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Multisystem Inflammatory Syndrome in Children (MIS-C) in Pediatric Patient Post Cardiac Surgery: A Case Report

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ABSTRACT

Introduction: Multisystem inflammatory syndrome in children (MIS-C) is a relatively new disease associated with recent infection of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2).

Case Report: We reported a 1-year-3-month-old girl with congenital heart disease since 1-month-old. Peripheral oxygen saturation was 89%, and systolic murmur was found from physical examination. Patient was assessed with ASA III physical status and planned to undergo re-route partial anomalous pulmonary venous return (PAPVR) and surgical atrial septal defect (ASD) closure under general anesthesia and cardiopulmonary bypass. During surgery, hemodynamic fluctuations were controlled. Post-operatively, she was transferred to the ICU, given sedation and analgesic. On night time, patient started to have fever with temperature 37.9^0C. On the second day, patient had bradypneu, bradycardia, re-intubated and was given CPR. On the third day, patient's SARS-CoV-2 Antibody was found to be reactive and diagnosis of MIS-C was made. On the fourth day, patient's condition begin to deteriorate on even though she was given of Dobutamine, Epinephrine, Norepinephrine and Vasopressin. Four hours later, patient did not respond after CPR and declared deceased.

Discussion: Early recognition of MIS-C is challenging because the initial symptoms appear in previously healthy patient, with several symptoms such as fever, abdominal discomfort, mucocutaneous involvement, neurologic symptoms, cardiorespiratory symptoms (shock, myocarditis, dyspnea) with evidence of a marked inflammatory state. Immunomodulators are the mainstay of the treatment, with additional therapy such as steroids and anticoagulant. This severe disease's mortality rate could be as high as 15% and more research must be done to better understand this disease.

Conclusion: MIS-C is a novel pediatric syndrome characterized by fever, multi-organ involvement and marked inflammatory state. Further study is required to provide consistent diagnosis criteria, therapy regimens, and long-term prognosis since this is a relatively new pediatric syndrome.

***Keywords*:** Multisystem inflammatory syndrome in children (MIS-C), SARS-CoV-2, pediatric

INTRODUCTION

Coronavirus disease 2019 (COVID-19) cases in children have persisted since the disease's initial outbreak, especially in Indonesia.[1] Children frequently exhibit mild symptoms with better outcomes. However, eight pediatric cases of hyperinflammatory shock were observed in mid-April 2020 in London. In contrast to other COVID-19 cases seen at the time, patients were extremely ill with multiple organ involvement. World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) assigned this condition the name multisytem inflammatory syndrome in children (MIS-C).[1,2] The definition used by all organization is based on six key elements:

age, persistence of fever, presence of inflammatory laboratory markers, manifestation of organ dysfunction, lacking an alternative diagnosis and temporal relation to COVID-19 infection or exposure. [3]

MIS-C typically manifests 4-6 weeks after SARS-CoV-2 infection, suggesting that the virus may serve as a trigger for people with certain genetic predispositions. Although not all patients exhibit SARS-CoV-2 RT-PCR positivity, majority show serological positivity.[4] There are several clinical presentation found in MIS-C patients, such as fever, mucocutaneous involvement, conjunctival alterations, gastrointestinal symptoms mostly abdominal pain, cardiovascular manifestations (tachycardia, hemodynamic shock, myocarditis, decreased LVEF), respiratory symptoms, thrombotic complications with elevated markers of inflammation and evidence of COVID-19 (RT-PCR, antigen test or serology positive).[5,6]

Over the course of the pandemic, MIS-C management has changed. Most MIS-C patients were treated with intravenous immunoglobulins and intravenous glucocorticoids, and additional interventions such as antithrombotic therapy and biologic therapy depend upon the severity of illness, constellation of findings, and response to initial therapy.[7] Supportive care may be required in the acute phase, including fluid resuscitation, inotropes, mechanical ventilation, and in most severe cases, extracorporeal membrane oxygenation (ECMO) support.[4] The overall prognosis for MIS-C appear good as most patient make a complete clinical recovery. However, many children with MIS-C require intensive care interventions during the disease course. Several studies report low mortality, but a study in Indonesia found a 15% mortality rate.[1] Here we present a case of a 1-year-3-month-old girl with history of congenital heart disease undergoes heart surgery, and was diagnosed MIS-C in the post-operative period.

CASE REPORT

We reported a case of a 1-year-3-month-old girl with history of congenital heart disease since 1-month-old which was identified during pre-vaccination screening. She consumed furosemide 3 mg/12 hours, digoxin 25 mcg/12 hours routinely, and underwent heart catheterization 1 month before admitted to the hospital. Peripheral oxygen saturation was 89% room air, with other vital sign within normal limit, pulse 102x/minute, RR 30 times/minute, temperature 36.9^{O}C. Significant findings from physical examination was systolic murmur. Complete blood count before surgery was within normal limits [WBC 11.60 x10^{3}/µL (6.0-14.0); HGB 11.70 g/dL (12-16); HCT 35.7% (36-49); PLT 346 x10^{3}µL (140-440)], hemostasis physiology examination was within normal limits [PT 10.6 (10-12.7) seconds; INR 0.93; aPTT 28.5 (23-34.7) sec], liver function test slightly higher than the upper liimit [SGOT 36.0 U/L (5-34); SGPT 17.70 U/L (11-50)], renal function test was within normal limits [creatinin serum 0.42 mg/dL (0.7-1.25); BUN 10.50 mg/dL (8-23)], electrolyte tests were slightly higher than the upper limit [Sodium 145 mmol/L (136-145); Chloride 111.9 mmol/L (94-110)]. On chest x-ray, cardiothoracic ratio was 57% with plethora.

