Dengue Hemorrhagic Fever with Acute Fulminant Hepatitis: A Case Report

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ABSTRACT

Dengue virus is estimated to cause over 100 million infections throughout the world annually. Although dengue infections can have a wide range of clinical pictures, atypical manifestations have been described recent years. The liver is a susceptible organ affected in dengue infection. Mild liver dysfunction is common in cases of dengue infection but severe liver function impairment and even encephalopathy are rare. The following is a case report of dengue hemorrhagic fever (DHF) with acute fulminant hepatitis. A 43-year-old woman has fulminant hepatitis on day 3 of treatment. Her AST level increased dramatically from 363 U/L to 3,246 U/L. The causes of other hepatitis infection has been excluded. Her dengue IgM-antibody level was reactive. Level of dengue IgM antibody reactive. Clinical improvement experienced by patient after supportive therapy and administration glisirizin or Stronger Neo-Minophagen-C (SNMC).

Keywords: *dengue haemorrhagic fever, fulminant, glycyrrhizin, hepatitis, infectione, stronger neo-minophagen-C, SNMC*

ABSTRAK

Virus dengue diperkirakan menyebabkan lebih dari 100 juta kasus infeksi dengue di seluruh dunia. Meskipun gambaran klinis bervariasi namun dewasa ini didapatkan manifestasi klinis yang tidak khas. Hati adalah organ yang rentan terkena dalam infeksi dengue. Gangguan fungsi hati ringan kerap dijumpai pada kasus infeksi dengue namun gangguan fungsi hati berat bahkan disertai ensefalopati jarang dijumpai. Berikut adalah laporan kasus demam berdarah dengue dengan hepatitis akut fulminan. Perempuan 43 tahun mengalami hepatitis fulminan pada hari ke-3 perawatan. Kadar SGPT meningkat drastis dari 363 U/L menjadi 3.246 U/L. Penyebab infeksi hepatitis lainnya telah disingkirkan. Kadar antibodi IgM dengue reaktif. Perbaikan klinis dialami pasien pasca terapi suportif dan pemberian glisirizin atau Stronger Neo-Minophagen-C (SNMC).

Kata kunci: *dengue berdarah dengue, fulminan, glisirizin, hepatitis, infeksi, stronger neo-minophagen-C, Stronger Neo-Minophagen-C (SNMC)*

INTRODUCTION

Dengue fever is an acute infection caused by dengue virus (DENV) through transmission of the mosquito *Aedes aegypti.* Tropical and subtropical countries are endemic locations of dengue infection with more than 100 million cases reported and 24,000 deaths annually.[1] Clinical features of dengue fever vary according to the age of patients, and clinically can be divided into five manifestations: non-specific fever; classical dengue; dengue fever; dengue hemorrhagic fever with *dengue shock syndrome;* and unusual clinical syndrome

(marked by presence of encephalopathy and severe liver dysfunction).[2-4] While mild hepatic dysfunction is commonly found in dengue fever.[2]

DENV infection can involve multiple organs, and the liver: is the most frequently affected organ in dengue fever. Manifestations of liver disorders are a direct result of toxic effects of the virus or in case of malfunction of immune system response. Clinical spectrum of liver disorder can be only mild transaminase enzyme up to severe conditions of encephalopathy and fulminant liver failure.[5] Glisirizin *(glycyrrhizin)* has been known in the world, including Indonesia, as a medical composition, which is biochemically, provide huge benefits for the improvement of liver function and histology. In Indonesia, this glisirizin known by the trademark SNMC® (Stronger Neo-Minophagen-C) by Dexa Medica. Several previous studies from Japan have demonstrated the efficacy of glisirizine in chronic hepatitis B and C as well as cases of fulminant hepatitis. While in Indonesia, the use of SNMC in chronic hepatitis C cases was reported by Sulaiman A et al (2002) and Lelosutan et al (2005) in chronic hepatitis B cases.[6]

This case report presents a case of dengue hemorrhagic fever experienced by a 43-year-old woman who on the second day of treatment, the patient had acute fulminant hepatitis conditions without any evidence of viral hepatitis infection. The patient's condition improved after giving SNMC ®. The focus of the discussion is more emphasized in the diagnosis and management of acute hepatitis complications of dengue hemorrhagic fever.

