Dengue Hemorrhagic Fever with Fulminant Hepatic Failure in an Immigrant Returning to Bangladesh

Stephen D. Lawn, Rosalinde Tilley, Graham Lloyd, Caroline Finlayson, Howard Tolley, Philip Newman, Philip Rice, and Thomas S. Harrison
Departments of Infectious Diseases, Intensive Care, Histopathology, and Microbiology, St. George’s Hospital Medical School, London, and Centre for Applied Microbiology and Research, Salisbury, United Kingdom

An immigrant from Bangladesh living in the United Kingdom presented with a nonspecific febrile illness after visiting his homeland and subsequently developed fulminant hepatic failure accompanied by hypotension, ascites, a generalized coagulopathy, and thrombocytopenia. Serology and detection of dengue virus serotype 3 by PCR established a postmortem diagnosis of hepatic failure secondary to dengue hemorrhagic fever.

Dengue viral infections are transmitted by the Aedes aegypti mosquito and affect up to 100 million individuals per year with two-fifths of the world population being at risk [1, 2]. The presentation of dengue infection can be classified into 5 main forms: nonspecific febrile illness, classic dengue fever (DF), dengue hemorrhagic fever (DHF), DHF with dengue shock syndrome (DSS), and unusual syndromes such as encephalopathy [2]. All 4 serotypes of dengue virus can cause DHF, but this is more likely to occur with secondary infections with a different serotype [1, 2]. Although the pathophysiology is incompletely understood, this phenomenon is thought to be mediated in part by antibody-dependent enhancement. Cross-reactive but non-neutralizing antibodies from a previous infection bind to the new infecting serotype and facilitate virus entry into cells [3]. The resulting higher peak viral titer causes more severe disease, possibly because of enhanced activation of cytokine cascades and the complement system, as well as increased endothelial dysfunction, platelet destruction, and consumption of coagulation factors [1].

The number of cases of dengue imported to countries where it is not endemic is rising as a result of increased travel and an increasing incidence of dengue worldwide. Most travelers from countries where dengue is not endemic have had no prior exposure to dengue virus and so, in general, develop uncomplicated primary infections. However, immigrants from countries where dengue is endemic who subsequently visit their homeland are at increased risk of secondary infection and DHF [4]. Here we report the case of a Bangladeshi man living in the United Kingdom who, after a visit to his homeland, developed DHF with the rare complication of fulminant hepatic failure.

CASE REPORT

The 59-year-old man had lived in Dhaka, Bangladesh, until the age of 35 years, when he moved permanently to the United Kingdom. He made annual visits to Bangladesh but had never knowingly had DF. He was generally fit, although he had well-controlled hypertension and noninsulin dependent diabetes mellitus (NIDDM) for >20 years, the latter being complicated by hyperlipidemia.

During the rain season in September 2002, he visited Dhaka, Bangladesh, and took no antimalarial prophylaxis.
laxis. Two days before returning to the United Kingdom, he developed a mild febrile illness characterized by sore throat, rhinorrhea, anorexia, lassitude, and a cough that was initially productive of a trace of yellow sputum. Although he returned to work after arriving back in the United Kingdom, he subsequently became increasingly weak with a persistent dry cough, fever, and nausea and vomiting. He was admitted to our institution on day 8 of his illness.

On examination, the patient was unwell, sweaty, and dehydrated. He was not jaundiced and was fully oriented. He had a temperature of 37.6°C, a pulse of 86 beats/min, and blood pressure of 125/70 mm Hg. His respiratory rate was increased, air entry was reduced at both lung bases, and inspiratory crepitations were audible at the right lung base. The only other positive clinical findings were mild tenderness in the right hypochondrium and scanty petechial hemorrhages over the shins.

Initial investigations revealed a normal hemoglobin concentration (15.8 g/dL) and hematocrit (0.46), marked thrombocytopenia (15 × 10^9 cells/L), a normal total WBC count (4.3 × 10^9 cells/L), a lymphopenia (0.6 × 10^9 cells/L), and a leucocytoblastic blood film. A clotting screen was normal apart from a prolonged activated partial thromboplastin time (APPT, 2.20 sec; normal range, 4.27–6.40 kPa), and a mixed metabolic acidosis and respiratory alkalosis. However, findings of a chest radiograph revealed hypoxia (PaO_2, 8.30 kPa; normal range, 0.54 mg/L, normal range <0.3 mg/L). Blood urea, creatinine, and electrolyte concentrations were normal. The serum C-reactive protein (CRP) level was elevated (143 mg/L; normal range, <10 mg/L) and the serum albumin level was reduced (27 g/L; normal range, 38–48 g/L). Serum concentrations of hepatic enzymes were increased; the alanine transaminase (ALT) level was 333 U/L (normal range, 5–40 U/L) and the alkaline phosphatase (ALP) level was 173 U/L (normal range, 30–100 U/L). The blood glucose concentration was 20.1 mmol/L but there was no ketonuria. Arterial blood gas measurement on air revealed hypoxia (PaO_2, 8.30 kPa; normal range, 11.1–14.4 kPa), hypocapnia (PaCO_2, 3.30 kPa; normal range, 4.27–6.40 kPa), and a mixed metabolic acidosis and respiratory alkalosis. However, findings of a chest radiograph and an electrocardiogram were normal.

