Rhabdomyolysis Associated with Dengue Virus Infection

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We describe 2 patients who developed rhabdomyolysis due to dengue virus infection. The first patient recovered with no sequelae, but the second developed multiple organ failure and died. Rhabdomyolysis is not well described as a complication of dengue virus infection and is probably under-recognized. All patients with severe dengue virus infection should undergo urinalysis, and serum creatinine kinase levels should be measured if urinalysis reveals heme.

Viral myositis leading to rhabdomyolysis and its complications are well described with several acute viral infections, most notably influenza A and B virus, HIV, coxsackieviruses, and cytomegalovirus [1–5]. To our knowledge, it has only twice previously been reported in association with acute dengue virus infection [6, 7] and is not mentioned as a potential complication of dengue fever by major textbooks or review articles [8–12]. We describe a man with proven acute dengue virus infection who developed rhabdomyolysis.

Case report. A 33-year-old previously healthy man (patient 1) was transferred to Royal Darwin Hospital (RDH; Darwin, Australia) in February 2002 from a clinic in Dili, East Timor, with a 5-day history of fever, malaise, and nausea. He was an Australian citizen who had been working in Dili as a mechanic for 8 months before admission to RDH. He had received all appropriate vaccines before travel and was receiving doxycycline, 100 mg/day, for malaria prophylaxis. He was re-

treated with intravenous normal saline, 6 L/day, to maintain a urine output of >150 mL/h.

CK levels peaked at 51,555 U/L on hospital day 2 and decreased to 14,524 U/L on day 4. He had an otherwise uncomplicated course and did not develop renal impairment. He was discharged home on day 4 feeling better.

Acute- and convalescent-phase serological tests were negative for influenza A and B viruses, HIV, Epstein-Barr virus, cytomegalovirus, leptospira, and rickettsiae. Results of blood cultures were negative. Serological analysis for detection of flavivirus by hemagglutination inhibition testing was negative (<10) on the day of admission to RDH and was strongly positive (>640) 10 days later. Dengue virus IgM titer was negative on hospital day 1 but positive on day 10. IgM titers for other relevant flaviviruses (Murray Valley encephalitis virus, Kunjin virus, and Japanese encephalitis virus) were negative. RT-PCR for detection of dengue virus RNA was performed on serum samples obtained on day 1 of hospitalization and was positive for dengue virus type 2 RNA. The possibility of a second unidentified infectious agent being responsible for the rhabdomyolysis cannot be ruled out; however, it is very unlikely, on the basis of the results of the investigations listed above.

Patient 1 was seen 2 weeks after discharge and was well. He had no muscle pain or weakness, and his serum CK level had returned to normal. Additional questioning revealed no personal or family history of myopathy.

Six months after the patient 1 was discharged, a retrospective chart review of patients with severe sepsis for an unrelated audit revealed a second patient (patient 2) with the same compli-
cation. This audit was looking at patients with septic shock admitted to RDH between January 2000 and May 2002. Among many other things, the etiologic agents of the sepsis and the peak serum CK levels were recorded for all of these patients. One hundred thirty patients were identified, 1 of whom (patient 2) had dengue virus infection.

Patient 2 was a 33-year-old African man who had been stationed in Dili, East Timor, with the United Nations. His medical history was unremarkable, and he was receiving no medications. He was admitted to RDH in February 2001 with suspected dengue hemorrhagic fever and acute renal failure. His serum CK level at admission was 17,548 U/L, with a normal CK MB isoenzyme level and a cardiac troponin I level of 0.2 ng/mL. He did not have a history of prolonged immobility or any other alternative cause of rhabdomyolysis. He later developed multiple organ dysfunction syndrome and died on hospital day 2. Blood RT-PCR was positive for dengue virus type 2 virus RNA. Results of blood cultures and blood films for malarial parasites were negative.

This second case is not clearly defined as rhabdomyolysis due to dengue virus infection. In the complex web of multiple organ dysfunction and systemic inflammatory response syndrome, it is difficult to demonstrate causality. Also, a second pathologic process other than the acute dengue infection cannot be excluded. However, given the compatible clinical illness and lack of a plausible alternative explanation, we think that acute dengue virus infection with secondary rhabdomyolysis is the most likely explanation of the illness and elevated serum CK level in patient 2.

Discussion. Rhabdomyolysis due to several viruses other than dengue virus has been well described [1–5]; however, the pathogenesis of acute viral myositis and consequent rhabdomyolysis has not been established. Direct invasion of muscle by virus has not been consistently demonstrated, and the most likely cause is thought to be myotoxic cytokines, particularly TNF released in response to viral infection [8, 13]. Studies of muscle biopsy specimens have revealed a range of findings, from mild lymphocytic infiltrate to foci of severe myonecrosis [14, 15].

Dengue virus infection shares several features with other viruses known to cause severe myositis. It causes a viremic illness associated with prostration and severe myalgia. It has been shown to cause increased production of TNF and IFN-α in humans [16, 17]. A series of findings from analyses of muscle biopsy specimens obtained from 15 patients with dengue fever has been published from Brazil. This study reported mild inflammatory PBMC infiltrates in 12 patients and foci of myonecrosis in 3 patients, which are very similar to findings reported for other viruses that cause severe myositis [15].

The absence of reports of rhabdomyolysis associated with
Dengue virus infection in the mainstream medical literature and textbooks suggests that this is a very rare complication. We suspect that this is not the case and that it may be underrecognized and underreported. The relatively common occurrence of rhabdomyolysis in association with influenza and other viruses and the above-mentioned similarities of dengue virus infection to these infections supports this view. Prospective reviews of serum CK levels in a large cohort of patients with dengue virus infection would be necessary to confirm this impression.

We suggest that urinalysis should be performed for all patients with severe dengue virus infection as a screening tool and that serum CK levels should be measured if urinalysis is positive for hemagglutination. If unrecognized, rhabdomyolysis is likely to lead to acute renal failure and electrolyte disturbances [18]. However, if recognized early, these complications can easily be prevented.

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References