DENGUE FEVER WITH WARNING SIGN (CASE REPORT)

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Abstract: Dengue Hemorrhagic Fever (DHF) is a disease infection caused by the dengue virus that enters the circulatory system through the bite of a vector, namely the Aedes aegypti, characterized by plasma leakage. Dengue virus infects endothelium, bone marrow, and Kupffer cells in the liver so that activates the immune system which occurs excessively. Thrombocytopenia occurs due to bone marrow suppression, destruction, and shortening of the life of platelets which interfere with the coagulation system, causing bleeding.

We describe a case of a 42-year-old man admitted to the intensive care unit who was diagnosed with dengue fever with a warning sign. In this case, besides complaint of fever, there is also the existence of pain in the pit of the heart, and gums bleeding. During the monitoring process in the room, there are other symptoms such as rash on the skin, nausea, vomiting, persistent heartburn, the difficulty for sleep, also minimal ascites. On laboratory result, hematocrit starts increasing and accompanied with the drop of platelets 50000/mm³ with Ht 49.8%, so that patient is transferred to ICU for monitoring intensively and prevent entering severe dengue.

This patient has platelets decrease until reaches 13,000/mm³ and hematocrit reached 48.1% shows the weight clinical that will be experienced patient. The patient who experiences ascites that becomes a predictor will occurrence of DSS so that has a prognosis of dubia. The prognosis for dengue without or with warning signs is generally good.

INTRODUCTION

Dengue infection is disease infectious disease caused by the dengue virus from the *genus Flavivirus, family Flaviviridae*. Dengue virus is transmitted through mosquito *Aedes Aegypty* which carries the DENV-1,2,3 and 4 viruses.³ Mostly infected patient character is asymptomatic or symptomatic in the form of fever, accompanied by painful muscle/joint, rash, leukopenia, lymphadenopathy, thrombocytopenia, and bleeding.

According to WHO, the incidence fever dengue hemorrhagic fever (DHF) increased 30 times over the last 50 years. Dengue virus infection is attacking developing countries especially area tropical nature endemic. In the 2000s in 12 Southeast Asian countries around 3 million people were infected with the Dengue virus every year years and 6000 patients experienced deadly each year consequences of Dengue infection.⁵ Indonesia was the country with the highest reported case of Dengue infection in Southeast Asia.⁶ The number of cases of dengue hemorrhagic fever in Indonesia occurred as many as 68,407 cases in 2017 with a death toll of 493 people. The death rate in Indonesia, which is more than one percent, is categorized high, with the province of West Java having a mortality rate of 0.58 percent.⁷

CASE REPORT

Anamnesis

A patient man 42 years old came to Dustira Hospital with a main complaint of fever. Fever was felt since 9 hours before and arouse tall suddenly and persistent continuously. The complaint was getting better with taking paracetamol but a few hours after that complaint arouse back.

Complaint accompanied with head dizziness, pain head, body feel aches, weakness, and pain in the pit of the stomach. The patient felt nauseous without accompanying the gag so the patient was only able to eat 2 spoons of rice. The patient had time to experience gum bleeding, nosebleed, no rashes, and spots, defecate and urinate were no complaints.

The patient has a history of disease hypertension already suffered for 1 year. The patient used to drink drug antihypertensive when there is a complaint like head dizziness. Drug taking antihypertensives patient is amlodipine 10 mg orally before sleep.

Family nor environment neighbor patient no anyone has complaint similar this patient moment. According to the patient, a lot of clothes hang at home and a lot of puddles around the house. The patient was then treated and for three days the patient feel the fever was already lost, however, start to arise spots red that doesn't disappear when pressed on both feet. His stomach felt full accompanied by nausea, vomiting, and heartburn. The patient became difficult to sleep.

Two days then from the inspection blood patient, the patient experienced a drop of thrombocyte so the patient was required to move from room care to ICU. The patient also felt his stomach becoming more bloated and feeling nauseous without accompanying vomit. *Physical examination*

Examination results physical on the patient obtained composment awareness with the impression of moderate pain. Inspection patient's vital signs showing patient experience Stage I hypertension with pressure blood reached 140/90 mmHg, whereas, for other vital signs in the normal limit, i. e. pulse 86x/min, respiration 22x/min, temperature $36,5^{\circ}C$, and $5p02\ 98\%$.

On examination of nutritional status, the patient experiences obesity with weight reaches 90 kg and height of 170 cm so that obtained mass body index as big as 31.14 kg/m^2 which shows that patient experience obesity.

On head examination did not find the presence of anemic conjunctiva, icteric sclera, epistaxis, or crust sanguinolenta. On the mouth, the examination did not find existence

bleeding in the gums. Inspection of the neck was no obtained gland enlargement or trachea deviation.

