A case of Multisystem Inflammatory Syndrome in adults in Malaysia

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SUMMARY

Multisystem Inflammatory Syndrome in Adults (MIS-A) is a rare but potentially life-threatening complication following SARS-CoV-2 infection. We present a Malaysian case of MIS-A in a 45 year old gentleman who developed cardiogenic shock following a mild SARS-CoV-2 infection.

INTRODUCTION

Multisystem Inflammatory Syndrome in Children (MIS-C) was first described in April 2020 as a hyperinflammatory syndrome with features resembling Kawasaki disease. Since June 2020, a similar syndrome for adults, Multisystem Inflammatory Syndrome in Adults, (MIS-A) has been increasingly reported worldwide. The Center for Disease Control and Prevention (CDC) published a report with a collection of 21 patients of MIS-A in the Morbidity and Mortality Weekly Report (MMWR) on 20 Oct 2020.[1] In this report we describe a local case of MIS-A in a 45-year-old gentleman who recently had COVID-19 infection. To the best of our knowledge this is the first case described in Malaysia.

CASE REPORT

A 45 years old gentleman who was diagnosed with asymptomatic COVID-19 through contact screening and yielded a positive combined nasopharyngeal (NPS) and oropharyngeal (OPS) swab rt-PCR for SARS-CoV-2. He is an active smoker with no known medical illness or previous admission. He was not vaccinated with SARS-CoV-2 vaccine previously.

He was initially quarantined in a low risk COVID-19 quarantine centre as per the Malaysian protocol at that time and was subsequently discharged well on day 12 of illness. His quarantine was uneventful for he did not require any oxygen therapy or medication.

Soon after discharge, at day 13 of illness based from PCR, he developed intermittent low grade fever, non-productive cough, sore throat, abdominal bloating and diarrhoea. Otherwise, he denied shortness of breath, chest pain, skin rashes, red eyes or haematuria. He consulted a general practitioner who prescribed him a course of empirical antibiotics for presumed infective diarrhoea. However, his symptoms persisted and he sought medical attention from the emergency department of Hospital Melaka, Malaysia six days later (day 19 from PCR).

Upon arrival in the emergency department, he was febrile (39 degrees Celsius), hypotensive (blood pressure 96/50mmHg) and tachycardia (heart rate 125 beats per minute). Otherwise, there was no hypoxia (pulse oximetry reading 98% under room air), with unremarkable examination including no rashes, mucositis or palpable lymphadenopathy except for appearing malaise.

Fluid resuscitation with crystalloid did not improve his haemodynamic status and intravenous infusion of noradrenaline was started. Blood investigations drawn on initial presentation revealed leukocytosis, thrombocytopenia, raised inflammatory markers, acute kidney injury, and mild hepatitis (as shown in Table I). Cardiac dysfunction was evident by raised cardiac biomarkers and echocardiogram findings. Repeated NPS SARS-CoV2 PCR during this admission was negative. No SARS-CoV-2 antibody taken during this admission.

He was admitted to the intensive care unit (ICU) for close monitoring and was started on empirical broad-spectrum antibiotics and venous thromboembolism chemoprophylaxis. However, there was no positive culture and the antibiotic was subsequently stopped. In view of the recent diagnosis of COVID-19 with unexplained multi-organ dysfunction and elevated inflammatory markers in shock, a diagnosis of MIS-A was considered and he was given a dose of intravenous immunoglobulin (IVIG) 2g/kg. There was a remarkable response post IVIG clinically. He felt better with improved blood parameters and we were able to wean off the inotropic support. He continued to improve and was discharged from ICU within 24 hours after IVIG. He was given diuretics for his failure symptoms and was well during his clinic appointment. His repeated transthoracic echocardiogram 2 months later revealed normal ejection fraction with resolved regional wall motion abnormality.

