacin and metronidazole for colitis, but symptoms continued to progress. The abdominal pain was achy, diffuse, and worst in the right lower quadrant. He experienced watery diarrhoea, ~10–15 bowel movements per day. In the ED, the patient had a high-grade fever of 102.7°F with accompanying chills and sweating. The patient was tachycardic (heart rate 130 b.p.m.) [see Figure 1 for Electrocardiography (EKG)] but normotensive with an oxygen saturation of 94% on arrival. On physical exam, the posterior oropharynx was erythematous with exudates. The patient had enlarged, tender, bilateral cervical and left inguinal lymphadenopathy, and diffuse abdominal tenderness. The patient was also noted to have a significant scleral injection with mild conjunctivitis bilaterally. Before transferring to our facility, the patient had a negative SARS-CoV-2 Polymerase chain reaction (PCR) by nasopharyngeal swab and a negative rapid antigen test in our ED. Lab work showed leukocytosis with lymphopenia, thrombocytopenia, elevated C-reactive protein (CRP) at 27.4 mg/dL, low fibrinogen level 133 mg/dL, and D-Dimer at 2270 ng/mL FEU. Infectious workup was negative, including blood and urine cultures, stool enteric panel by PCR, and a respiratory viral panel. Computed tomography of the abdomen and pelvis indicated right-sided colitis, right mesenteric lymphadenopathy, and mild hepato-splenomegaly (see Figure 2A). His chest X-ray (CXR) was normal. On admission, the patient was started on piperacillin–tazobactam for suspected colitis. Over the next 24 h, the patient remained tachycardic with intermittent fevers >102°F with the development of hypotension that was initially responsive to intravenous (IV) fluid boluses. He was subsequently transferred to the medical intensive care unit (MICU) for possible septic shock and was started on IV norepinephrine. The patient developed mild respiratory distress with a drop in oxygen saturation to 85%, requiring nasal cannula. A repeat CXR revealed bilateral pulmonary oedema, raising concern for cardiac dysfunction (see Figure 2B). Pro-brain natriuretic peptide (BNP) was
Troponin T high sensitivity was also increased at 148.9 ng/L. Trans-thoracic echocardiography showed dilated cardiac chambers, reduced left ventricular (LV) systolic function of 40–44% with mild global hypokinesis, normal right ventricular systolic function, normal aortic root, and small pericardial effusion with no evidence of tamponade physiology. All visualized valves appeared normal in structure and motion. Colour and Doppler analysis showed mild pulmonic and tricuspid regurgitation (see Videos 1 and 2). This raised the concern for possible myocarditis. The infectious disease team was consulted, and on repeat discussion with the patient, it was found that he had been diagnosed with COVID-19 8 weeks prior. Given that the patient was not improving, the constellation of acute colitis, myocarditis, lymphadenopathy, conjunctival injection, and negative infectious workup, the diagnosis of MIS-C/MIS-
A was concluded. Based on currently available data and case reports, the patient was treated with intravenous immunoglobins (IVIG) 2 g/kg (dose was divided into 1 g/kg q24 h for two doses due to his depressed ejection fraction) and IV methylprednisolone 125 mg IV q12 h. Within 4 h of receiving the medications, the patient’s heart rate normalized, he defervesced, and he reported improvement in his abdominal pain. Over the next 24 h, he was weaned off norepinephrine and, the following day, was transferred out of the MICU. This confirmed the MIS-C/MIS-A diagnosis after adequate response to the treatment. After 5 days, his IV methylprednisolone was transitioned to oral prednisone 60 mg/day and tapered over 3 weeks. Regarding his heart failure with reduced ejection fraction, he was started on IV furosemide and angiotensin-converting enzyme inhibitor. He was discharged on lisinopril, carvedilol, and furosemide for heart failure. The patient was seen at follow-up after 3 months and has a complete resolution of symptoms, and was scheduled for trans-thoracic echocardiogram (TTE) but has not been done yet.

