Case report

A fatal course of multiple inflammatory syndrome in children coinfection with dengue. A case report from Indonesia

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\textbf{A B S T R A C T}

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or corona virus disease 2019 (COVID-19) is a currently ongoing global pandemic. Children tend to show milder symptoms of infection compared to adults. Concurrently, in April 2020, there was reported an escalation of Kawasaki cases like disease in children treated in the intensive care unit and showing polymerase chain reaction (PCR) SARS CoV-2 positive. Those children had a hyperinflammatory response, which caused the failure of multi-organ and shock. Several countries have reported similar cases since then. Here we describe a case of a patient with COVID-19 and concurrent dengue infection presenting MIS-C. A 6-year-old male with no past medical history looked pale with fatigue and brought to an emergency room from a referral hospital. The patient presented with fever, acute abdominal pain, shock, and deteriorate quickly, confirmed with the serology of SARS CoV-2 IgM was reactive, serology of anti-dengue IgM was reactive and PCR SARS CoV-2 was negative. Possibly it is MIS-C coinfection with severe unusual dengue infection or MIS-C with false-positive dengue serologic test leading to a fatal outcome.

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\textbf{Introduction}

The corona virus (SARS CoV-2) was first identified in Wuhan, China, back in December 2019. The spread has been out of control, and it is resulting in a pandemic around the world. In the fifth month of the pandemic, the U.K.'s latest report found eight cases of children with Kawasaki-like disease symptoms admitted to the pediatric intensive care unit (PICU) \cite{1}. The clinical profiles of such cases were hyperinflammatory, which causing failure of multi-organ and shock. Several countries have reported similar cases since then. The Center for Disease Control and Prevention (CDC) released a Health Advisory on severe complications from COVID-19 children called Multisystem Inflammatory Syndrome in Children (MIS-C) together with World Health Organization (WHO) develops an understanding of multisystem hyperinflammatory cases in children and adolescents. Herein we describe a six-year-old male with COVID-19 presenting as MIS-C and coinfection with dengue infection leading to became a fatal case.

\textbf{Case report}

A 6-year-old male with no past medical history, with fatigue, looks pale and brought to the pediatric emergency department from the referral hospital. In the initial presentation, the patient presented with shock. The parents reported that the patient complains of fever for five days and abdominal pain. There was no history of cough, breathing difficulties, bleeding, or rashes. The patient had no history of traveling or contact with COVID-19 patients. He was still an active child two days before admission, and the symptoms abruptly worsened afterward.

The patient presented with shock and altered consciousness (Glasgow Coma Score/GCS 12), heart rate of 135 beats per minute, blood pressure 70/40 mmHg, respiratory rate 40 breaths per minute, temperature 36.5°C, and prolonged capillary refill time >2 s. Oxygen saturation checked was 83 %, receiving oxygen 5 L/minutes via a simple mask. From the physical examination, there is no enlargement of the spleen and liver. Fluid resuscitation and transfusion were performed as pediatric surviving sepsis protocol. Hemodynamic monitoring, inotropic agent administration, and subsequent orotracheal intubation were performed according to the COVID-19 protocol.

The laboratory tests showed complete blood counts, hemoglobin of 2.9 g/dL, hematocrit 9.3 %, leucocyte 18 × 103/μL, basophil 0 %, eosinophil 0 %, neutrophil band 1 %, neutrophil segment 55 %.
lymphocyte 33 %, monocyte 4 %, erythrocyte 1.13 × 1012/L, and platelets counts 213 × 103/μL, albumin 1.96 g/dL, urea 46.2 g/dL, serum creatinine (S-Cre) 1.15 mg/dL, aspartate transaminase (AST) 510 U/L, alanine transaminase (ALT) 173 U/L, potassium 6 mmol/L, sodium 123 mEq/L, C-reactive protein (CRP) 0.09 mg/dL, procalcitonin 0.78 ng/mL. The blood gas analysis revealed pH 6.8, pO2 24.2 mmHg, pCO2 27.2 mmHg, HCO3 4.8 mmol/L, TCO2 5.6 mmol/L, BE -2.78 mmol/L and SO2 17.3 %, lactate dehydrogenase 10.6 mmol/L. Peripheral blood smear revealed normochromic erythrocytes, anisopoikilocytosis (ovalocyte, pencil cell) microcytic, and leukocytic hypersegmentation. An additional blood test for serum iron was 157 mcg/dL with a Total Iron Binding Capacity (TIBC) of 207 mcg/dL, and ferritin of 3985 ng/mL. The rapid test SARS Cov-2 IgM was reactive and IgG non-reactive (specificity 95.74 %, sensitivity 69.05 %). Polymerase Chain Reaction (PCR) of SARS Cov-2 was negative. The IgM anti-dengue was reactive and the IgG anti-dengue was non-reactive. No abnormalities noted on the chest x-ray (Fig. 1).

