CASE REPORT

MORTALITY FROM SEPTIC SHOCK IN A DENGUE INFECTED PATIENT: A CASE REPORT

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Abstract. Dengue infection can be associated with secondary infections which may be challenging to recognize due to the overlap with the symptoms of dengue infection. We report here the case of a 48 year old Chinese female with dengue fever with a fatal secondary bacterial infection due to *Enterococcus faecium*.

Keywords: dengue, complications, hemorrhage, *Enterococus faecium*

INTRODUCTION

Dengue is an important vector-borne human disease in tropical and subtropical regions. Currently, there is no available preventive vaccine or therapeutic treatment for dengue infection. Supportive care is the current method of managing this disease. The nonspecific symptoms and signs of this disease make it sometimes difficult to diagnose and manage. Dengue infection may be associated with bone marrow (BM) suppression (Bierman and Nelson, 1965). Patients may seek help late in the illness when the clinical presentation and diagnosis may be more challenging (Tsai *et al*, 2012). Although secondary infections in dengue infected patients have been documented (Lee *et al*, 2005; Chai *et al*, 2007; Ong *et al*, 2007; Larbcharoensub *et al*, 2011; Lee *et al*, 2012), they may be difficult to diagnose and their extent is unclear. We describe a fatal case of such a patient.

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CASE REPORT

A 48 year old Chinese female presented to the hospital with fever, malaise, rhinorrhea, sore throat, and poor appetite

Table 1
Laboratory results of patient.

Date	12/8	12/11	12/12	12/14	12/15	12/16	12/17	Normal range
DOI	2	5	6	8	9	10	11 (expired)	
Platelets (x1,000/ l)	97	36	48		158	256		150-400
WBC (/ l)	4,900	8,200	12,800		11,300	22,100		4,000-11,000
CRP (mg/l)	32.64				5	6.12		< 5
SGPT (IU/l)	256	99			41	1,384		< 40
SGOT (IU/l)	454	128			51	6,491		< 40
PT (INR)		1.0				3.7		0.85-1.15
PTT (seconds)		36.8 (c:28.5)				49.2 (c:28.5)	56.4 (c:28.2)	24-36.8
BNP (pg/ml)						393		<100
D-dimer (mg/l)						11.01		<0.55
Fibrinogen (mg/dl)						54		170-410
Haptoglobin (mg/dl)							<5.83	36-195
Uric acid (mg/dl)						18.9		2.6-7.2
Stool OB				N		3+		

DOI, day of illness; SGPT, serum glutamic-pyruvic transaminase; SGOT, serum glutamic oxaloacetic transaminase; PT, prothrombin time; PTT, partial thromboplastin time; c, healthy control; OB, occult blood; IU, international units; INR, international normalized ratio; BNP, brain natriuretic peptide; N, negative.

for 2 days. She had a past medical history of diabetes mellitus, hypertension, ischemic heart disease and renal failure, for which she had been receiving hemodialysis for nearly three years. She had suffered a non-ST elevation myocardial infarction one year previously. On physical examination, she had a fever of 37.8ºC, a blood pressure of 161/89 mmHg, a pulse rate of 88/min and a respiratory rate of 20/min. She had no rash or gastrointestinal symptoms.

Laboratory investigations revealed an elevated C-reactive protein (32.64 mg/ml), an elevated aspartate aminotransferase level (454 IU/l), an elevated alanine aminotransferase level (256 IU/l), a leukocyte count of 4,900 cells/mm^3 with 73.9% neutrophils, and a platelet count of 97,000 cells/mm^3 (Table 1). Chest x-ray revealed borderline cardiomegaly. A single blood culture and influenza test were both negative. Computerized tomography of the abdomen revealed a fatty liver, cholelithiasis and evidence of an intraabdominal infection but no abscess formation. Intravenous ceftriaxone and metronidazole were empirically administered (Table 2).

On the fifth day of illness, she was afebrile but her platelet count rapidly declined (Table 1). Because of a recent diagnosis of dengue fever in her neighborhood, she was tested for dengue infection on the sixth day of illness. She had a positive test for dengue IgG but negative test for dengue RNA with a RT-PCR, a

Table 2
Clinical management.

