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RESEARCH ARTICLE

Potential severe pediatric SARS-CoV-2-induced multisystem inflammatory syndrome resembles dengue infection

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ABSTRACT

We describe a child with acute fever and abdominal pain who developed rash and edema of extremities. Blood test revealed thrombocytopenia, lymphopenia, positive dengue-IgM, and hypoalbuminemia with elevated procalcitonin. Right pleural effusion revealed from chest x-ray. Diagnosed as dengue hemorrhagic fever (DHF) grade 1, however, at 7th day of illness, altered mental status, respiratory and circulatory failure occurred. Laboratory examination showed marked thrombocytopenia, transaminitis, metabolic acidosis, elevated D-dimer, decrease fibrinogen, and elevated cardiac marker (troponin I and CKMB). The patient then developed catecholamine-resistant shock and did not survive after 48 hours. Although rapid test of SARS CoV-2 infection was negative, rapid deterioration with some unusual clinical feature suggest multisystem inflammatory syndrome in children (MIS-C) related to SARS-CoV-2 infection. This case raises an awareness of MIS-C that clinical features resemble dengue infection.

Keywords: MIS-C; inflammatory syndrome; Covid-19.

INTRODUCTION

SARS-CoV-2 infection shows various clinical manifestations. The inflammatory process has an important role in symptom occurrence, with systemic inflammation associated with poor outcomes (Yuki *et al.*, 2020) SARS-CoV-2 infection in children has been suggested to be milder (5.8% severe cases) than in adults (18.5% severe cases) (Dong *et al.*, 2020). In severe pediatric cases of SARS-CoV-2 infection, systemic inflammation, known as Multisystem Inflammatory Syndrome in Children (MIS-C) may occur. MIS-C has clinical features similar to other diseases, such as toxic shock syndrome, Kawasaki disease, and even dengue infection (Henderson *et al.*, 2020; Wu *et al.*, 2020; Yan *et al.*, 2020).

MIS-C has to be suspected in children (0-19 years) with persistent fever (≥38.0°C for ≥24-72 hours), any organ dysfunction (mucocutaneous inflammation, shock, cardiac involvement, acute gastrointestinal symptoms, coagulopathy), laboratory evidence of inflammation (high CRP, procalcitonin, ESR, fibrinogen, D-dimer, ferritin), and link to SARS-CoV2 (positive serology, antigen test, PCR, or likely COVID-19 contact) (Radia *et al.*, 2020). Some clinical manifestation, such as persistent fever, abdominal pain, rash, thrombocytopenia, and lymphopenia are also commonly seen in dengue. Circulatory failure could be developed in MIS-C, similar to Dengue Shock Syndrome (DSS). Previous reports from Singapore and China even revealed some patients who were serologically positive for dengue, were later confirmed to have SARS-CoV-2 infection (Wu *et al.*, 2020; Yan *et al.*, 2020).

CASE PRESENTATION

A 7-years-old girl presented to the Emergency Department with a high fever and abdominal pain for the previous 5 days. She also experienced nausea, vomiting, headache, peripheral erythema, and extremity pain. She had taken acetaminophen for five days, but the fever persisted. On examination, she had fever (38.9°C), slight hypotension (94/50 mmHg) tachycardia (120/min), tachypnea (26/min), but normal oxygen saturation (98%) and warm extremities. She had non-pitting edema and erythematous rash over all extremities [Figure 1]. Blood tests showed marked thrombocytopenia and lymphopenia (absolute lymphocyte counts 357/mm^3) as well as increased procalcitonin (75.5 ng/mL) [Table 1]. Mild hypoalbuminemia, hypocalcemia, and hyponatremia were also noted. IgM anti-Dengue was also positive. Chest X-Ray showed patchy infiltrates in the AP position and pleural effusion in the right lateral decubitus (RLD) position [Figure 2]. The patient was diagnosed with dengue hemorrhagic fever grade 1 and treated with maintenance fluid therapy and antipyretics.

