CASE REPORT

Case series of multisystem inflammatory syndrome in adults in Melaka, Malaysia

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SUMMARY

Multisystem inflammatory syndrome in children (MIS-C) is a post-viral immunological or hyperinflammatory complication of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection commonly seen in older children.[1] During the course of COVID-19 pandemic, reports of new MIS-C cases have been increasing worldwide since it was first described in April 2020. Since June 2020, several cases of Multisystem Inflammatory Syndrome in Adults (MIS-A) have been reported by Chau et al.[2], Magro et al.[3] and Oxley et al.[4] The first MIS-A case in Malaysia was diagnosed in July 2021 and reported on January 2022, by Seow et al.[5] This review describes in detail three additional MIS-A cases up to February 2022 that were subsequently diagnosed since the first reported case in Hospital Melaka, Malaysia. All cases were diagnosed via case definition by Centers for Disease Control and Prevention (CDC).

CASE PRESENTATION

Case Report 1

A 45-year-old gentleman who was an active smoker with no known medical illness was diagnosed with COVID-19 infection Category 1 through contact screening. He was then quarantined for 2 weeks in a low-risk COVID-19 quarantine centre as per Malaysian protocol at that time. The quarantine was uneventful, for he did not develop any symptoms or warning signs or require any medical intervention, and he was discharged well.

On day 13 of his illness, he developed intermittent low-grade fever, non-productive cough, sore throat, abdominal discomfort and diarrhoea. Despite a short course of empirical antibiotics for presumed infective diarrhoea prescribed by a general practitioner, his symptoms persisted, and he sought medical attention from the Emergency Department of Hospital Melaka, Malaysia. There, he required inotropic support due to hypotension that did not respond to fluid resuscitation, albeit still able to saturate well under room air. Blood parameters revealed thrombocytopenia, raised inflammatory markers and evidence of multi-organs damage, including raised cardiac enzymes, hepatitis and non-oliguric acute kidney injury (KDIGO-AKI Stage 2).

Despite the initiation of empirical broad-spectrum antibiotics, his condition did not improve, and there were no positive bacterial cultures to suggest an acute infection. As he fulfilled the MIS-A diagnostic criteria (one primary clinical criterion [a] + three secondary clinical criteria [b, c, d] + two laboratory criteria [A, B]), he was given a dose of intravenous immunoglobulin (IVIg) on day 2 of admission. There were remarkable clinical and biochemical improvements, where the inotropic support was weaned off on day 4 after the given IVIg dose, improving transaminitis and kidney injury. Inflammatory markers also showed a decreasing trend. He continued to improve and was discharged after seven days of hospitalization.

Case Report 2

A 73-year-old Malay gentleman who was an active smoker with no known medical illness was diagnosed with COVID-19 infection Category 1 through contact screening and subsequently quarantined for 2 weeks at a quarantine centre. His quarantine was uneventful, and he did not require any medical intervention.

He was asymptomatic and well until day 17 of the illness, when he developed a fever with chills and rigours, gradual onset of shortness of breath and lethargy for three days at home. As symptoms worsened, he was brought to the emergency department, where he was intubated and started on inotropic support due to severe acute respiratory distress syndrome (ARDS with PaO_2/FiO_2 < 100) and cardiogenic shock. Blood investigations reported thrombocytopenia, raised inflammatory markers and evidence of multi-organ damage, including raised cardiac enzymes, hepatitis and non-oliguric acute kidney injury (KDIGO-AKI Stage 2).

He was started on empirical broad-spectrum antibiotics and anticoagulant for venous thromboembolism prophylaxis. However, his condition did not improve, and there were no positive bacterial cultures to suggest an acute infection. With a recent history of COVID-19 infection and overall clinical picture suggestive of hyperinflammatory syndrome, the diagnosis of MIS-A was considered, and he was later found to fulfil the diagnostic criteria (one primary clinical criterion [a] + two secondary clinical criteria [b, d] + two laboratory criteria [A, B]). He was given a dose of IVIg on day 2 of admission with corticosteroids. Despite the reduction in inflammatory markers, he succumbed to death on day 3 of admission due to fulminant multi-organ failure.

