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Case report

Acute myocarditis in dengue hemorrhagic fever: a case report and review of cardiac complications in dengue-affected patients

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SUMMARY

We report a case of dengue hemorrhagic fever (DHF) complicated by acute myocarditis and review the literature. A 65-year-old woman experienced DHF due to dengue virus serotype 3, complicated with acute myocarditis and acute pulmonary edema. Clinically this masqueraded as acute myocardial infarction, with an electrocardiographically depressed ST segment in precordial leads and elevated serum cardiac-specific troponin I level. Under supportive management, the patient recovered 3 days later. A total of 18 pertinent articles involving 339 dengue-affected patients with cardiac complications were found by PubMed search. Clinical manifestations of cardiac complications varied considerably, from self-limiting tachy–brady arrhythmia to severe myocardial damage, leading to hypotension and pulmonary edema. Although rare, a fatal outcome was reported in some cases of dengue with cardiac complications. To avoid otherwise preventable morbidity and mortality, physicians should have a high index of suspicion for cardiac complications in patients with dengue illness and should manage this accordingly.

1. Introduction

Dengue is one of the most important mosquito-borne viral diseases in the world.[1] Clinically, a non-specific afebrile illness, a mild-form dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) are commonly encountered in dengue epidemics. Of note, a variety of cardiac complications have been reported in dengue-affected patients,[2–8] which include atrioventricular conduction disorders,[5] supraventricular arrhythmia,[6] and myocarditis.[7,8] During a dengue outbreak in southern Taiwan in 2006, among 107 patients with dengue illness admitted to Chang Gung Memorial Hospital-Kaohsiung (CGMH-KS; a 2500-bed facility serving as a primary care and tertiary medical center), one was found to be complicated with acute myocarditis and acute pulmonary edema. We report this case, review the literature, and discuss the implications of cardiac complications in dengue patients. A better understanding of cardiac complications will potentially improve the treatment of dengue illness by avoiding otherwise preventable morbidity and mortality in the affected patients.

2. Case report

A 65-year-old woman presented to the emergency department of CGMH-KS because of a 3-day fever, malaise, and bleeding gums. She did not have any systemic disease, nor did she have a family history of cardiovascular disease. Upon arrival, her ear temperature was 39.8 °C, pulse rate (PR) 119/min, respiratory rate (RR) 20/min, and blood pressure (BP) 150/80 mmHg; her body weight was 52 kg, and multiple petechiae were found on bilateral legs. Laboratory data disclosed that her peripheral white cell count was 10.7×10^9/l (normal range $3.9–10.6 \times 10^9$/l) with 61% polymorphonuclear cells, hemoglobin 14.5 g/dl (normal range 12–15 g/dl), hematocrit 42.4% (normal range 35–45%), platelet count 11.0×10^9/l (normal range $150–400 \times 10^9$/l), prothrombin time 10.2 s (control, 10.6 s), activated partial thromboplastin time (aPTT) 71.4 s (control, 30.2 s), aspartate aminotransferase (AST) 2016 U/l (normal value <40 U/l), alanine aminotransferase 947 U/l (normal value <40 U/l), and albumin 2.3 g/dl (normal range 3.0–4.5 g/dl). A chest radiograph disclosed normal lungs and a slightly enlarged heart size with a cardiothoracic ratio (CTR) of 0.65 (normal value for adults <0.5).[9] Clinical examination and history taking did not reveal any signs and/or symptoms suggestive of heart failure. A tentative diagnosis of DHF was made based on the findings of fever, bleeding gums, and petechiae, thrombocytopenia

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($<100 \times 10^9$/l), and hypoalbuminemia.[10] Intravenous fluid supplementation with 0.9% normal saline infused at a rate of 2 ml/h/kg was started. Twelve units of platelets (50 ml/per unit) were transfused for thrombocytopenia, and 3 units of fresh frozen plasma (125 ml/per unit) were infused daily for three successive days for coagulopathy.

Despite a high fever (ear temperature 39.3 °C), the normal saline infusion was reduced to a rate of 0.4 ml/h/kg 17 h after her arrival because of stable vital signs (BP 121/63 mmHg; PR 80/min; RR 17/min). Her condition remained uneventful until day 3 when her blood pressure dropped abruptly to 78/51 mmHg, coupled with a PR of 119/min. After intravenous fluid challenge with 800 ml normal saline, her blood pressure was increased to 100/67 mmHg with PR of 88/min. An inotropic agent was not administered. Her urine output was not recorded. Because of relative hypotension and persistent fever (ear temperature 38 °C), cefazolin and gentamicin were parenterally administered after blood sampling for culture.

