登革熱併發急性肝炎和急性呼吸窘迫症候群—案例報告

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摘要

登革熱是最流行的蚊蟲媒病感染，全世界每年發生超過 3.9 億例登革熱感染。登革熱病毒感染的表現形式廣泛，從高熱病到登革出血熱或登革熱休克綜合徵。也描述了涉及心臟，肝臟，中樞神經系統和肺部的非典型表現。在這裡，我們報告一嚴重的登革熱伴急性肝炎和急性呼吸窘迫綜合徵之案例。一名 76 歲的女性入院 10 天，出現發燒，血小板減少症，肝功能指數升高，肝性腦病變，急性腎功能衰竭和急性呼吸困難，被診斷為急性呼吸窘迫綜合徵。由於頑固性休克和多重器官功能衰竭，她的病情隨後惡化並最終死亡。我們回顧了有關急性肝炎和急性呼吸窘迫綜合徵的登革熱病毒感染的文獻。

關鍵詞：登革熱； 急性肝炎； 急性呼吸窘迫綜合徵

Acute Hepatitis and Acute Respiratory Distress Syndrome Complicated in Dengue Fever: A Case Report

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Abstract

Dengue fever is the most prevalent arboviral infection with more than 390 million dengue infections throughout the world annually. Dengue virus infections have a wide range of manifestations from febrile illness, dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) to atypical manifestations related to hearts, livers, central nerve systems or lungs. Here, we report a case of severe dengue fever with acute hepatitis and acute respiratory distress syndrome (ARDS). A 76-year-old female was admitted for 10 days. She developed fever, thrombocytopenia, liver function elevation, hepatic encephalopathy, acute renal failure and acute breathlessness. She was diagnosed to be ARDS. Her condition deteriorated and eventually died due to refractory shock with multiple organ failures. We review the literature on dengue virus infections with acute hepatitis and ARDS.

Keywords: Dengue Fever, Acute Hepatitis, Acute Respiratory Distress Syndrome

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I. Introduction

Mosquito-borne diseases remain a major cause of morbidity and mortality across the tropical regions and arboviruses-most notably dengue-are responsible for a rising burden of disease[1] . Dengue fever is the most prevalent and rapidly spreading mosquito borne viral illness transmitted by Aedes mosquito in the world. Recently, it has been estimated that more than 390 million dengue infections occur each year throughout the world[2]. The dengue infections could have diverse clinical symptoms, ranging from asymptomatic infection to dengue fever, dengue hemorrhagic fever (DHF), or dengue shock syndrome (DSS). Unusual manifestations have been described such as hepatitis, myocarditis, encephalitis, and acute respiratory distress syndrome (ARDS). Acute hepatitis due to dengue infection is not uncommon. However, dengue fever is rarely considered as a cause of acute liver failure. ARDS is a heterogeneous clinical syndrome comprising of severe hypoxemia and decreased lung compliance caused by inflammatory lung injury that leads to increased pulmonary vascular permeability. Dengue fever presenting with ARDS has not been reported widely. Here, we report a case of dengue hemorrhage fever with acute fulminant hepatitis and severe ARDS.

II. Case

A 76- year- old female, resident of Tainan city presented to our emergency department with three day history of fever, myalgia with bone pain, and abdominal discomfort with vomiting. She had a past medical history of hypertensive cardiovascular disease with regular medication control. The patient had normal vital signs at emergency department but some skin rash over both legs noted. She denied any tarry stool or bloody stool passage or coffee ground substance vomitus. The laboratory tests revealed thrombocytopenia (platelet count: 54x103/ uL) and deranged liver functions [aspartate transaminase (AST): > 2500 U/L; alanine transaminase (ALT): >1200 U/L; Bilirubin T: 2.72 mg/dl; Bilirubin D: 1.91 mg/dl]. Dengue NS1 antigen was tested and revealed positive and dengue RT-PCR test also showed positive. Under the impression of severe dengue fever with impairment of liver function, the patient was immediately admitted to intensive care unit. Liver function test deteriorated (AST: 7881 U/L; ALT: 2721 U/L; Bilirubin T: 3.26 mg/dl; Bilirubin D: 2 mg/dl; Ammonia: 73 umol/L) with progressive conscious disturbance (GCS: E1V2M4 at illness day 6). Non-invasive ventilation by bi-level positive airway pressure (BIPAP) was used due to desaturation of arterial blood gas and reduced ventilator effort two days after admission to the hospital. Abdominal sonography showed an increased echogenicity of the liver parenchyma, a gallbladder stone but no evidence of common bile duct or intrahepatic ducts dilation and there was no ascites present. Diagnostic approach to patient with acute viral hepatitis including Anti-HAV IgM, Anti-HCV, and HBsAg revealed negative. Bacterial pneumonia was suspected because of leukocytosis (WBC count:10.9x103/ uL), elevation of C-reactive protein (CRP: 71.3 mg/L), elevation of Procalcitonin (PCT: 0.73 ng/ml) and x-ray of chest showing new infiltrates at bilateral lower lung fields. Extended- spectrum antibiotic treatment with piperacillin-tazobactam was administered intravenously for suspicious of dengue virus co-infection with bacterial pneumonia. However, three sets of blood and sputum cultures were tested, but showed only normal mixed flora in sputum specimens and negative in blood samples. Three days after admission, coffee ground vomitus drained from nasogastric tube and proton-pump inhibitor (PPI) infusion therapy was used. Renal function deterioration, shock, and desaturation of arterial blood gas developed despite BIPAP using on the seventh day after admission. Therapies with continuous veno-venous hemofiltration, vasopressors, and intubation with mechanical ventilation were applied. ARDS developed with x-ray of chest revealed bilateral diffuse infiltrates (Figure 1), PaO2/FiO2 ratio < 200 (Table 1), and decrease lung compliance. Ventilator setting with low tidal volume and high positive end expiratory pressure (PEEP) was initiated. Nevertheless, profound shock progressed despite high dose vasopressors and the patient expired on tenth day after admission.

