Expanded Dengue Syndrome with Hemolytic Anemia: A Case Report

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ABSTRACT

Introduction: Expanded Dengue Syndrome is an atypical manifestation of dengue hemorrhagic fever with compliciation of other organs such as the liver, spleen, and kidney. Haemolytic anemia is a rare complication that can occur in dengue haemorrhagic fever and the case has not been widely reported.

Patient and methods: This case report will discuss a 45-year-old man who presented with severe dengue haemorrhagic fever with atypical manifestations to the other systems such as haematology, hepatology, nephrology, and gastrointestinal problems.

Results: The patient was diagnosed with dengue hemorrhagic fever with the positive result of NS-1 antigen, IgG, and IgM dengue. Patient was diagnosed with severe anemia in conjunction with dengue infection. Examination of the peripheral blood smear, reticulocytes, and LDH was done with the result is haemolytic anemia. Coombs test was found negative. Transfusions of Packed Red Cells and Thrombocytes Concentrate were given as a treatment of severe anemia and thrombocytopenia. Patient recovered without further complications and was discharged home.

Conclusion: The condition of hemolytic anemia in EDS is a rare condition and should be aware of. Further examination in dengue hemorrhagic fever patients with severe anemia should be considered with the presence of hemolytic anemia.

Keywords: Dengue Hemorrhagic Fever, Anemia, Thrombocytopenia, Expanded Dengue Syndrome.

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Introduction

Dengue Hemorrhagic Fever (DHF) is a self-limiting arboviral infection. It is caused by dengue virus, a single stranded RNA Flaviviridae. Four serotypes of dengue virus (DEN-1, DEN-2, DEN-3, and DEN-4) possess its own viral genome that encodes three structural proteins (capsid C, membrane protein M and envelope glycoprotein E) and seven nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5).[1–4] There were no reports on dengue infection rate[5], but approximately 390 million people in 128 countries are at risk.[6] According to the World Health Organization (WHO), there are approximately 500.000 cases per year that progress to a higher severity, and 2.5% of them experience death.[7,8] The Indonesian Health Data Profile in 2011 shows that dengue infection ranks second out of ten inpatient diseases in hospitals with a Case

Fatality Rate (CFR) of 0.55%. The number of dengue cases in Indonesia reached 65.432 with an incidence rate (IR) per 100.000 population of 27.56 and a case fatality rate (CFR) of 0.91%. Bali is one of the provinces with the highest incidence rate per 100.000 population with a figure of 75.42 after South Sulawesi which reached 76.16. The number of cases that occurred in Bali reached 2.996 with a CFR of 0.23%.[9]

DHF complications could involve several important organs such as the brain, liver, heart, lung, and kidney and have unusual and atypical clinical manifestations in each individual. Expanded Dengue Syndrome (EDS) is a new category from the WHO classification in 2012, namely, severe DHF with unusual manifestations of other organ such as liver, kidneys, and other organs. Patients with comorbid, pregnancy, infants, elderly, and immunocompromised are more prone to developing EDS conditions.[10,11] Hemolytic anemia is a rare complication of EDS where the mechanism of association has not been widely reported.

Case Illustration

A 48-year-old man came to Dharma Yadnya General Hospital with continuous fever and shiver. In addition, the patient complained of nausea, vomiting, joint pain, and headache. The patient denied any complaints of abdominal pain, myalgia, retroorbital pain, or other systemic complaints. Previously, the patient went to the primary care facility and was given antibiotics (Amoxicillin), NSAIDs (Methylprednisolone), and acetaminophen. The patient had no history of dengue fever. The patient was compos mentis (GCS 15), with a blood pressure of 130/80 mmHg, a pulse of 80 beats/minute, a respiratory rate of 22 times/minute, and a temperature of 39.4oC. Physical examination did not reveal any red spots or active bleeding. Physical examination, either systemic or another general, found no abnormalities. The diagnosis of dengue hemorrhagic fever was made based on NS1 examination on the first day of fever and anti-dengue immunoglobulins in the form of IgM and IgG which were positive on day 9 of fever.

