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CASE REPORT

DENGUE HEMORRHAGIC FEVER AND ACUTE RESPIRATORY DISTRESS SYNDROME

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ABSTRACT

Dengue fever is one of the major public health problems in the tropical countries and the adjacent subtropics. Dengue hemorrhagic fever (DHF) is a serious form of this disease. As this infection is becoming more and more common, the incidence of unusual presentations associated with dengue hemorrhagic fever is increasing. Except for the pleural effusions, pulmonary manifestations are highly unlikely in this disease. Acute respiratory distress syndrome (ARDS) in DHF is very rarely reported in the medical literature. We report a case of 19 year old female with DHF who presented with acute onset of breathlessness which was diagnosed to be due to ARDS according to the Berlin definition. After ruling out almost all possible causes of ARDS in this female, dengue hemorrhagic fever (DHF) was considered as the cause of this complication. The need of the hour is to make the medical practitioners in dengue fever endemic areas aware of this atypical complication of DHF so that proper diagnostic and treatment steps can be taken at the earliest possible convenience and the lives of such patients can be saved.

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INTRODUCTION

Dengue is a mosquito borne infection which is endemic in the tropics and the adjacent subtropics (Murray *et al.*, 2013). This viral hemorrhagic fever has humans and monkeys as the host reservoirs (Weaver, 2005). Human race is possibly aware of the deadly nature of this arboviral infection since 265 – 420 AD during which the people of Chin Dynasty had symptoms compatible with dengue fever (Gubler, 1998). Today, this infection affects around 200 million people annually and is keeping 2.5 billion people at risk. With 500 thousand hospitalizations each year, its severe form causes the death of over 20 thousand people annually (Murray *et al.*, 2013). The severe forms of dengue fever are the dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) manifesting as fluid accumulation, plasma leakage, severe hemorrhage or multi-organ involvement (Maria *et al.*, 2013; Jain *et al.*, 2014). The common complications of these severe forms of dengue are encephalitis, acute liver and renal failure, myocarditis,

Guillain-Barre syndrome, hemophagocytic syndrome and lupus erythematosus (Gupta *et al.*, 2012). Acute respiratory distress syndrome associated with dengue virus infection has not been widely reported in the literature.

The first such case was reported in 1999 (Sen *et al.*, 1999). We report a case of ARDS complicating severe dengue.

Case Report

A 19 years old female presented in emergency department of Capital Development Authority (CDA) Hospital with high grade fever associated with rigors and chills, severe retro-orbital pain, myalgia, skin rash and itching all over the body for last 5 days. She was taking medications prescribed to her by a local general practitioner who then referred her to the Capital Hospital on account of her shortness of breath for 1 day. She was irritable and unable to complete sentences while speaking. Her previous medical, surgical, family, socioeconomic, menstrual and allergic history was unremarkable.

On examination, she had tachycardia (PR = 120 bpm) and hypotension (Blood pressure = 90/50 mm Hg). Her temperature

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and respiratory rate were recorded as 101°F and 40/minute, respectively. Her oxygen saturation was 86% at the time of admission to hospital. Crepitus were present all over the chest along with petechiae on both arms but there was no neurological deficit. She was immediately intubated and put on a ventilator in the intensive care unit (ICU) of the hospital. A series of laboratory studies revealed leukopenia, thrombocytopenia and proteinuria. Blood complete picture showed hemoglobin 11.5gm/dl, total leukocyte count 3000/cmm, lymphocytes 40%, platelet count 73000/cmm and ESR 15. Chest x-ray PA view showed bilaterally diffused infiltrates with sparing of costophrenic angle. Arterial blood gases (ABG'S) revealed PO₂:FiO₂ <200mmHg. Serum fibrinogen degeneration products were increased. Echocardiography was absolutely normal. Alanine aminotransferase (ALT) level was 70 IU/L while Aspartate aminotransferase (AST) was 57 IU/L. The urine examination showed proteinuria.

Activated partial thromboplastin (APTT) was 40 seconds (Ref. range 33 Seconds) and Prothomin time (PT) was recorded as 24 seconds (Ref. range 13 Seconds). NS1Ag was positive, which confirmed diagnosis of dengue fever. Acute respiratory distress syndrome (ARDS) secondary to dengue fever was suspected which was confirmed when other causes of ARDS were ruled out by various laboratory tests. These included the normal hepatitis serology, blood culture, urine culture, typhidot, MP smear, renal function test (RFT'S), antibodies to leptospira and ultrasound of abdomen and pelvis.

Next day of admission her investigations revealed serum creatinine 2.1mg/dl, serum urea 105 mg/dl, Alanine aminotransferase (ALT) 120 IU/L, Aspartate aminotransferase (AST) 97 IU/L, Activated partial thromboplastin (APTT) 70 sec and Prothomin time (PTT) 36 sec. Serology revealed positive IgM against dengue virus antigen. She developed multi-organ failure even with close monitoring and vigorous supportive treatment. She was managed with fluid resuscitation, antibiotics and fresh frozen plasma for correction of coagulopathy. Her condition did not improve and finally she succumbed to her illness.

