Multisystem inflammatory syndrome in an adult (MIS-A) due to SARS-CoV-2 infection presenting to a South African hospital

Sarvesh Balkaran, 1 Samuel Peres Surdut, 2 David Morris Rose, 2 Robert Freercks 3

SUMMARY
Kawasaki-like multisystem inflammatory syndrome related to SARS-CoV-2 infection is a well-described condition in children and adolescents (MIS-C) and now also in adults (MIS-A). We report a case of MIS-A in a previously well woman in her mid-30s who presented with vasopressor-dependent shock 2 weeks after initial recovery from suspected SARS-CoV-2 infection, accompanied by fever, vomiting, diarrhoea, weakness, arthralgia, rash, cough and headache. Examination was notable for fever, tachycardia, hypotension, cervical lymphadenopathy, mucocutaneous involvement, neck stiffness, pansystolic murmur and bilateral crepitations. Inflammatory markers were elevated. Echocardiogram showed mitral regurgitation with preserved ejection fraction. She was treated with vasopressors, admitted to the intensive care unit and subsequently required invasive mechanical ventilation. Both PCR and antibodies for SARS-CoV-2 were positive. Treatment with intravenous methylprednisolone and intravenous immunoglobulin was initiated with rapid improvement in clinical condition and inflammatory markers. She has since made a full recovery with normal echocardiogram 8 months later.

BACKGROUND
To date, COVID-19 caused by SARS-CoV-2 has resulted in over 200 million cases and over 4 million deaths worldwide. 1 During the early stages of the pandemic, reports emerged of a multisystem inflammatory syndrome occurring in children and adolescents, with features similar to Kawasaki disease (KD), KD shock syndrome and toxic shock syndrome. 2–4 The syndrome, later termed multisystem inflammatory syndrome in children (MIS-C), is characterised by fever, elevated inflammatory biomarkers and multiorgan involvement. 2–5 The condition typically presents at least 2 weeks after acute SARS-CoV-2 infection, although not all patients give a history of preceding symptomatic infection. 7 While not fully understood, the prevailing theory underpinning the pathophysiology is that of excessive post-infectious immune activation resulting in an aberrant inflammatory response, autoantigen recognition and subsequent tissue damage and end-organ dysfunction. 3 8–10 PCR for SARS-CoV-2 is frequently negative in such patients and positive serological testing suggests evidence of recent infection, 2 11 12 though persistent PCR positivity in these patients is well described. 3 8 9 13 A similar syndrome has subsequently been recognised in adults 7 8 11 13–21 and a case definition for multisystem inflammatory syndrome in adults (MIS-A) was published by the Centers for Disease Control and Prevention (CDC) in May 2021. 22 However, few cases of MIS-A have been reported in Africa, where unique challenges exist which may limit the recognition and prompt appropriate management of this life-threatening condition. Our aim in writing this report is to contribute to the growing body of literature around MIS-A and provide a South African perspective with regard to its identification and treatment in day-to-day clinical practice within a resource-limited context.

CASE PRESENTATION
A woman in her mid-30s was referred by her primary healthcare doctor to the emergency department at a tertiary hospital in South Africa in late 2020. She presented with a febrile illness and circulatory shock, was started on vasopressor support with epinephrine and was subsequently transferred to the acute medical admissions resuscitation area. Three weeks prior to her admission, she developed a sore throat, myalgia and fatigue which resolved spontaneously after 2–3 days. However, 2 weeks later, she developed fever, vomiting, diarrhoea, generalised weakness, arthralgia, a rash, dry cough and intermittent headache, prompting a visit to her general practitioner. She had no history of COVID-19 illness, and a SARS-CoV-2 PCR test performed on relapse of her symptoms 5 days prior to her presentation was negative. Other than an episode of non-severe malaria in early childhood, she had been well up until this illness. She is a non-smoker and does not use ethanol.

On physical examination, she was alert and oriented, had a temperature of 39°C, heart rate of 140 beats/min, blood pressure of 70/58 mm Hg and features of poor peripheral perfusion. The jugular venous pulse was not elevated. She had a respiratory rate of 28 breaths/min and peripheral oxygen saturation of 97% in room air. She was pale, dehydrated, mildly icteric and not oedematous. Submandibular and cervical lymphadenopathy was present, as were angular cheilitis, non-purulent conjunctivitis and a transient non-tender erythematous macular rash on her legs. Auscultation revealed a 3/6 pansystolic murmur consistent with mitral regurgitation (MR) and bilateral basal crepitations. There was no evidence of peritonitis, joint effusions or synovitis. Neck stiffness was present, but there was no focal neurological deficit. ECG (figure 1)
A case report showed a sinus tachycardia and PR depression in standard lead II consistent with acute pericarditis; there was no evidence of myocardial ischaemia.

