Expanded Dengue Syndrome Presenting with Encephalitis Dengue, Acute Liver Failure, Acute Kidney Injury in a 32-Year-Old Man: a Case Report

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Abstract: Introduction: Expanded dengue syndrome is a manifestation of dengue fever which involves various complications to other organs such as the brain, liver, kidneys, and heart.

Case presentation: A 32-year-old man was referred with altered mental status. He complained of fever, vomiting, headache and myalgia since two days before hospitalized for five days in previous hospital. On admission in our hospital he was delirium E2M5V2, normal other vital signs, and jaundice. Laboratory parameters showed Hb 15.9 g/dl, Ht 37%, WBC 26170/µl, platelet 16000/µl, creatinine 2.04 mg/dl, ureum 103 mg/dl, ALT 3711 U/l, AST 7961 U/l, total bilirubin 13.3 mg/dL, direct bilirubin 7.80 mg/dL, positive serum NS-1 antigen, anti-dengue IgM and IgG, while negative seromarkers for hepatitis A, B, and C, malaria and IgM Salmonella. The head CT scan examination was suggestive of cerebral edema. The abdominal ultrasound results was fatty liver. The patient was given 1 g daily of intravenous methyl prednisolone tapering off, curcuma xanthorrhiza, and intravenous stronger neo-minophagen C. The patient had good response and was discharged after 8 days of hospitalization.

Conclusion: This case report establishes expanded dengue syndrome with multiple organ involvement. Prompt diagnosis and treatment and elimination of differential diagnoses is crucial..

1 INTRODUCTION

Expanded dengue syndrome is the phenomenon coined by the World Health Organization for cases of dengue fever (DF) with rare but dangerous consequences. Expanded dengue syndrome mainly leads to complications involving the vital organs, thus is also associated with a higher mortality rate.1 The World Health Organization (WHO) came up with the term "expanded dengue syndrome" (EDS) to designate cases which do not fall into either DHF or DSS, with unusual manifestations in other organs such as the cardiovascular system, the nervous system, the kidneys, the gut, and the hematological system, which have been increasingly reported and called EDS.2

Dengue fever (DF) is a mosquito-borne tropical disease caused by female Aedes aegypti. Belonging to the Flavivirus family, it has 4 unique serotypes (DEN1–4). The incubation period is 7 to 10 days.1 Dengue is caused by one of four single-stranded, positive-sense RNA viruses (dengue virus type 1 through dengue virus type 4), also referred to as serotypes) of the genus flavivirus (family Flaviviridae). Infectious virus and the virus-encoded NS1 are present in blood during the acute phase, and high-level early viremia and NS1 antigenemia have been associated with more severe clinical presentations.3-5 The detection of NS1 is also the basis for commercial diagnostic assays. 6

Dengue fever is the fastest-spreading mosquito-borne viral disease worldwide, affecting over 100 million people annually. This disease also leads to 20 to 25,000 deaths, primarily among children, and is prevalent in more than 100 countries. Epidemics occur yearly in the Americas, Asia, Africa, and Australia. 7

We describe a case of a 32-Year-Old Man with expanded dengue syndrome who presented with altered mental status and jaundice. This case report is reported how to establish a diagnosis by eliminating other differential diagnoses and evaluation of organs related to this disease. Proper diagnosis and therapy will have a positive impact in patient.