DISCUSSION

Dengue fever is caused by dengue virus, a member of flaviviridae (Leyssen *et al.*, 2000). The principle vector is the *Aedes aegypti* mosquito (Scott, 2010). Infection may range from asymptomatic seroconversion to symptomatic dengue fever or DHF/DSS, the more severe forms (Rajapakse, 2011). The high fever, bleeding manifestations usually with the hepatomegaly and circulatory failure characterize the DHF (Tsai *et al.*, 2013). Its distinctive laboratory finding is mild-to-moderate thrombocytopenia along with concurrent hemoconcentration (Kabra *et al.*, 1999). An acute increase in vascular permeability leading to leakage of plasma into the extra vascular compartment is the major pathophysiological change that is useful in determining the severity of disease in DHF and to differentiate it from dengue fever (Devarajan *et al.*, 2008). The resulting hemoconcentration and decreased blood pressure is thought to be histamine and cytokine mediated (Setlik *et al.*, 2004; Gubler, 1998). It thus, manifests as elevated hematocrit, hypoproteinemia or serous effusion

(Handbook for clinical management of dengue, 2012). Our case was diagnosed as DHF according to the World Health Organization criterion.

Case definition for dengue hemorrhagic fever: the WHO criteria (Handbook for clinical management of dengue, 2012)

The following must all be present:

1. Fever or history of acute fever, lasting 2 - 7 days, occasionally biphasic.
2. Hemorrhagic tendencies, evidenced by at least one of the following:
 - a positive tourniquet test
 - petechiae, ecchymoses or purpura
 - bleeding from the mucosa, gastrointestinal tract, injection sites or other locations
 - hematemesis or malena
3. Thrombocytopenia (100,000 cells per cu mm or less).
4. Evidence of plasma leakage due to increased vascular permeability, manifested by at least one of the following:
 - a) A rise in the hematocrit equal to or greater than 20% above average for age, sex and population;
 - b) A drop in the hematocrit following volume replacement equal to or greater than 20% of baseline
 - c) Signs of plasma leakage such as pleural effusion, ascites, and hypoproteinaemia

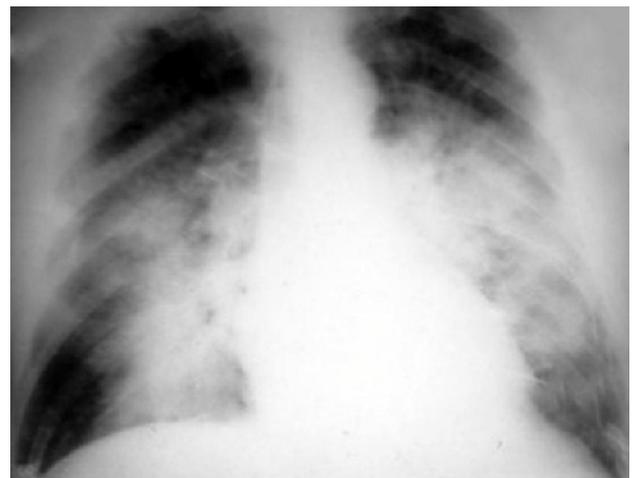


Figure 1. X-ray showing ARDS (which showed bilateral diffused infiltrates with sparing of costophrenic angle)

Confirmation of the diagnosis is by Polymerase Chain Reaction (PCR) or serology (Chua *et al.*, 2011). Symptomatic management is the only way of improving the condition of such a patient (Rajapakse *et al.*, 2012). Acute respiratory distress syndrome (ARDS) is characterized by pulmonary edema caused by the increased permeability of alveolar capillary barrier (Matthay and Zimmerman, 2005). This manifests clinically as acute hypoxemic respiratory failure and arises as a complication of a widespread systemic response to the acute injury or inflammation (Matthews and Noviski, 2001). The precipitating factors include conditions ranging from direct injury such as aspiration, diffuse infection to indirect injury like sepsis or non-thoracic trauma (Ware and Matthay, 2000; Wyncoll and Evans, 1999). Almost all infectious agents have been reported to trigger ARDS (viruses, bacteria, fungi and parasites) (Sheu *et al.*, 2010). To diagnose

ARDS and establish its cause, complete clinical evaluation is required. Besides treating the primary causative agent, it is managed by ventilator and hemodynamic support (Matthay and Zeman, 2011).

Dengue virus is not known to be a well known cause of ARDS. In our case, a diagnosis of ARDS was made on the basis of respiratory distress within 1 week of dengue fever, chest X-ray findings, which showed bilateral diffused infiltrates with sparing of costophrenic angle (Figure-1), normal echocardiographic findings, and arterial blood gases (ABG'S), which revealed PO₂:FiO₂ <200mmHg. This was in accordance with the Berlin definition of ARDS (Fanelli *et al.*, 2013). Our patient had acute breathlessness and was treated as ARDS but the patient was having extreme morbidity as a result of this critical complication of DHF and finally died. In the absence of any other cause identified, we concluded that DHF was the cause of acute respiratory distress syndrome in this patient.

Conclusion

Severe dengue in both forms (DHF/DSS) is a fatal illness. Although, many atypical presentations of Dengue Fever have been documented in medical literature, but ARDS still remains an unusual and a deadly complication of Dengue Fever. However, if immediate attention is taken in diagnosis of the complications by imaging and laboratory tests and extreme suspicion, there are chances that the patient can be saved from damage by its fatal complications. The need of the hour is to make the medical practitioners in dengue fever endemic areas aware of this atypical complication of DHF so that proper diagnostic and treatment steps can be taken at the earliest possible convenience and the lives of such patients can be saved.

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