Broad-spectrum intravenous (IV) antibiotic cover was initiated on admission but she continued to deteriorate over the first 24 hours and she was transferred to the intensive care unit (ICU) for further management, requiring intubation and mechanical ventilation shortly thereafter due to escalating vasopressor requirements and severe tachypnoea, although she did not require supplemental oxygen. Chest radiograph (figure 2) on admission to ICU showed bilateral, though predominantly right-sided, perihilar and basal ground-glass opacifications consistent with pulmonary oedema.

INVESTIGATIONS

Initial laboratory investigations (table 1) showed an elevated white cell count with neutrophilia and lymphopenia, elevated C reactive protein, lactate dehydrogenase, procalcitonin (PCT), ferritin and highly sensitive troponin I, as well as Kidney Disease Improving Global Outcomes Stage 2 acute kidney injury and mild elevation of aminotransferase enzymes. Pregnancy was excluded. Cerebrospinal fluid analysis did not suggest meningitis. Point-of-care echocardiography showed moderate to severe MR and a left ventricular ejection fraction (LVEF) of 62%, with no regional wall motion abnormalities. No left ventricular dilatation or endocardial vegetations were noted.

A SARS-CoV-2 PCR done on presentation to the emergency unit was later found to be positive, as was qualitative testing for SARS-CoV-2 nucleocapsid IgG antibodies, supporting a diagnosis of MIS-A. Antinuclear antibodies, rheumatoid factor and serological tests for HIV and viral hepatitis were negative. Blood cultures done on admission and serially throughout the patient’s stay in the ICU remained negative.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included septic shock, acute rheumatic fever, systemic lupus erythematosus, adult-onset Still’s disease and acute viral infections, including severe SARS-CoV-2 infection and HIV seroconversion. Ultimately, a diagnosis of Kawasaki-like multisystem inflammatory syndrome associated with SARS-CoV-2 infection complicated by myopericarditis and shock was established, as supported by the clinical features and SARS-CoV-2 antibody positivity.

TREATMENT

The primary mode of treatment for patients with MIS-A is supportive care with prompt and early organ support. The patient was started on IV methylprednisolone 500 mg daily for 3 days on day 2 of admission, IV immunoglobulin (IVIg) 2 g/kg administered over 2 days, as well as colchicine 0.5 mg two times per day and aspirin 300 mg daily. Oral prednisone 0.5 mg/kg daily was initiated after completion of the methylprednisolone pulse. Standard adjunctive COVID-19 treatment as per the hospital and national guidelines at the time, including zinc, vitamin D, vitamin C, niacin and prophylactic low-molecular-weight heparin was also initiated. Antibiotics were continued for 5 days, although no bacterial source of sepsis was ever identified.

OUTCOME AND FOLLOW-UP

Response to the above therapy was dramatic, with rapid improvement in blood pressure and cessation of vasopressor support within 48 hours of starting immunosuppressive therapy. Her inflammatory markers improved steadily after initiation of treatment, as did her renal function and anaemia (see table 1). She developed transient atrial fibrillation on day 5 of her admission which was successfully electrically cardioverted. Her ventilatory support was eventually weaned and she was successfully extubated to room air on day 7 of admission. Her ICU stay was further complicated by a transient but marked delirium. This was thought to possibly be due to the disease entity itself, high-dose steroid therapy, ICU delirium or a combination thereof. She was transferred to a general medical ward on day 8 for ongoing treatment and rehabilitation by our multidisciplinary team, including physical, occupational and speech therapy and dietetics. She was discharged home 1 week later on aspirin, low-molecular-weight heparin and a tapering course of prednisone for 2 weeks. She has since made a full recovery. Repeat echocardiogram at 1 month demonstrated complete resolution of the MR and good systolic function with preserved LVEF. She was completely well at her 6-month review and has now returned to full-time employment with

Figure 1 Features of acute pericarditis—PR depression in standard lead II.

Figure 2 Chest radiograph showing bilateral perihilar and lower zone opacifications suggestive of pulmonary oedema. Date: 31 August 2021.
Underlying pathophysiological mechanisms are not yet fully understood. Shock are common in both MIS-C and MIS-A, though the presence of moderate to severe MR, making an accurate assessment of the left ventricular function difficult in this instance.

Cardiac injury and myocardial involvement. Myocardial injury is evident in view of the raised troponin and may explain the transient significant MR that fully resolved at follow-up. Several case reports and series report shock and reduced LVEF to be prominent features in patients with MIS-A. Though at least one report mentions features of profound clinical shock with preserved LVEF on echocardiography, suggesting a potential mechanism for shock other than left ventricular dysfunction. Although the LVEF in our patient was measured as 62%, this is likely an overestimate given the presence of moderate to severe MR, making an accurate assessment of the left ventricular function difficult in this instance.