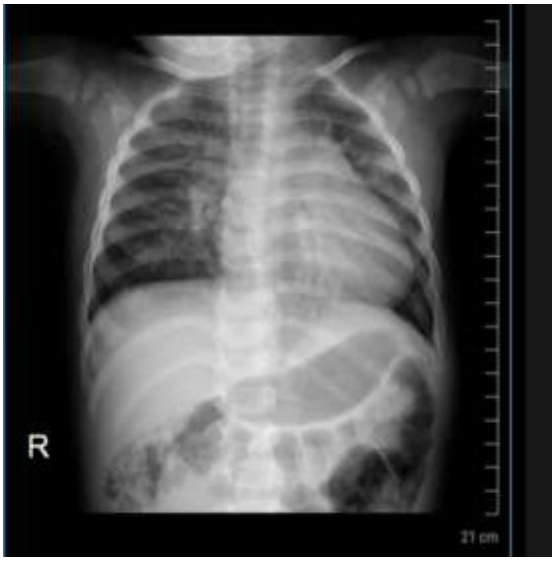

Figure 1. Chest x-ray showing plethora with normal CTR

Based on echocardiography, the impression was suspected intracardiac right PAPVR, small sinus venosum ASD, mild relative valvular pulmonary stenosis (PS), trivial pulmonary regurgitation (PR), moderate tricuspid regurgitation (TR). During recent cardiac catherization was found intracardiac partial anomalous of right pulmonary venous return, small sinus venosum ASD (5.4 mm), low flow (FR 1,31) and low resistant (PARI 1.03).

Patients was assessed with ASA III physical status and planned to undergo re-route PAPVR and surgical ASD closure under general anesthesia and cardiopulmonary bypass. She was positioned in the supine position and pre-medicated with Midazolam 1 mg IV and Ketamine 5 mg IV. During induction, she was given O2 : Sevoflurane. In addition, she was also given Fentanyl 45 mcg IV, Rocuronium 10 mg IV, Heparin 2700 IU IV, Protamine 36 mg IV, and Calcium Gluconas 90 mg IV. Anesthesia was maintained with a combination of O2; compressed air; Sevoflurane; Fentanyl; and Rocuronium 0.2 mg/kg every 45 minutes. She was bleeding as much as 200 mL, with a urine output of 140 mL. She was then resuscitated with 800 ml of crystalloid, 61 ml of thrombocyte concentrate (TC), 100 ml of fresh frozen plasma (FFP), and 120 ml of packed red cells (PRC).

Post-operatively, she was given Morphine 5 mg volume 20 ml (1 ml/hour), Dexmedetomidine titrates from 0.3 mcg/kg/hour as analgesic. She was then treated in the intensive care unit for three days and received additional therapy, such as Cefazoline 250 mg/24 hours, and Dobutamine 6 mcg/kg/minute. Routine laboratory tests after surgery showed hypokalemia (3.02 mmol/L) and thrombocytopenia (115/mcL), Tranexamic Acid 100 mg/8 hours was given. On night time, patient started to have fever with temperature 37.9ºC. On the next day, added therapy were Furosemide 5 mg/24 hours, Hydrocortisone 20 mg/24 hours, Paracetamol 150 mg/8 hours, Meprovent nebulization 1 respule/24 hours. Later in the morning, patient had bradypneu and bradycardia (115 times/minute → 50 times/minute). One ampule of Atrophine Sulfate was given, continued with CPR and re-intubation. Calcium Gluconas 300 mg, Levofloxacine 75 mg/12 hours, Ibuprofen 100 mg/8 hours, Cefepime 400 mg/8 hours, Gentamicin 40 mg/24 hours were added to the regimen. On the third day, patient's SARS-CoV-2 Antibody was found to be reactive (11804.0 AU/ml) and diagnosis of MIS-C was made. On the fourth day, patient was hypotensive and begin to deteriorate. Four hours later, patient's blood pressure cannot be measured, bradycardia with SpO2 80%, continued with 10 cycle of CPR but patient did not respond until pupil was found maximally dilated and patient was declared deceased.