2 CASE PRESENTATION

A 32-Year-Old Man was referred to our hospital with altered mental status and jaundice. He complained of fever, vomiting, headache and myalgia since two days before hospitalized for five days in previous hospital. During previous hospitalization, the patient became jaundiced on the second day of treatment. On admission in our hospital he was delirium E2M5V2, jaundice, and no fever. There was no deficit neurological. At the emergency room , his blood pressure 120/70 mmHg, heart rate was 72 bpm, respiratory rate was 20 time/minute, body temperature was 36.6̊ C, body weight was 80 kg, body height was 170 cm, and BMI was 27.7 kg/m2. There were jaundice sclera and hematoma on the foot. Other physical examinations were normal

Blood examination revealed Hb 15.9 g/dl, Ht 45%, WBC 26170/µl, platelet 16.000 µl, basophil 0%, eosinophil 0%, neutrophils 67 %, lymphocyte 17%, monocytes 16%, AST 7961 U/L, ALT 3711 U/L, Total bilirubin 13.30 mg/dL, direct bilirubin 7.80 mg/dL, Indirect bilirubin 5.50 mg/dL, ureum 103 mg/dL, creatinine 2.04 mg/dL, Glucose 112 mg/dL, INR 2.57, APTT 38.2 second, PT 33.6 second, fibrinogen 149 mg/dL, D-dimer 3.00 µg/mL. Electrolyte examination revealed Natrium 138 mEq/L, Kalium 4.9 mEq/L, calcium 8.3 mg/dL. Serology laboratory results dengue IgG positive, dengue IgM positive, dengue NS 1 antigen reactive, IgM Salmonella typhi negative. Malaria test result was negative. There was no proteinuria. The head CT scan examination was decreased white matter-gray matter differentiation, suggestive of cerebral edema, there was no ICH or cerebral infarction. A chest radiograph results was normal.

The patient was given crystalloid 5cc kg/hour tapering off within 2 days and continued with maintenance dose crystalloid. Injection Methylprednisolon 1 gr/ day was given for three days, infusion 40 ml/day of SNMC during hospitalization, Curcuma xanthorrhiza capsule every 8 hour, Branched Chain Amino Acid infusion/ day, injection lansoprazole 30 mg/ day. Injection methyl prednisolone tapering off after three days from1 gr/ day to 500 mg for 1 day, and then the dose was reduced to 250 mg for 1 day. During 5 days hospitalization, his condition and symptoms were improving. He could be able to communication and good consciousness. Injection methyl prednisolone was reduced 62,5 mg/ day.

Eliminating the cause of jaundice Laboratory tests are performed to eliminated differential diagnosis, HbsAg nonreactive, AntiHCV nonreactive, antiHAV nonreactive, HIV nonreactive, IgM Anti leptospira negative. The result of abdominal USG was fatty liver. After one week treatment in our hospital, the patient was evaluated by performing a head MRI. The results of head MRI was normal. Repeat blood examination showed Hb 12.4 g/dl, Ht 37%, WBC 13390/µl, platelet 75.000 µl, total bilirubin 16.60 mg/dL, direct bilirubin 11.10 mg/dL, Indirect bilirubin 5.50 mg/dL, AST 197 U/L, ALT 523 U/L, ureum 71 mg/dL, creatinine 0.94 mg/dL. He has been discharged from hospitalization is still being monitored. After 5 days discharge from hospitalization, the laboratory result was total bilirubin 8.6 mg/dL, direct bilirubin 4.8 mg/dL, Indirect bilirubin 3.8 mg/dL. Two weeks after hospitalization, the laboratory result was total bilirubin 3.6 mg/dL, direct bilirubin 1.5 mg/dL, Indirect bilirubin 2.1 mg/dL. The jaundice was healed and he can do activities normally as usual.

3 DISCUSSION

Expanded dengue syndrome is a term announced by the WHO in 2011 to cover the uncommon expressions of dengue involving severe damage to the liver, kidneys, bone marrow, heart, or brain.8 The WHO presented the term "expanded dengue syndrome" to designate cases that do not fall into either dengue shock syndrome or dengue hemorrhagic fever. The most common are cardiac and neurological manifestations and dengue encephalitis is a significant cause of the fatal outcome. The sensible knowledge about EDS helps to establish the diagnosis and prompt the appropriate treatment for dengue with unusual manifestations.9