On the second day, the signs and symptoms persisted, but the laboratory results showed decrease of hemoglobin, hematocrits, and platelets. On the third day (7th day of illness), distributive shock occurred. The patient had

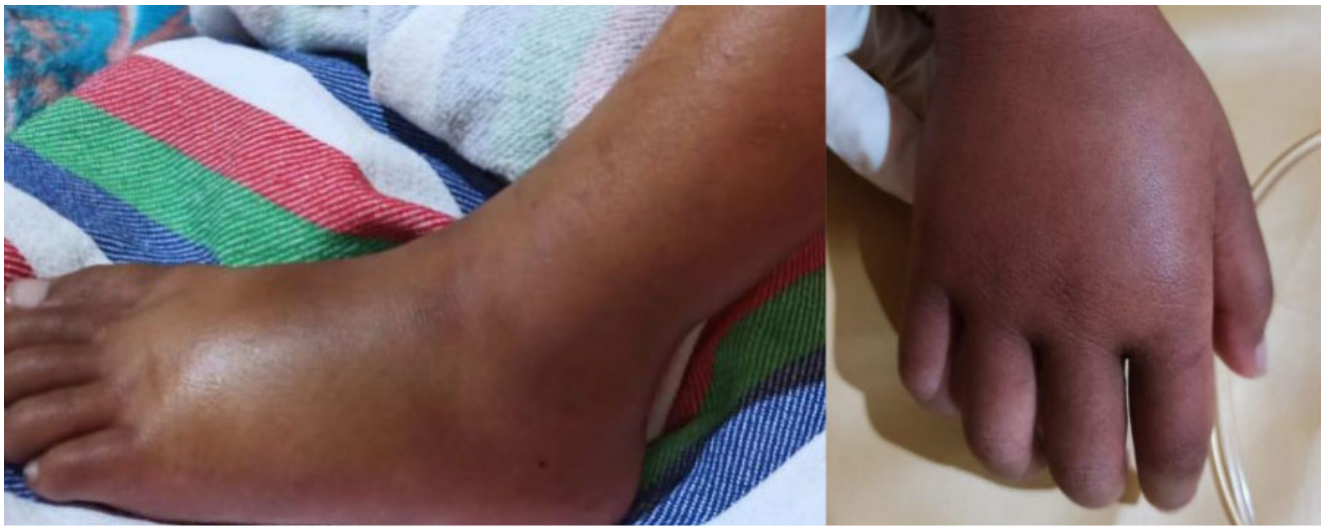

Figure 1. Edema in both extremities. Erythematous rash and swollen feet and hands on the first day of admission. The edema was non-pitting and mildly tender.

Table 1. Laboratory results during hospitalization

Parameter tested	1st day	2nd day	3rd day
Complete blood count			
• Hemoglobin (ref: 11.4-15.1), g/dL	14.8	10.6	9.6
• Hematocrit (ref: 38-42), %	39.1	29.4	26.2
• Leucocytes (ref: 4.7-11.3), $x10^3/\mu L$	5.25	7.66	9.54
• Diff. count, %			
• Neutrophils (ref: 51-67)	86.4	80.9	76.9
• Lymphocytes (ref: 25-33)	6.8	13.7	15.9
• Platelets (Ref: 142-424), $x10^3/\mu L$	36	19	17
Clinical blood chemical			
• Albumin (ref: 3.5-5.5), g/dL	2.86	–	1.96
• AST (ref: 0-32), U/L	350		5261
• ALT (ref: 0-33), U/L)	75		673
• BUN (ref: 7-20), mg/dL	35		44.9
• Creatinine (ref: <1.2), mg/dL	0.88		1.00
Serum electrolytes			
• Sodium (ref: 135-145), mEq/L	116	117	124
• Potassium (ref:3.5-5.0), mEq/L	4.00	3.85	3.89
• Chloride, mEq/L	91	92	99
• Calcium, mEq/L	7.1	6.7	6.2
• Phosphorous, mEq/L		3.2	4.4
Hemostatic tests			
• PTT (s)	12.2	–	22.8
• INR	1.19		2.33
• APTT (s)	37.6		62.6
• Fibrinogen (Ref: 154-398), mg/dL			71.8
• D-dimer (Ref: <0.5), mg/L			33.67
Blood gas analysis			
• pH	7.28	–	7.24
• $PaCO_2$ (mmHg)	32.2		10.4
• PaO_2 (mmHg)	82.4		56.2
• HCO_3 (mmol/L)	15.2		4.5
• Base excess (mmol/L)	-11.8		-23.0
• SaO_2 (%)	94.7		85.2
Infection marker			
• Procalcitonin (ng/mL)	75.52		16.59
• Anti-streptolysin O (ASO)	Negative		
• Anti-dengue IgM	Positive		
• Anti-dengue IgG	Negative		
• Blood culture			Absent bacterial growth
Cardiac marker			
• Troponin-I (Ref:<0.03), µg/L			0.9
• CK-MB (Ref: 7-25), U/L			1075

