Case Report

Hantavirus Pulmonary Syndrome Coexistent with Dengue

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ABSTRACT

Dengue is an arthropod-borne disease caused by viruses of *Flaviviridae* family. It poses a major public health burden in tropical and sub-tropical regions. Clinical features of dengue vary from a mild flu-like disease and rash, to a potentially lethal haemorrhagic fever or shock syndrome. Hantavirus pulmonary syndrome is a rodent-born disease emerging in the American continent and is caused by viruses of the *Bunyaviridae* family. Potential reservoirs of these agents were described in Brazilian Central Plateau. Dengue infection is transmitted by mosquitoes, while hantaviruses are acquired by contact or inhalation of aerosolised excreta of infected rodents. Dengue and hantavirus infections have also been considered as emerging public health problems in some Indian areas; moreover, other infections mixed with dengue have been documented. The case of a Brazilian patient with hantavirus pulmonary syndrome and serologic evidence of dengue infection is described.
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Key words: Co-infection, Dengue, Hantaviruses, Hantavirus pulmonary syndrome.

INTRODUCTION

Hantavirus pulmonary syndrome (HPS) is an emerging disease caused by agents of *Bunyaviridae* family and carried by rodents of subfamily *Sigmodontinae*, and constitutes an important public health problem in the new world. In the vast majority of cases, HPS follows infections by close contact or inhalation of aerosolised excreta of the reservoir rodents; although possible, person-to-person transmission is very rare. Recently, HPS was reported in a male patient infected at periphery area of Brasilia-DF.[1]

Dengue is one of the main tropical diseases. This mosquito-borne illness is caused by viruses of *Flaviviridae* family, that has increased in importance among public health challenges in urban and semi-urban areas of developing countries.[2] Dengue epidemics as well as human hantavirus infections have been described in India; [2-4] moreover, other infections mixed with dengue have also been documented in overlapping endemic areas.[2,5-8] Co-infections can be under-appreciated because of similar clinical or laboratory data. We present a case of dengue co-infections with HPS to increase the awareness of the possibility.

CASE REPORT

A 48-year-old male was attended in another hospital in June 2009, presenting with high fever, headache, arthralgia, myalgia, abdominal pain, and absence of skin rash. Analgesics were prescribed and he returned to home. About 48 hours later, because of symptoms persistence, fever and fainting, he was transferred to the Emergency Department and soon admitted to the intensive care unit of our hospital. He was previously healthy and non-alcoholic, but was a cigarette smoker (pack-years: 46) and had a body mass index (BMI) of 35kg/m^2. He lived in the Brasilia-DF urban region and denied recent permanence in rural or forest environments. He had signs of severe sepsis with hypotension, acute renal failure, metabolic acidosis and was in respiratory distress with cyanosis. He was mechanically ventilated and administered fluids, antibiotics (imipenem plus metronidazole), iontropes, diuretics and enoxaparin. He had thrombocytopaenia and was transfused cryoprecipitates, platelet concentration and fresh plasma. Computed tomography of the chest showed bilateral alveolar and interstitial opacities in the perihilar and peribronchovascular regions, accentuated bilateral pleural effusion, while the heart

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area was within the normal limits (Figure A to D). Later vancomycine was added in place of metronidazole. With this treatment, the patient was recovered and entubated on the seventh day. The patient was discharged to the clinical ward, with improvement in general condition, except for residual signs of right-sided pleural effusion, and mild oedema in lower extremities.

The plasma levels of the aminotrasferases, CK and CKMB persisted elevated. After two weeks, blood samples were taken for serologic tests (hantavirus, dengue and leptospirosis). Evidence of dual infection with dengue virus and hantavirus was observed with seroconversion in acute phase of febrile illness (positive dengue vírus immunoglobulin (Ig)-M and negative IgG by immunochromatography (WAMA Diagnóstica, São Carlos-SP, Brazil), and positive (ANDES virus) hantavirus IgM capture enzyme linked immunosorbent assay (ELISA) Instituto Adolfo Lutz, São Paulo-SP, Brazil). Leptospira infection was ruled out by negative IgM/IgG specific immuno-enzymatic assay (Central Laboratory of Health, LACEN-DF, Brazil). Serologic tests for syphilis and human immunodeficiency virus (HIV)-1/HIV-2 infections were negative. Investigations for viral hepatitis were not remarkable, except for anti-HAV IgG, that was positive. Hemocultures were negative. The electrocardiogram (ECG) was normal, and urinalysis was unremarkable. **C**hest radiography now revealed normal features (Figure E and F). He was discharged to outpatient surveillance entirely asymptomatic; however, there was anemia, and the levels of liver and muscle enzymes persisted slightly elevated.