**Discussion**

The pathophysiology of MIS-C is not well understood. One theory postulated an abnormal immune response to COVID-19 occurring after acute infection. The study involved peripheral leucocyte phenotyping in children with MIS-C. High levels of interleukins 6, 8, 10, 17 and high CD64 and Human Leukocyte Antigen – DR isotype (HLA-DR) expression were observed in the acute phase of the infection. This indicated potential immune dysregulation leading to MIS-C in COVID-19 infected children. We would also like to shed light on the mechanisms of myocardial injury in MIS-C. Different possible causes have been identified, namely, viral myocarditis, stress cardiomyopathy, hypoxia, systemic inflammation, and rarely ischaemia. A subset of MIS-C patients presented with hypotension and shock along with more common symptoms.

The presenting symptoms of MIS-C patients cover a wide spectrum from persistent fever, gastrointestinal symptoms, conjunctivitis, respiratory symptoms (cough, shortness of breath), neurological symptoms, rash, and lymphadenopathy. Common clinical findings observed are shock, hypotension, myocardial dysfunction, acute respiratory failure, and pleural/pericardial effusions. The laboratory findings include pancytopenia, elevated cardiac markers including troponin and BNP, increased inflammatory markers (CRP, Erythrocyte sedimentation rate, D-Dimer, fibrinogen, and interleukin-6), hypoaalbuminaemia, hypertriglyceridaemia, and high liver enzymes. Common cardiac imaging findings with TTE include decreased LV function as well as coronary artery aneurysms and pericardial effusion. Abdominal ultrasound and computer tomography often reveal ascites, mesenteric inflammation, and adenopathy. The diagnosis should be made after excluding other possibilities.

Similarly, cases of MIS-A presenting with fever, elevated inflammatory markers, gastrointestinal symptoms, shock, and LV systolic dysfunction. Chau et al. reported a case series of young adult males with COVID-19 who presented with shock, hyperinflammatory biomarkers, and multi-organ failure, including bi-ventricular failure. Morris et al. reported 27 adults with cardiovascular, gastrointestinal, dermatologic, and neurologic symptoms who concurrently tested positive for COVID-19. A retrospective study in paediatrics reviewed confirmed cases of MIS-C. Many of the patients experienced thrombocytopenia, high BNP and D-Dimer, and increased inflammatory markers. Immunomodulatory therapy, including IVIG (71%), corticosteroids (61%), and the IL-1 receptor antagonist anakinra (18%), provided clinical improvement in all the cases. Moreover, another study included MIS-C patients with symptoms, such as fever, acute myocardial dysfunction, gastrointestinal symptoms, and conjunctivitis. The management of these patients included immunomodulatory therapy and cardiac support. On a similar note, surveillance targeted across paediatric health centres in the USA for MIS-C provided results like our patient. Different organ systems were affected: gastrointestinal system (92%), respiratory (70%), cardiovascular (80%), mucocutaneous (74%), and haematologic (76%). We aimed to report this case to shed light on the need for early diagnosis and treatment in those patients and report that MIS-C can occur in adults, and immunoglobulin and corticosteroids greatly improve the outcome.
Lead author biography

I am Nitish Mittal, a third year medical student at Texas Tech University Health Sciences Center, Lubbock, TX, USA. I have performed clinical research for past 3 years and cultivated my knowledge base through different projects, ranging from transcatheter aortic valve replacement (TAVR) and anti-platelets to multi-system inflammatory syndrome in adults (MIS-A). I have given several oral/poster presentations in various conferences, namely Cardiovascular Research Technologies and New Cardiovascular Horizons. I completed my high school in India followed by Bachelor of Science in Chemistry from Texas Tech University. In free-time, I enjoy playing tennis/cricket and love spending time with family and friends.

Supplementary material

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

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

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

**Conflict of interest:** The authors have no financial conflicts of interest to disclose.

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