CASE REPORT

Dengue Hemorrhagic Shock and Disseminated Candidiasis

Satoshi Suzuki¹, Takatoshi Kitazawa¹, Yasuo Ota¹, Shu Okugawa¹, Kunihisa Tsukada¹, Yoko Nukui¹, Shuji Hatakeyama¹, Daisuke Yamaguchi², Shinji Matsuse², Takeshi Ishii², Takehiro Matsubara², Chisako Yamauchi³, Satoshi Ota¹, Naoki Yahagi³, Masashi Fukayama³ and Kazuhiko Koike¹

Abstract

Dengue fever, one of the common endemic viral fevers, often presents with fever, rash, and mild liver dysfunction. However, plasma leakage induced by dengue virus infection can lead to dengue hemorrhagic fever and dengue shock syndrome, and it can cause severe complications including liver failure and encephalopathy. Infection of dengue virus with other pathogens is an unusual but serious complication. We report a case of dengue shock syndrome with liver failure and impaired consciousness. The patient developed a disseminated Candida tropicalis infection, which may have been due to translocation of the fungus from the intestine damaged by the dengue virus.

Key words: dengue shock syndrome, Candida tropicalis, liver failure, encephalopathy

(DOI: 10.2169/internalmedicine.46.6354)

Introduction

Dengue infection, which is one of the hemorrhagic fevers caused by the arbovirus, is epidemic in many tropical and subtropical countries. The number of the reported cases in Japan with dengue virus infection has been gradually increasing and 73 cases were reported in 2005. The clinical presentations include non-specific febrile illness, dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. Dengue fever presents as an acute fever with headache, rash, and thrombocytopenia. Dengue hemorrhagic fever is characterized by an increase in capillary permeability and haemostatic changes, which result in effusions, ascites, and bleeding. Dengue shock syndrome is associated with hypotension caused by severe plasma leakage.

With dengue infections, liver injury is not an uncommon presentation, though in many dengue fever cases, liver enzyme elevations are mild to moderate (1, 2). As well, encephalopathy and coinfection with other pathogens are rare complications (3-5). We present a fatal case of dengue shock syndrome with acute liver failure and impaired consciousness accompanied by severe systemic fungal infection. Coinfection with dengue virus and fungus has not been previously reported. Given the histological findings, candidemia may have occurred as a result of translocation from the intestine that had been damaged by the dengue virus infection.

Case Report

A 53-year-old Japanese man presented with fever and headache on August 21, 2005. He had been working in Colombo, Sri Lanka, for 2 years with no episodes of infectious diseases that are endemic to the area. He was admitted to a local hospital in Colombo on August 25th due to a prolonged fever of 39°C. On admission, the patient had a skin rash; there were no signs of neurological, respiratory, or gastrointestinal abnormalities. Laboratory data were almost normal, except that the platelet count was 8.5 × 10⁴/mm³, and the liver enzymes were mildly elevated (aspartate aminotransferase (AST) 113 IU/L, alanine aminotransferase (ALT) 67 IU/L). Serum immunoglobulin M (IgM) antibody for dengue virus was positive on enzyme-linked immunosorbent assay (ELISA), and dengue virus RNA was detected on polymerase chain reaction (PCR) assay. Gingival bleeding and petechiae on the extremities were noted on August

¹Department of Infectious Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, ²Department of Emergency and Critical Care Medicine, The University of Tokyo, Tokyo and ³Department of Pathology, Graduate School of Medicine, The University of Tokyo, Tokyo
Received for publication November 7, 2006; Accepted for publication February 6, 2007
Correspondence to Dr. Yasuo Ota, yasuota-tky@umin.ac.jp

1043
The patient was given a platelet transfusion because his platelet count had decreased to $2.6 \times 10^4/\text{mm}^3$. On August 27, the patient’s systolic blood pressure dropped below 60 mmHg and the hematocrit level was increased by 53.2%. Although his blood pressure recovered shortly after fluid therapy, meropenem was started because septic shock was suspected. However, blood cultures were negative. On August 29, the patient’s urine volume was significantly diminished, and daily hemodialysis was initiated. On August 31, the patient developed dyspnea. Significant elevation of the transaminases and creatine was noted (AST 3,980 IU/L, ALT 910 IU/L, creatine 6.7 mg/dl). The patient’s consciousness level became gradually disturbed; eventually, he only responded to pain stimulation. However, computed tomography (CT) of the brain showed no abnormal findings. On September 4, the serum ammonia level was elevated to 116 μg/dL. The patient was transferred from Sri Lanka to our hospital in Japan for further treatment.

On arrival at our hospital in early September, the patient’s blood pressure was 50/20 mmHg, and his body temperature was 39.6°C. The patient had severe jaundice and petechiae. Breath sounds were decreased bilaterally, and his abdomen was distended with a large amount of ascites. Laboratory findings included leukocytosis, anemia, and thrombocytopenia. Both the prothrombin time (international normalized ratio, INR) (1.63) and the partial thromboplastin time (69 s) were extremely prolonged, which suggested disseminated intravascular coagulation. Furthermore, type-3 dengue virus RNA was still positive on PCR assay performed essentially as previously described (6). In addition, neutralizing antibodies against both type-3 and type-4 dengue virus showed high titers in a plaque assay. On chest and abdominal CT, progressively worsening infiltrations in both lungs and massive amounts of fluid in the pleural and peritoneal cavities were found. On brain CT, high density areas with surrounding low density areas in the right sylvian fissure and in the right cerebellar hemisphere were present. Hemodialysis and plasma exchange were done due to acute renal failure and hepatic failure. On September 8, fungus was isolated from blood cultures that had been taken immediately on admission; the fungus was later identified as *Candida tropicalis*. Amphotericin-B and fluconazole were administered intravenously. Although the patient was aggressively treated for dengue and fungal infection, his bleeding tendency did not improve; the patient’s brain hemorrhage and edema worsened markedly. The patient died on September 9.