Case Report 3

A 55-year-old Malay gentleman who was an active smoker with underlying hypertension was diagnosed with RVD disease during his current admission. He was initially treated for COVID-19 pneumonia Category 5, for which he was intubated for severe respiratory distress. In view of his newly diagnosed retroviral disease (RVD) with low CD4 counts, compatible chest X-ray changes and difficulty weaning

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Table I: Case definition of Multisystem Inflammatory Syndrome in Adults (MIS-A)

Definition of MIS-A by CDC[6]
A patient aged ≥21 years hospitalised for ≥24 hours, or with an illness resulting in death, who meets the following clinical and laboratory criteria. The patient should not have a more likely alternative diagnosis for the illness (e.g., bacterial sepsis, exacerbation of a chronic medical condition).
Clinical criteria
Subjective fever or documented fever (≥38.0 C) for ≥24 hours prior to hospitalisation or within the first 3 days of hospitalisation* and at least three of the following clinical criteria occurring prior to hospitalization or within the first 3 days of hospitalization*. At least one must be a primary clinical criterion.
A. Primary clinical criteria
1. Severe cardiac illness Includes myocarditis, pericarditis, coronary artery dilatation/aneurysm or new-onset right or left ventricular dysfunction (LVEF<50%), 2nd/3rd degree A-V block or ventricular tachycardia (Note: cardiac arrest alone does not meet this criterion)
2. Rash AND non-purulent conjunctivitis
B. Secondary clinical criteria
1. New-onset neurologic signs and symptoms include encephalopathy in a patient without prior cognitive impairment, seizures, meningeal signs or peripheral neuropathy (including Guillain-Barré syndrome)
2. Shock or hypotension not attributable to medical therapy (e.g., sedation, renal replacement therapy)
3. Abdominal pain, vomiting or diarrhoea
4. Thrombocytopenia (platelet count <150,000/ microliter)
Laboratory evidence
The presence of laboratory evidence of inflammation AND SARS-CoV-2 infection.
A. Elevated levels of at least TWO of the following: C-reactive protein (CRP), ferritin, IL-6, erythrocyte sedimentation rate and procalcitonin
B. A positive SARS-CoV-2 test for current or recent infection by RT-PCR, serology or antigen detection

NOTE: *These criteria must be met by the end of hospital day 3, where the date of hospital admission is hospital day 0.

oxygen support, he was also treated for *Pneumocystis Jirovecii pneumonia*. He had a prolonged history of ventilation during this hospitalization, complicated by severe COVID-19 infection and sequential ventilator-associated pneumonia. He also developed pulmonary embolism (PE), as evidenced by computed tomography pulmonary angiogram (CTPA), with additional findings of bronchiectasis and fibrotic lung changes, which were suggestive of underlying chronic lung disease. He responded well to treatments given for infections and PE thus was subsequently planned for tracheostomy, followed by a period of rehabilitation to optimise his conditions prior to discharge.

Towards the end of the sixth week from the date his SARS-CoV-2 PCR was positive, he suddenly deteriorated as he developed fever and breathlessness, followed by cardiac arrest, and required cardiopulmonary resuscitation. During resuscitation, he had refractory ventricular tachycardia that required multiple electrical and chemical cardioversions. A repeat CTPA showed worsening of pre-existing PE with new emboli seen in another pulmonary artery branch, despite being on a therapeutic dose of anticoagulant. In view of poor GCS recovery post-resuscitation, computed tomography (CT) brain imaging was performed and showed features of vasculitis with intraparenchymal bleeds and thrombus within intracranial vessels. An echocardiogram showed akinesia over the mid-apex anteroseptal wall; in this case, it might be contributed by coronary artery involvement.

Blood investigations showed raised inflammatory markers, coagulopathy and evidence of multi-organ damage, including raised cardiac enzymes, hepatitis and acute kidney injury. Overall clinical, biochemical and radiographical findings were suggestive of possible vasculitis affecting multiple organs (brain, heart and lungs), although acute kidney injury and transaminitis might be multifactorial due to post-cardiac arrest and/or vasculitis.