CASE ILLUSTRATION

A 43-year-old woman came with the main complaint of high fever since two days before admission to the hospital. Fever is felt throughout the day but improved by administration of paracetamol. Patient complains of nausea with vomiting every meal. Patient also complains of headaches, pain behind the eyes, and the body feels sore as exercising. There was no spontaneous or menstrual bleeding in this patient. There is no significant comorbidity of other diseases in this patient. There was no history of smoking and no history of traveling out of town in the last two weeks. The patient is a housewife and is not pregnant. The health insurance fund guarantee is the National Health Insurance (JKN).

Physical examination revealed compos mentis, blood pressure of 130/80 mmHg, tachycardia (115 beats per minute) and fever (temperature 38.9˚C). The patient's weight is about 50 kg. No jaundiced images of the sclera or skin of the patient. Skin turgor examination showed normal results and examination of tongue mucosa showed a shiny (wet) tongue. The acral is felt warm and the presence of petechies in the lower limbs in this patient. On abdominal examination, there is no enlarged liver or spleen. Epigastric pain is present in this patient. Examination of other organs does not show any abnormality.

Results of laboratory tests currently in emergency unit showed hemoglobin 14.5 g/ dL, hematocrit 43%, leukocytes 6500/mm^3 and platelets 68,000/mm^3. Liver transaminase examination results showed an increase of aspartate-aminotrasferase (AST) 509 U/L and alanine-aminotrasferae (ALT) 363 U/L (normal value: < 40 U/L). Electrolyte examination showed sodium of 131 mEq/L; potassium 3.1 mEq/L and chloride 92 mEq/L. Blood glucose level showed normal values of 97 mg/dL. Examination of renal function showed urea yield 38 mg/dL and serum creatinine 1.6 mg/dL. Chest radiological examination showed no abnormality whereas electrocardiogram result only shows the existence of sinus tachycardia.

The diagnosis of dengue hemorrhagic grade-II with day-3 onset (with hepatic and renal involvement of the liver organ) is established in this patient as a major problem. A routine peripheral blood every 12 hours, routine of liver function and kidney function every two days are planned in this patient. Serological dengue blot and hepatitis marker was performed in this patient in order to make sure the cause of hepatitis. An abdominal ultrasound examination is also scheduled for this patient. Five hundred cc of *Normal saline is given* every 6 hours. Symptomatic drugs are also given such as lansoprazole 30 mg twices iv, sucralfate 15 cc thrice to four times, domperidone 10 mg thrice and oral hepato-protector which is combination of *silymarin* and curcuma, thrice. Patient is encouraged not to get out of bed, not to brush her teeth or to scrape her nose with her fingers. On the second day of treatment (fever onset day-4), hematocrit levels increased to 43% and platelet counts decreased to 27,000/mm^3. In general, the patient's condition is not found abnormalities and also did not get any spontaneous bleeding in patient. Serological results of IgM dengue antibodies showed positive results while dengue IgG antibodies showed negative results. All markers of hepatitis examined also showed negative results (IgM antiHAV, HBsAg and IgM anti-HCV).

During the 3rd or 5th day care of fever onset, the patient's awareness becomes apathetic, speech

bubbling and behaving agitatively. Value scale of *Glasgow Coma Scale* (GCS) at the time showed 13 (of 15). No abnormalities of vital signs, as well as no signs of spontaneous bleeding. The laboratory results showed hematocrit levels of 41% and amounted to 17,000 platelets/mm$^{3.}$ Repeated liver function showed a significant increase in the amount of AST 1,624 U/L and ALT 3,276 U/L. Random blood glucose level was normal as normal as total bilirubin levels, level of prothrombin time (PT) and activated partial Trhomboplastin Time (aPTT). Urgent consultation to psychotherapist colleague shows the condition of the patient at that time due to organic mental disorders.

