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Case report

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**Dengue Hemorrhagic Fever with Acute Liver Failure,  
A Case Report with Total Plasma Exchange Therapy**

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**Abstract**

Nowadays, dengue hemorrhagic fever has atypical presentation. These include acute liver failure and encephalitis. Morbidity and mortality were higher in this patient. We report a dengue patient with acute liver failure and hepatic encephalopathy grade III who was supported with total plasma exchange (TPE)

and N-acetylcysteine (NAC). The good clinical response was shown after the sixth day of treatment.

**Keywords :** dengue hemorrhagic fever, acute liver failure, total plasma exchange, N-acetylcysteine

**บทคัดย่อ**

ในปัจจุบัน ไข้เลือดออกพบมีอาการแสดงที่ไม่เหมือนกับปกติ เช่น ตับวายเฉียบพลัน สมองอักเสบ โดยผู้ป่วยที่มีอาการเหล่านี้จะมีความรุนแรงของโรคสูงและมีโอกาสเสียชีวิตสูง ผู้เขียนนำเสนอตัวอย่างผู้ป่วยไข้เลือดออกที่มีตับวายเฉียบพลัน และมีอาการทางสมองจากโรคตับ

ระดับสาม ซึ่งได้รับการรักษาด้วยการแลกเปลี่ยนน้ำเหลืองและให้ยาเอ็นอะเซทิลซิสเทอีนทางเส้นเลือด โดยมีผลการรักษาที่ดีในวันที่หกของการรักษา

**คำสำคัญ:** ไข้เลือดออก ตับวายเฉียบพลัน การแลกเปลี่ยนน้ำเหลือง เอ็นอะเซทิลซิสเทอีน

## Introduction

Dengue virus infection is a tropical disease, potentially life threatening infectious disease. The disease has wide spectrum from mild to severe disease. In severe case, the immune response was trigger and cascade to phenomenon of plasma leakage and bleeding,<sup>1,2</sup> Elevated interferon- $\gamma$  (IFN- $\gamma$ ) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) were found in dengue hemorrhagic fever patient.<sup>1</sup> In vitro study, both cytokines had synergistic effect on endothelial cell cultures by increasing monolayer permeability, which might play a role in capillary leakage.<sup>3,4</sup> Activation of coagulation and fibrinolytic systems were pronounced in severe dengue infection.<sup>5</sup> This may be another role of hemorrhagic manifestation in dengue hemorrhagic fever other than thrombocytopenia and vasculopathy. Dengue infection also had other unusual manifestations.<sup>6</sup> Acute liver failure, encephalopathy and encephalitis were commonly found in severe dengue case.<sup>7-10</sup>

## Case report

A Thai female, aged 25, had high grade fever, myalgia and nausea for 2 days. She was admitted at a private hospital. The laboratory test shown leukopenia and mild elevated liver enzyme. Tourniquet test was done. The result was positive. She was treated with supportive treatment, included intravenous fluid, motilium, omeprazole, air-X, dramamine and

acetaminophen. Serial complete blood count shown atypical lymphocyte and thrombocytopenia. She still had high grade fever about 39 °C, abdominal discomfort and nausea. The liver enzyme was followed and had high elevated. On the fifth day after admission (the 7<sup>th</sup> of fever), she looked drowsiness. The laboratory test shown hemoconcentration and very high elevated liver enzyme as shown in table 1. The diagnosis was dengue hemorrhagic fever with acute hepatic failure. She was transferred to Prapokklao (PPK) Hospital due to financial problem. During five days of admission, she received 24-tablet acetaminophen. She had previously healthy and social drinking. She had no history of jungle travel and no herbal medicine use. Physical examination showed BT 39.4°C, BP 139/82 mmHg, pulse rate 116/min and respiratory rate 34/min. She had anicteric sclera, no pallor, no cervical lymphadenopathy, no oral candidiasis, normal breath sound and heart sound. Liver was enlarge about 3 FB BRCM, of which span was 13 cm. Spleen could be palpated. There were no all skin lesion included eschar. Neurological examination showed that she had stupor, normal pupils and light reflex while eye ground and other cranial nerves could not be evaluated. Motor power were all grade V, deep tendon reflex were all 1+, Babinski 's sign was negative and stiff neck was negative.