IV methylprednisolone and IVIg have been proposed and used as initial treatment options for MIS-C. MIS-A has been successfully treated with either or both of the agents, with the majority of patients surviving and demonstrating a return to normal cardiac function.

### DISCUSSION

This patient presented with a severe multiorgan inflammatory state 3 weeks after a transient viral illness which was likely to have been acute SARS-CoV-2 infection given the positive antibodies. The positive PCR on admission is likely due to persistence of the viral nucleic acid and has been described in this setting, although a negative PCR as occurred 5 days prior to her admission is also commonly seen. While the timing is supportive of MIS-A, the main alternative diagnosis considered was septic shock. There is no reliable way to rule out sepsis at the initial presentation and this remains a diagnosis of exclusion. However, clinicians should suspect MIS-A where patients have a history of COVID-19 and who present with cardiogenic shock or multiorgan dysfunction in the absence of hypoxaemia. The presence of a raised PCT is in fact supportive of MIS-A where the mean PCT level in a case series of MIS-C was 5.4 µg/L. While the extrapulmonary manifestations of COVID-19 are protean, these are generally always accompanied by respiratory failure, thus highlighting the need to consider MIS-A in the absence of respiratory compromise. The CDC case definition for MIS-A is presented in table 2. Our patient fulfils the age and timing criteria and both primary clinical criteria, showing evidence of myopericarditis (as demonstrated by the initial ECG findings and elevated troponin I) as well as a rash and non-purulent conjunctivitis. In addition, she meets all secondary criteria except for thrombocytopenia (although the initial platelet count was not accurately obtainable due to platelet clumping as noted in table 1). Laboratory evidence of inflammation and SARS-CoV-2 infection was also present. No alternative diagnosis was more likely especially given the lack of response to IV antibiotics and negative serological testing for other plausible conditions. Cardiac injury and shock are common in both MIS-C and MIS-A, though the underlying pathophysiological mechanisms are not yet fully understood. Our patient had evidence of pericardial and myocardial involvement. Myocardial injury is evident in view of the raised troponin and may explain the transient significant MR that fully resolved at follow-up. Several

### Table 1  Serial laboratory investigations

| Test (reference range) | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 |
|------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| White cell count (3.9–12.6×10⁹/L) | 25    | 25.4  | 18    | 13.9  | 10.5  | 10.0  | 10.2  | 15.3  |
| Neutrophil count (1.6–8.3×10⁹/L) | 21.8  |       |       |       |       |       |       |       |
| Lymphocyte count (1.4–4.5×10⁹/L) | 1.00  |       |       |       |       |       |       |       |
| Haemoglobin (120–150g/L) | 100.6 | 70.9  | 70.3  | 70.1  | 70.5  | 80.5  | 90.6  | 100.6 |
| Platelets (186–454×10⁹/L) | Clumped | 195   | 290   | 267   | 256   | 272   | 316   | 348   |
| Creatinine (49–90µmol/L) | 116   | 81    | 71    | 83    | 70    | 50    | 40    | 33    |
| C reactive protein (<10mg/L) | 410   | 309   | 275   | 155   | 80    | 45    | 44    | 33    |
| Procalcitonin (<0.1µg/L)  | 9.17  | 6.8   | 5.07  | 2.41  | 1.17  | 0.58  | 0.37  | 0.29  |
| Lactate dehydrogenase (100–190U/L) | 304   |       |       |       |       |       |       |       |
| Ferritin (11–307µg/L)  | 21.8  |       |       |       |       |       |       |       |
| Troponin I (<18ng/L) | 445   |       |       |       |       |       |       |       |
| D-dimer (<0.25mg/L)  | 4.79  |       |       |       |       |       |       |       |
| Total bilirubin (5–21µmol/L) | 42    | 30    | 11    |       | 10    | 13    | 16    |       |
| Conjugated bilirubin (0–3µmol/L) | 18    |       |       |       |       |       |       |       |
| Alanine transaminase (7–35U/L) | 61    |       |       |       |       |       |       |       |
| Aspartate transaminase (13–35U/L) | 60    |       |       |       |       |       |       |       |

### Table 2  CDC case definition for MIS-A—a patient aged ≥21 years, hospitalised for ≥24 hours or with illness resulting in death, without a more likely alternative diagnosis and who meets the following clinical and laboratory criteria

| I. Clinical criteria—subjective or documented fever (≥38°C) and at least 3 of the following clinical criteria present for ≥24 hours prior to admission or within 3 days of admission |
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| A. Primary clinical criteria (at least 1 must be present) |
| 1. Severe cardiac illness—including myocarditis, pericarditis, coronary artery dilatation/aneurysm, or new-onset right or left ventricular dysfunction (<50%), 2nd/3rd degree A-V block, or ventricular tachycardia. Cardiac arrest alone does not meet this criterion. |
| 2. Rash AND non-purulent conjunctivitis |
| B. Secondary clinical criteria |
| 1. New-onset neurological signs and symptoms—including encephalopathy in a patient without prior cognitive impairment, seizures, meningeval signs or peripheral neuropathy (including Guillain-Barré syndrome) |
| 2. Shock or hypotension not attributable to medical therapy (eg, sedation, renal replacement therapy) |
| 3. Abdominal pain, vomiting or diarrhoea |
| 4. Thrombocytopenia (<150 000/µL) |