On autopsy, hepatic enlargement and cholestasis were observed. Hepatocellular necrosis was seen in the midzonal and centrilobular regions (Fig. 1A). In the brain, multiple hemorrhagic infarctions were present. Cellular infiltration that would have suggested encephalitis was not observed. In the kidneys, fibrin thrombi were formed in glomerular capillaries, and tubular necrosis was observed. Dengue virus RNA was detected in the liver, but not in the brain, lung, kidney, intestine or spleen, on Reverse Transcriptase (RT)-PCR assay performed essentially as previously described (6) (Fig. 1B). Fungus bodies were detected throughout the body, including the brain, liver, lungs, kidneys, enlarged mesenteric lymph nodes, pleural effusions, pericardial fluid, ascitic fluid, and nodules in the left atrium (Fig. 1C).

**Discussion**

Fever, hemorrhagic tendencies, thrombocytopenia and evidence of plasma leakage were observed in this case. Dengue hemorrhagic fever was diagnosed according to the WHO criteria (7). In addition, the antibodies to type-3 and type-4 dengue virus were both positive, indicating this was his second infection with dengue virus, although the patient had no recollection of getting infected with dengue virus before.

Among the complications of dengue virus infection, co-infection with other pathogens is a rare but severe complication. Previously identified co-infecting organisms have included *Escherichia coli*, *Salmonella*, *Streptococcus pneumoniae*. 
niae, Mycobacterium tuberculosis, Mycoplasma pneumoniae, Shigella sonnei, Klebsiella pneumoniae, Enterococcus faecalis, Moraxella lacunata and herpes virus (3, 4, 8). However, there have been no reports of fungal coinfections in dengue patients. Most coinfeting pathogens are normally found in the intestinal tract. Enterobacteriaceae, enterococci, and streptococci generally have been found to more readily translocate than other gram-positive and anaerobic bacteria (9). In patients with dengue virus infection, dengue virus induces apoptosis of endothelial cells due to the antibodies produced (10). A recent study demonstrated the evidence of intestinal mucosal injury in patients with dengue infection (11). Therefore vulnerability of intestinal mucosa due to dengue virus infection may lead to translocation of organisms into the blood stream. Candida tropicalis, which was isolated from the present patient, normally inhabits the skin and intestinal tract (12, 13). In a mouse model, Candida spp. translocation from the intestine to other organs was lower than that of bacteria (14); however, in one study involving a healthy volunteer, oral administration of Candida spp. lead to fungemia and funguria (15). The presence of an intravenous catheter has known to be one of the risk factors of candidal bloodstream infection. Although culture of the intravascular catheter tip was not examined in this case, it is possible that Candida tropicalis could have invaded the bloodstream through an intravenous catheter. However, it is more likely that Candida tropicalis infection occurred due to translocation from the secondarily damaged intestine, since there was enlargement of the mesenteric lymph nodes due to candidiasis. Lee et al investigated the clinical characteristics of concurrent bacteremia with dengue infection in adults (3). They identified the following independent risk factors: acute renal failure, prolonged fever, altered consciousness, dengue shock syndrome, older age, and gastrointestinal bleeding. The present case had 4 of these risk factors. It is also possible that the use of broad-spectrum antibiotics is a risk factor for coinfection with Candida spp. In an animal model, the use of antibiotics facilitated the colonization of the intestine and the dissemination of Candida albicans (16). Steroid, which is also known to promote infection with Candida spp., was not used in our patient.

Before Candida tropicalis was isolated, the patient presented with unusual manifestations of dengue virus infection, including liver failure and consciousness disturbance. Since Candida tropicalis was also detected in these organs, it was difficult to determine whether these manifestations were due to the dengue infection itself or to candidiasis. In previously published histopathological studies of dengue fever cases with liver failure, hepatocellular necrosis was noted in the midzonal and centrilobular regions, and dengue virus antigen was detected in the hepatocytes located in the necrotic areas (17). In the present case, hepatocellular necrosis was also observed in the midzonal and centrilobular regions, and dengue virus was detected in the liver on PCR assay. On the other hand, the identified areas with Candida tropicalis were not consistent with the necrotic regions. Given these findings, the liver damage in our case might be more likely caused by dengue infection. The patient’s consciousness was disturbed, and he had an elevated serum ammonia level before he developed a hemorrhagic brain infarction. The pathological findings of dengue-related encephalopathy include cellular infiltration, diffuse endothelial thickening of capillaries, and detection of virus component (18); these findings were not seen in this case. Therefore, this patient’s neurological damage was likely due to hepatic encephalopathy rather than dengue virus-related brain involvement or hemorrhagic infarction due to intravascular invasion of Candida tropicalis.

We would like to thank Mie Kataoka for preparing the manuscript. We would also appreciate Dr. Shiraz Hassen and the staff of Apollo Hospitals in Colombo, Sri Lanka, for providing medical information on our patients.

References