Table 1 Laboratory test

LAB.	Day of fever							
	2nd	4th	5th	6th	7th *	8th	9th	10th
Hct	41	39	37	45	53	42.8	29.3	24.4
WBC	2,840	2,190	2,350	4,320	7,610	9,820	12,960	13,670
PMN	53	52	70	52	56	62.6	73.7	66
LYM	43	41	24	38	34	25.7	15.6	20.9
ATYP LYM	-	5	3	5	6	-	-	-
PLT	182,000	126,000	69,000	41,000	48,000	25,000	51,000	117,000
AST					13,600	10,784	928	932
ALT	63			610	3,370	3,197	591	443
TB					3	1.7	1.5	1.6
DB					1.23	1	0.7	0.9
PT						18.9	15.2	13.9
INR					1.55	1.66	1.33	1.22
BUN					29.3	41	63	74
Cr					0.1	2.1	4.6	7.3

Remark \* Day 7 : August 30, 2012

Laboratory test : Malaria pigment - negative, UA : protein 3+, glucose-negative, Sp.Gr. 1.033, RBC - negative, WBC 3-5/ HPF, granular cast 20-30 / LPF, AntiHAV IgM - negative, HBsAg - negative, AntiHCV - negative, Dengue titer IgG and IgM - negative (7th day of fever), Hemoculture - no growth.

### Clinical course and outcome

She had severe acute hepatitis with hepatic encephalopathy grade III and was immediately transferred to PPK ICU at the first day. CT brain shown diffused brain swelling without intracerebral hemorrhage. She was intubated and treated with propofol, 3% NaCl, 30°-elevated head, hyperventilation and lactulose. She was received NAC 9,000 mg in 5% D/N/2 100 ml drip in 1 hr then 3,000 mg in 5% D/N/2 200 ml drip in 4 hr and then 6,000 mg in 5% D/N/2 500 ml drip in 16 hr due to history of suspected acetaminophen overdose.

She also received total plasma exchange (TPE) with fresh frozen plasma 3,000 ml for corrected hepatic encephalopathy. The second day of admission, she gained consciousness but still had confusion. The third day, her liver function was much improved. However her renal function was worsen and hemodialysis was started on the third day and was continued on the fifth, eighth and thirteenth day. The fourth day, she had spontaneous breathing. The ventilator setting was change to continuous positive airway pressure (CPAP). The fifth day, she could slowly response to following

command. The sixth day, she was alert and endotracheal tube was taken off. On the seventh day, she was transfer to general medicine ward. Dengue titer IgG and IgM were repeated and shown positive result. She was discharged on the eighteenth day. Two weeks later, she was followed up. Her clinical and renal function were absolutely resolved.

### Discussion

Dengue infection usually has liver involvement. In dengue hemorrhagic fever, the transaminase level was usually less than five-times of upper normal limit.<sup>11</sup> The transaminase value that was five-fold above normal value were usually observed in dengue hemorrhagic fever more than in classical dengue.<sup>12</sup> The level of AST was higher than that of ALT.<sup>9,11,13</sup> The peak of transaminase was found in critical phase.<sup>9,13</sup> During this phase, systemic vascular leakage caused inadequate tissue perfusion and led to multi-organ failure.<sup>2,14</sup> However, direct invasion from dengue virus could damage organ failure. In fatal cases, dengue virus was identified in liver tissue.<sup>15-16</sup> In our case, acute liver failure occurred during the critical phase. However, acetaminophen overdose may be another cause of liver failure. Total acetaminophen consumption, more than 8 gram in dengue patient was associated with increased serum transaminases.<sup>17</sup> Medication use should be awareness including of safety dose of acet-

aminophen. Non-steroidal anti-inflammatory agents (NSAIDs) may aggravate gastritis or bleeding in dengue infection and was recommended not to be used.<sup>18</sup>

In present, antiviral drugs for treatment of dengue infection are not available.<sup>18</sup> Treatment remains supportive therapy with careful fluid management. In case series, outcome of acute liver failure in dengue infection with standard medical therapy was reported excellently.<sup>19</sup> However, the complicated disease with acute liver failure increased morbidity and mortality.<sup>7-10,15-16,20</sup> Adjuvant therapy may improve outcome in some case. Intravenous administration of NAC in the early stage of liver failure was shown benefit.<sup>21</sup> Currently, liver support systems can correct coagulopathy and remove hepatotoxins in the experimental study.<sup>22</sup> Molecular adsorbent recirculating system (MARS) led to rapid reversal of biochemical profile and encephalopathy in dengue with acute liver failure.<sup>23</sup> TPE was considered for temporary liver support until recovery of liver or liver transplantation.<sup>24</sup> Owing to rapid deterioration of our patient, intravenous NAC and TPE were administrated within the first twenty four hour of admission. Her liver function was much improved in the third day and her encephalopathy was resolved in the sixth day. As previous report, intravenous administration of NAC in hepatic encephalopathy grade III – IV shown no benefit.<sup>21</sup> The good clinical response

in our patient may attribute to total plasma exchange. Besides supportive treatment in dengue hemorrhagic fever, early detection and management of complication should be considered.

In conclusions, TPE may be an alternative therapy for dengue hemorrhagic fever patients with acute liver failure.

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