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Case Report

Exploring the Therapeutic Potential of Glycyrrhizic Acid in Liver Implication in Dengue Infection: A Case Report

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ABSTRACT

Dengue is one of the most common infectious diseases affecting humans. The virus is transmitted between humans by the *Aedes* mosquito. It occurs hyperendemically in tropical and subtropical climates worldwide. Dengue infection can affect numerous organs, with the liver being the most frequently affected organ. The clinical spectrum of liver disorders ranges from mild elevation of transaminase enzymes to severe conditions such as acute liver failure. Several mechanisms have been proposed to describe hepatic dysfunction observed in dengue fever and dengue hemorrhagic fever, such as immunological injury, hypoxic injury, and direct viral damage due to reduced hepatic perfusion during shock. Glycyrrhizic acid, extracted in the form of glycyrrhizin from the root of the licorice plant *Glycyrrhiza glabra*, is referred to as Stronger Neo-Minophagen-C (SNMC®). It has shown effectiveness in reducing serum aminotransferase and bilirubin levels, attenuating hepatocyte apoptosis, and producing endogenous interferon. The following is a case report of a 23-year-old woman with dengue fever and elevated liver enzyme level. The patient's vital signs were stable. A physical examination revealed no abnormalities. A complete blood count test showed thrombocytopenia without an elevation of the hematocrit. AST level was 901 U/L after admission. Causes of other hepatitis infections, such as hepatitis A, B, and C, were excluded. The dengue IgM and IgG antibody levels were reactive. After several days of hospitalization, the patient experienced clinical improvement after supportive therapy and the administration of glicyrrhizic acid or SNMC®.

Keywords: : Dengue Infection, Elevated Liver Enzyme, Glycyrrhizic Acid, Hepatic Dysfunction, and SNMC®.

Highlights: This report highlights the use of glycyrrhizic acid in the prevention of acute liver failure in dengue infection with liver involvement.

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INTRODUCTION

Dengue fever, an acute infectious disease transmitted between humans by the *Aedes* mosquito, and is caused by dengue virus (DENV). This RNA virus belongs to the genus Flavivirus and family Flaviviridae, with four distinct serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. Although these serotypes share some antigenic similarities, their significant differences lead to the provision of cross-protection for only a limited period following infection with any one among the four. Secondary infections with a distinct serotype or the occurrence of several infections involving other serotypes can initiate extreme forms of dengue.[1,2] Furthermore, dengue infection occurs hyperendemically in tropical and subtropical climates worldwide, particularly in urban and semi-urban regions.[3] The occurrence of dengue has shown a substantial surge, experiencing an eight-fold increase over the last two decades. The cases climbed in 2000 from 505,430 to exceeding 2.4 million in 2010 and further escalated to 4.2 million by 2019.[3,4]

Dengue can affect numerous organs, with the liver being the most frequently affected. The clinical spectrum of liver disorders ranges from mild elevation of transaminase enzymes to severe conditions such as acute liver failure.[5] Several mechanisms have been proposed to describe hepatic dysfunction observed in dengue fever and dengue hemorrhagic fever, such as immunological injury, hypoxic injury, and direct viral damage due to reduced hepatic perfusion during shock.[6–8]

Glycyrrhizic acid, extracted in the form of glycyrrhizin from the root of the licorice plant Glycyrrhiza glabra, is referred to as Stronger Neo-Minophagen-C (SNMC®) by Dexa Medica in Indonesia. It is a triterpene glycoside majorly comprising flavonoids, hydroxyl coumarins, and β-sitosterol, alongside glycyrrhetinic acid, which has various pharmacological and biological activities.[9] Additionally, it is effective against viral hepatitis, specifically chronic viral hepatitis, and is capable of stimulating endogenous interferon production.[10] Glycyrrhizic acid derivates were reported to have anti-dengue activities by conjugating with amino acids. The introduction of aromatic acyl hydrazide residues into the carbohydrate part also strongly influenced on the antiviral activity of glycyrrhizic acid against DENV2.[11] In vitro analyses by Crance et al.[12] using human hepatoma cells demonstrated that glycyrrhizin could inhibit hepatitis A virus penetration, probably by changing the fluidity of the cell membrane.[12] Moreover, glycyrrhizin can help reduce elevated liver enzyme levels by inhibiting phospholipase A2 activation and controlling changes in hepatocyte membrane[13] permeability, which represses the production of hepatitis B surface antigen (HBsAg).[14]

This report presents a case of dengue fever in a 23-year-old female with liver implications, without any evidence of viral hepatitis infection. The focus of this discussion centers on the diagnosis and management of the liver affected by dengue infection.