In view of his recent SAR-CoV-2 infection, the diagnosis of MIS-A was considered. IVIg was not given due to concerns about multiple thrombosis; thus, he was given high-dose steroids; unfortunately, he succumbed to death after three days of steroids.

Case Report 4

A 65-year-old Malay gentleman with type 2 diabetes mellitus was hospitalized and treated for COVID-19 infection Category 4 with a short course of corticosteroids. He was discharged home on day 17 of his illness after weaning off oxygen support.

On day 27 of his illness, he was admitted again with a fever (40 °C), shortness of breath for 2 days, and clinically in shock, resulting in multi-organ dysfunction. Despite elevated inflammatory markers, platelet count and troponin-I were still within normal range. He was initially treated for septic shock secondary to pneumonia with an empirical antibiotic, but there was no improvement and no positive bacterial culture.

Subsequent blood investigations showed a reduction in platelet count with an increase in inflammatory markers. Cardiac dysfunction was evident by the pericardial effusion noted on the echocardiogram with a markedly raised repeated troponin-I level. A retrospective review concluded that he had MIS-A as he fulfilled the criteria (one primary clinical criterion [a] + two secondary clinical criteria [b, d] + two laboratory criteria [A, B]) on day 3 of admission. In view of his poor kidney function and urine output and the fact that he was intolerable of dialysis, physicians opted for high-dose steroids instead of IVIg. Unfortunately, he succumbed to death soon after the initiation of high-dose steroids due to irreversible multi-organ failure.

Table II: Summary of all cases with investigations

Summary of the MIS-A cases									
Date of admission	**Age (years), sex, race, COVID-19 vaccination status**	**Underlying medical conditions**	**Clinical signs/ symptoms**	**Previous SARS-CoV-2 testing and disease category (CAT)***	**SARS-CoV-2 testing on MIS-A admission**	**Laboratory studies (upon diagnosis)**	**Imaging/ other diagnostic studies**	**Treatments given**	**Outcome**
13/7/2021	45, male, Malay, not vaccinated	Nil	Fever, cough, sore throat, abdominal bloating, diarrhoea for 1 week Admitted with signs of shock associated with multi-organs dysfunction including myocarditis, hepatitis and acute kidney injury (KDIGO-AKI stage 2).	Yes/PCR (+) CAT 1 20 days prior to MIS-A presentation	Yes/PCR (-)	Platelet 85 cells/μL, CRP 260 mg/L, Ferritin 7830.2 pmol/L, Procalcitonin 24.35 ng/mL, Trop-I 5700.51 ng/L	CXR: clear lung fields ECHO: mild global hypokinesia with ejection fraction 45%, no pericardial effusion ECG: sinus tachycardia with mild T inversion at precordial leads USG Abdomen: no significant abnormality detected	IVIg x1, corticosteroids, empirical antibiotic, inotropes, anticoagulants	Liver and kidney injury started to improve on day 2 post-IVIg Off inotrope on day 4 post-IVIg Discharged after 7 days of admission
23/8/2021	73, male, Malay, not vaccinated	Nil	Fever (38°C) with chills and rigours, dyspnoea, lethargy x 3 days Admitted with respiratory distress and cardiogenic shock, complicated with acute kidney injury (KDIGO-AKI stage 2) and hepatitis	Yes/PCR (+) CAT 1 20 days prior to MIS-A presentation	Nil	Platelet 80 cells/μL, CRP 155 mg/L, Ferritin 9287 pmol/L, Trop-I 3275 ng/L	CXR: cardiomegaly, bilateral peripheral ground glass opacity ECHO: posterior wall hypokinesia with ejection fraction 45%, no pericardial effusion, no signs of pulmonary PE, all valves were normal. ECG (serial): sinus tachycardia, dynamic and ischemic changes over II, III, aVF, v2 to v6	IVIg x1, corticosteroids, empirical antibiotic, inotropes, antiplatelet, anticoagulants	Deceased on day 3
6/11/2021	55, male, Malay, not vaccinated	HTN, RVD	Admitted initially for COVID-19 CAT 5 and PJP, complicated with VBP and PE, which was well treated. On 7th weeks from last positive SARS-CoV-2 PCR result, developed sudden onset of fever (38°C), breathlessness, cardiac arrest and refractory VT that required multiple cardioversions. Poor GCS recovery post-resuscitation.	Yes/PCR (+) CAT 5 6 weeks prior to MIS-A presentation	Nil	Platelet 223 cells/μL, ESR 45 mm/hr, Ferritin 36300 pmol/L, Trop-I 1449 ng/L	CXR: bilateral diffuse reticular opacification CTPA (7th week admission): PE involving segmental branches of bilateral descending pulmonary artery (previously only right descending). ECHO: Akinesia over mid-apex anteroseptal wall, consisted with severe CAD ECG: ventricular tachycardia CT brain: features of vasculitis with intraparenchymal bleed and thrombus within intracranial vessels	corticosteroids, empirical antibiotic, inotropes, antiplatelet, anticoagulants	Deceased on day 3