AST: aspartate transaminase; ALT: alanine transaminase; PTT: partial thromboplastin time; APTT: activated partial thromboplastin time; INR: international normalized ratio; CK-MB: creatinine kinase-MB.

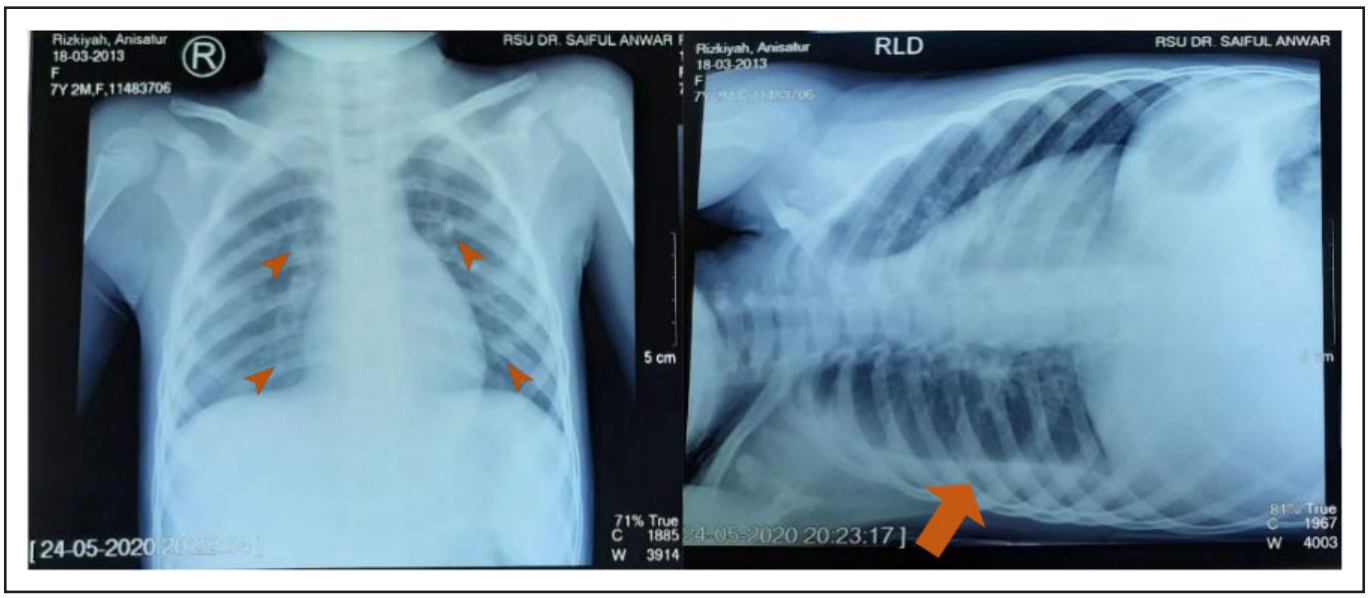

Figure 2. Chest x-ray (A) symmetrically distributed patchy infiltrates in the AP position (left photo, noted by arrowheads); (B) pleural effusion (right photo, noted by arrow) in the RLD position.

