

# FATAL RHABDOMYOLYSIS IN DENGUE HEMORRHAGIC FEVER: A CASE REPORT

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**Abstract.** Dengue hemorrhagic fever is caused by dengue virus infection. The classical manifestations consist of fever, thrombocytopenia, and hemoconcentration. However, its unusual complications may be fatal, such as prolong shock, massive bleeding, volume overload, and unusual manifestations, for example, severe rhabdomyolysis. Here we report a case of 17-year old Thai man who was referred to our hospital because of 7-day fever with thrombocytopenia, hemoconcentration and right pleural effusion. The serology tests confirmed to be dengue infection. He developed various complications: severe hepatitis, coagulopathy, and heavy proteinuria; encephalopathy that needed a respiratory ventilator. On day 12 of fever, he had myalgia and passed dark urine. Serum creatinine and serum creatinine phosphokinase (CPK) were found abnormally high. He was diagnosed as severe rhabdomyolysis with acute kidney injury, and immediate hemodialysis was performed. He did not respond to treatment and expired within three hours. Although the mechanism of severe rhabdomyolysis in dengue fever is not clearly known, it may theoretically be proposed such as direct muscle cell injury leading to myositis by dengue virus, myotoxic cytokines which are produced in response to viral infection, dehydration or hypophosphatemia.

**Keywords:** dengue hemorrhagic fever, fatal rhabdomyolysis

## INTRODUCTION

Dengue infection is the very common viral infection in tropical areas particularly in rainy season. Mosquitoes, mainly *Aedes aegypti*, transmit it. Its clinical manifestations include dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. In the case of classical dengue hemorrhagic fever, there are three phases: febrile, toxic, and recovery, as follows: after

having acute fever for 3-5 days, the patients will develop thrombocytopenia due to immune complex including platelet destruction and hemoconcentration due to the leakage of the intravascular volume during the toxic phase. Before accessing the recovery phase within 1-3 days, the minority of the patients may develop the unusual or severe complications such as renal failure, acalculous cholecystitis, conduction abnormalities (Nimmagadda *et al*, 2014), dengue shock syndrome, dengue encephalopathy (Hendarto and Hadinergoro, 1992), acute hepatic failure, severe pancreatitis (Jain *et al*, 2014) or fatal rhabdomyolysis (Karaku *et al*, 2007).

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Rhabdomyolysis or lysis of the striated muscle cells is characterized by the dark urine due to myoglobinuria, weakness of muscle, myalgia, high serum creatine phosphokinase (CPK), and possibly renal failure. It can result from various factors, such as drugs, severe strenuous exercise, or viral infections, for example, influenza, HIV, coxsackievirus, and CMV. The report of rhabdomyolysis in patient with dengue fever has been occasionally reported (Sargeant *et al*, 2013). Herein, we report a case of proven dengue hemorrhagic fever complicated by fatal rhabdomyolysis.

### CASE REPORT

A 17-year old Thai man was referred to Maharat Nakhon Ratchasima Hospital because of confusion for six hours. Seven days before the referral, he had high-grade fever with poor appetite, and two days later, he was found to have low platelet ( $100,000/\text{mm}^3$ ); the diagnosis of dengue fever was proposed, and fluid therapy was cautiously initiated at the community hospital. The platelet was followed daily and found to decrease until it finally reached  $27,000/\text{mm}^3$ . The hematocrit rose from 45% to 55%, and the patient started becoming confused on the day of referral. The physical examination on the day of admission, day 7 of fever was as follows: blood pressure, 126/79 mmHg; pulse 89, beats/min; body temperature,  $38.0^\circ\text{C}$ ; and respiratory rate, 30 breaths/min. He looked drowsy with poor compliance, and he had mild jaundice, decreased breath sounds with dullness on percussion at the RLL field, stiffness of neck, no hepatosplenomegaly, and no petechiae.

Investigations on the 1st day of ad-

mission, day 7 of fever: a hematocrit of 55.3%, a white blood cell count of  $10,000/\text{mm}^3$  with 52% neutrophils, 23% lymphocytes, 12% monocytes, 13% atypical lymphocytes and a platelet count of  $9,000/\text{mm}^3$ . Blood chemistry revealed 21.1 mg% of BUN, 1.16 mg% of creatinine, 2.6 mg% of total bilirubin, 1.5 mg% of direct bilirubin, 3,823 IU/l of AST, 1,657 IU/l of ALT, 69 IU/l of ALP, 2.9 g% of albumin, 2.3 g% of globulin, 7.2 mg% of Ca, 1.0 mg% of P (normal 2.7-4.5).

Further investigation results were: negative for dengue virus antigen (immunochromatography), weakly positive for dengue IgM, positive for dengue IgG, negative for leptospira IgG and IgM, less than 1:50 for scrub and murine typhus IgG and IgM, negative for *O. tsutsugamushi*, HBsAg, anti-HCV or anti-HIV, no growth for hemoculture.