With these new clinical and laboratory findings, the diagnosis of acute fulminant hepatitis with encephalopathy in dengue hemorrhagic fever is established. Patient could not be transferred to the intensive care unit (high care unit HCU; intensive care unit ICU) because both HCU and ICU were full-bed. A 500 cc of comafusin hepar every 12 hours was administered to this patient. Then three ampoules of SNMC dissolved in 250 cc of 5% dextrose liquid which administered continuously for 1 hour in this patient. This SNMC was given once a day and planned for the next three consecutive days. Six hours after administration of fluid therapy Comafusin Hepar and SNMC, awareness of patient had improvement and finally achieve to compos mentis. Repeated results of serial peripheral blood tests on the 3rd day of the treatment showed decreased levels of hematocrit 39% with severe thrombocytopenia 6,000/mm$^{3.}$ Vital signs of the patient were stable, no fever or signs of bleeding. Transfusion of 5 units of thrombocyte concentrate (TC) is given to prevent spontaneous bleeding due to her low platelet counts. Level of creatinine also improved ie 0.6 mg/dL.

At day 4 treatment (day 6 of fever onset), hematocrit levels showed 36% and platelet level increased after transplanting platelet transfusions. Level of liver transaminase also decreased significantly after the administration of SNMC. ALT level decreased to 2,560 U/L (from 3,276 U/L) and AST to 1,560 U/L (from 1,624 U/L). Then, the second administration of SNMC therapy was continued in this patient.

Day 5 treatment (7th day of fever onset), hematocrit level showed 34% increase in platelet level increased to 47.000/mm^3. Improvements in transaminase levels were also demonstrated after two series of SNMC therapy ie AST 648 U/L and ALT 822 U/L. In general, clinical improvement was felt by patient in this day (day-5).

Platelet level at day 6 of treatment (or day 8 onset of fever) increased to 114,000/mm^3. Hematocrit levels still showed results 34%. After three series of SNMC administration, liver transaminase levels showed improvement in the value of AST 327 U/L and ALT 490 U/L. The patient is discharged with a recommendation back to outpatient clinic after one week, and also for peripheral blood and liver transaminase examinations. Unfortunately, abdominal ultrasound examination in the patient can not be implemented because it is still waiting for the queue schedule. Patient are equipped with hepatoprotector drug containing *silymarin* and Curcuma thrice a day for a week.

One week after treatment, the patient come to internal medicine outpatient clinic to perform routine blood tests and liver transaminases. The patient's condition, in general, looks good, no significant complaints are experienced post-treatment. The results of routine blood showed hemoglobin level of 11.5 g/dL, hematocrit 37%, leukocytes 4,300/mm^3 and platelets 354,000/mm$^{3.}$ As for the liver function, obtained AST 77 U/L and AST 188 U/L. Oral hepatoprotector drug is administered for this patient thrice a day.

DISCUSSION

The diagnosis of dengue hemorrhagic fever in these patients is established according to the criterias of WHO, which are: sudden onset of fever 2-7 days, petechiae, platelets level below 100,000/mm^{3,} as well as signs of plasma leakage.[7] Signs the leakage of plasma (plasma leakage) in this patient marked by increasing of hematocri level > 20%. Regard to no history of hematocrit data before the illness, the evaluation of hematocrit elevation was obtained from a decrease in hematocrit levels after fluid therapy. A decrease in hematocrit levels by 20,9% was obtained in these patients from the following calculations: [(43% -34%) / 43%] x 100% = 20,9%. The presence of symptoms of malaise obtained in this patient such as headache, body-ache, back of the eye pain, in line with the constitutional symptoms of dengue infection. Even so, in the last few years, dengue fever can show an unspecific clinical picture.[8] The positive results from dengue IgM antibodies, as an acute primary infection, confirm the diagnosis of dengue hemorrhagic fever in this patient.

General management of dengue hemorrhagic fever is by administration of fluid therapy with symptomatic medication. Patient is given maintenance therapy fluid for amount of 2,000 cc of normal saline per day. This is in accordance with the guidance which the need for maintenance fluids in patients with dengue

hemorrhagic fever without shock is 1,500 cc + 20 x kg body-weight.[9] Given the patient's weight is 50 kg, then the fluid needs is obtained by a 1,500 cc + 20 (50) cc = 2,500 cc. Lack of 500 cc of fluid is expected to be overcome from fluid intake orally.