tachycardia (145-150/min), wide pulse pressure (90/35 mmHg), warm extremities, and brisk capillary refill. She also became agitated and had increased respiratory rate, without marked chest retractions. She was then intubated and mechanically ventilated. We applied pressure-controlled mode, frequency 25/min, peak inspiratory pressure (PIP) 10 cmH_2O, positive-end expiratory pressure (PEEP) 6 cmH_2O, and FiO_2 0.5 to achieve tidal volume (TV) 5-7 mL/kg.

A crystalloid fluid bolus was also given. A total of 40 mL/kg lactated ringer (LR) was administered; nonetheless, circulatory failure persisted. Ultrasonic cardiac output monitor (USCOM) examination revealed high cardiac output (cardiac index 8.3 L/min/m^2) and low systemic vascular resistance (SVRI 853 ds/cm^5/m^2). Norepinephrine was then added; starting at 0.05 µg/kg/min and titrated every 30-60 minutes.

The patient was suspected to have MIS-C related to SARS-CoV-2 infection, Kawasaki disease (KD) with shock, septic shock, or toxic shock syndrome (TSS). Laboratory examination showed deterioration, i.e., marked thrombocytopenia, increased liver enzymes, decreased renal function, hypoalbuminemia, metabolic acidosis, prolonged prothrombin time (PT), and partial thromboplastin time (PTT) [Table 1]. The cardiac marker test showed a marked increase of troponin-I (0.9 µg/L) and CK-MB (1075 U/L). Another abnormal laboratory result was elevated D-dimer (33.67 mg/L) and CRP (24.52 mg/dL), but decreased fibrinogen (71.8 mg/dL). The antibody test for SARS-CoV-2 (ECLIA-anti-SARS-CoV-2) was negative in both IgG and IgM.

Rapid deterioration occurred despite giving the maximum doses of norepinephrine (1 µg/kg/min) and epinephrine (0.5 µg/kg/min). The patient had decreased level of consciousness and oxygen desaturation. Her blood pressure fell to 70/20 mmHg. USCOM examination showed decreased cardiac index (6.3 L/min/m^2) and systemic vascular resistance (SVRI 450 ds/cm^5/m^2). Because of catecholamine-resistant shock, the patient experienced cardiac arrest and passed away despite cardiopulmonary resuscitation.

DISCUSSION

This case of suspected MIS-C illustrates that it may mimic the clinical features of dengue infection. Our patient had vasoplegic shock on the 4th day of defervescence (7th day of illness), an uncommon manifestation of dengue shock syndrome (DSS). Despite strong evidence of dengue infection (right pleural effusion, thrombocytopenia, and positive Dengue IgM), the later onset of shock with rapid deterioration and multiorgan inflammations was uncommon. Thus, we assumed another disorder was involved other than severe dengue. In the midst of the SARS-CoV-2 pandemic, MIS-C should be taken into consideration. Our case highlights the similarity of several clinical features of dengue infection and MIS-C; Hence, awareness should be raised in dengue-endemic areas in order to distinguish between conditions.

Recently, children have been admitted to intensive care because of rare multisystem inflammatory syndromes, called MIS-C, which has been hypothesized to be associated with SARS-CoV-2 infection. Presenting signs and symptoms, such as acute fever, rash, and multisystem inflammation (especially cardiac involvement), resemble Kawasaki disease (KD) and toxic shock syndrome (TSS) (Jonat *et al.*, 2020; Whittaker *et al.*, 2020). About 150 suspected MIS-C cases have been reported in EU/EEA countries and the UK in 2020, including one mortality (Whittaker *et al.*, 2020). In dengue-endemic areas, such as Southeast Asia and South America, MIS-C could present with similar clinical signs as severe dengue infection, as reported in cases in Singapore and Thailand (Joob & Wiwanitkit, 2020; Wu *et al.*, 2020; Yan *et al.*, 2020). It would augment the awareness and complexity of managing dengue in the pandemic era.