The patient experienced sudden onset of chest pain and shortness of breath 22 h after the emergence of hypotension. On examination, she was conscious but febrile (ear temperature 38.1 °C), with a PR of 98/min and a BP of 134/95 mmHg. Auscultation revealed coarse rales throughout her chest. A follow-up chest radiograph showed progressive cardiomegaly (CTR was 0.79), perihilar haze, and congestion over bilateral lower lung fields, suggestive of pulmonary edema. The total volume of intravenous fluid supplement and transfused blood components was estimated to be 5000 ml thus far. Intravenous fluid was immediately discontinued. Laboratory data revealed that her peripheral white cell count was 16.8×10^9/l, hemoglobin 11.0 g/dl, hematocrit 32.3%, platelet count 80×10^9/l, aPTT 39.6 s (control, 30.2 s), and albumin 2.0 g/dl, and she had a remarkably elevated serum cardiac-specific troponin I of 7.23 ng/ml (normal value <0.4 ng/ml).[11,12] An electrocardiogram showed ST segment depression (>1 mm) in precordial leads V3–V6. A diagnosis of acute myocardial injury was made by a cardiologist based on electrocardiographic findings and the high serum cardiac-specific troponin I level.[12] Despite suspicion of an acute myocardial infarction or viral myocarditis, a coronary angiogram for differential diagnosis and to determine the need for primary coronary angioplasty was deferred because of thrombocytopenia and coagulopathy with active bleeding. In addition to oxygen supplement, albumin 25% and furosemide (40 mg) was intravenously infused for her pulmonary edema. An echocardiogram performed the following day disclosed a suboptimal left ventricular function with an ejection fraction of 62% and end-diastolic volume of 79 ml. She continued receiving intravenous albumin plus furosemide for a further 2 days. Defervescence occurred on day 5 and her peripheral white cell count was 13.2×10^9/l, hematocrit 37.1%, and platelet count 144×10^9/l.

The patient's blood culture was negative for bacterial growth, and a serological test was positive for dengue virus (DEN)-specific immunoglobulin M antibody. A reverse transcriptase-polymerase chain reaction was positive for dengue virus serotype 3 (DEN-3). Clinically she felt much better and refused further coronary angiographic investigations. Subsequent serum troponin I values were not available. She was discharged from the hospital on day 7. Two days later, follow-up laboratory data at the outpatient clinic showed that her peripheral white cell count was 7.8×10^9/l, AST 61 U/l, and albumin 3.2 g/dl. Clinically, she did not have any signs of heart failure when she was last seen on day 27 after the onset of dengue illness.

3. Literature review

We searched the PubMed database for articles published between January 1975 and August 2008 in the English-language literature. Medical subject headings (MeSH) including dengue, myocarditis, pericarditis, arrhythmia, and myocardial were cross-referenced in the search, which was supplemented with a secondary manual search.

A total of 18 pertinent articles involving 339 patients were found from the PubMed search.[2–8,13–23] The information retrieved, including DEN serotype, demographics, cardiac manifestations, and clinical outcomes is summarized in Table 1.[2–8,13,15,19–21,23] Where DEN serotype(s) was mentioned, DEN-2 and DEN-3 had been identified.[2–5] Differing clinical severities were found, resulting from a wide spectrum of cardiac manifestations, which included self-limiting tachy–brady arrhythmia[2,5,6,13,20] and myocardial damage with decreased left ventricular ejection fraction, leading to hypotension and pulmonary edema.[3,4,7,8,15,19,21,23] Most of the affected patients were supportively treated for symptomatic relief;[3,4,7,8,15,19,21,23] some patients with left ventricle failure required parenteral inotropic agents (i.e., dopamine and/or dobutamine) for their cardiogenic shock.[3,4] Although rare, a fatal outcome was reported in dengue-affected patients with cardiac complications.[19,23]

4. Discussion

The incidence of cardiac complications in patients with dengue illness varies greatly from one series to another. From India, Agarwal et al. reported that only one of 206 patients subjected to cardiovascular evaluation experienced cardiac symptoms;[14] Wali et al., reported that 70% of 17 patients with DHF/DSS who underwent myocardial scintigraphic study suffered diffuse left ventricular hypokinesis with a mean ejection fraction of 40%;[4] and Kabra et al., reported that 16.7% of 54 children with dengue illness had a decreased left ventricular ejection fraction of <50%.[7] A recent report from Sri Lanka showed that 62.5% of 120 adults with dengue fever (DF) had an abnormal electrocardiogram.[3] These series suggest that cardiac complications in patients with dengue illness are not uncommon, and might have been under-diagnosed because most of the cases with cardiac complications are clinically mild and self-limited.[2]