Table 1 Labortory test results of the severe dengue patient, according to the day of illness

	Day 4	Day 5	Day 6	Day 7	Day 9	Day11	Day13	Day14
AST (U/L)	2,563	5,039	7,881	6,431	4,715	2,384	705	-
ALT (U/L)	1,230	2,197	2,721	2,493	1,752	1,057	419	-
Total bilirubin (mg/dl)	2.72	3.01	3.26	4.08	7.04	10.05	11.56	-
Direct bilirubin (mg/dl)	1.91	2	-	-	5.23	7.69	8.35	-
Ammonia (umol/L)	-	-	73	-	74	-	-	-
Albumin (g/dl)	3.1	-	-	-	2.4	-	2.1	-
BUN (mg/dl)	16	-	-	33	57	83	-	-
Creatinine (mg/dl)	0.76	-	-	1.58	4.92	8.56	-	-
CRP (mg/L)	71.3	-	-	-	144	-	108.8	-
Leukocytes (x103/uL)	10.9	9.3	-	-	10.9	-	13.7	-
Hgb (g/dL)	11.8	11.1	10.6	10.1	9.7	-	5.7	-
Hct (%)	33.2	-	29.6	28.9	28	-	-	-
Platelets (x103/uL)	56	56	59	56	67	72	55	-
INR (InR)	1.76	-	1.4	-	1.44	-	-	-
ABG base excess	-1.5	-	-	-6.9	-6.8	-10.8	-3.4	-4.0
P/F ratio	-	-	-	-	-	237	132	82.8

AST: aspartate aminotransferase; ALT: alanine aminotransferase; BUN: blood urea nitrogen; CRP: C-reactive protein; Hgb: hemoglobin; Hct: hematocrit; INR: international normalized ratio; ABG: arterial blood gas; P/F ratio: PaO2/FiO2 ratio