Our patient had acute fever, thrombocytopenia, positive anti-dengue IgM, and vascular leakage (pleural effusion), which are pathognomonic signs of dengue hemorrhagic fever (DHF). Additional symptoms, such as headache, nausea, vomiting, and myalgia, are also common in dengue infection. Therefore, we treated the patient with maintenance fluid

and antipyretics. No special treatments were done to correct her thrombocytopenia or pleural effusion since bleeding and respiratory distress did not occur. Moreover, we predicted that the illness would resolve in the subsequent days.

A few cases of DSS may occur in 2-7 days; however, mostly occur between 3-5 days. Shock in dengue may initially be compensated with a normal systolic blood pressure (BP), elevated diastolic BP, narrow pulse pressure, and features of hypoperfusion, such as cold mottled skin. In addition, increase of hematocrit is usually occur (Guzman *et al.*, 1999; Shann, 2005; Ranjit & Kissoon, 2011). In our case, circulatory failure progressively occurred on the 7th day of illness, accompanied by the decrease of hematocrit and hemoglobin level, without any bleeding sign. Decrease diastolic BP and wide pulse pressure, without any sign of skin hypoperfusion, occurred in initial phase of shock. It was not relevant with shock manifestation in dengue, thus led us to re-evaluate the diagnosis. Bacterial sepsis or toxic shock syndrome (TSS) was considered, and broad-spectrum antibiotics were administered. However, because of the patient's normal leukocyte count, negative anti-streptolysin O (ASO), and decreased procalcitonin level, we thought another disease was present rather than infection. Based on the clinical signs of acute fever, erythematous rash, swelling, and circulatory failure accompanied by multiorgan inflammation (neutrophilia; hypoalbuminemia; elevated CRP, D-dimer, and aminotransferase; persistently decreased platelet count, and fibrinogen), we suspected either MIS-C related to SARS-CoV-2 infection or Kawasaki disease with shock (Belhadjer *et al.*, 2020; Riphagen *et al.*, 2020).

According to the 2004 American Heart Association (AHA) guidelines, the patient did not fulfill the criteria of classic KD, since only two clinical features were apparent, i.e., fever and erythematous rash of the extremities (Newburger *et al.*, 2004). Unfortunately, we could not perform echocardiography to evaluate for coronary artery abnormalities in order to establish a diagnosis. A case series demonstrated that KD-shock compared to MIS-C, revealed lower age in the KD group [median: 3.8 (IQR: 0.2-18) vs 9 (5.7-14) years respectively], CRP [median 19.3(IQR: 8.3-23.7) vs 22.9(15.6-33.8) mg/dL respectively], and troponin [median 10 (IQR: 10-30) vs 45 (8-294) ng/L respectively] (Whittaker *et al.*, 2020).

Our patient was 7 years old; she had marked increase of CRP [24.52 (reference range <0.3) mg/dL] and cardiac marker [troponin I: 0.9 (reference range: <0.1) µg/L and CK-MB: 1075 (reference range: 7-25) U/L]. Moreover, the patient had been residing in an area with SARS-CoV-2 community transmission; hence raising the probability of MIS-C. Despite the negative ECLIA-anti-SARS-CoV-2 test result, the MIS-C could not be ruled out. Some case series reported that 9-20% of MIS-C patients had negative antibody and PCR examination results (Cheung *et al.*, 2020; Whittaker *et al.*, 2020). We did not perform PCR because of diagnosis of MIS-C not expected initially and the patient's condition deteriorate rapidly. Antigen rapid test was also not yet done when this case occurred.

