Case Report: Dengue Infection in a Human Immunodeficiency Virus-1 Positive Patient Chronically Infected with Hepatitis B Virus in Western Mexico


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Abstract. Human immunodeficiency virus (HIV) and dengue coinfection has not been extensively studied. We report herein a case of dengue serotype 1 infection in an HIV-1-positive patient coinfected with hepatitis B virus (HBV) in Colima State, Mexico. CD4+ cells and HIV-1 viremia remained at normal levels, and no severe complications were observed during this multiple viral infection. The alanine transaminase and aspartate transaminase values were elevated before and during dengue infection. Surprisingly, these parameters were significantly reduced 2 months later. Because of the lack of evidence regarding this multiple viral interaction, further research is required to understand the biologic and clinical course of dengue infection in HIV-1/HBV coinfected patients, especially in tropical regions where dengue virus transmission is highly active.

INTRODUCTION

Human immunodeficiency virus/hepatitis B virus (HIV/HBV) coinfection is common throughout the world. Previous reports have estimated that 10% of HIV-positive patients are coinfeected with HBV worldwide, which may accelerate progression of liver failure. Moreover, the interaction of HIV with other tropical agents is associated with accelerated HIV/acquired immunodeficiency syndrome (AIDS) disease progression. For example, malaria and HIV coinfection is related to CD4+ cell activation and an increase in the levels of proinflammatory cytokine expression. This enables rapid HIV-1 replication and a consequently accelerated progression of HIV/AIDS disease.

Dengue is a tropical and subtropical mosquito-borne disease. According to the World Health Organization, 2.5 billion persons are at risk for contracting dengue infection, resulting in an estimated incidence of 50–100 million cases per year worldwide. There are four different dengue virus serotypes (DENV-1 to 4) that cause infection. They are genetically different, but share similar epidemiologic behavior.

HIV/DENV coinfection has not been extensively studied. To date, six clinical reports have described the clinical presentations of dengue infection in HIV-1-infected patients. These reports suggest that HIV/DENV coinfection results in a benign clinical progression of dengue disease, as well as suppression of HIV-1 replication during the acute phase of dengue infection. Here in we report a case of DENV-1 infection in an HIV-1-positive patient chronically infected with HBV in Colima State, Mexico, an endemic tropical region for DENV transmission.

CASE REPORT

In 2009, a 52-year-old woman infected with HIV-1 and HBV was admitted to the Regional Hospital of Colima with clinical suspicion of dengue infection. Upon admission, the patient had 2-day progression of intermittent fever (> 38.2°C), intense headache (especially behind the eyes), fatigue, muscle and joint pain (ankles, knees, and elbows), and abdominal bloating. The patient was alert and oriented to person, place, and time, and her general condition was good. The conventional tourniquet test did not show the presence of capillary fragility (6 petechiae/in²). Physical examination was unremarkable, except for hyperemic oropharynx. On the 4th day, her state of health improved, fever disappeared, and she was asymptomatic. During this event, the patient continued to take highly active antiretroviral treatment (HAART; lamivudine, zidovudine, and efavirenz), and only oral acetaminophen 500 mg tablet every 8 hours was added to her management. Dengue diagnosis was confirmed through detection of the DENV NS1 antigen with the SD Bioline Dengue Rapid Duo Test® (Yongin-si, Gyeonggi-do, Republic of Korea), following the manufacturer’s instructions. The molecular identification carried out with reverse transcription polymerase chain reaction (RT-PCR) and automated sequencing at McLab (San Francisco, CA) showed the presence of DENV-1 strain DENV-1/MX/BID-V3664/2006 (GenBank no. GQ868499), with a similarity of 99%. Follow-up of the HIV viremia in the INDRE (Department of Health, Mexico) showed undetectable levels (< 40 HIV-1 RNA copies/mL) during dengue infection and 6 months after the multiple viral infection. Blood hematologic, viremia, and serum biochemical values before, during, and after dengue infection are shown in Table 1. The values before dengue infection were obtained from the medical records of the study patient. The chronicity of HBV infection was corroborated through serologic tests, and the patient was found to be positive for hepatitis B surface antigen (HBsAg) and anti-hepatitis B core (anti-HBc) and negative for IgM anti-HBc.

The patient voluntarily agreed to participate in this study, signing statements of informed consent, and it was approved by the Ethics Committee of the School of Medicine, University of Colima, and the Institutional Review Board of the Department of Health (Colima State, Mexico).