DISCUSSION

MIS-A is a rare yet life-threatening condition. Diagnosis of MIS-A requires evidence of current or recent COVID-19 infection with severe dysfunction involving one or more extrapulmonary organs and raised inflammatory markers.[1] The patient should not have another more likely alternative diagnosis.[1] Previously those patients with severe pulmonary disease were excluded to avoid inclusion of patients in which organ dysfunction might be the result of tissue hypoxia.[1] However this exclusion criteria was not in the latest case definition of MIS-A, published by CDC in May 2021 (Table

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Table I: Relevant investigation during hospitalization

Blood investigation (Units)	Day 1 of admission	Day 4 of admission (24 hours after IVIG)	Prior to discharge (72 hours after IVIG)
Total white blood cells count (cells/μL)	34.8	20.3	13.1
Absolute neutrophil count (cells/μL)	32.3	16.4	9.7
Absolute lymphocyte count (cells/μL)	1.5	2.5	2.0
Platelets count (cells/μL)	85	254	245
Serum Urea (mmol/L)	23.7	16.7	9.3
Serum Creatinine (μmol/L)	219	116	79
Alanine transaminase (U/L)	128	151	139
Aspartate transaminase (U/L)	130	105	-
CRP (mg/L)	260	117	22
D-dimer (mg/L)	32.49	-	-
Procalcitonin (ng/mL)	24.35	2.9	-
Ferritin (pmol/L)	7830.2	-	-
High sensitivity Troponin I (ng/L)	5700.51	-	-
NT-proBNP (pg/mL)	10324	-	-
Peripheral blood film	Normochromic and normocytic red blood cells (RBC), no fragmented cells or nucleated RBC seen. As for white blood cells (WBC) count, it is increased predominantly neutrophils. Many neutrophils show toxic granulation. Some dysplastic neutrophils observed. Reactive lymphocytes are easily seen. Left shift seen. No blast. Platelet count was adequate with few large platelets and occasional giant platelets seen. Few small platelet clumps present. No evidence of microangiopathy hemolytic anaemia (MAHA).		
Microbiological and serological investigation			
Nasopharyngeal swab for SARS-CoV-2 PCR	Negative		
HIV Ag-Ab, HepBsAg and Anti-HCV	Negative		
Blood, urine and stool culture	No growth		
Imaging			
ECG	Sinus tachycardia with mild T inversion at precordial leads		
Transthoracic echocardiogram	Mild global hypokinesia with ejection fraction 45%, no pericardial effusion		
Chest radiography	Clear lung fields (as shown in Figure 1)		
Ultrasound abdomen	No significant abnormality detected		

Table II: Multisystem Inflammatory Syndrome in Adults (MIS-A) case definition information for healthcare providers[2]

Case definition of MIS-A by CDC
A patient aged ≥21 years hospitalized 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 hospitalization or within the first three days of hospitalization and at least three of the following clinical criteria occurring prior to hospitalization or within the first three days of hospitalization. At least one must be a primary clinical criterion. A. Primary clinical criteria a. 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) b. Rash and non-purulent conjunctivitis B. Secondary clinical criteria a. New-onset neurologic signs and symptoms Includes encephalopathy in a patient without prior cognitive impairment, seizures, meningeal signs, or peripheral neuropathy (including Guillain-Barré syndrome) b. Shock or hypotension not attributable to medical therapy (e.g., sedation, renal replacement therapy) c. Abdominal pain, vomiting, or diarrhea d. Thrombocytopenia (platelet count <150,000/ microliter)
Laboratory criteria
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, ferritin, IL-6, erythrocyte sedimentation rate, procalcitonin B. A positive SARS-CoV-2 test during the current illness by RT-PCR, serology, or antigen detection