On the first day of treatment, the patient complained of discomfort during urinating. Urine chemical analysis showed elevated pH (7 [normal: 5-6,5]), microscopic sediment examination showed 2-3 erythrocytes per HPF(normal: negative), leukocytes 3-5 /HPF, squamous epithelial cells 0- 1 /LPF (normal: negative), positive bacteria (+1)/LPF (normal: negative) so that the diagnosis of urinary tract infection was confirmed. In addition, the patient also complained of diarrhea on the fourth day of treatment. Diarrhea 5 times a day, yellow in color, watery, smells, sour, and with mucus but no blood. Complete fecal examination showed that there was mucus on macroscopic examination, and microscopic examination showed the following results: erythrocytes 4-5/HPF (normal: negative), leukocytes 1-2 /HPF (normal: negative), positive bacteria (+3) (normal negative). From these data, the patient was also diagnosed with acute liquid diarrhea et causa bacterial infection. Renal function was examined on the second day of treatment and showed elevated creatinine, namely, 1.45 mg / dL. Blood Urea Nitrogen (BUN) was normal.

On the sixth day of treatment, the patient complained of nausea, vomiting, and bloated. Upon examination, there was a pain in almost all abdomen region along with abdominal distension. Abdominal X-Ray was performed on the patient and showed no abnormalities

in the abdomen. Bloating and abdominal distention was felt to be getting worse, so the patient was consulted with a surgeon and was getting an ultrasound examination. There was free fluid in the abdominal cavity, and but no visible abnormalities in other organs such as the kidneys, liver, and spleen were observed. Laboratory examination showed elevated ALT and AST, then an HBsAg examination was performed with negative results.

Examination of bleeding time on a ninth day found prolonged PT and a PTT. Complete blood count was performed every day, and platelet was found decreased in every test. On the 6th day of treatment, the platelet count was 5x103 µL (normal 150-440 103/uL), so that 5 bags of Thrombocyte Concentrates (TC) were transfused. Platelet levels after transfusion were 13x103 µL and then increased gradually. However, after the Platelets gradually increased, the patient's hemoglobin level gradually decreased.

On a ninth day, the hemoglobin result was 6,1 g/dl (normal 13,2-17,3 g/dL), and PRC transfusion was administered. Hemoglobin levels after the first transfusion were 8,5g/dL. A second PRC transfusion was performed the next day, and the hemoglobin level after the second transfusion was 10,2 g/dL. Reticulocyte examination found an increase of 1,66% (normal 0,43 to – 1,36%) and absolute reticulocyte 0,0933x10^6/µL (normal 0,023 to – 0,07x10^6 / µL), levels of Immature Reticulocyte Fraction (IRF) 26,8% (normal 1,6 – 10,5%). Examination of Lactate Dehydrogenase found an increase of 611 U/L (normal 240-480 U / L). Blood smear examination found normochromic normocytic erythrocyte cells with cell polychromasia (+) and normoblast (+). Coomb's test was negative, both direct and indirect. Bilirubin results were within the normal range.

The patient's hemodynamic status was stable. The patient received 3 mL/KgBW crystalloid in the first 4 hours, with daily monitoring of vital signs, clinical status, and complete blood counts. Maintenance fluid therapy is carried out by giving the same dose or reducing it by 1-2 ml / KgBW which was determined based on vital signs. The patient's urine output was evaluated every day to monitor fluid administration.