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Table II: Summary of all cases with investigations

Summary of the MIS-A cases									
Date of admission	**Age (years), sex, race, COVID-19 vaccination status**	**Underlying medical conditions**	**Clinical signs/ symptoms**	**Previous SARS-CoV-2 testing and disease category (CAT)***	**SARS-CoV-2 testing on MIS-A admission**	**Laboratory studies (upon diagnosis)**	**Imaging/ other diagnostic studies**	**Treatments given**	**Outcome**
11/2/2022	65, male, Malay, not vaccinated	Type 2 DM	Lethargy and poor oral intake for 2 weeks, fever and shortness of breath for 2 days Admitted with severe respiratory distress and signs of distributive shock, complicated with oliguric acute kidney injury (KDIGO-AKI stage 3) and hepatitis	Yes/PCR (+) CAT 4 27 days prior to MIS-A presentation	Nil	Platelet 103 cells/μL, CRP 61.6 mg/L, Ferritin 3807.2 pmol/L, Trop-I 3735.62 ng/L	CXR: bilateral ground-glass opacity ECHO: hyperdynamic heart with ejection fraction 49%, pericardial effusion ± 0.5cm ECG: sinus tachycardia USG Abdomen: fatty liver with hepatomegaly, bilateral renal parenchymal disease	Corticosteroids, empirical antibiotic, inotropes, anticoagulants, diuretics	Deceased on day 6

*Disease category (CAT) by Malaysia clinical practise guidelines for COVID-19 infection
- CAT 1: asymptomatic
- CAT 2: symptomatic, no pneumonia
- CAT 3: symptomatic with pneumonia
- CAT 4: symptomatic with pneumonia and require supplemental oxygen
- CAT 5: critically ill with or without other organ failures

Abbreviations: PCR, polymerase chain reaction; CRP, C-reactive protein; Trop-I, troponin-I; CXR, chest X-ray; ECHO, echocardiogram; ECG, electrocardiogram; USG, ultrasonography; IVIg, intravenous immunoglobulin; HTN, hypertension; RVD, retroviral disease; DM, diabetes mellitus; PJP, Pneumocystis Jirovecii pneumonia; VAP, ventilator-associated pneumonia; ESR, erythrocyte sedimentation rate; CTPA, computed tomography pulmonary angiography; CT brain, computed tomography of brain.

DISCUSSION

With the surge of SARS-CoV-2 infection cases worldwide due to the global pandemic, clinicians and public health officers are not only dealing with the disease itself but also the complications that follow. MIS-A is a rare yet life-threatening condition that follows the SARS-CoV-2 infection. Its fatality is due to multi-organ dysfunction resulting from hyperinflammation. Three out of four patients who have been diagnosed with MIS-A reported in this review are deceased. In our review, which consisted of patients aged between 45 and 73 years old, all were Malay males. In the case series of MIS-A in UK, the findings show that adults of all ages who were infected with SARS-CoV-2 are at risk of developing MIS-A.[7] A study concerning the race and ethnicity of COVID-19 MIS-C was conducted, and it reports a disproportionate burden of MIS-C among Black and Hispanic children in NYC.[8] However, there was also a disproportionate burden of COVID-19 hospitalisations among Black and Hispanic children; thus, it is still unclear whether this signifies a fact. As Malays are the majority of the Malaysian population, it is not clear whether Malays have a relatively increased risk or burden of MIS-A, although all cases in our review are Malays.

