# Dengue Hemorrhagic Fever and Acute Hepatitis: A Case Report

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**Dengue fever is the world's most important viral hemorrhagic fever disease, the most geographically wide-spread of the arthropod-born viruses, and it causes a wide clinical spectrum of disease. We report a case of dengue hemorrhagic fever complicated by acute hepatitis. The initial picture of classical dengue fever was followed by painful liver enlargement, vomiting, hematemesis, epistaxis and diarrhea. Severe liver injury was detected by laboratory investigation, according to a syndromic surveillance protocol, expressed in a self-limiting pattern and the patient had a complete recovery. The serological tests for hepatitis and yellow fever viruses were negative. MAC-ELISA for dengue was positive.**

**Key Words: Dengue, dengue hemorrhagic fever, hepatitis.**

Dengue fever is the world's most important viral hemorrhagic fever disease; it is the most geographically wide-spread of the arthropod-born viruses, especially in the Americas, the Pacific islands and on continental Asia [1]. Dengue virus infection can present a diverse clinical spectrum, ranging from asymptomatic illness to dengue shock syndrome, as well as unusual manifestations, such as hepatitis, encephalitis, myocarditis, Reye's syndrome, hemolytic uremic syndrome and thrombocytopenic purpura [2].

Liver injury due to dengue infection is not uncommon and has been described since 1970 [3]. However, in the Americas, this clinical presentation is poorly documented. Painful hepatomegaly, the main clinical symptom observed, is seen in up to 30% of patients. It is most commonly associated with dengue hemorrhagic fever (DHF), and its magnitude has no relationship with the severity of the disease. On the other hand, an increase in aminotransferases can be seen in up to 90% of persons with dengue infection, with levels of aspartate aminotransferase (AST) higher than those of alanine aminotransferase (ALT) [4-6].

Acute liver failure is a severe complicating factor in dengue infection, predisposing to life-threatening hemorrhage, disseminated intravascular coagulation and encephalopathy. The association of liver impairment and neurological manifestations in a patient with DHF indicates a very poor prognosis, often culminating with death [7-11].

In Latin America, the superimposed geographical areas for malaria, viral hepatitis and yellow fever represent a challenge for identifying the etiology of acute febrile syndrome complicated by hepatitis. During the DHF outbreak of 2001 in Manaus, the capital of Amazonas state in the Brazilian rain forest, we identified an unusual case with acute febrile hemorrhagic syndrome, followed by severe hepatic injury. Although dengue fever is an emergent and epidemic disease in parts of the Americas, little is known about its clinical presentations in this region. This case was a serious but fortunately atypical presentation of DHF.

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## Case Report

A 28-year-old white man was admitted to our hospital in February 2001. He had a personal history of regular alcohol use and of dengue fever three years earlier. Five days before admission, he developed fever, headache, chills, myalgias and arthalgias, and he took acetaminophen at standard dosages on his own. On the fourth day of symptoms, after a decrease in fever and headache, he had diffuse abdominal pain, repeated vomiting, hematemesis, epistaxis and diarrhea.

On evaluation in the emergency department, he was well-nourished, anicteric, and he had normal vital signs. A few petechial lesions were observed on the upper extremities and mildly painful liver enlargement was evident. There were no signs of active bleeding or cavitary effusions. The tourniquet test was not performed since the patient already had evidence of spontaneous bleeding.

The patient was hospitalized and submitted to a management protocol for suspected DHF cases [6]. He was given oral fluids and intravenous saline solution. The results of laboratory tests are shown in Table 1.

During the first 24 hours of hospitalization the patient had rare episodes of epistaxis, right upper abdominal pain and vomiting, but he remained hemodynamically stable all the time. He was discharged after two days of hospitalization, with a clinical diagnosis of grade II DHF [2] and acute liver failure.

On follow-up evaluation, he had no complaints and the laboratory examinations were normal. Serological tests for viral hepatitis (A, B and C) and yellow fever were negative, as were blood cultures for bacteria. Thick blood film was negative for malarial parasites. The MAC-ELISA and the ELISA Inhibition of Agglutination tests for dengue virus were both positive. Isolation of dengue virus was not attempted because of its low positivity after the fourth day of disease.

## Discussion

Although liver involvement by dengue virus has been frequently described in Asia and the Pacific islands, and to a lesser degree in the Americas, the pathogenic mechanisms are not yet fully elucidated. Some believe that it is related to combined interactions of the virus, the host and the duration of disease [11].