Date	12/8	12/11	12/12	12/14	12/15	12/16	12/17
DOI	2	5	6	8	9	10	11 (expired)
Resuscitation						X	
Antibiotics	IV: ceftriaxone 2g Q12h per day for 6 days; metronidazole 500 mg (3X per day) for 6 days; followed by unasyn 375 mg 1#Q12h for 1 day					IV: antibiotics after resuscitation: piperacillin + tazobactam	
Hemodialysis	X				X		
Chest x-ray	X						
Abdominal CT	X						
Abdominal ultrasound	X			X			
Blood culture	N						*Enterococcus faecium*
Dengue test			RT-PCR, NS1 antigen, and IgM were negative; IgG+			IgG+Confirmed: dengue virus infection	

DOI, day of infection; N, negative.

negative test for dengue, non-structural protein 1 (NS1), a negative test for dengue IgM. An acute dengue infection was confirmed by a four-fold increase in dengue IgG titer with the second sample (day 10 of illness), using the standard dengue IgG test recommended by the Taiwan CDC (Shu *et al*, 2003). The patient had clinical improvement and an increase in her platelet counts between day 6 and 9 of illness; therefore the antibiotics were discontinued on day 9 of her illness.

On the evening of the 9th day, the patient passed tarry stool after hemodialysis. The next morning, the patient lost consciousness. The patient was suspected of having an acute myocardial infarction. Laboratory investigations revealed a higher hematocrit level but the CK-MB and Troponin I were within normal limits. The brain natriuretic peptide was elevated (Table 1). The patient developed sudden cardiac arrest and she was successfully resuscitated. A chest x-ray revealed only increased pulmonary vascularization.

A peripheral blood smear obtained on the 10th day of illness showed hemophagocytosis (Fig 1A), a high D-dimer, a low fibrinogen level and prolonged PT and PTT, indicating disseminated intravascular coagulation. The stool for occult blood was positive. Due to the low amount of haptoglobin in the circulation, hemolysis was suspected. The patient also had a high uric acid level but no history with gouty arthritis. The patients was dialyzed, and started on piperacillin-tazobactam.

The patient developed shock and *Enterococcus faecium* was recovered from two sets of blood cultures on the 11th day

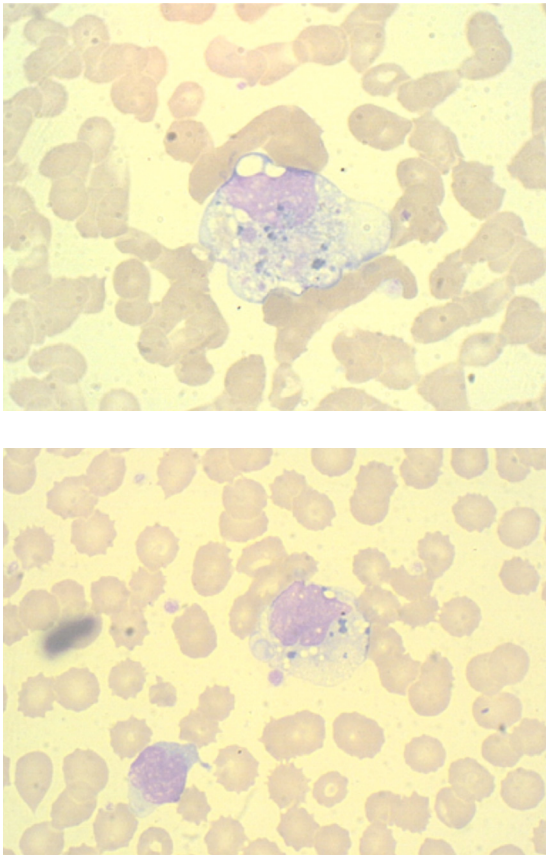

Fig 1–Peripheral blood smear. (A) Hemophagocytosis in a blood smear obtained on the 10th day of illness. Numerous cellular debris and platelets are seen in the cytoplasm of activated macrophage/monocytes (Wright's stain), 1,000X. (B) Cytokine levels obtained on the 6th and 10th days of illness.

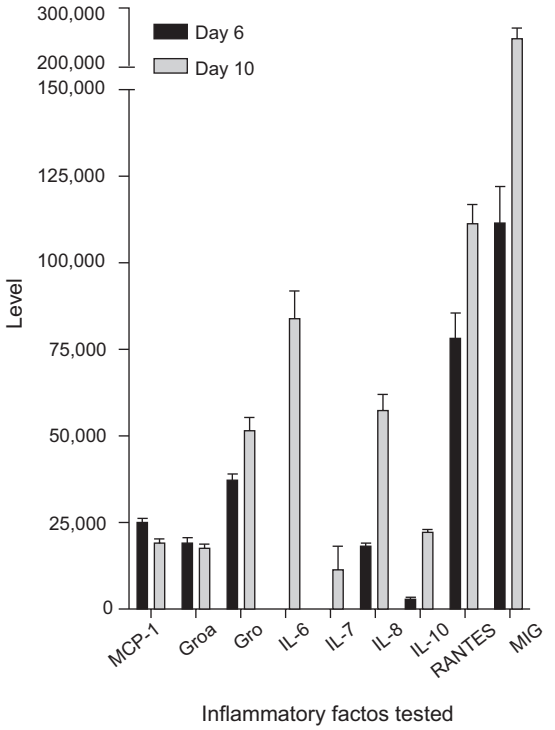

Fig 2–Inflammatory factor levels on days 6 and 10.