Initially, the patient was diagnosed with a refractory septic shock that leads to aggressive fluid resuscitation, administration of a broad-spectrum antibiotic, and inotropic agents according to sepsis guidelines in children. Hemodynamic instability progressed to the point of multiple organ failure and passed away within 14 h in the pediatric emergency unit.

Discussion

Children with COVID-19 typically will have a mild to moderate course of illness. Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 is characterized by hyper inflammation, fever, abdominal symptoms, conjunctivitis, and rash, and multiple organ dysfunction after ruling out other possible causes of infection [3,4]. The MIS-C has a clinical profile that similar to inflammation found in moderate to severe Kawasaki disease with shock, staphylococcal, and streptococcal toxic shock syndromes, bacterial sepsis, and macrophage activation syndrome [1,5]. Our patient presented without the classic upper respiratory symptoms of COVID-19, conjunctivitis, or rash, but presented with fever, acute abdominal pain, shock, and deteriorate quickly. All children with suspected moderate to severe COVID-19/MIS-C with signs of septic shock or other sepsis-associated organ dysfunction should timely perform blood culture, fluid bolus, and broad-spectrum antibiotics without waiting for culture results [6]. We treated this patient with broad-spectrum antibiotics and other septic shock procedures applied as well. Even though based on the previous studies, microbe was not found in the vast majority of septic shock cases, only 35–50 % of patients presented with a positive culture [6,7].

Our patient is a six-year-old male with a ferritin plasma level of 3985 ng/mL following Pouletty et al. found the prognostic factors for the development of severe disease were age over five years and ferritinemia >1400 μg/L [5]. Feldstein et al. is suggesting that the organ-system involvement included the gastrointestinal system 92 %, cardiovascular in 80 %, hematologic in 76 %, mucocutaneous in 74 %, and respiratory in 70 % for MIS-C, and may become a fatal case, 4 (2%) died [8]. Predominant symptoms of stomach and prevalence of cholestasis than the liver injury hypothetically caused by the higher expression of angiotensin-converting enzyme-2 receptors in the gastrointestinal epithelium cells and cholangiocytes than in hepatocytes [9]. Our patients had circulatory shock requiring subsequent inotropic support, similar to the study of MIS-C by Kest et al. in New Jersey, United States of America/USA [10].

Laboratory findings showed severe anemia, hypoalbuminemia, hyperferritinemia, elevated liver enzyme, urea, and creatinine, slightly increased procalcitonin, and confirmed with the serology of SARS Cov-2 IgM was reactive even though PCR for SARS Cov-2 was negative. Feldstein et al. reported their study of MIS-C in the United States, there is only 70 % that PCR was positive [8]. Leukocytosis was found, this is following the research by Kest et al.,

![Fig. 1. The chest x-ray was within normal limits.](image-url)
which in his research all patients with MIS-C was leukocytosis [10]. Our case had severe anemia and leukocytosis, but lymphocytopenia was not found. The serological examination revealed IgM antibody reactive for dengue and SARS-CoV-2, the same case as reported from Singapore, where reactive serology found between the two examinations. This fact may explain the false positive or coexistence between COVID-19 and dengue infection [11]. The patient screened for anti-dengue serology, with reactive results. However, Indonesia is an endemic country of dengue, but only a serologic examination available for diagnosing it.

We also performed a chest x-ray and no infiltrates or pleural effusion were found. This finding is appropriate with study from Xiaoping et al. in China, found no obvious abnormality in chest X-ray from pediatric patients nine-years-old with COVID-19 [12]. Abnormal respiratory findings might be small pleural effusions, patchy consolidations, focal consolidation, and atelectasis [8]. However, since the early imaging manifestation of COVID-19 is ground-glass opacity (GGO), chest X-ray could be missed due to its low-resolution nature and projection overlapping [13]. We also do electrocardiography, and no abnormality has been found. However, we have no chance to do an echocardiography examination and we can not perform abdominal ultrasound examinations as there is no portable ultrasound and consider the patient rapidly deteriorating condition.