The illness was thought most likely to be infective, with possible causes including malaria, atypical pneumonia, typhoid fever, viral hepatitis, dengue fever, leptospirosis, or meningococcemia together with complicating disseminated intravascular coagulation or an immune-mediated thrombocytopenia. Hematological malignancy, vasculitis, a drug reaction, and Henoch-Schonlein purpura were considered to be less likely possibilities. The patient was treated with intravenous cefotaxime and erythromycin, intravenous crystallloids, an insulin infusion, high-flow oxygen, and blood product support.

No malaria parasites were seen in blood samples obtained from the patient. Cultures of blood, urine, and a throat swab were sterile. The results of serologic tests for hepatitis A, B, C, and E were negative, as were the results of serologic tests for cytomegalovirus, Epstein-Barr virus, and Legionella spp. The results of complement fixation tests for Mycoplasma pneumoniae, Chlamydia pneumoniae, Coxiella burnetti, and Leptospira spp. were also negative. Within 24 h of admission to the hospital, the patient became hypotensive (85/50 mm Hg). He developed a generalized consumptive coagulopathy and was transferred to the intensive treatment unit (ITU). A bone marrow aspirate was normal. An abdominal ultrasound revealed a very fatty liver of normal size with normal blood flow within the hepatic portal vein and a small amount of ascites around the liver and within the pelvis. Increasing oxygen requirements necessitated endotracheal intubation and ventilation. By 36 h after admission to the hospital, there was evidence of hepatic failure; the blood ALT concentration was 802 U/L, the aspartate transaminase (AST) level was 4067 U/L (normal range, 0–40 U/L) and the lactate dehydrogenase level (LDH) was 3508 U/L (normal range, 0–175 U/L). Blood paracetamol levels were undetectable. The patient developed a profound lactic acidosis (lactate, 16.5 mmol/L) and hemofiltration was commenced to correct this. Findings of an echocardiograph revealed excellent left ventricular systolic function, but a noradrenaline infusion was required to maintain the circulation.

On day 3 of hospitalization, the patient developed marked ascites with worsening liver failure and coagulopathy. In view of progressive clinical deterioration despite maximal medical support, an exploratory laparotomy was performed to exclude bowel ischemia or perforation. The only abnormal findings were a grossly enlarged and congested liver with fatty infiltrates together with gross ascites. Despite full supportive care on ITU the patient died on the fourth day of hospitalization. A postmortem examination revealed no other abnormality. Liver histology revealed marked steatosis and a florid hepatitis with necrosis (figure 1). A low titer of IgM antibodies and a high titer of IgG antibodies to dengue virus were subsequently detected in the patient’s serum, and dengue virus serotype 3 was detected by PCR. A postmortem diagnosis was made of DHF complicated by fulminant hepatic failure.

**DISCUSSION**

This patient presented with a nonspecific febrile illness without the prominent headache, generalized myalgia, and retro-orbital pain that characterize classical uncomplicated DF. However, this illness was entirely consistent with the diagnosis of DHF complicated by DSS and fulminant hepatic failure. No other infection was identified. Multiple serotypes of dengue virus are known to have been present in Bangladesh for >30 years [5]. However, outbreaks of DHF associated with dengue virus serotype 3 have recently been reported from Bangladesh [6, 7]. It is likely that our patient had previously had an asymptomatic
Figure 1. A, Photomicrograph of the postmortem liver biopsy specimen (original magnification × 200) showing marked macrovesicular fatty change, midzonal hepatocellular necrosis (N), and focal lymphocytic and polymorphonuclear leucocyte infiltration. A portal tract (PT) is indicated. B, Photomicrograph of liver biopsy specimen (original magnification × 600) showing marked hepatocellular necrosis and the presence of numerous Councilman (apoptotic) bodies (CB). These appearances are consistent with hepatitis caused by dengue virus.
dengue infection with a different serotype, leading to a more severe secondary infection on this occasion. The presence of high serum titers of IgG antibody to dengue virus on day 8 of the illness is highly suggestive of this possibility [1].

Dengue virus has been identified within liver tissue and dengue antigen identified within Kupffer cells of infected individuals [1]. However, although elevation of serum concentrations of liver transaminases is almost invariably in individuals with DHF [8], hepatic failure is rarely reported. Hepatic failure following DHF has been described in 2 adults who subsequently recovered [9, 10] and in 8 children in Malaysia, 1 of whom died [11]. Nonfatal Reye’s syndrome confirmed by liver biopsy has also been described as a complication of DHF [12, 13]. However, to our knowledge, this is the first report of fatal hepatic failure in an adult arising as a complication of DHF. Our patient was not encephalopathic before ventilation, and the histological pattern of fatty infiltration was macrovesicular, rather than the microvesicular pattern characteristic of Reye’s syndrome. It is possible that the marked steatosis observed was instead a result of the patient’s longstanding diabetes mellitus and hyperlipidemia, and this may have predisposed him to this severe hepatic complication of DHF.

This case illustrates the importance of physician awareness of patterns of infectious disease outbreaks around the world. Hepatic failure is a rare but important complication of DHF, and DHF should be included in the differential diagnosis of infective hepatitis in individuals who have recently been in an area in which dengue is endemic. Immigrants from countries where DF is endemic may be at risk for DHF as they travel back to their home countries, and advice concerning assiduous avoidance of mosquito bites is important, especially when there is a known outbreak of DHF at their destination.

References