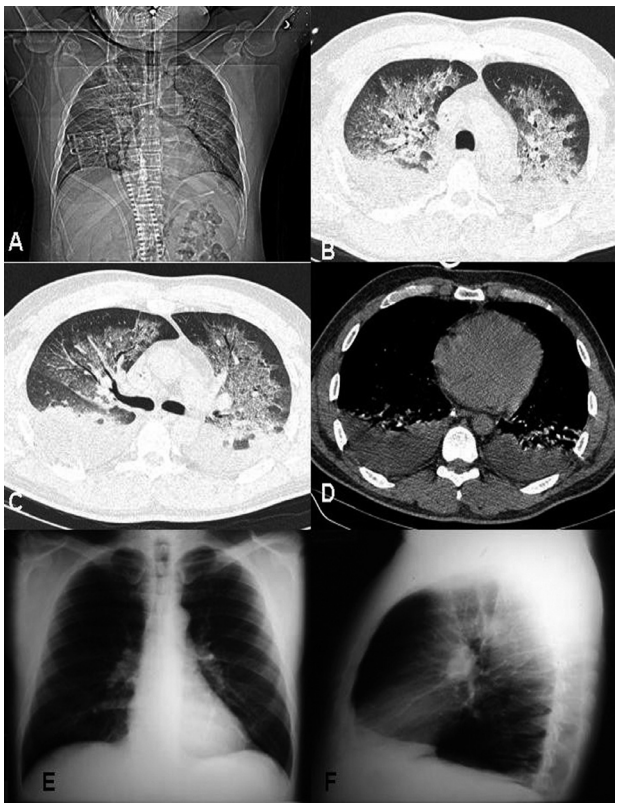

Figure. (A) Digital chest radiography showing bilateral alveolar and interstitial opacities in perihilar and peribroncho-vascular regions; (B) and (C) chest CT images at aortic and carina levels showing bilateral peribronchovascular opacities, and inspissation of septal and intralobular interstitium; (D) bilateral pleural effusion on CT; (E) and (F) normal findings showed on the chest radiograph on recovery

After about a two-month follow-up, laboratory control tests had normal results, including haemoglobin, liver and muscle enzymes. A positive dengue virus IgG was also detected in the patient blood samples taken during the convalescent phase of his disease. At present, the patient is under routine ambulatory surveillance, in a good health and continuing his normal activities with no restriction.

DISCUSSION

Association of dengue with protozoan, bacterial, and other viral infections have been rarely described.[2,5-8] *To the best of our knowledge, the present report is the first communication about dengue-hantavirus co-infection detected in our country.* Notwithstanding, the initial concern about eventual dengue false-positive reaction, as more definitive tests (virus isolation and the specific reverse transcriptase-polymerase chain reaction [RT-PCR]) were not available due to high costs as in most of the developing countries.[9,10] Moreover, Behera *et al*[2] described a patient with co-infections (including dengue, leptospira and hepatitis-E), in which both dengue virus isolation and RT-PCR were negative, while dengue IgM was positive. Therefore, many dengue co-infections previously reported were confirmed by positive dengue-specific IgM.[2,5,7,8] Abbasi *et al*[5] reported 26 cases (23.21%) of dual dengue and malaria infection among 114 patients studied in Karachi. The authors utilised serologic data (positive dengue-specific IgM) as unique criteria to confirm the diagnosis of dengue infection.[5] Chai *et al*[6] studied nearly 4,000 cases of dengue admitted in a Singaporean hospital, and described concurrent *Staphylococcus aureus* bacteremia in five patients. The authors commented that bacterial blood cultures are not routinely done in viral illnesses, and speculated the possible role played by dengue in predisposition to other infections. In addition, fever lasting more than a week was emphasised as a clue for search for co-infections.[6] Dual infection with dengue virus and HIV was reported in two Cuban patients, and dengue was also confirmed by the detection of dengue-specific IgM (MAC-ELISA). The authors commented about possible under appreciated co-infections due to overlapping of endemic dengue regions and HIV high

incidence areas. They also hypothesised about immunopathological interactions during dengue and HIV co-infection.[8]

Additional concern could be about the absence of rash in the present case. In fact, skin changes can provide useful clues for differential diagnosis in patients with dengue. However, as in Brazilian patients, cutaneous manifestations have been decribed in less than 50% of Indian patients with dengue;[9] and may be absent in individuals presenting dengue with diverse concurrent infections, as well.[2,6,8]

Our patient had clinical and serological evidence of HPS, concurrent with the detection of dengue-specific IgM. The serologic investigations followed the same methodology applied in our recent report about HPS;[1] additionally, the epidemiological and clinical features were similar. Although the management of non-cardiogenic pulmonary oedema required endotracheal intubation and mechanical ventilation, he improved rapidly and the outcome was good.

Occurrence of acute renal failure, leukocytosis, low platelets, and hemoconcentration, in addition to changes in liver and muscle enzymes as in our case must be distinguished from other febrile illnesses (OFI) in endemic areas, including haemorrhagic fever with renal syndrome, leptospirosis, and severe dengue infection.[1,10] Serologic data ruled out leptospirosis and hepatitis and confirmed HPS and dengue.[2,5,7,8]

Frequently, studies performed in endemic regions do not follow a consensual algorithm to differential diagnosis of dengue, and the origin of OFI remains unclear.[10] Although different transmissible diseases are prevalent in overlapping areas with endemic dengue, the occurrence of dual infections has been very rarely reported.[2,5-8] One possible explanation could be the difficulty in distinguishing between clinical features and laboratory changes respectively caused by other agents and due to dengue infection. Considering that concurrent infections might be under appreciated or under reported, the authors believe that case studies may increase the suspicion index of health workers about co-infections,[2,5-8] especially in less typical cases that may otherwise be neglected.[1,10] High suspicion index constitutes the first step to elaborate diagnosis algorithm.

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