The virus may have a replication phase in hepatocytes, causing hepatic injury, stimulating apoptosis, microvesicular steatosis and the development of Councilman-Rocha Lima bodies, similarly to yellow fever infection and other viral hemorrhagic diseases [9,11,12]. The histopathological observation of liver specimens is restricted to fatal cases because of the risk of bleeding diathesis in acutely ill patients. Some viral strains also seem to have a prominent liver tropism, especially DEN-1 and DEN-3 [2].

Chronic liver disease, alcoholic steatonecrosis, hemoglobin disorders and hepatotoxic drug use (e.g.: salicylates, acetaminophen and antiemetics) during dengue infection may predispose to and even increase liver injury. These drugs may become toxic in patients with dengue-associated hepatitis or hypoperfusion, although some authors did not observe a correlation between acetaminophen overdose and the development of liver failure [3].

From 1973 to 1982, the observed liver involvement due to dengue infection in Thailand and Malaysia was mild, and it manifested exclusively as elevated liver enzymes. But after this period, several cases of fulminant hepatitis with high mortality rate have been reported, mainly in children and young adults [9]. The increase in aminotransferases, mainly AST, has been associated with disease severity and may serve as an early indicator of dengue infection. Indeed, liver injury is a good positive predictive factor for the development of DHF [5]. This increase usually happens within the first nine days of symptoms and normalizes in about two weeks. Increased levels of alkaline phosphatase and serum bilirubin are noted in a smaller proportion of cases [8].

In this case report, the patient's regular alcohol ingestion and previous dengue infection, as well as the oral intake of acetaminophen, may have favored liver injury. Nevertheless, despite a remarkable increase in aminotransferases, there was no cholestasis and recovery was favorable. The ingestion of other

**Table 1.** Laboratory results of a dengue hemorrhagic fever patient, according to the day of illness. The patient first sought medical care on day 5

| | **Day$_5$** | **Day$_6$** | **Day$_7$** | **Day$_9$** | **Day$_{15}$** |
|---|---|---|---|---|---|
| Leukocytes (x $10^3$/μL) | 9.6 | 24.8 | 34.3 | 26.1 | 10.5 |
| Neutrophils (%) | 64 | 61 | 49 | 60 | 45 |
| Lymphocytes (%) | 23 | 29 | 41 | 30 | 40 |
| Red blood cells (x $10^6$/μL) | 4.1 | 4.0 | 3.5 | 3.4 | 3.8 |
| Hemoglobin (g/dL) | 14.0 | 12.7 | 11.0 | 10.7 | 11.2 |
| Hematocrit (%) | 42.1 | 38.2 | 32.6 | 31.3 | 33.6 |
| Platelets (x $10^3$/μL) | 16 | 27 | 55 | 106 | 208 |
| Prothrombin activity (%) | - | - | 14 | 69 | 88 |
| Albumin (g/dL) | - | - | 2.7 | 2.5 | 3.4 |
| AST (U/L) | - | - | 7,082 | 2,565 | 101 |
| ALT (U/L) | - | - | 2,129 | 1,380 | 266 |
| ALP (U/L) | - | - | 139 | 176 | 132 |
| gGT (U/L) | - | - | 194 | - | 153 |
| LDH (U/L) | - | - | 5,054 | 2,020 | - |
| Total bilirubin (mg/dL) | - | - | 1.54 | 1.68 | 0.83 |
| Direct bilirubin (mg/dL) | - | - | 0.59 | 0.60 | 0.37 |
| Creatinine (mg/dL) | - | - | 1.4 | - | 1.1 |
| Glucose (mg/dL) | - | - | - | 105 | 88 |

potential hepatotoxic substances was exhaustedly investigated.

Jaundice in dengue infection has been associated with fulminant liver failure and by itself is already a poor prognostic factor [10]. Despite an increased risk of hemorrhagic manifestations, because of reduced prothrombin activity, our patient showed only mild and self-limited bleeding.

The progressive decrease in hematocrit levels after intervention, as well as thrombocytopenia, hypoalbuminemia, spontaneous bleeding and positive serological tests confirmed the diagnosis of DHF. The hypoalbuminemia found in this case was probably a result of both capillary leakage induced by dengue infection and liver failure. Leukocytosis was attributed to extensive acute hepatocyte necrosis [13]. Bacterial infection was ruled out by negative microbiological tests and the favorable outcome without antimicrobial therapy. Hepatitis E and G viruses were not tested.

The detection of liver injury would probably have been delayed if this patient had not been enrolled in a syndromic surveillance protocol for acute hemorrhagic febrile diseases, which resulted in early intervention with fluid therapy, continuous medical support and sequential laboratory exams.

The endemic areas for viral hepatitis throughout the world are most often superimposed on areas with dengue fever, and one must rule out this infection whenever a patient with hepatitis of unknown origin is attended.

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