CASE DESCRIPTION

A female aged 23 years presented at the emergency department with a primary complaint of high-grade fever persisting for three days, accompanied by myalgia and retro-orbital pain. Nausea and vomiting occurred four times daily, while spontaneous bleeding, such as epistaxis and gingival bleeding, was not reported. There was no history of previous illnesses, including hepatitis, diabetes mellitus, or allergies. No family members exhibited similar symptoms, and the patient had not recently traveled to another city.

Upon admission, consciousness was observed, along with the following vital signs: blood pressure (BP) 100/60 mmHg,

pulse per minute at 100 beats, respiratory rate per minute at 18 breaths, oxygen saturation at 98% in room air, as well as 37.7°C body temperature. Physical examination revealed petechiae in the upper extremities and mild tenderness in the right upper quadrant and epigastric region. Laboratory tests indicated 14.0 g/L (11.7-15.5 g/L) hemoglobin (Hb), 39% hematocrit (Hct); white blood cell count (WBC), 5.1x10^3/µL, platelet count (PC) of 32x10^3/µL, alanine aminotransferase (ALT), 255 U/L (normal < 35); aspartate aminotransferase (AST), 901 U/L (normal < 35); and 123 mmol/L (135–147) serum sodium. Hepatitis markers were all negative, while clinical suspicion of dengue fever was verified by positive anti-dengue antibodies (IgM and IgG), as detailed in Table 1.

Table 1. Laboratory Test During Admission.

Examination	Result
Blood cell count	
Hb	14 g/dL
Hct	39%
WBC	5.1 × 10^3/µL
PC	32 × 10^3/µL
Blood chemistry	
AST	901 U/L
ALT	225 U/L
BUN	35 mg/dL
Creatinine	0.66 mg/dL
Glucose	85 mg/dL
Na	123 mmol/L
K	4.4 mmol/L
Cl	97 mmol/L
Immunoserology	
IgM anti-HAV	Negative
IgG anti-HAV	Negative
HBsAg	Negative
Anti – HCV	Negative
IgM anti-dengue	Positive
IgG anti-dengue	Positive

Hb, hemoglobin; Hct, hematocrit; WBC, white blood cell; PC, platelet count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; IgM, immunoglobulin M; IgG, immunoglobulin G; HAV, hepatitis A virus; HCV, hepatitis C virus.

Chest radiological examination showed no abnormalities, while abdominal ultrasound indicated achalculous cholecystitis (blue arrow) are shown in Figure 1 and 2.

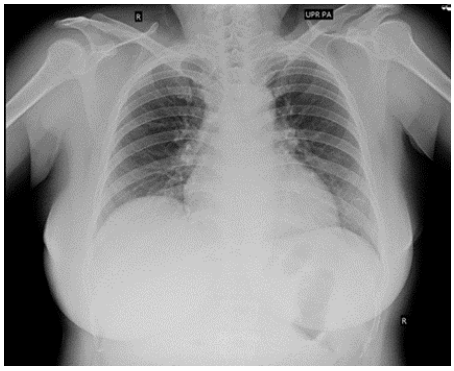

Figure 1. Chest X-Ray of The Patient.

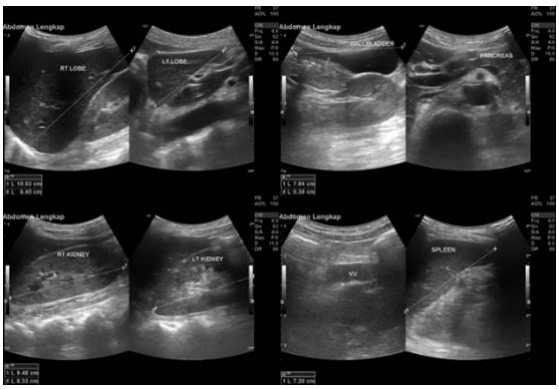

Figure 2. Abdominal ultrasound of the patient.

A diagnosis of dengue fever with liver involvement was established. The patient received appropriate fluid therapy and symptomatic medication, along with glycyrrhizic acid infusion of two ampules daily for five days to correct serum sodium levels. The complete blood count (CBC) was monitored every 24 h, and liver enzyme levels were evaluated after completion of the infusion as detailed in Table 2.

Table 1. Laboratory Test During Hospitalization.

	Day of hospitalization								
Markers	0	1	2	3	4	5	6	7	8
Hb	14	10.7	10.5	11.3	11.3	10.9	11.0	11.8	11.5
Hct	39	30	30	32	32	30	32	33	33
WBC	5.1	3.8	4.0	4.4	5.0	4.9	4.8	5.1	5.5

PC	32	26	34	27	36	42	65	89	120
AST	901				806				88
ALT	285				282				56
Na	123		134						
K	4.4		3.8						
Cl	97		108						

*) Hb, hemoglobin; Hct, hematocrit; WBC, white blood cell; PC, platelet count; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Following five days of glycyrrhizic acid infusion, the liver enzyme levels showed slight improvement. The infusion was continued for an additional five days, with the addition of curcumin, containing curcumin and lysin, three times daily. After a total of 10 days, the liver enzyme levels exhibited significant improvement, and the patient was asymptomatic, leading to discharge.