Laboratory diagnosis of dengue is established directly by detection of viral components in serum or indirectly by serologic means. The sensitivity of each approach is influenced by the duration of the patient's illness.10 After an incubation period of 3 to 7 days, symptoms start suddenly and follow three phases; an initial febrile phase, a critical phase around the time of defervescence, and a spontaneous recovery phase.11 During the febrile phase, detection of viral nucleic acid in serum by means of reverse-transcriptase–

polymerase-chain-reaction (RT-PCR) assay or detection of the virus-expressed soluble nonstructural protein 1 (NS1) by means of enzyme-linked immunosorbent assay (ELISA) or the lateral-flow rapid test (not currently available in the United States) is sufficient for a confirmatory diagnosis. For primary infections in persons who have not been infected previously (which is typical in the case of most travelers), the diagnostic sensitivity of NS1 detection in the febrile phase can exceed 90%, and antigenemia may persist for several days after the resolution of fever.12-14 Serologic diagnosis of dengue relies on the detection of high levels of serum IgM that bind dengue virus antigens in an ELISA or a lateral-flow rapid test; IgM can be detected as early as 4 days after the onset of fever.15 The patient had positive results for dengue IgG and IgM, and also positive NS1 on the seventh day since the onset of fever.

Neurological manifestations are less common in dengue, encephalitis and encephalopathy are the most common neurological presentations of dengue infection.16 Encephalitis is due to the direct viral invasion of the brain and can manifest with altered sensorium or personality, seizures, and localized neurological signs.17

Soares et al.18 have proposed following criteria to diagnose dengue encephalitis:

a. Presence of fever;

b. Acute signs of cerebral involvement such as altered consciousness or personality and/or seizures and/or focal neurological signs;

c. Reactive IgM dengue antibody, NS1 antigen, or positive dengue polymerase chain reaction in serum and/or CSF;

d. Exclusion of other causes of viral encephalitis and encephalopathy.

Only few case reports and case series featuring dengue encephalitis describe extensive MRI brain findings. They mostly report involvement of bilateral thalamus, brainstem, cerebellum, basal ganglia, medial temporal lobes and cortical and cerebral white matter.[19] Typically, a head CT scan reveals areas of increased density within brain tissue, suggesting spontaneous microhemorrhages, alongside regions of decreased density in the thalami and basal ganglia. Brain MRI is useful in identifying specific anatomical regions of involvement and confirming a diagnosis of dengue encephalitis in individuals exhibiting the aforementioned neurological signs. Commonly affected areas include the basal ganglia, hippocampus, temporal lobes, cerebellum, thalamus, and cerebral white matter, with T2 sequences often showing hyperintensities. Occasionally, similar lesions are detected in the brainstem (especially the substantia nigra) and cerebellum.[21-24] In this patient, symptoms of fever and decreased consciousness were found. Laboratory results showed IgG and IgM dengue and also NS 1 positive. A CT scan of the head showed decreased white matter-gray matter differentiation which was suggestive of cerebral edema.

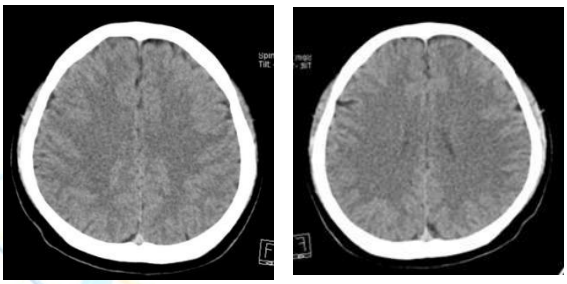

Figure 1 : Head CT scan at admission, decreased white matter-gray matter differentiation, suggestive of cerebral edema

No specifc treatment is available for encephalopathy or encephalitis. There is no proven value of corticosteroids or antiviral agents.