On the thorax, examination obtained normal lungs marked with form and movement symmetrical chest wall, voice percussion sonor on both roomy lungs, the respiratory sound tree was the same VBS in the lungs right and left, as well as no found existence ronchi or wheezing on both roomy lungs so that no pleural effusion. Inspection heart was showing a normal heart marked with sound heart I and II were regular, pure, and no murmurs found.

On abdominal examination, the abdomen was convex with protruding umbilicus to in. On auscultation, bowel sounds had a frequency of 15x/minute. Palpation obtained pain of epigastrium, deafness moved (+) minimal, liver and spleen difficult to assess.

On the extremities, patient was not found existence a marked abnormality with warm akral, less CRT from 2 seconds, no edema, and the petechiae already started fading on both extremity bottom.

Laboratory test

Inspection routine blood obtained Hb 15.7 g/dl, erythrocytes 4.9×10^6 /mm³, leukocytes 6470/mm³, hematocrit 41.5%, platelets 142.000/mm³, MCV 84 fl, MCH 31.8 pq, MCHC 37.8 g/dl, basophils 0.5%, eosinophil 0.6%, neutrophil segment 73.1%, lymphocytes 14.4%, monocytes 11.4%, and GDS 128 mg/dl.

On the 4^{th} day ICU laboratory obtained Hb 19 g/dl, erythrocytes $6x10^6/mm^3$, leukocytes $5640/mm^3$, hematocrit 49.8%, platelets $13,000/mm^3$, MCV 82.5 fl, MCH 31.5 pq, MCHC 38.2 g/dl, basophils 1.1%, eosinophil 0.2%, neutrophil segment 34.3%, lymphocytes 35.5%, monocytes 28.9%.

On the 5th day laboratory obtained Hb 17.4 g/dl, erythrocytes 5.5x10⁶/mm³, leukocytes 7320/mm³, hematocrit 44.8%, platelets 23.000/mm³, MCV 81.2 fl, MCH 31.5 pq, MCHC 38.8 g/dl, basophils 0.8%, eosinophil 0.0%, neutrophil segment 52.2%, lymphocytes 37.2%, monocytes 9.8%, sodium 124 mmol/L, potassium 3.8 mmol/L, chloride 97 mmol/l, NS-1 nonreactive.

Diagnosis

Based on history, physical examination, and laboratory tests for the patient this could be diagnosed with Dengue with warning signs accompanied by hyponatremia, minimal ascites, hypertension grade I, and obesity II. The differential diagnosis in the patient is severe dengue.

Therapy

During patient was treated in the room care, the patient was given the number of supportive and symptomatic treatments; Ringer's Lactate 24 drops/minute, Psiidi 3x1mg, Omeprazole 2x40 mg, Ondansetron 2x4mg, Sucralfate 3x1spn, and PCT 3x500 mg.

After the patient enters the ICU on the day 6th care, the patient start to get a number of other treatments, that include IVFD 3000 cc: gelafusal 500 cc/24 hours (6:1), Omeprazole 2 x 40 mg, Sucralfate 3 x 1 spn, Domperidone 3 x 1, Curcuma 3 x 1, Amlodipine 0-0-5 mg. The patient has also paired a catheter for urine monitoring and blood tests every 12 hours.

DISCUSSION

Dengue fever is caused by the dengue virus that enters the circulatory system through the bite of a vector, namely the Aedes aegypti or Aedes albopticus mosquito, which is characterized by plasma leakage.⁸ Dengue virus has almost the same characteristics as other flavivirus genera. The dengue virus genome consists of (Ribo-Nucleic-Acid) RNA with a single chain, the RNA is surrounded by an icosahedral nucleocapsid and enclosed by an envelope with a lipid composition. This virus is rod-shaped, thermolabile, sensitive to inactivation by diethyl ether and sodium deoxycholate, and stable at 70°C. There are 4 serotypes of the virus, namely DEN-1, DEN-2, DEN-3, and DEN-4.⁸ Factor possible risks increase the occurrence of dengue, as following: age or young age, body immunity, population density, hanging clothes, house humidity, poor environmental sanitation, housing quality, and nutritional status.⁹

Dengue virus infects endothelium, bone marrow, and Kupffer cells in the liver, thereby releasing various mediators that activate the immune system, which occurs excessively, which will cause various signs and symptoms of the dengue virus. 10,11 Secondary infection is the main risk factor for Dengue Hemorrhagic Fever/Dengue Shock Syndrome due to antibody-dependent encryption. The inflammatory process that occurs makes vascular permeability increase where plasma that is in the intravascular comes out into the extravascular so that plasma leakage occurs which if it occurs continuously will cause hypovolemic shock. 11,12 The cause of plasma leakage occurs not only due to the release of inflammatory mediators, but can also occur due to activation of the C3a and C5a complement systems by the virus-antibody complex. 13