DISCUSSION

The diagnosis of dengue fever in the patient was confirmed based on the criteria set by the WHO in 2011, including sudden onset of fever within 2-7 days, presence of petechiae, platelet count <150,000/mm^3, and absence of plasma leakage signs. Additionally, the observed malaise symptoms such as headache, body aches, and retro-orbital pain were consistent with the conventional manifestations of dengue infection.[2] The identification of acute primary infection through positive results for dengue IgM antibodies further confirmed the diagnosis of dengue.

Defective liver function in the patient was attributed to dengue fever infection, considering the negative consequences of hepatitis virus marker examinations. When a person has a dengue infection, their liver dysfunction can range from minor (as indicated by an increase in aminotransferases alone) to severe (as indicated by jaundice and even fulminant hepatic failure).[15]

This was in line with existing studies showing that the liver was repeatedly affected by dengue fever.[5] Hepatitis is discovered in 60-90% of dengue fever cases, characterized by mild to moderately elevated transaminase levels almost five times above the normal value. Meanwhile, severe hepatitis, characterized by transaminase levels surpassing 10 times the upper limit of normal, is only encountered in a mere 3-11% of cases.[16] The distinctive feature of liver cell damage is the elevation of ALT levels over AST levels, distinguishing it from liver damage caused by the hepatitis virus.[5,17]

The liver damage pathophysiology in dengue remains incompletely comprehended but is generally related to interactions between the host, viruses, as well as the time of disease. Hepatocytes and Kupffer cells are primary viral targets.[5] The virus attaches to the hepatocyte cell surface receptor, and protein E plays a crucial role in this process. Sulfate sulfur is also recognized to facilitate DEN virus entry into liver cells, referred to as HepG2. Liver cells in the G2 phase are sensitive to the disease, enabling viral multiplication. Subsequently, liver lesions, microvesicular steatosis, apoptosis, as well as the appearance of Councilman-Rocha Lima bodies, comparable to the conditions in yellow fever as well as different hemorrhagic viral infections are presented.[18,19] Liver damage may result from direct viral effects on hepatocytes, as previously described, or due to disruptions in the response of the host immune system toward the virus; additional factors contributing to liver injury include ischemia or hypoxia in hepatocytes initiated by circulatory disorders. Furthermore, drug administration, including paracetamol or acetaminophen, which are frequently used to manage fever or discomfort in dengue, tends to promote liver damage.[5,16]

No specific therapy is available for hepatitis in dengue cases; however, the primary treatment objectives focus on viral clearance, seroconversion, and reducing inflammation.[20] In contrast to viral hepatitis, achieving viral clearance and seroconversion in dengue hepatitis treatment is not feasible, making mitigation of inflammation the primary target. Glycyrrhizin is known to have anti-inflammatory, antioxidant, and hepatocyte membrane-stabilizing properties.[20] Additionally, it exhibits anti-hypertransaminase effects by disrupting the release of transaminase enzymes into the bloodstream of patients with liver parenchymal damage or inflammation, namely, hepatocyte necrosis.[21] SNMC® in Indonesia is available in the form of ampoules (20 ml) comprising 40 mg of glycyrrhizin, 400 mg of glycine, and 20 mg of L-cysteine (BPOM).

In case of dengue fever, SNMC® was administered at two ampoules (40 ml) for a total of eight consecutive days. This is in accordance with the recommended dosage displayed in the package insert, which suggests 40-60 ml but does not exceed 100 ml daily (BPOM). The observed advancement in liver function was similar to the significant enhancement in transaminase activity reported by Lin et al (2015) after administering 100 ml of SNMC® for five days in a case of acute exacerbation of hepatitis B.[22]

STRENGTH AND LIMITATION

The strength of this study is that it demonstrated the effectiveness of SNMC® as an anti-inflammatory agent in liver involvement in dengue infection. A limitation of this study is that future large-scale studies are required.

CONCLUSIONS

In conclusion, this case report shows the potential efficacy of glycyrrhizic acid treatment, known as SNMC®, in managing dengue hepatitis. However, there is a need to conduct further extensive and well-designed research focusing on the use of SNMC® in dengue hepatitis.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTION

Data curation, writing–review and editing, and validation: ISP. Data curation, supervision, and validation: PR.

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