Symptomatic treatment such as anti-seizure medications and mannitol or diuretics for raised intracranial pressure should be provided in an intensive care setting. The immune-mediated manifestations generally respond well to immunomodulators like high doses of corticosteroids or intravenous immunoglobulin therapy.21 The pharmacologic treatment of cerebral edema should be guided whenever possible by the underlying pathology. Corticosteroids appear to be helpful in reducing cerebral edema in patients with bacterial meningitis, but not ICH.25 In this case, the patient was given high-dose corticosteroids 1gr/ day for three days and tapered off. There was improvement in terms of consciousness.

Dengue has been related to various forms of renal involvement. These include electrolyte imbalance, acute kidney injury (AKI), proteinuria, glomerulonephritis, alanine aminotransferase (IgA)

nephropathy, hemolytic uremic syndrome, and acute tubular necrosis.26

The incidence of renal manifestations varies from 17% to 62%.27 Current data show that AKI is present in 0.9% to 69.4% of dengue patients with variations based on the population studied and the criteria for the diagnosis of AKI adopted.28-31 The most widely used laboratory parameters include serum creatinine (SCr) levels, changes in urine output, and glomerular filtration rate.32-34

Several mechanisms have been proposed to account for the etiopathogenesis of dengue fever-induced AKI, including direct action by the virus, hemodynamic instability, rhabdomyolysis, hemolysis and acute glomerular injury.35

Dengue causes an intense inflammatory process that involves the release of inflammatory cytokines, activation of the complement system and platelets, and endothelial injury, which results in increased vascular permeability with a consequent loss of intravascular fluid.36,37

This process might cause hemodynamic instability and even shock, resulting in AKI due to a reduction of renal perfusion and acute tubular injury.38 Viral infection-induced renal injury might be due to a direct cytopathic effect of the viral protein on the glomerular and tubular cells, an in situ immune-mediated mechanism triggered by viral antigens bound to glomerular structures, tissue injury caused by immune complexes composed of viral antigens and antiviral antibodies and damage caused by inflammatory mediators released in response to the glomerular or tubular cytopathic effects of the viral antigens.39

Careful assessment of the warning signs of severe dengue and the patient's blood volume are crucial for the prevention of AKI. Fluid replacement should be performed carefully to avoid overload producing a consequent worsening of intravascular fluid extravasation, which might increase morbidity and mortality. Fluid replacement must be initially performed with crystalloid solutions, while use of colloids should be restricted to cases of unresponsive shock.40 Adequate fluid is the main therapy in the treatment of dengue fever. Patients received therapy of crystalloids 5cc/kg/24 hours tapered off, and continued with a maintenance dose.

Patients with chronic renal failure or end-stage renal failure treated by dialysis are characterized by multiple disturbances of amino acid (AA) metabolism, which particularly involve BCAA (Branched-Chain Amini Acid). In renal failure patients, abnormal BCAA metabolism is a consequence of: 1) the disappearance of the normal role of kidneys in AA metabolism; 2) the impact of renal failure on both peripheral and hepatosplanchnic nitrogen metabolism; and 3) the possible effects of underlying renal disease on protein and AA metabolism. The abnormalities of BCAA and branched-chain keto acid (BCKA) metabolism result in BCAA depletion, as reflected by the decrease in the concentrations of plasma BCAAs and cellular valine. Abnormal plasma BCAA and BCKA may be responsible for disturbances in organ amino acid exchanges and subsequent organ dysfunction. Therefore, BCAA supplements were proposed in CRF and dialysis patients to improve plasma AA and nutritional status.

Moreover, as protein restriction was reported to slow the progression of renal failure, essential AA and KA supplements, including BCAA and BCKA, were proposed to decrease protein intake as much as possible while maintaining protein status. This article refers to recent reviews on BCAA metabolism and therapeutic use during renal failure.41,42 One of research states among adult patients undergoing cardiac surgery, infusion of amino acids reduced the occurrence of AKI.43

This patient had acute kidney injury, with urea 103 mg/dL, creatinine 2.04 mg/dL. BCAA infusion was given to this patient once a day during treatment and also adequate fluid therapy. There was a decrease urea 71 mg/dL and creatinine 0.94 mg/dL in one week of hospitalization.