of illness. This *E. faecium* was sensitive to streptomycin, teicoplanin, tigecycline, vancomycin and linezolid. Endotoxin levels were measured in sequential serum samples using a commercial endotoxin assay kit (GenScript, Piscataway, NJ). No endotoxin was detected in the serum samples collected on days 5 and 6, but high levels of endotoxin were found on days 10 and 11 (2.25 and 1.5 EU/ml, respectively). Interleukin (IL)-6, IL-7, IL-8, IL-10, and Monokine Induced by Interferon gamma; also known as CXCL-9 (MIG), were elevated days 6-10, but were especially high on day 10 (Fig 2). The clinical picture and laboratory findings suggest sepsis with DIC, combined with hypovolemia from a gastrointestinal bleeding and a sudden increase in cytokines resulted in a cardiac arrest.

DISCUSSION

This case shows the complexity of managing a case of dengue infection with sepsis. Although dengue IgG was positive, dengue viral RNA, dengue IgM and

dengue NS1 antigen were all negative. A difficult challenge is timely diagnosis to enable prompt, appropriate treatment. Most patients do not seek health care at the first sign of a febrile illness (Tsai *et al*, 2012). This patient did not develop a high grade fever. There are several possible reasons for this: the hemodialysis reduced the likelihood of fever, there was some fluctuation in the temperature at the time it was measured, and the immunocompromised state of the patient prevented a febrile response. Bleeding, shock and multiorgan failure are common in severe dengue infections.

The factor that influenced the clinical picture in this case was the sepsis caused by *Enterococcus faecium*. Enterococci are facultatively anaerobic, gram-positive cocci, commensal to the gastrointestinal tract. In recent years, it has been reported as a major cause of nosocomial infections with a high mortality rate (Jett *et al*, 1994; Johnson, 1994; Suffredini and Munford, 2011). Reports suggest dengue patients are more vulnerable to blood-stream invasion by bacteria from the intestinal tract (Lee *et al*, 2005; Ong *et al*, 2007; Lee *et al*, 2012). Bone marrow suppression caused by the dengue virus (Bierman and Nelson, 1965) may have increased the likelihood of more severe sepsis due to the *Enterococcus faecium*. Dengue endotoxemia has been detected on the day of maximal vascular permeability in 50% of patients with severe dengue infection (Usawattanakul *et al*, 1986). Enterococcal bacteria can cause sepsis following translocation from the gut in animal models (Mason *et al*, 2011) and produce a bacterial toxin that can induce large transendothelial cell macroaperture tunnels, rupturing the host endothelial barrier, leading to bacterial dissemination (Maddugoda *et al*, 2011). Bacteria in damaged guts may leak into circulation and cause sepsis. The levels of lipopolysaccharide in serum of dengue patients have been correlated with disease severity (van de Weg *et al*, 2012). This hypothesis needs to be further explored.

Hemophagocytic activity may contribute to abnormal cytokine production (My *et al*, 2010), which can be a hallmark of lethal bacterial infections. Unusual cytokine responses (Papasian *et al*, 2002) and high fatality rates have been documented in patients who have received hematopoietic stem cell transplants and have developed hematological disorders resulting from enterococcal infections (Almyroudis *et al*, 2005; Todeschini *et al*, 2006; Fossati *et al*, 2010; Suffredini andMunford, 2011).

The patient's underlying diseases likely contributed to the fatality in this case. Bacterial infections have been documented in dengue patients (Wang *et al*, 2007; Araujo *et al*, 2010; Larbcharoensub *et al*, 2011), but the role of secondary enterococcal infections in dengue infections is unknown. Bone marrow suppression, along with impairment of humoral and cellular immunity, has been documented in dengue patients, but its clinical significance is unclear.

The death of this patients was unexpected, especially after the initial clinical improvement. The cause of death was sepsis due to enterococal bacteremia with underlying dengue infection. The underlying diabetes mellitus type 2, chronic renal failure and ischemic heart disease were also contributing factors. Clinicians should be aware of the potential additive risks for gastrointestinal bleeding, ischemic heart disease in patients undergoing hemodialysis. Empiric antibiotics should be considered in dengue infected patients at high risk of developing bacteremia. A strong index of suspicion should be

maintained in dengue infected patients with immune suppression.

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