| II. Laboratory evidence—the presence of laboratory evidence of inflammation AND SARS-CoV-2 infection |
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| A. Elevated levels of at least 2 of the following: CRP, PCT, IL-6, Erythrocyte sedimentation rate, ferritin |
| B. A positive SARS-CoV-2 test during the current illness by PCR, serology or antigen detection |

CDC, Centers for Disease Control and Prevention; CRP, C reactive protein; IL-6, interleukin 6; MIS-A, multisystem inflammatory syndrome in adults; PCT, procalcitonin.
to premorbid function at later review. However, no definitive treatment guidelines for MIS-A currently exist. Our patient showed a rapid improvement in clinical condition and inflammatory markers on initiation of combination therapy with glucocorticoids and IVIg. Tocilizumab, a monoclonal antibody directed against the interleukin 6 receptor, has also been used in some reports. Although tocilizumab is available in our facility, there is still little evidence to support its use in MIS-A. In addition, in the context of a high community prevalence of latent tuberculosis as well as the possibility of intercurrent sepsis and severe ICU-acquired infections, it was felt that the potential benefits of tocilizumab use did not outweigh associated risks. It should also be noted that access to tocilizumab remains limited in many parts of South Africa and other similar low/middle-income countries worldwide.

Close to 3 million cases of COVID-19 have so far been diagnosed in South Africa, yet only a few isolated reports of MIS-A in the country have been published to date. One reason for this may simply be a lack of knowledge about the condition among adult clinicians, resulting in patients with seemingly disparate features of MIS-A not being considered as part of a single clinical entity and a potential for underdiagnosis. Another factor is the lack of appropriate national infrastructure which limits patients’ access to healthcare services. For those patients who would present with compatible clinical features, there are often significant delays in evaluation, diagnosis and management owing to pervasive resource constraints and lack of availability of appropriate diagnostic investigations (such as specialised laboratory tests, echocardiography and other advanced imaging) and treatment modalities (such as ICU facilities, IVIg and monoclonal antibodies). It is unlikely that these obstacles will be overcome in the near future and clinicians need to maintain a high index of suspicion for MIS-A in patients presenting with the appropriate time course.

With these above challenges in mind, this report will hopefully aid in further disseminating knowledge about COVID-19-related MIS-A and facilitate its swift recognition and treatment.

Patient’s perspective

At first, I could say mine were mild symptoms, where I felt like any flu but with a running tummy for one day, tiredness, sweating and simple cough. I never had either loss of smell or loss of taste. After about 15 days since the first symptom, I noted my lymph node under my right ear was swollen. Gradually the swelling increased and started to give headache and pain below my chest, for which I visited a GP. The doctor prescribed me antibiotics and syrup and I was told am COVID-19 negative. After 5 days I went back for a checkup, but by then my situation had worsened. For example, my fingers and toes were freezing and I was pale. That is when I decided to visit another GP, from which I was admitted to hospital. During the ICU stay, even though I had no feeling of pain as I was sedated, I had hallucinations. Following my discharge to the recovery ward, my body was numb and my voice gone. However, because of all the extraordinary care and support I get from the doctors and nurses, for which I am so grateful, I recovered and had hope that I will make it through. My strength and health condition progressed speedily and today I am as healthy as I was before COVID-19.

Learning points

► Multisystem inflammatory syndrome in adults (MIS-A) is a severe, complex and potentially life-threatening complication of COVID-19, typically occurring several days to weeks after resolution of initial acute infection with SARS-CoV-2 and is characterised by fever, multiorgan involvement and raised inflammatory markers.
► Clinicians should always consider MIS-A in the context of the COVID-19 pandemic in patients who present with cardiogenic shock or multiorgan dysfunction in the absence of hypoxaemia. This will allow earlier initiation of appropriate therapy after exclusion of common alternatives.
► Not all patients have a history of preceding symptomatic infection underscoring the importance of adjunctive serological testing.
► Shock requiring support with vasopressors is a common and important manifestation of MIS-A, but usually improves with appropriate treatment. Initial treatment with intravenous methylprednisolone and IVIg has been successful in many reported cases.
► Diagnosis and treatment of MIS-A may be delayed or not possible in healthcare settings with limited resources, such as many low/middle-income countries, and clinicians should remain vigilant in order to recognise this important clinical syndrome.

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ORCID iD Robert Freercks http://orcid.org/0000-0002-7939-1352

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