Complete Blood Count	Day-1	Day-2	Day -3	Day-4	Day-5	Day-6 08.56 am	Day- 6 16.52 pm	Day-7	Day-8	Day-9	Day-10	Day-11	Day-12	Normal Value
Hemoglobin	14.2	13.1	12.9	13.5	14.4	14.7	13.1	10.7	7.4	6.1	8.5	10.2	10.2	13.2-17.3 g/Dl
Red Blood Cell Count	4.88	4.51	4.41	4.59	4.96	5.08	4.49	3.69	2.54	2.07	2.96	3.32	3.42	4.4-5.9 x 10^6/uL
Hematocrit	41.3	38	36.7	38.1	41.1	41.6	36.7	30.6	20.2	17.5	25.5	29.6	29.6	40 – 52 %
White Blood Cell Count	10.6	6.1	4.3	3.7	4.4	4.7	8.8	9.7	2.9	17.9	17.3	11.5	11.5	3.8 – 10.6 x 10^6/uL
Platelets	166	130	114	55	13	5	13	24	62	231	341	348	348	150-440 x 10^3/uL
Reticulocyte									1.66					0.43 – 1.36 %
Absolut Reticulocyte										0.0933				0.023-0.0701 x 10^6/ uL
IRF										26.8 %				1.6 – 10.5 %
LDH										611				240-480 U/L
Coomb's test	No Auto immune antibody coated on patient's erythrocyte detected (Direct: negative) No Irregular free Allo-Antibody in patient's serum (Indirect: negative)													
Peripheral blood smear	Erythrocyte : Normochromic, normocytic, polychromasia (+), normoblast (+) Leukocyte : Elevated count, predominant with segment neutrophil no immature granulocyte, toxic granule (-), no immature cell Thrombocyte : Normal count, giant thrombocyte (-) Interpretation : Leukocytosis, normochromic normocytic anemia													

Table1. Complete Blood Count during the Treatment

Variable	Day-2	Day-6	Day-8	Day-9	Day-10	Normal Value
ALT	27	143	75		53	10-40 U/L
AST	17	108	78		55	10-55 U/L
HBs Ag		Negative				Negative
Creatinine	1.45	1.25				<1.2 mg/dL
Blood Urea Nitrogen (BUN)	13	10				8-25 mg/dL

Total Bilirubin			0.78			<1.3
Direct Bilirubin			0.35			<0.5
Immunoserology						
NS1	Positive					Negative
Anti-Dengue IgG			Positive			Negative
Anti-Dengue IgM			Positive			Negative
Hemostasis						
Bleeding Time				2'00''		1-3 Minutes
PT				11.4		Differences to control PT< 2 seconds
PT Control				14.5		
INR				0.86		0.85-1.22
APTT				23.8		Differences to control < 7 seconds
APTT Control				36.6		

Table2. Other Laboratory Examination during the Treatment

Discussion

The manifestation of EDS can vary. Although some cases are asymptomatic, serious complications may arise with unusual clinical manifestations. EDS may manifest as various symptoms such as neurological, hepatology, nephrology, and cardiology, as well as targeting various organs related or conditions associated with secondary infections or co-infections with various pathogens.[12] The gastrointestinal and other systems that have mucosal lining are the main targets for capillary leakage and one of the clinical manifestations is diarrhea. In this case, the patient had gastrointestinal infections that manifest as diarrhea and urinary tract infection caused by Gram-negative bacteria. There are some literature related to the existence of two infections between the dengue virus and bacteria.[13,15] Approximately, 0.18 to 7% of dengue infections are associated with a bacterial infection.[16,18] How dengue infection predisposes to super infection and bacteremia has not been determined, but several hypotheses such as low immunity, severe neutropenia, and microbial translocation may be related to dengue superinfection.[19,21]

Dengue infection can cause immunosuppression during acute infection and can reduce proliferative response stimuli in T cells by impairing the function of antigen-presenting cells, reduce phagocytic activity and migration of spleen and peritoneal macrophages and suppress the presence of interferon signaling pathways through different down-regulation.[19,22,24] In addition, modulation effects of Lipopolysaccharide (LPS), endotoxin on Gram-negative outer membrane is also associated with active replication of dengue virus. Chen et al (2002) observed that when LPS was added to in vitro culture of human monocytes and macrophages after dengue virus infection, viral replication increased and prolonged[25] and a similar conclusion was reached by one study in cell culture of the Aedes aegypti mosquito.[26] The presence of Gram-negative coinfection associated with active replication of the dengue virus may

temporarily worsen or be prolonged after starting antibiotic therapy because of the release of large amounts of LPS from killed bacteria.[27]