The pathophysiology of MIS in both adults and children remains elusive. "Updated Management Protocol for MIS-C" concluded that the most postulated mechanism is the abnormal immune or inflammatory response triggered by SARS-CoV-2 infection.[1] This theory is evidenced by the manifestation of MIS signs and symptoms two to six weeks after SARS-CoV-2 infection, multisystemic involvement of cytokine storms and hyperinflammation, positive SARS-CoV-2 serology in the majority and prompt response to immunomodulation therapy.[1]

While MIS-A also mimics the presentation of extrapulmonary manifestations in severe SARS-CoV-2 infection with elevated inflammatory markers and coagulopathy associated with damaged organs, it is distinct in that it presents with new symptoms after an acute infectious illness that is often followed by a period of recovery.[9] As the studies on the disease nature are still ongoing, the case definition of MIS-A has been revised, and the latest version was published by CDC in May 2021 (Table I). All the patients described here were proven to be infected with SARS-CoV-2 prior to their current illness and developed a new onset of fever and signs of cardiac, kidney and liver damage, with one of them having diarrhoea that suggested gastrointestinal system involvement and one of them having multifocal thromboembolic events (cerebral and myocardial infarction and PE). Although the patient from case 3 did not fulfil the CDC criteria for MIS-A (clinical criteria did not occur within the first three days of hospitalization), there were definite clinical, biochemical, and radiological signs of multisystemic (cardiovascular, pulmonary and neurological) hyperinflammation and coagulopathy, which is highly supportive for the diagnosis of MIS-A as all other possible pathologies had been well treated. Case 3 patient had been fit and planned for discharge prior to the new onset of clinical deterioration, which happened around 6 weeks post-SARS-CoV-2 infection. Consequently, the diagnosis of MIS-A should be considered among patients with signs of hyperinflammation and severe extrapulmonary multiorgan dysfunction, particularly cardiovascular, occurring within 2-5 weeks after the initial SARS-CoV-2 infection, when alternative diagnoses for the illness are excluded. RT-PCR and serologic testing for SARS-CoV-2 antibodies may aid in the diagnosis of MIS-A.[9]

In contrast with MIS-C, there is no existing management protocol or guideline for MIS-A.[7] As the hypothesised pathophysiology of both MIS-A and MIS-C is the dysregulation of immune or inflammatory responses, immunomodulators have become the pillar of treatment. Evidenced by the anti-inflammatory and beneficial effects of reducing coronary artery aneurysm in Kawasaki's disease, in COVID-19 fulminant myocarditis, and in various case reports of MIS-C, IVIg is especially widely recommended.[10] Combination of IVIg with glucocorticoids in a stepwise approach has also proven to have faster recovery of myocardial function and reduced length of hospital stay.[10] A systemic review reported the application of these treatments as well for MIS-A.[9] In our review, there were two patients given a combination of IVIg and corticosteroids, while the other two received only corticosteroids. Only one of the patients who received combination therapy survived, who had a milder degree of organ damage at presentation.

The true incidence of MIS-A is unknown, which is highly likely to be underreported, given that there is difficulty in distinguishing it from sepsis at initial presentation. During this COVID-19 pandemic era, clinicians should maintain a high index of suspicion for MIS-A among patients who present with hyperinflammatory syndrome and thus should investigate for current or previous SARS-CoV-2 infection at presentation. Earlier identification of disease and prompt initiation of appropriate treatment will improve outcomes. Further study of the pathophysiology of MIS in both adults and children is desired for a better understanding of the disease, thus more targeted therapy can be applied. Clinical trials for the use of biological agents are required, thus providing more alternate treatment options, especially in adults where we still have limited data for the efficacy of IVIg and corticosteroids.

CONCLUSION

This review describes four cases of MIS-A diagnosed in Malaysia, and one of them shows good clinical outcomes with a trial of IVIg combined with corticosteroids. Hopefully, this review will be able to raise awareness of MIS-A among clinical practitioners, and thus, more clinical trials on treatment will be made to improve survival.

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