Urinalysis found a specific gravity of 1.025, protein 4+, sugar-negative, blood (RBC, Hb or myoglobin) 3+, ketone-negative. Coagulogram showed: PT 21.4 seconds (normal 8.9-15.1), INR 1.82, aPTT 79.1 seconds (normal 21.9-34.5), and TT >120 seconds.

A chest x-ray film showed moderate amount of right pleural effusion, no cardiomegaly, or pulmonary congestion. The computerized tomography of the brain showed diffuse brain swelling.

He was definitely diagnosed as dengue hemorrhagic fever with right pleural effusion. Other possible diagnoses included dengue or hepatic encephalopathy, coagulopathy, hypocalcemia with hypophosphatemia, and heavy proteinuria with hypoalbuminemia.

The treatment was immediately started

with fresh frozen plasma 100-200 ml/hr, platelet concentrate transfusion, parenteral fluid, and meropenem 2g every 8 hours. The hypocalcemia and hypophosphatemia were corrected. The blood pressure and urine output could be maintained, but his impaired consciousness was not improved; finally, his respiration was supported with ventilator.

On days 9-11 of fever, with fully supportive treatments, he still had high-grade fever, confusion, occasionally shiver, and urine output was adequate, although the urine color was dark. Hematocrit and platelets could be kept between 36%-45% and 9,000-40,000/mm<sup>3</sup>, respectively.

On day 12, he developed more confusion with concurrent fever, creatinine level rose from 1.16 to 3.93 mg%, and CPK 151,760 U/L. The chest film showed pulmonary congestion without cardiomegaly. The diagnosis of acute renal failure as well as severe rhabdomyolysis was established, and emergency hemodialysis on double lumen at the right femoral vein was immediately performed. Three hours after dialysis, he became more comatose, developed tachypnea, hypotension, and ventricular tachycardia, and did not respond to inotropic drugs, and finally expired. The autopsy was not allowed.

## DISCUSSION

Our case was diagnosed as secondary dengue infection, based on the clinical syndrome of acute fever for a few days, with subsequent thrombocytopenia, hemoconcentration and right pleural effusion and immunologically confirmed by the positive tests of dengue IgM and IgG antibodies (CDC, nd). In addition, he de-

veloped unusual but severe complications, for example, severe hepatitis (ALT >300 U/L) (Parkash *et al*, 2010), coagulopathy without clinical bleeding symptom, acute encephalopathy, heavy proteinuria, severe rhabdomyolysis, acute kidney function impairment, and finally death. All of these derangements may possibly be due to the direct involvement of the virus, because the dengue virus antigen can be demonstrated in the kidney, liver, heart, lung, and spleen in cases of fatal dengue infection (Póvoa *et al*, 2014).

Rhabdomyolysis has been occasionally reported in cases of dengue fever. Although, the exact mechanism is not known, many theories are proposed, for instance, rhabdomyolysis is the direct effect of the dengue virus itself, because it shares several features with other viruses that are well-known causes of severe myositis and finally rhabdomyolysis, such as influenza A and B, coxsackievirus, Epstein barr virus (EBV), and HIV, although the dengue virus has not been demonstrated in muscle cell, thus far. Other possibilities may be myotoxic cytokines, especially the tumor necrosis factor and the interferon alpha (Sargeant *et al*, 2013) that generally respond to viral infection.

Rhabdomyolysis can happen in case of dehydration, our case runs quite longer course than usual. In general, acute febrile phase of dengue fever lasts for two to seven days (Chaturvedi and Nagar, 2008), and toxic phase usually takes 1-3 days. During toxic phase, the main pathogenesis is the fluid leakage leading to hemoconcentration and right pleural effusion and the fluid is needed to keep enough intravascular volume and urine output.

In case of hypophosphatemia (serum

phosphate < 2.0 mg%), rhabdomyolysis can also commonly occur. although it has been corrected, but severe hypophosphatemia can be masked because of the ongoing rhabdomyolysis (Singhal *et al*, 1992).

Most patients with dengue fever complicated by rhabdomyolysis always have myalgia and dark urine as the warning symptoms. And, they may subsequently develop renal failure due to concentrated myoglobinuria interacting with Tamm-Horsfall protein, leading to the high mortality rate (around 29%) (Sargeant *et al*, 2013). If a dengue fever patient is complicated by azotemia and heavy proteinuria without rhabdomyolysis, he should generally have self-resolution (Hutspardol *et al*, 2011).

In summary, a 17-year old man presented with a high-grade fever for a few days; he developed subsequent thrombocytopenia, hemoconcentration, and right pleural effusion. The diagnosis of dengue infection was confirmed with serology tests. During the toxic phase, he developed severe hepatitis, coagulopathy, heavy proteinuria, and encephalopathy followed by severe rhabdomyolysis with acute kidney injury. The immediate hemodialysis was performed, but we could not save the patient's life. The only warning symptom of this fatal complication was dark urine.

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