Renal function examination showed an increase in creatinine parameters, but the BUN test was normal. There is often increased kidney function due to tissue damage in severe DHF.[28] The possible mechanism is the cytopathic effect of the dengue virus on glomerular and tubular cells. In intravascular hemolysis, when free hemoglobin is filtered through the glomerulus and enters the proximal tubule where the hem and globin are separated, an increase in intracellular proteins in the hem group can result in nephrotoxicity due to renal hypoperfusion, direct cytotoxicity or intrarenal vasoconstriction leading to acute tubular necrosis.[29] In this case, serum creatinine was increase1,2 times, with normal BUN results. An increase in serum creatinine is not necessarily the result of impaired kidney function but rather the damage to muscle tissue due to the production of myotoxic cytokines from dengue. Acharya et al. found in dengue patients with muscle weakness, biopsy examination revealed inflammation of muscle cells.[30]

The patient complained of abdominal pain accompanied by nausea and vomiting with abdominal distension. Free fluid in the abdominal cavity was found, without any abnormalities in other abdominal organs. Ascites often occur in DHF due to plasma leakage. Endothelial cell damage accompanied by the release of inflammatory mediators, namely IL-6, IL-8 and Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES), as well as activation of adhesion molecules such as ICAM-1 by the dengue virus can also increase vascular permeability and lead to plasma leakage. Endothelial cell damage can also because by apoptotic mechanisms triggered by TNF alpha and cytokines from the immune response related to dengue infection.[31] The certain cause of abdominal pain, in this case, is still unknown because there were no abnormalities in the abdominal organ. The most likely mechanism of pain is the presence of ascites, which can cause pain in which there is abdominal pain in 2.39% of patients with ascites.[32]

Involvement of liver damaged had been reported in expanded dengue fever.[33] Bijaya et al. found that 57.5% of EDS patients showed an increased ALT and AST in the first 4 days and slowly decreased thereafter.[34] Several mechanisms of liver disorders have been proposed, one of which is cellular apoptosis. Dengue virus invasion of hepatocyte and kupffer cells will cause these cells to undergo apoptosis. Other mechanisms that may involve are the presence of viral cytopathy, defects in mitochondria, and cytokine storm.[33,35] This is indicated by an increase in liver enzyme levels, where AST levels are said to increase more frequently than ALT. However, AST is not specific to the liver compared to ALT, because muscle cells, erythrocytes, and heart cells may release AST when damage occurs. Therefore, the ALT level is more related to the severity of dengue.[36,38]

In our case, PT and PTT were prolonged. APTT prolongation is associated with symptom severity, mortality rate, and length of stay in DHF patients.[39] The study by

Kannan et al. Explained that thrombocytopenia is associated with a PTT prolongation without PT abnormalities is due to reduced intrinsic factors caused by defects in the synthesis process of coagulant factor.[40] The patient's hemoglobin level on the first day was normal and tended to be stable until the 6th day and inversely proportional to the patient's platelet level on the first day then decreased every day. The transfusion of Tc was performed according to WHO guidelines, namely platelet transfusion can be administered when platelets reached<10.000 in patients without bleeding manifestations as a prophylactic measure.[41] The dengue virus can change the antigen from the erythrocyte membrane and trigger a cross-reaction of the antibody against the virus.[28] The pathophysiological process of thrombocytopenia in dengue fever is still debated, but some hypothesized that bone marrow depression may directly cause viral invasion of monocytes and platelets leads to increased consumption and destruction processes, with red blood cells becoming susceptible and resistant to virus invasion.[42] Six hours after TC administration, platelet was increased, but Hb levels decreased, so PRC transfusion was performed. PRC transfusions were given when there was Hb <7g / dL or evidence of hemolysis.[43]

