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ARTICLE

SEVERE DENGUE OR COVID-19-RELATED MIS-C? DIAGNOSTIC CHALLENGES IN RESOURCE-LIMITED AND DENGUE-ENDEMIC REGIONS

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ABSTRACT

Besides serological cross-reactivity and co-infection between dengue and SARS-CoV-2, diagnostic challenges arise because many people have had positive dengue IgG in dengue-endemic regions, and patients usually come after 4-5 days of fever. We report a case of 9-year-old girl, diagnosed with dengue with warning signs on admission because of fever, severe abdominal pain, thrombocytopenia, and positive dengue IgG. The subsequent course of the illness was not consistent with dengue infection because the shock happened during the febrile phase concurrent with rising leucocyte and platelet counts, the fever continued for longer than seven days, and there was bilateral non-purulent conjunctivitis with subconjunctival hemorrhage. She was diagnosed with COVID-19-related MIS-C because of positive SARS-CoV-2 IgG and hyperinflammatory markers. Her clinical condition improved progressively after steroid administration. Clinical awareness about MIS-C is required to avoid misdiagnosis and improper treatment during or after the COVID-19 pandemic. Every clinician should consider MIS-C as a differential diagnosis if patients have inconsistencies with the course of dengue illness.

Keywords: dengue, MIS-C, SARS-CoV-2, COVID-19, child

АБСТРАКТ

Помимо перекрестной серологической реактивности и коинфекции между денге и SARS-CoV-2, возникают диагностические трудности, поскольку в эндемичных по денге регионах многие люди имеют положительный денге IgG, а пациенты обычно поступают после 4-5 дней лихорадки. Мы сообщаем о случае с 9-летней девочкой, у которой при поступлении был поставлен диагноз денге с тревожными признаками из-за лихорадки, сильных болей в животе, тромбоцитопении и положительного IgG денге. Последующее течение болезни не соответствовало инфекции денге, так как шок произошел во время лихорадочной фазы, одновременно с повышением количества лейкоцитов и тромбоцитов, лихорадка продолжалась более семи дней, и был двусторонний негнойный конъюнктивит с субконъюнктивальным кровоизлиянием. Ей был поставлен диагноз COVID-19-связанный MIS-C из-за положительных IgG SARS-CoV-2 и маркеров гипервоспаления. После приема стероидов ее клиническое состояние постепенно улучшилось. Во избежание ошибочного диагноза и неправильного лечения во время или после пандемии COVID-19 необходима клиническая осведомленность о MIS-C. Каждый клиницист должен рассматривать MIS-C в качестве дифференциального диагноза, если у пациентов имеются несоответствия с течением болезни денге.

Ключевые слова: денге, MIS-C, SARS-CoV-2, COVID-19, ребенок

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INTRODUCTION

The Coronavirus Disease-19 (COVID-19) pandemic has become a serious health problem globally, with more than 200 million people having been infected by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) all around the world.[1] There have been more than 3 million confirmed COVID-19 cases in Indonesia until August 2021, and 12.9% were under 18 years old.[2] Small groups of children present with severe multisystem inflammation associated with SARS-CoV-2 infection, named multisystem inflammatory syndrome in children (MIS-C). The incidence of MIS-C is still uncertain, but an estimated incidence of 0.6% among laboratory confirmed COVID-19 patients has been reported in New York.[3]

In addition to the COVID-19 pandemic, several countries are also struggling with endemic dengue. Serological cross-reactivity and co-infection between COVID-19 and dengue have been documented in some investigations. It may be challenging to distinguish between severe dengue and MIS-C because of overlapping clinical and laboratory characteristics.[4-6] Laboratory diagnostics of dengue infection in Indonesia are frequently based on rapid diagnostic tests, especially IgM/IgG rapid test. Difficulty in interpreting the laboratory results may have contributed to overdiagnosed or missed dengue diagnosis.[6,7] In severe cases, we need to differentiate between dengue and COVID-19 related MIS-C to determine the appropriate treatment.

CASE REPORT

A 9-year-old female child, 34 kg, came to emergency department (ER) with high fever, persisted after routine paracetamol, since 5 days before admission. The patient also had generalized severe abdominal pain, nausea, and diarrhea 2-3 times a day. She had sore throat and a little bit of cough, but had never felt shortness of breath. She already did a SARS-CoV-2 rapid antigen nasopharyngeal swab, and the result was negative. However, she lived in high local transmission area of COVID-19, where many of her neighbors had been in self-isolation since 8 weeks ago. About 6 weeks before, she had low-grade fever with cough but the SARS-CoV-2 rapid antigen nasopharyngeal swab was negative. She had never been diagnosed with dengue infection before.