DISCUSSION

Since mid-2020, European and North American countries have reported pediatric case with severe multisytem inflammatory syndrome associated with SARS-CoV-2. Early description revealed as significant clinical variability that was unique from well-known inflammatory disorders while also sharing some characteristics with Kawasaki disease or toxic shock syndrome. This condition is known as multisystem inflammatory syndrome in children (MIS-C).[5]

Median age of MIS-C patients is usually 8-9 years with no preexisting medical conditions. It is essential to recognize signs of possible MIS-C patients, but this can be challenging because the initial symptom appears in previously healthy patient, resembles those of other viral diseases.[8] Fever >38ºC, abdominal discomfort, vomiting or diarrhea, erythematous skin rash, mucocutaneous involvement, and conjunctival alterations are the most frequent signs and symptoms. Other symptoms include sore throat, neurologic symptoms (fatigue, disorientation or headaches), lymphadenopathy and swollen hands and feet.[4] One third patient had cardiovascular symptoms, such as tachycardia, hemodynamic shock or

hypotension, myocarditis, mild or severe reduced left ventricular ejection fraction. Respiratory symptoms were present in half of cases, including dyspnea, upper respiratory tract symptom, and radiological infiltrates.[5,7,9] If patient does not recover from surgery within acceptable period of time or exhibits new clinical indicators included in the case definition, MIS-C should be taken as a differential diagnosis.[10] During the first day of post-operative period, our patient had already been extubated with no significant problem. On the evening, patient begin to develop fever. On the second day, patient patient had bradypneu, bradycardia and was re-intubated. Since then, patient's condition and hemodynamic began to deteriorate eventhough she was given high dose Dobutamine, Epinephrine, Norepinephrine and Vasopressin.At least four inflammatory markers (C-reactive protein, neutrophil count, ferritin, procalcitonin, fibrinogen, interleukin-6, and triglycerides) were elevated in the majority of patients. There have also been reports of thrombocytopenia and lymphopenia. Children with MIS-C frequently exhibit high D-dimer levels, but thrombosis event is uncommon. Heart involvement is indicated by high level of troponin, brain natriuretic peptide (BNP) or pro-BNP. Cardiac and inflammatory biomarkers not only point to MIS-C but also might indicate severity of illness.[4] With RT-PCR and/or serological assays (IgG/IgM/IgA), presence of recent or active SARS-CoV-2 infection was determined. Study shown that two-thirds of patients were IgG-positive and only 37.5% had positive respiratory RT-PCR.[4,8] Since re-intubation, further analysis of laboratory investigations revealed lymphopenia (28.70%), thrombocytopenia (82.00 x 10^3/µL), and significant elevation in inflammatory markers; high procalcitonin (18.47 µg/Ml), high neutrophil count (55.1%), high CRP 34.60 mg/dL, high ferritin 336.95 mg/dL, low fibrinogen 97.60, high D-dimer level (2.55 mg/mL) and reactive Anti-SARS-CoV-2 IgG (11804.0 AU/mL). Troponin I level were as high as 35103.6 pg/mL, suggesting heart involvement in our patient. Our laboratory findings aligned with other study on MIS-C patients, suggesting that occurrence of fever, hemodynamic changes and substantial coagulopathy may be attributable to a defect in the innate immune system.

Published guidelines for treatment are based on expert consensus due to lack of supporting data. Most patients had pharmacological management with intravenous immunoglobulins (IVIG), with half of them receive intravenous steroids.[7] Our patient received intravenous IVIG 2 gr/kg over 12 hours and methylprednisolone 2 mg/kg/day after MIS-C diagnosis was confirmed. Immunomodulators are the main treatment for MIS-C, which suggests that postinfectious immunological dysregulation is the primary cause of this condition. The dosing for IVIG differ from each study, with dose range from 1-2 gr/kg as single infusion over 8-16 hours.[9,11–13] One study found that multiple IVIG doses were needed in 11.0% MIS-C cases.[5] High dose IVIG either alone or in combination with corticosteroids have been successfully used to treat MIS-C cases. These regimens were based on Kawasaki disease recommendations, and combining IVIG with corticosteroids led to a lower rate of treatment failure. Additional first-line treatment included antiplatelet medications and anticoagulants.[4,5,9] An independent predictor of thrombosis was markedly high D-dimer (>5 times the upper normal limit). Severe MIS-C patient with age >12 years requiring immobilization, central lines, and PICU care could be administered prophylactic-dose anticoagulant therapy if bleeding risk is low.[12,14,15] Interleukin-6 inhibitors, anti tumor necrois factor, and interleukin-1Ra inhibitors are other drug that have been descried in MIS-C case series.[4]

Mortality rate of MIS-C differs from each study, ranging from 1.7 – 15%.[1,3,16,17] The group that did not survived had more frequent ferritin levels above 500 ngr/mL, more cardiovascular complications, need for mechanical ventilation support and renal replacement therapy.[17] Lower mortality rate

can be due to greater understanding of MIS-C, reflected in the rapid diagnosis of MIS-C in those study with lower mortality rates.

CONCLUSION

The diagnosis of MIS-C should be taken into consideration given the significant number of SARS-CoV-2 infection in recent years. MIS-C is a novel pediatric syndrome characterized by fever, multi-organ involvement and marked inflammatory state. Further study is required to provide consistent diagnosis criteria, therapy regimens, and long-term prognosis since this is a relatively new pediatric syndrome.

Declaration by Authors

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