Thrombocytopenia occurs due to bone marrow suppression, destruction, and shortening of the life of platelets which interfere with the coagulation system, causing bleeding.¹³ Massive bleeding can occur if there is interference with blood clotting factors and Disseminated Intravascular Coagulation (DIC). Bleeding and shock will affect each other which can develop into irreversible shock accompanied by severe bleeding.¹¹

Diagnosis of dengue hemorrhage fever is established if there is a fever with 2 clinical manifestations accompanied by the existence of plasma leakage and thrombocytopenia. Clinical manifestation referred to fever 2-7 days that arise suddenly, high, continuous; bleeding manifestations either spontaneously such as petechiae, purpura, ecchymosis, epistaxis, bleeding gums, hematemesis and/or melena, or in the form of a positive tourniquet test; headache, myalgia, arthralgia, and retroorbital pain; cases of dengue fever were found either in the school environment, at home, or around the house; there is plasma leakage which is characterized by one of the following signs/symptoms: an increase in the hematocrit value > 20% from the initial examination or from population data according to age, the presence of pleural effusion, ascites, hypoalbuminemia, hypoproteinemia, thrombocytopenia < 100,000/mm³, and hepatomegaly.

Diagnostic classification of Dengue fever divided dengue without a warning sign, dengue with a warning sign, and severe dengue fever. The warning signs of dengue fever include: abdominal pain, persistent vomiting, present bleeding mucosa, and the presence of enlargement liver (hepatomegaly).¹⁴

Investigations that can be carried out in cases of dengue fever are as follows:

General check-up

Complete blood counts that are carried out routinely are hemoglobin levels, hematocrit, and platelet counts. In DHF patients, hemoconcentration or an increase in hematocrit >20% indicates hypovolemia due to plasma leakage. Thrombocytopenia in DHF can be found where the platelet count is <100,000 cells/ μ L. Leukopenia generally occurs in the febrile phase and is sometimes also accompanied by lymphopenia.

Nonstructural Protein-1 (NS1)

Nonstructural Protein-1 (NS1) is a nonstructural glycoprotein synthesized by the Dengue virus which is secreted into the blood of patients infected with the Dengue virus. NS1 antigen can be detected in the early days of fever from the first to the eighth day with a sensitivity of 63%-93.4% and a specificity of 100%.

Dengue IgM and IgG antibodies

Dengue virus IgM antibodies were detected from days 3-5. It reaches peak levels in the second week, then decreases slowly and can remain detectable 2-3 months later. IgG antibodies can be detected above 5-7 days and can stay positive for years.

Other laboratory tests

Other examinations that need to be carried out in cases of DHF aim to determine complications. The examinations needed include blood gas analysis, especially in DSS patients for monitoring complications of metabolic acidosis. Radiological examination (upright PA chest X-ray and right lateral decubitus) was performed with the aim of seeing the presence or absence of pleural effusion. Ascites and pleural effusion can also be detected by ultrasound examination.

In the case of dengue infection based on existing clinical findings should be determined if the patient needs to be treated or repatriated. Criteria of Dengue fever is necessary conducted to cover "warning sign" or another special condition.¹⁷ Warning signs can be in the form of abdominal pain, vomiting, mucous bleeding, lethargy or restlessness, liver enlargement >2cm, fluid accumulation fluid, and hematocrit enhancement compared previously together with a fast drop of platelets. Other special conditions include pregnancy, infant, old age, overweight or obesity, presence of other diseases such as heart disease or diabetes mellitus, living alone, or staying far from the health facility.

In this case, besides complaint of fever, there is also the existence of pain in the pit of the heart, and gums bleeding. During the monitoring process in the room, there are other symptoms such as rash on the skin, nausea, vomiting, persistent heartburn, the difficulty for sleep, also minimal ascites. On laboratory result, hematocrit starts increasing and accompanied with the drop of platelets 50000/mm³ with Ht 49.8%, so that patient is transferred to ICU for monitoring intensively and prevent entering severe dengue.

Indication of the patient allowed for going home is must fulfillment criteria in the form of no fever for 48 hours, improvement of clinical status, thrombocyte tends to increase >50000/mm³, and hematocrit stable without giving fluid intravenously.