On admission, the patient was alert with normal vital signs and oxygen saturation, but her temperature was 38^0C. She had generalized abdominal tenderness, mostly in epigastric region. Her laboratory examination showed leucocytosis, thrombocytopenia, positive dengue IgG, and positive SARS-CoV-2 IgG (Table 1). A chest x-ray showed mild bilateral perihilar and pericardial infiltrates. She was diagnosed with dengue fever with warning signs and was given lactate crystalloid at 3 mL/kg BW/hour. On the second day of hospitalization, the patient looked drowsy, with a blood pressure of 70/35 mmHg, pulse rate of 135 bpm, and cold extremities. There was no apparent active bleeding, but the gastric residual fluid was dark-colored. She was treated for dengue shock with oxygen supplementation, fluid resuscitation (20 ml/kg BW), and dobutamine inotropic support (5 mcg/kg BW/min). The laboratory results revealed decreased hematocrit level, increased leucocyte and thrombocyte counts, moderate hyponatremia, and high c-reactive protein (CRP) level. Ceftriaxone, 50 mg/kg BW/day, was administered to her intravenously (IV) as an empiric antibiotic.

On the third day of hospitalization, the patient was still not fully alert, and her fever persisted. The inotropic dose was increased to 7.5 mcg/kg BW/min to maintain systolic pressure at the fifth percentile of her age, and 3 liters of IV fluid were given in 24 hours. There was bilateral non-purulent conjunctivitis and subconjunctival bleeding in her eyes. On the fourth day, the blood pressure was stable and the inotropic dose was slowly reduced. However, the patient remained in tachycardia (130 bpm), and her fever increased to 39.4^0C. She still complained about abdominal pain, but the gastric residual

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fluid was clear, so a fluid diet was started gradually. She was then suspected of having COVID-19-related MIS-C and worked up for laboratory evidence of hyperinflammation. The results showed very high d-dimer, fibrinogen, and slightly increased erythrocyte sedimentation rate (ESR). She received intravenous methylprednisolone at 2 mg/kgBW/day, divided into 2 doses, but the heparinization was postponed because of the history of gastrointestinal and subconjunctival bleeding.

After 3 doses of methylprednisolone, no fever was observed. The patient had no more abdominal pain, the feeding tolerance was good, and her conjunctivitis disappeared. Repeated dengue serology showed dengue IgM remained negative and IgG was positive. The laboratory evaluation after five days of methylprednisolone showed a negative CRP level, normal fibrinogen, and dramatically decreased d-dimer. On the tenth day of hospitalization, the patient underwent an echocardiography examination, and the result was normal. The methylprednisolone was switched to oral, and the patient was discharged on the eleventh day.

DISCUSSION

In dengue-endemic regions, such as Indonesia, there is a great possibility of misdiagnosis between severe dengue and COVID-19-related MISC-C. There have been reports of severe dengue co-infection with COVID-19-related MIS-C, as well as serological cross-reactivity between dengue and SARS-CoV-2 infection.[4-6,8,9] During the COVID-19 pandemic, non-structural 1 (NS1) antigen appeared to be more reliable to confirm dengue infection than serology IgM/IgG dengue.[4,9,10] However, patients frequently presented to healthcare facilities after 4-5 days of fever which is the transition time between viremia and the appearance of serological dengue markers.[11] On days 1-5 of fever, the positive rates for NS1 antigen and dengue IgM were 81% and 37%, respectively. While IgM detection increased to 73% on days 6-10, NS1 antigen detection declined to 42%.[12]

Another challenge in using serology dengue test in dengue-endemic regions, besides the possibility of cross-reactivity with SARS-CoV-2, is that many people have already been exposed to dengue infection and therefore have positive dengue IgG antibodies. Post-infection dengue antibody responses can last for a long time, IgM circulates in the body for up to 2 to 6 months, while IgG persists longer, generally up to 2 months to 2 years after primary infection.[10] A study by Utama et al showed that by age 5, more than 40%, and by age 12, more than 90% of patients had serologic evidence of prior dengue exposure.[7] Dengue IgM/IgG ratio or IgG titers are important in differentiating between recent and past infection, but these diagnostic tests may not be available in some laboratory facilities. The NS1 antigen and the IgM/IgG rapid tests are the most common laboratory diagnostic tools for clinicians in Indonesia.[7]