The patient lived in a dengue-endemic area and showed a reactive for IgM anti-dengue, non-reactive for the IgG anti-dengue, but no hemorrhagic or plasma leakage was observed. According to WHO guidelines 2011, these manifestations commonly suitable for dengue fever, but this patient probably had the primary dengue infection which rarely causing a dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS), or unusual manifestation/expand ed dengue syndrome (EDS), in a few cases it has also been documented in primary dengue infections. Unusual manifestations of patients with severe organ involvement such as liver, kidneys, brain, or heart associated with dengue infection have been increasingly reported in DHF and also in dengue patients who do not have evidence of plasma leakage. These unusual manifestations may be associated with coinfections, comorbidities, or complications of prolonged shock [14].

Different from adults, Vakili et al. reported of 34 cases of children infected with SARS-CoV-2 getting different leukocyte counts, most cases (82 %) showed normal numbers, lymphopenia, and neutropenia were only found in one case, respectively. A normal or temporary elevated CRP, conflicting WBC count results, and procalcitonin elevation are the most important laboratory reports of COVID-19 infected children [15]. Lippi and Mattuzzi reported that mean hemoglobin difference of the four individual studies, in all except one of these four investigations, the hemoglobin value was found to be significantly lower in COVID-19 patients with the severe disease than in those with milder forms, yielding a weighted mean difference (WMD) of –7.1 g/L; 95% CI, –8.3 to –5.9 g/L). A progressive decrease in hemoglobin concentration may reflect a worse clinical progression [16]. Our patient had a significant decrease in hemoglobin concentration and a slight increase in procalcitonin levels were found, but the CRP level was not increased.

This case was the first MIS-C patient in Dr. Hasan Sadikin hospital on June 30th, 2020. As of 01 July 2020, according to WHO, the Government of Indonesia announced 57,770 confirmed cases of COVID19, and 2934 (5.08 %) deaths, and 25,595 recovered cases from 452 districts across all 34 provinces [17]. At the time, according to the National Task Force for COVID-19, the COVID-19 cases confirmed in children 1–5 years-old and 6–18 years-old were 2.7 % and 8 % (0.8 % and 0.9 % confirmed deaths) respectively [18]. In our case, all criteria related to MIS-C have fulfilled, except no escalation of CRP. Besides COVID-19 coinfection with unusual dengue, it might be an open possibility of differential diagnosis with other secondary viral infection.

This case met the six criteria of MIS-C defined by WHO [1] and also CDC [2], a six- year-old male with a fever of five days (although different in duration, CDC case is subjective or objective fever at least 24 h and WHO case is fever at least 3 days), severe illness (CDC’s case definition states that children have severe symptoms that require hospitalization, but the WHO case definition does not), multisystem organ involvement (altered mental state, abdominal pain, and shock), laboratory evidence of inflammation (severe anemia, leukocytosis, increase of hepatic enzymes and procalcitonin, hyperferritinaemia, and hypoaubuminemia), and evidence of infection with SARS-CoV-2 based on antibody testing (the Rapid test SARS CoV-2 was reactive for IgM and non-reactive for IgG) but PCR of SARS CoV-2 was negative, he had no history exposure to persons with COVID-19 but he was lived in the crowded area with the evidence of circulating COVID-19. The patient also had the reactive of IgM anti-dengue with the unusual dengue infection manifestation. Many things to learn more about COVID-19 and MIS-C in children, it explained that the spectrum of diseases ranges from mild to severe. The COVID-19 with coinfection might be presented with severe illness and even fatal outcome as well as dengue infection.

Conclusion

The COVID-19 pandemic warns all of the clinicians, paramedics, and health care workers should consider any possibilities of MIS-C for any children presenting with a fever of more than three days (or even if there is a history of fever), severe symptoms and signs. Multisystem inflammatory syndrome in children might be led to serious and life-threatening illnesses in previously healthy children, especially if coinfection was found.

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Declaration of Competing Interest

The authors report no declarations of interest.

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