Cytokine and inflammatory dysregulation have key roles in viral infections and MIS-C immunopathology. This severe manifestation of SARS-CoV-2 infection has been associated with increased proinflammatory cytokines and chemokine levels (Ye *et al.*, 2020). While cells of the respiratory tract lining are prone to infection as the viral port of entry, lymphocytes may be infected as well. ACE-2, the binding target of SARS-CoV-2 on human cells, is highly expressed on the surface of both cell types. This event produces a rapid increase of Angiotensin II, which can enhance local inflammation and platelet activation (Leisman *et al.*, 2020). In our case, neutrophilia accompanied by lymphopenia and increased of procalcitonin from the first day of admission were indications of the immunopathogenic process of MIS-C.

Dysregulated inflammation and platelet activation in SARS-CoV-2 infection initiates widespread endothelial injury and coagulation (Hennon *et al.*, 2020). Low platelet count with high D-dimer in our patient reflected the systemic activation of coagulation which produced microvascular thrombosis. This combination of dysregulated inflammation and platelet activation also causes increased vascular permeability and plasma leakage subsequently. Systemic inflammation also induces persistent macrophage activation, which in turn causes multiple organ dysfunction (MODS) (Carcillo *et al.*, 2017). This pathogenesis is similar to that of macrophage activation syndrome (MAS) and Kawasaki Disease. Low platelet count and rapid progressive plasma leakage could be used to distinguish between MAS-KD and MIS-C (Licciardi *et al.*, 2020).

Recent available guidelines only recommend empirical therapy for MIS-C. Large clinical trials in the pediatric population are lacking. Intravenous immunoglobulin (IVIG), steroids, interleukin (IL-1) receptor antagonist (ra), IL-6 ra, tumor necrosis factor (TNF)-α ra, and anticoagulants are the suggested medication for treating severe MIS-C (Jonat *et al.*, 2020; Rimensberger *et al.*, 2021). Unfortunately, our case occurred in the middle of May 2020, when the MIS-C phenomenon was newly recognized and no therapeutic guideline published. Therefore, our therapeutic management was inadequate and done to merely resolve circulatory failure. We did not consider any additional therapy recommended for MIS-C.

Despite the maximum dose of epinephrine, norepinephrine, and hydrocortisone, the circulatory failure persisted. The patient rapidly deteriorated and had cardiac arrest. Recently, most MIS-C patients generally have a good prognosis, with mortality ranging from 0-2% (Cheung *et al.*, 2020; Whittaker *et al.*, 2020). We are uncertain whether our patient's death was due to the inappropriate therapy or higher severity of the disease. As of this time, there have been few studies on the mortality predictors for SARS-CoV-2 associated with MIS-C.

The positive IgM anti-dengue result in the initial laboratory examination raises the suspicion of co-infection between severe dengue infection and MIS-C. Indonesia is also an endemic area for dengue infection, so there was a high chance of the patient developing both dengue and SARS-CoV-2 infection. However, MIS-C should be considered as the causation of the fatality in this case. The clinical manifestation and pathologic timeline were more compatible with MIS-C than DSS. Previous reports also reported false-positive dengue serology tests and the cross-reactivity was reported as high as 22% in patient with SARS-CoV-2 infection. In-silico analysis of outer protein chain between Dengue virus and Covid-19 virus reported high similarity of chain in the spike and envelope protein, which associated with immunoglobulin production (Carcillo *et al.*, 2020; Lustig *et al.*, 2020).

In conclusion, SARS-CoV-2 infection in children could lead to a delayed phase of systemic inflammation, such as MIS-C. Its clinical features are similar to those of severe dengue infection, except for the later onset of circulatory failure. More awareness, that is history of SARS-CoV-2 contact, early recognition of inflammatory signs, PCR or antigen testing of SARS-CoV-2, are mandatory; especially in dengue-endemic areas, to prevent misdiagnosis of MIS-C and delayed specific treatment.

Conflict of Interest

The authors declare that they have no conflict of interest.

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