Hemolytic anemia is a rare complication of EDS and the mechanism remains unclear. Physical examination and patient previous history could be important clues to diagnose haemolytic anemia.[44] In our case, haemolytic anemia was confirmed on the ninth day of treatment. Peripheral blood examination showed normocytic normochromic erythrocytes with cell polychromasia (+) and normoblast (+) and increased reticulocytes and IRF (immature reticulocyte fraction), which corresponds to the criteria for hemolytic anemia.[45] In the case of acquired hemolytic anemia characterized by an increase in IRF and absolute reticulocyte indicating an increase in erythropoiesis.[46] The destruction of RBC is characterized by increased bilirubin, as well as LDH. However, in our case, LDH levels were increased but the total and direct bilirubin levels were normal. Increased bilirubin occurs in hemolytic anemia due to increased hemoglobin catabolism in the RES resulting in unconjugated bilirubin formation[42] and LDH as well as hemoglobin enters the bloodstream when red blood cells are destroyed.[41]

It is known that high haemoglobin and hematocrit in DHF patients are caused by plasma leakage due to cross-reactions between pro-inflammatory mediators such as tumor necrosis factor (TNF)-alpha and anti-NS1 antibodies with proteins on the surface of endothelial cells, causing apoptosis of these cells. When the patient is rehydrated, haemoglobin will return to its original state.[46] This is one of the reasons that often cause a delay in diagnosis and treatment. The mechanism of hemolytic anemia associated with dengue virus infection remains unclear. A predictable possibility is the presence of cold-type autoimmune haemolytic anemia, which is caused by complications of several infections that are characterized by the destruction of antibody-coated red blood cells. However, the initiation of the production of the autoantibodies remains unclear. The key that plays a role in this process is the regulation of cytokines that trigger the activation of T lymphocyte

immunoregulatory activity in dengue infection haemolytic anemia.[47]

In this study, the Coomb test was negative. Hemolytic anemia with a negative Coombs test is known to be related to the hemolysis process that is based on Ig A antibodies.[48] Antibody examination was not done in our study due to limited resources in our facility. This is similar to Medagodaetal's study on negative coomb test in Dengue Shock Syndrome patients.[49] but in contrast to the study of Ayeetal and Nurul et al that showed positive indirect coomb's test in dengue patients.[28,36] Cold agglutinin is an antibody contained in the structure of the carbohydrate antigen of erythrocytes, which will be active at low temperatures (<37oC) with most consist of IgM antibodies.[49] Polyclonal IgM is usually acquired after infection-causing generalized hemolysis and is self-limiting, but requires transfusion in some cases. There is no previous evidence regarding the association of cold agglutinin hemolytic anemia with dengue virus infection, in which bleeding manifestations are one of the characteristic features of increased vascular permeability, thrombocytopenia, and hemoconcentration.[50]

The cause of hemolytic anemia in dengue virus infection is the result of transient depression of the bone marrow and a form of bleeding complications that occur.[51] Atypical manifestations of dengue infection have increased in diagnosis, in line with the ability to form transient polyclonal antibodies directly against erythrocytes antigens which in turn result in complement-mediated hemolysis.[45] The recovery process from dengue infection will also result in there solution of a hemolysis.[52]

Conclusion

EDS is a rare atypical form of DHF. The involvement of EDS with damage to various specific organs is still an important matter for further study. In anemia where there is no bleeding, it is necessary to suspect a hemolysis process that may occur due to an autoimmune process or direct infection of a virus. As practitioners in both hospital and primary health care, it is important for doctors to recognize and diagnose the presence of EDS associated with haemolytic anemia early before the occurrence of further complications.

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