DISCUSSION

The high incidence of dual infections of HIV with other tropical agents is an important problem that requires...
special attention. The results presented herein (Table 1) suggest that there were no severe clinical complications during this multiple viral infection. CD4+ cells remained at normal levels during dengue infection. Despite the fact that there is presently no evidence about the clinical complications of dengue infection in HIV-1/HBV coinfected patients, previous reports have shown that HBV infection leads to an increase in liver failure in HIV-positive patients treated with HAART.\(^2,14\) Our results showed that alanine transaminase and aspartate transaminase hepatic enzyme values were high before dengue infection, due to the HBV infection. However, a slight increase during dengue infection was observed. After 2 months, the hepatic enzyme levels were normal (Table 1). Most certainly, dengue infection is associated with acute liver failure in both HIV-uninfected patients and HBV-infected patients,\(^15,16\) thus suggesting an alteration in cytokine production. This was supported by the observation of low levels of interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) in patients with dengue and HBV infection and similar levels of IL-10, IL-4, and interferon γ expression in both the group of dengue patients with HBV infection and the group without HBV infection.\(^17\) It is possible that the altered cytokine production profile plays an important role in regulating the inflammatory response,\(^18\) which could lead to an unpredictable clinical course and unknown progression of liver failure in patients infected with HIV, HBV, and DENV. At this point, it is unclear whether dengue infection results in accelerated liver failure progression in HIV/HBV coinfected patients. Our observations suggest that dengue infection did not cause significant liver damage, but a significant decrease in the levels of hepatic enzyme expression was observed 2 months after the multiple viral infection. We cannot explain this phenomenon, given the existing lack of evidence on this particular subject. Such information is crucial to the biologic and clinical understanding of this multiple viral infection, as well as its implications in liver failure progression. Therefore, further studies are required to understand the main role of dengue infection in HIV/HBV coinfected patients treated with HAART.

In regard to HIV-1/DENV coinfection, our results coincide with those previously reported in which no severe complications attributable to dengue infection were observed.\(^8-11\) This behavior is possibly due to the effect of HAART treatment, which could be protecting the patient against dengue; this is according to a previous report that suggests a decrease of hepatitis C disease progression associated with HAART treatment in HIV-1-infected patients in Thailand.\(^19\) Even though the effect of HAART treatment during dengue infection remains unknown, the attenuation of certain cytokines in HIV-1-infected patients treated with HAART, such as IL-10 and TNF-α, could play an important role in decreasing dengue disease progression in HIV-1-positive patients.\(^20,21\) Both IL-10 and TNF-α are strongly associated with severe dengue infection.\(^22\)

The HIV-1 viral loads in our patient remained at normal levels (< 40 HIV-1 RNA copies/mL) during DENV-1 infection and 6 months later. Watt and others\(^8\) have reported a reduction in the HIV-1 viral load in an HIV-1-positive patient without HAART treatment who presented with dengue infection in Thailand, and demonstrated that HIV-1 replication was suppressed during the acute phase of the infection. The antiviral mechanism involved has not been described, but previous reports\(^23-25\) have shown that DENV-1 and DENV-2 NS5 protein expression inhibits HIV-1 replication in Jurkat CD4+ T cells. This antiviral effect has been associated with an increase instromal cell-derived factor 1 (SDF-1) cytokine expression and a decrease in CD4 and CXCR4 expression.\(^24,25\) SDF-1 is the principal ligand for the co-receptor CXCR4 and blocks HIV fusion and entry into the CD4+ T cell.\(^26\) The fact that DENV NS5 protein expression could induce signaling pathway activation through the cell membrane should not be ruled out. This would produce a transcriptional modification, such as that occurs during SDF-1 cytokine overexpression. There is currently no evidence of such a phenomenon, but the NS3 protein of the hepatitis C virus (HCV) has been reported to have an affinity for a 14-amino acid immunodominant epitope of the CD4+ T cell. This could prevent the immune system attack, enhancing the efficiency of HCV replication and a consequent increase in disease severity.\(^27\) The analysis of the effect of DENV protein expression on HIV-1 replication would therefore provide necessary evidence for
understanding the mechanism by which the DENV interferes on HIV replication in T lymphocytes.

A limitation of the present study is the fact that the HBV viral load was not determined. We suggest that the viremia of all coinfecting agents should be measured in future studies on patients similar to ours to have a better understanding of the clinical course of the pathology.

In conclusion, our results showed no severe clinical complications during this multiple viral infection. No significant behavior of the HIV-1 viral loads was observed, because the patient was treated with HAART and the viral load remained undetectable. Although previous reports show evidence that tropical diseases can accelerate HIV/AIDS disease progression, our results showed that HIV-1 viral load levels apparently remained normal during the follow-up. Similarly, no side effects attributable to HBV infection were observed. However, there was a significant decrease in hepatic enzyme levels 2 months after dengue infection. Further studies with a greater number of patients are required. In addition, experimental studies evaluating the main role of dengue in HIV-1/HBV coinfected patients treated with HAART are needed. They could also explore its possible implications in the development of coadjuvant therapies for HIV/HBV coinfected patients, as well as new models enabling a more detailed study of the biology of these combined RNA viral infections.

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