Our patient was diagnosed with dengue with warning signs at admission because of her physical clinical manifestations, and laboratory results of thrombocytopenia and positive dengue IgG antibody. Besides gastrointestinal manifestations, the patient also had respiratory manifestations, such as cough and sore throat. Upper respiratory tract manifestations were not uncommon in dengue infection, some studies reported that 20-30% of patients with dengue infection had cough and/or cold.[13,14] However, there was leucocytosis with dominance of segment neutrophil, which was not very usual in dengue infection, especially in acute febrile phase. Decreasing white blood cell and platelet counts make the diagnosis of dengue very likely, and leukopenia usually precedes the onset of critical phase.[11] The patient's course of illness was not supportive of dengue infection, as the shock manifestation occurred in febrile phase, parallel with increasing leucocyte and platelet count. The fever also persisted for more than seven days, and there was bilateral non-purulent conjunctivitis with

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subconjunctival bleeding. The ocular involvement in dengue is not frequent, and the pathophysiology is still unclear. Subconjunctival hemorrhage is the most frequently reported ocular manifestation, as a result of marked thrombocytopenia.[15] In our case, conjunctivitis and subconjunctival hemorrhage appeared while thrombocyte was increasing. Repeated dengue serology on the sixth day of hospitalization yet showed negative dengue IgM serology. This result ruled out dengue primary infection in our patient. Even though secondary infection could not be determined by this serology result, her clinical manifestations did not support dengue infection.

COVID-19-related MIS-C was considered in our patient as she met the WHO criteria, and the response to high dose corticosteroid was good. The positive SARS-CoV-2 IgG and negative SARS-CoV-2 rapid antigens showed evidence of COVID-19 post-infection. Ideally, a SARS-CoV-2 RT-PCR nasopharyngeal swab should be performed rather than rapid antigen test, but the Indonesia Ministry of Health permitted the use of SARS-CoV-2 rapid antigen test in certain conditions, such as when sampling delivery to the referral laboratory is more than 24 hours and the RT-PCR result is more than 48 hours, because of emergencies. Although the pathophysiology of MIS-C is not clearly understood, it has been suggested that it is a post-infectious process triggered by abnormal immunophenotype and cytokine release syndrome.[15] A systematic review by Hoste et. al. showed that two-thirds of patients with MIS-C were IgG positive, and only about 30% of patients had positive respiratory RT-PCR.[16] MIS-C is commonly found in children with a median age of 8 (5-13) years and previously healthy children after 4-6 weeks after the peak of COVID-19 transmission in the country.[3,16-18] Our patient was 9 years old, and her clinical manifestation timeline was consistent with a peak incidence of COVID-19 in Indonesia.

As the COVID-19 infection is still ongoing, the number of MIS-C cases is also expected to increase. Clinical alertness about MIS-C is required to avoid misdiagnosis and delayed treatment. Every clinician in dengue-endemic regions should think about MIS-C as a differential diagnosis if the suspected dengue patient has inconsistent clinical manifestations and/or laboratory findings with the course of dengue illness. The positive SARS-CoV-2 IgG antibody is an important clue to consider an MIS-C diagnosis in symptomatic children.

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CONFLICT OF INTEREST

The authors declare no conflict of interest of this study

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Table 1. Patient's clinical manifestations and laboratory results

Hospitalization	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 9
Clinical manifestations								
Fever (^{0}C)	38.0	37.9	38.8	39.4	38.2	36.7	36.9	36.7
Altered mental status	-	+	+	-	-	-	-	-
Cough	+	+	+	+	+	+	-	-
Conjunctivitis/ subconjunctival bleeding	-	-	+	+	+	-	-	-
Abdominal pain	+	+	+	+	+	-	-	-
Laboratory results								
Hemoglobin (g/dL)	11.6	9.1	10.5	10.7				
Hematocrit (%)	33	25	31	29				
Platelet (10^3/mm^3)	98	108	118	117				
Leucocyte(10^3/mm^3)	12,54	18.27	18.33	18.14				
Basophil (%)	0		0					
Eosinophil (%)	5		4					
Neutrophil (%)	80		81					
Lymphocyte (%)	14		10					
Monocyte (%)	1		5					
Dengue IgM	Negative					Negative		
Dengue IgG	Positive					Positive		
SARS-CoV-2 antigen				Negative				
SARS-CoV-2 IgM	Negative							
SARS-CoV-2 IgG	Positive							
Salmonella Typhi IgM			Negative					
CRP (mg/dL)		>128				32-64		Negative
Fibrinogen (mg/dL)				433				169
D dimer (µg/dL)				3.62				0.63
Glucose (mg/dL)	124							
Sodium (mmol/L)		128	135			131		
Potassium (mmol/L)		2.9	2.9			4.5		
Chloride (mmol/L)		100	105			100		
Urea (mg/dL)		41						
Creatinine (mg/dL)		0.7						
Aspartate aminotransferase (U/L)		34						
Alanine aminotransferase (U/L)		27						

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