The presence of impaired liver function in this patient is thought to be part of dengue fever infection, regard to negative results of hepatitis virus marker examination. This is consistent with the literature which shows that the liver is the organ most frequently affected in dengue fever.[5] Hepatitis can be found in 60-90% of cases of dengue fever, which is dominated by mild to moderately elevated transaminase (transaminase levels < 5 times the normal value). While severe hepatitis where transaminase levels rise more than 10 times the upper limit value of normal is only found at 3-11%.[10] Characteristic features of liver cells damage in dengue is ALT levels higher than AST. This condition is different from liver damage due to hepatitis virus.[8,13,14]

The pathophysiology of liver damage to dengue infection is not fully understood. But in general, it is associated with the interaction between the host, viruses, and duration of illness.[12,13] Hepatocyte cells and Kuppfer-cell are the main target cells of dengue infection.[13] Dengue virus would attach to the cell surface receptor of hepatocytes. Protein E is known to have a role in attaching the virus to the cell. Sulphate sulfur, also known to play an important role in the process of entry of DEN virus into liver cells (HepG2). The liver cells when in G2 phase are susceptible to infection and facilitate replication of the virus. Once dengue virus successfully performed a phase of virus replication in hepatocytes cells, then the next step is a lesion in the liver, apoptosis, micro-vesicular steatosis and body formation: *Councilman-Rocha Lima,* which is similar to the infection of yellow fever and other hemorrhagic viral infection.[12] Liver damage can occur due to a direct effect of virus into liver cells, as previously described, or as a consequence of the disruption of the host-immune system response against the virus.[13] Other causes of liver injury are due to ischemic liver or hypoxic conditions in hepatocyte cell due to circulatory disorders. In addition, the usage of drugs such as acetaminophen or paracetamol are often used to overcome the fever or stiffness in dengue, also contributes to liver damage.[10,12]

The diagnosis of acute fulminant hepatitis in this patient is established on the third day of treatment based on rapid liver dysfunction (elevated fastly of liver transaminase levels) with encephalopathy, in patients without prior liver disease history (no evidence of viral hepatitis involvement).[11] Levels of transaminases, especially ALT, in this patient has increased from the beginning of treatment (day 3 of the initial onset of fever) and increased dramatically in the 5 th day of the onset of fever. This is not much different from the literature that suggests that ALT began to increase on day 3 of the disease and its peak levels on the 7th day of disease onset.[8]

Although there is no specific therapy for fulminant hepatitis in dengue cases, but in general, the objectives of the treatment of hepatitis are: viral clearance, seroconversion, and reduce inflammation.[15] Unlike the case of viral hepatitis, viral clearance and seroconversion component certainly can not be met in the treatment of hepatitis dengue. Then, the main thing to do is to reduce inflammation process. Glycyrrhizin is known to have anti-inflammation effects, anti-oxidant effects, and hepatocyte cell membrane stabilization effects.[15] Glycyrrhizin also has anti-hypertransaminase namely by disrupt bondage of transaminase enzymes in the blood circulation in patients with parenchymal damage or inflammation of the liver (hepatocyte necrosis).[16] SNMC in Indonesia, provided in the form of ampoules 20 ml with the composition are: 40 milligrams of Glycyrrhizin, 400 milligrams of glycine, and 20 milligrams of L-cysteine.[17]

In this case, SNMC therapy was given with a dose of 3 ampoules (60 mL) for three consecutive days. The patient's transaminase level improved dramatically after three days of SNMC dosing. This is in line with the recommended daily dosage indicated in the package insert, that is 40-60 mL SNMC but can not exceed 100 mL per day.[17] Improvement of liver functions in this case, not much different from the reports of Ling et at, who reported a significant improvement transaminase function in the case of an acute exacerbation of hepatitis B after administration of 100 mL SNMC for 5 consecutive days.[18.] Thus, this case report shows the effectiveness of SNMC as anti-inflammatory in the treatment of acute fulminant dengue hepatitis, although it still requires research on a larger scale, in the future.

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