Hepatic dysfunction is a crucial feature seen in dengue virus infection. Hepatocytes and Kupffer cells are prime targets for dengue virus infection.44-46 An eventual outcome of hepatocyte infection by dengue virus is cellular apoptosis, a phenomenon demonstrated both in vivo and in vitro.47 After apoptosis, what stays of the cells are the Councilman Bodies.48 The various pathways involved in this apoptotic process include viral cytopathy, hypoxic mitochondrial dysfunction, the immune response.49 A wide spectrum of hepatic histological changes have been noted in dengue. This comprises fatty change (micro vesicular), hepatocyte necrosis, hyperplasia and destruction of Kupffer cells, Councilman Bodies

and mononuclear cell infiltrates at the portal tract.50,51

Traditionally, C. xanthorrhiza have been greatly harnessed all over its local distribution area as an ingredient of jamu (Indonesian herbal supplement and medicine) or to medicate and control numerous of sickness and disorders since ancient time including lack of appetite, stomach illness, liver ailments, constipation, bloody diarrhea, dysentery, arthritis, children's fevers, hypotriglyceridemic, hemorrhoids, vaginal discharge, rheumatism, and skin eruptions.52-57 The efficacy of C. xanthorrhiza for treating various diseases has been confirmed due to having pharmacology properties such as anti-inflammatory, antibacterial, antioxidative, neuroprotective, nephroprotective, antitumor, and hepatoprotective activities.58-66

Stronger Neo-Minophagen C (SNMC) is a glycyrrhizin-containing preparation that is approved in Japan for the treatment of chronic hepatic diseases and is marketed in Japan, China, Korea, Taiwan, and India.67 In Japan, SNMC has been used as a treatment for chronic hepatitis for more than 30 years. In a multicenter double-blind study, alanine aminotransferase (ALT) levels in serum have been shown to significantly decrease in patients received 40 ml/day of SNMC for four weeks ($P<0.001$).68,69 To investigate the neuroprotective effects of SNMC in cerebral ischemia, SNMC was administered intravenously (i.v.) at 1 ml/kg at 30 minutes before or 30 minutes, 3 hours, and 6 hours post-MCAO (60 minutes) and mean infarct volumes were assessed at 2 days post-MCAO. SNMC 1 ml/kg, which contains 2 mg/kg glycyrrhizin, is within the accepted dose range for the treatment of patients with chronic hepatic disease.68,70 One of research states branched-chain amino acid infusion may improve the prognosis of hepatic encephalopathy in patients with end-stage kidney disease, particularly those with lower liver function.71

The patient's laboratory results at admission were AST 7961 U/L, ALT 3711 U/L Total bilirubin 13.30 mg/dL, direct bilirubin 7.80 mg/dL, Indirect bilirubin 5.50 mg/dL. The patient was given curucuma tablets three times a day. The patient was also given SNMC 40 ml drip every day for one week of hospitalization. Laboratory results after receiving curcuma and SNMC found direct bilirubin 11.10 mg/dL, Indirect bilirubin 5.50 mg/dL, AST 197 U/L, ALT 523 U/L. The patient was given medicine to be consumed at home curucuma three times a day for 3 days. Two weeks after hospitalization, the laboratory results in another hospital were total bilirubin 3.6 mg/dL, direct bilirubin 1.5 mg/dL, indirect bilirubin 2.1 mg/dL.

4 CONCLUSIONS

Expanded dengue syndrome is a disease that involves several organs. Establishing a proper diagnosis and eliminating differential diagnosis are things that must be done. Collaboration needs to be carried out with other divisions. Comprehensive treatment and specific organs involved therapy are important to achieve good outcomes

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