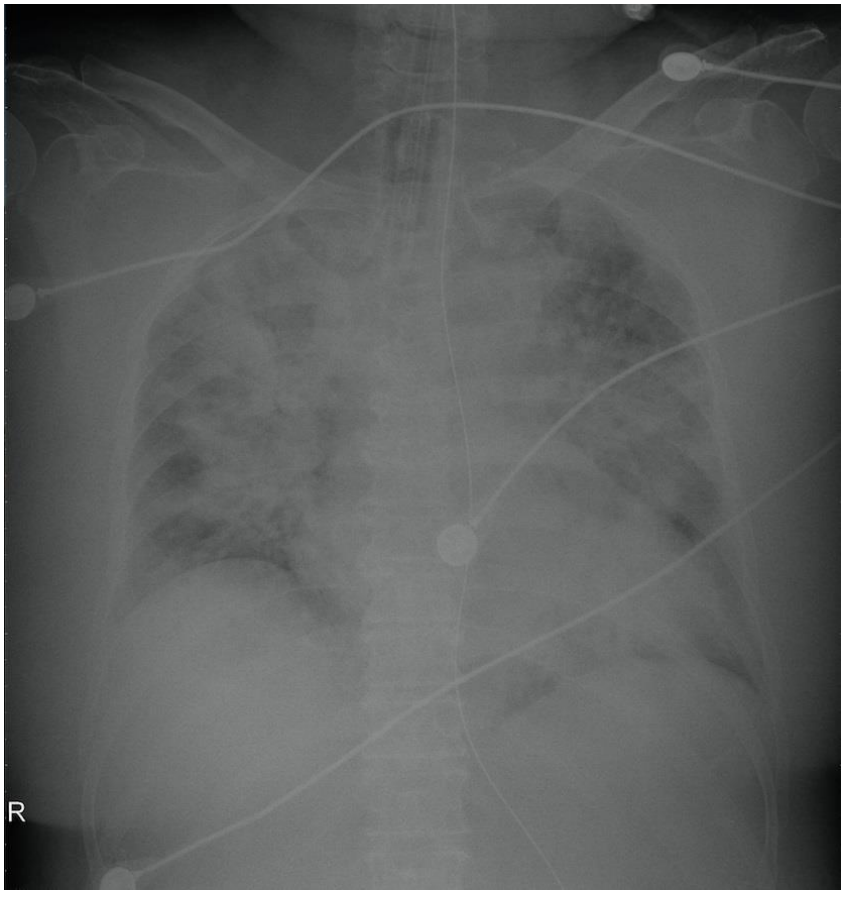

Fig.1 X-ray of chest showing bilateral diffuse infiltrates suggestive of ARDS

III. Discussion

The World Health Organization (WHO) classified symptomatic dengue virus infections into three categories: undifferentiated fever, classic dengue fever (DF), and dengue hemorrhagic fever (DHF) before 2009. However, these categories have been criticized for some reasons and the WHO Special Program have adopted a revised classification of "dengue" and "severe dengue"; "severe dengue" is applied to patients who show severe plasma leakage, severe hemorrhage, or severe organ impairment, similar to the clinical presentation of this patient. There is no specific therapy currently available for dengue virus infections, however early recognition of severe dengue and management of significant bleeding, plasma leak, shock, and vital organs support are important for patient survival.

ARDS is a life threatening critical condition characterized by hypoxemia respiratory due to increased permeability of alveolar capillary membrane related pulmonary edema, and stiff lungs[3–4]. Severe dengue could cause plasma leakage syndrome, pleural effusion, and ascites. Soluble NS1 protein, which can be detected in the serum during acute infection, has been reported to activate cells through toll-like receptor 4 signaling and to induce endothelial permeability and disrupt the glycocalyx[5–6]. However, ARDS in adult has not been well known caused by dengue virus[7] . In our case, a diagnosis of severe ARDS was made on the basis of chest x-ray findings of bilateral opacities, the PaO2/FiO2 ratio < 100 on ventilator settings that include a PEEP > 5 cmH2O and the respiratory distress of patient cannot be fully explained by cardiac failure or fluid overload, in accordance with the Berlin definition of ARDS[8] . Treatment of ARDS consists of hemodynamic support and ventilator setting of low tidal ventilation except treating the primary causing agent. Evidence suggests that the early application of low tidal volume ventilation improves mortality in patients with ARDS[9–10]. However ARDS is still associated with high mortality, with estimates ranging from 26 to 58 percent[11–12] . We added sedative agents and began protective lung strategy with low tidal (4-6 ml/kg) soon after ARDS developed; however, her condition still rapidly deteriorated and died.

Liver function tests have been frequently modestly (2 to 5 times the upper limit of normal values) elevated in both adults and children with dengue virus infection, but marked elevations are seldom noted[13–14] . It is different from conventional viral hepatitis, the level of AST is higher than that of ALT in dengue fever; and it has been suggested that the cause may be the excess release of AST from damaged myocytes involved by dengue infections[15]. However the pathogenic mechanisms of interaction between liver cells and dengue virus are not yet elucidated. The dengue virus can have a direct effect on hepatocytes stimulating apoptosis and microvascular steatosis or a consequence of dysregulated immune response in host against the virus[16–17] . In fetal cases of dengue related hepatitis, histological findings include fatty change with or without focal hemorrhage, mononuclear cell infiltration in the portal tract and necrosis of hepatocytes and Councilman-Rocha Lima bodies[18–19] . Fulminant hepatitis occasionally occurs in dengue fever. In our patient, the diagnosis of acute hepatitis caused by dengue virus was based on marked liver enzyme elevations and jaundice. Progressive conscious disturbance and elevated ammonia were highly suggestive of hepatic encephalopathy and it occurred within 8 weeks of acute hepatitis; However, there was co-infection of pneumonia which may contribute to conscious disturbance. The diagnosis of fulminant hepatitis caused by dengue fever could not be completely confirmed in this patient. Mortality with acute hepatitis was higher in those with thrombocytopenia, bleeding disorder, respiratory failure and circulatory failure, like the clinical presentation of this patient.

IV. Conclusion

Dengue hemorrhagic fever is characterized by high fever, thrombocytopenia with hemorrhagic manifestation and shock syndrome. However, recently the reports of rare manifestations of liver, renal, encephalopathy and

ARDS have become more common and carry high mortality rate. In the absence of any other pathogen /cause identified, we believe that acute hepatitis and ARDS in this case were caused by severe dengue fever. We suggest that clinicians should be made aware of unusual complications with high mortality of dengue fever.

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