

## Primary dengue virus infection with hemorrhagic manifestations in a patient chronically infected with Hepatitis C virus

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### ABSTRACT

Dengue virus is the most important vector-borne virus worldwide. It can cause simultaneous infections with two distinct dengue virus serotypes in a single patient, also causing concomitant infections with other arboviruses and hepatitis C virus. The simultaneous combinations of infections exacerbate diagnostic problems, due to causing a range of clinical signs and confused clinical diagnostic results. Our report illustrates these points. This report provides information on a patient chronically infected with two hepatitis C virus genotypes, who became coinfecting with dengue virus, and presented hemorrhagic manifestations.

**Key words:** dengue hemorrhagic fever, HCV

### RESUMEN

**Infección primaria de dengue con manifestaciones hemorrágicas en un paciente crónico infectado con virus de hepatitis C**

El virus dengue es el virus transmitido por vector de mayor importancia a nivel mundial. La infección simultánea con diversos serotipos del virus dengue en mismo paciente ha sido reportada, al igual que la coinfección por diversos arbovirus

y el virus de la hepatitis C, esto a su vez; exacerbando los cuadros clínicos observados y por tanto potencializando la confusión al momento del diagnóstico. En este reporte hacemos énfasis en dicha observación. Este reporte provee información de un paciente con una infección crónica con dos genotipos distintos del virus de hepatitis C y que presentó una coinfección primaria del virus dengue con manifestaciones hemorrágicas.

**Palabras clave:** dengue hemorrágico, fiebre, HCV

### INTRODUCTION

There are four known serotypes of dengue viruses which are classified as dengue serotype 1, 2, 3 and 4. Each of them can cause similar clinical signs and symptoms. Dengue infections can be asymptomatic or can induce clinical manifestations such as fever, capillary permeability and thrombocytopenia, regardless of which of the four dengue virus serotypes is the infecting agent. Dengue virus also can cause the most severe clinical displays of the disease, known as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) (1). Hepatitis C virus (HCV) is classified in the family *Flaviviridae*, as the sole member of the genus *Hepaci-*

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*virus*. Chronic infections in the majority of cases (80-85%) are responsible for long-term hepatic damage. One of the most common problems associated with HCV chronic infection with hepatic fibrosis is recurrent thrombocytopenia resulting from several factors as bone marrow inhibition, decrease of liver thrombopoietin production and the autoimmune mechanism (2) resulting from production of antiplatelet antibodies (3, 4). In cases of coinfection, this may potentiate any hemorrhagic manifestations caused by primary dengue virus infection.

Coinfection during primary dengue infection with either two different dengue virus serotypes, or other pathogens have been detected previously (5, 6) with the potential problem of exacerbating a range of clinical signs during illness and therefore confusing the accuracy of clinical diagnostics. Unfortunately coinfections are generally not considered during initial diagnosis and therefore are seldom reported.

Here we described a non-fatal case of dengue hemorrhagic fever in a patient with chronic hepatitis C. During an outbreak of dengue, a 29-year-old woman from the city of Merida, Mexico was admitted to a local clinic on October 13, 2009 with a temperature of 40°C, headache, myalgia, arthralgia, retro-orbital pain, and generalized weakness. On admission, a blood sample was taken (written informed consent was obtained from the patient), and sent immediately to the Arbovirology laboratory at the Centro de Investigaciones Regionales "Dr. Hideyo Noguchi, Universidad Autonoma de Yucatan. Epidemiological data indicated that her house was located in a high dengue transmission area within the city of Merida, Yucatan, Mexico.

Laboratory findings demonstrated leukopenia (3,500/ $\mu$ L) (normal values 4,000–9,000), thrombocytopenia (67,000/ $\mu$ L) (normal values 150,000–450,000) and slightly elevated hematocrit (42.1%) (normal value 36–40%). Liver enzymes were not measured at this time because no suspicion of liver involvement was considered.

All other findings during the clinical examination were normal including a tourniquet test, which was negative at the time to the admission to the clinic.

Dengue virus serology, using standard MAC-ELISA IgM and IgG tests five days post initial symptoms, were negative. NS1 platelia test (Bio-Rad, Marnes-la-Coquette, France) was positive.

Three days following onset of the symptoms, the patient developed a rash and generalized petechiae. The patient was given supportive care and recovered completely after a week. Thrombocytes and leukocytes were not measured at a follow-up examination. Since there was no evidence of HCV involvement during the acute dengue infection, and because she did not voluntarily report the condition to the medical personnel, HCV tests were not performed at that time.

A frozen blood sample from this patient was examined retrospectively in a parallel study to identify different risk factors associated with hemorrhagic manifestations and liver involvement in primary dengue hemorrhagic cases. Positive PCR reactivity for HCV was noted using specific primers, as well detecting anti-HCV IgG antibody (Accutrack, Xiamen, China). Further studies based on envelope gene amplification demonstrated simultaneous active infection of HCV genotypes 1 and 4 (7).

Hepatitis C virus and dengue infection are serious public health concerns in Mexico. There are previous observations indicating a role of hepatitis coinfection exacerbating liver damage associated with dengue infection in adults, which greatly complicates the care given to these patients due to vascular leakage and bleeding. (8). In case of HCV chronic infection of the liver with fibrosis, it is known to be a risk factor to developed thrombocytopenia (2), resulting in production of antiplatelet antibodies, elevated liver enzymes and coagulopathies. This in turn, could severely affect one of the major coagulation systems of the body, increasing the risk of potential hemo-

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rhage during dengue infections. Since previous observations demonstrated that infection by HCV can result in similar hemorrhagic manifestations (9), infection with HCV should be considered an important risk factor in complicating primary dengue infections in the form of hemorrhagic manifestations in patients with liver involvement especially those with liver fibrosis and cirrhosis. In conclusion, these findings emphasize the need to determine whether dengue infection in patients chronically infected with HCV and with suspicion of liver damage could represent an unrecognized cause of disease severity in dengue endemic areas.

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### DISCLOSURE STATEMENTS

No competing financial interests exist for any of the authors.

### BIOETHICS DISCLAIMER

Research with human subjects has been carried according to the Ethical principles of Medical research based on the Helsinki declaration. The protocol was reviewed and approved by the Ethical Committee of Centro de Investigaciones Regionales Dr. Hideyo Noguchi (CIR), Universidad Autónoma de Yucatán, México

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