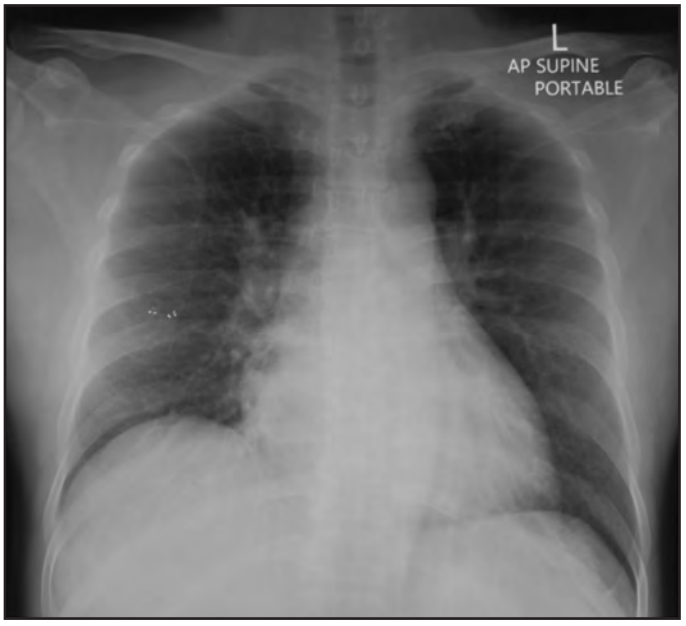

Fig. 1: This chest X-ray was taken on the day of admission.

II).[2] Our patient fulfilled both old and new case definition of MIS-A.

Pathophysiology of MIS-A is still not well understood. Postulated mechanisms of extrapulmonary manifestations in COVID-19 included endothelial damage and thromboinflammation, dysregulation of immune responses, and maladaptation of ACE2-related pathways.[3] Possible similar mechanisms responsible in the pathophysiology of MIS-A.[1] In a case report published by Boudhabhay and colleagues, the renal biopsy of the reported case with MIS-A revealed a thrombotic microangiopathy (TMA) picture with mainly neutrophil interstitial infiltrate.[4] Another unfortunate MIS-A case, autopsy findings of the heart revealed endotheliitis and vasculitis which involved the small cardiac vessels and extending into the surrounding epicardial fat and interstitial spaces.[5] The most interesting finding in this autopsy is that the coronary arteries were spared from the inflammatory cells infiltration, unlike the typical findings of coronary artery involvement in childhood Kawasaki disease.[5,6]

The interval between COVID-19 and the development of MIS-A symptoms was reported to be between 2–5 weeks.[1] In a retrospective cohort study of a single center, patients with MIS-A were in a younger age group compared to those with acute COVID-19.[7] One third of those patients with MIS-A (5 out of 15) required intensive care treatment.[7] Another case series of 51 patients with MIS-A showed that cardiovascular abnormalities were the most frequently reported findings (82.5%), followed by fever (80.4%), gastrointestinal symptoms (72.5%) and respiratory symptoms (54.9%).[8] Only 2 reported mortality out of 51 patients with MIS-A in that particular case series.[8]

As the postulated pathophysiology of MIS-A is a dysregulated immune response, various immunomodulatory medications have been tried, for examples glucocorticoid (especially intravenous methylprednisolone), intravenous immunoglobulin (IVIG), anakinra (Interleukin-1 inhibitor), tocilizumab (Interleukin-6 inhibitor) and eculizumab (monoclonal anti-C5 antibody).[1,4,5,7-9] In a case series written by Bastug and colleagues, the majority of reported cases (60.8%) were treated with glucocorticoids and 37.3% of the reported cases were treated with IVIG.[8] However, at the moment there are no widely accepted treatment guidelines available for MIS-A in contrast with MIS-C. American College of Rheumatology suggested a stepwise approach of immunomodulatory therapies in MIS-C where IVIG is the first-tier therapy and glucocorticoid is used as adjunctive therapy in patients with severe disease or those with a refractory course of disease.[10]

Clinicians are more acutely aware of MIS-C among the paediatric population, but adults are not excluded from getting this complication of COVID-19. In this difficult time with increasing cases of COVID-19 beleaguering Malaysia and the rest of the world, clinicians should be aware of such an entity and have a high index of suspicion for early diagnosis and management to improve outcome. The diagnosis of MIS-A in patients with no clear epidemiology history of SARS-CoV-2 infection can be challenging, as some patients can be asymptomatic of COVID-19 but develop MIS-A subsequently.[1] Thus for these patients, SARS-CoV-2 serology is an important investigation in reaching the diagnosis of MIS-A.

CONCLUSION

We report here a case of MIS-A who responded well to IVIG and to the best of our knowledge, is the first reported case in Malaysia. Hopefully, through this case report, this will be able to increase the awareness of MIS-A as it is likely underdiagnosed during this pandemic.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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