Management of the patient, in this case, is given therapy group B. At the start comes inpatient could be given therapy fluid orally accompanied intravenous 0.9% saline or ringer's lactate with dose maintenance in accordance body weight, here given fluid RL 24 gtt/min, then administration of paracetamol as antipyretic if fever >38 °C, omeprazole

injection including group proton pump inhibitor (PPI) and administration of sucralfate as a mucoprotector for resolve heartburn complaint, ondansetron injection as an antiemetic for relieving nausea and vomiting, and psidii for increasing platelets, as well as conducted monitoring pattern fever, the volume of fluid in and out, urine *output*, the presence of warning signs, and inspection of blood especially hematocrit, leukocytes, and platelet count.

At the time monitoring found clear warning sign, with enhancement hematocrit >20%, give isotonic solutions, such as 0.9% saline or RL start with 5-7 mL/kg/hour for 1-2 hours, then lower to 3-5 mL/kg/hour for 2-4 hours, then lower to 2-3mL/kg/hour, then subtract or upgrade in accordance with response clinical. Reassess clinical status, Ht, and review speed suitable liquid as well as do monitoring vital signs and perfusion periphery every 1-4 hours up to patient go out from critical phase, urine output every 4-6 hours, Ht (6-12 hours), blood glucose, and other organ functions (examination) laboratory of kidney, liver, coagulation, or in indication. At the moment Ht the more increased and platelets amount lower, patients can be added colloid to help reduce continuous plasma leakage. Patients have had a history of hypertension since 1 year ago and no drink the cure by routine. During treatment, blood tension several times up so given amlodipine as an antihypertensive, taken at night.

In general, most DHF patients will recover without complications within 24-48 hours after shock. Signs of the patient entering the healing phase are the general condition improving, increasing appetite, stable vital signs, stable Ht and decreasing to 35-40%, and adequate diuresis. In the healing phase, confluent petechial rash (30%) or sinus bradycardia due to myocarditis may be found, which generally do not require treatment.

Based on data from the study with 69 patients who experienced complications, between days 1 and 4 after disease onset, the three most common warning signs found are stomach ache, vomiting, and the presence of pleural effusion. Minor gastrointestinal bleeding was noted at coming to the hospital. Complications journey that can be found are gastrointestinal bleeding, acute kidney injury, encephalopathy, severe hepatitis with ALT and AST >1000U/L, rhabdomyolysis, pneumonia, disseminated intravascular coagulopathy and acute hemolytic anemia.

Dengue fever prognosis is determined by the degree of disease, whether or not treatment is given quickly, age, and nutritional status. Dengue prognosis without and with warning sign is generally good. Severe dengue fever if it can be detected quickly then the patient can be helped. The mortality rate in uncontrolled shock is around 40-50 % but with proper fluid replacement therapy, it can be 12%. DHF in adults is generally milder than in children. In cases of DHF accompanied by complications such as DIC and encephalopathy, the prognosis is poor.

The diagnosis of DHF and the course of the disease must be done accurately. In patients with DHF, laboratory tests showed thrombocytopenia and hemoconcentration.²¹ The number of platelets and hematocrit levels are often used as indicators of the severity of the disease. The number of leukocytes to see the cause of infection (virus/bacteria). The relationship between hematocrit levels and the severity of DHF has a strong relationship. This means that the higher the hematocrit level, the more severe the clinical degree of DHF.

This patient has platelets decrease until reaches 13,000/mm³ and hematocrit reached 48.1% shows the weight clinical that will be experienced patient. The patient who

experiences ascites that becomes a predictor will occurrence of DSS so that has a prognosis of dubia.

CONCLUSION

Dengue Hemorrhagic Fever (DHF) is a disease infection caused by the dengue virus that enters the circulatory system through the bite of a vector, namely the Aedes aegypti or Aedes albopticus mosquito, characterized by plasma leakage.

Dengue virus infects endothelium, bone marrow, and Kupffer cells in the liver so that it releases various mediators that activate the immune system which occurs excessively, which will cause various signs and symptoms of the dengue virus. Thrombocytopenia occurs due to bone marrow suppression, destruction and shortening of the life of platelets which interfere with the coagulation system, causing bleeding.

Investigations that can be carried out in cases of dengue fever include a complete blood count, which is routinely carried out on hemoglobin levels, hematocrit, and platelet counts. Patients had respiratory failure requiring mechanical ventilation. DSS patients with the presence of pleural effusion, gastrointestinal bleeding, and vomiting were the three most common warning signs on arrival. The prognosis for dengue without or with warning signs is generally good. If severe dengue can be detected quickly, the patient can be helped.

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Declaration Of Interests

The authors have no competing interests to declare that are relevant to the content of this article.

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