The clinical manifestations of cardiac complications in dengue illness vary considerably.[2–8,13–23] At one end of the clinical spectrum, patients are asymptomatic or have mild cardiac symptoms despite relative bradycardia, transient atrioventricular block, and/or ventricular arrhythmia.[2,6,5,13,20] At the other severe end, patients may experience acute pulmonary edema and/or cardiogenic shock due to severe myocardial cell damage with left ventricular failure.[3,4,7,8,15,19,21,23] Myocarditis can masquerade as acute myocardial infarction.[23,24] The diagnosis of acute myocardial infarction could be made based on a rise in biochemical markers of myocardial necrosis (serum creatine kinase-MB and/or cardiac troponin I), coupled with ischemic symptoms and/or electrocardiographically developed Q waves or ST segment elevation/depression.[25] When it comes to indicators of myocardial necrosis, troponin I is more sensitive and more specific than creatine kinase-MB.[12] As for the cardiac complication in this reported patient, the differential diagnosis included acute myocardial infarction and acute myocarditis; the former is characterized by a blockage of the coronary arteries, while the latter has patent coronary arteries.[26] The bleeding tendency in this patient posed a high risk for an invasive procedure and thus precluded an angiographic study for the differential diagnosis and for angioplasty in the case of myocardial infarct. However, rapid clinical improvement after the development of hypotension and acute pulmonary edema unequivocally indicated that this was a case of myocarditis.[26] Myocarditis is not uncommonly found in viral infections other than dengue.[26]

With respect to volume replacement for DHF patients with a >20% increase in hematocrit, the World Health Organization

Table 1
Summary of demographic details, cardiac manifestations, and outcomes in dengue-affected patients with cardiac manifestations reported in the English-language literature

Author(s), year of publication [Ref.]	No. patient(s)	Gender or sex ratio/age (years)[a]	Cardiac manifestations[b] (*n* [%])	Dengue serotype	Outcome
Present case	1	F/65	Myocarditis, LVEF <62%	DEN-3	Survived
Lee et al., 2008 [23]	1	M/25	Myocarditis, pulmonary congestion and hypotension	ND	Died
Kularatne et al., 2007 [3]	75	M:F = 25:50/ median 34	Tachy–brady arrhythmia (58 [77%]), hypotension (17 [23%]), and LVEF <55% (5 [6.7%])	DEN-3 infection in three patients and DEN-2 in one with data available	All survived
Ravindral et al., 2007 [2]	61	ND/ND	Tricuspid regurgitation (35 [57%]), left ventricular dilatation (13 [21%]) and dual chamber dilatation (10 [16%])	DEN-2	Not reported
Khongphatthanayothin et al., 2007 [21]	30 DF, 36 DHF, 25 DSS	ND/mean 9.6 ± 2.8 (patients with DF); ND/mean 11.4 ± 2.7 (patients with DHF); ND/mean 10.3 ± 3.1 (patients with DSS)	LVEF <50% in two (6.7%) patients with DF, five (13.8%) with DHF and nine (36%) with DSS	ND	All survived
Lateef et al., 2007 [20]	50	M:F = 39:11/mean 32.8 ± 10.8	Relative bradycardia	ND	ND
Malavige et al., 2006 [19]	2	ND/ND	Low LVEF, pulmonary edema, hypotension and tachycardia	ND	Died
Promphan et al., 2004 [8]	1	M/13	Hypotension with junctional rhythm and bradycardia and LVEF <40%	ND	Survived
Horta Veloso et al., 2003 [6]	1	M/61	Acute atrial fibrillation	ND	Survived
Khongphatthanayothin et al., 2003 [15]	24	M:F = 13:11/mean 10.8 ± 2.8	Mean LVEF 53.3 ± 9.0%	ND	ND
Khongphatthallayothin et al., 2000 [5]	1	M/7	Mobitz type I 2nd degree atrioventricular block	ND	Survived
	1	F/7	Mobitz type I 2nd degree atrioventricular block	DEN-2	Survived
Wali et al., 1998 [4]	17	M:F = 12:5/mean 29.76	Mean LVEF, 41.69 ± 5.04% with global hypokinesia in 12 patients (70.59%) (detected by radionuclide ventriculography) and 47.06 ± 3.8% (detected by echocardiogram)	DEN-2	All survived
Kabra et al., 1998 [7]	9	ND/<12	LVEF <50%	ND	All survived
Chuah, 1987 [13]	1	M/31	Transient ventricular bigeminy	ND	Survived

M, male; F, female; ND, no data available; DEN, dengue serotype; DF, dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome; LVEF, left ventricular ejection fraction.
[a] In the event of case series, age is either median or mean age of the dengue-affected patients with cardiac manifestations.
[b] One patient might have had more than one cardiac manifestation; ventricular ejection fraction was determined by echocardiogram unless stated otherwise.

recommends intravenous infusion with 5% glucose in physiological saline at 6 ml/h/kg for the initial 1–2 h, followed by 3–5 ml/h/kg, which may be discontinued at 24 to 48 h depending on the normalization of hematocrit, pulse rate, and blood pressure.[10] Overhydration may lead to fluid overload, resulting in respiratory distress in patients with dengue.[10] In the present case, despite improvement in the serial hematocrit after fluid therapy, hypotension developed on the third day of treatment suggesting that this resulted from cardiac dysfunction rather than insufficient intravenous fluid replacement, thus indicating that the patient's pulmonary edema was cardiogenic due to impairment of left ventricular function.[27]

Myocardial dysfunction has been reported to be more severe in patients with DSS when compared to those with DF or non-shock DHF.[21] The pathophysiology of myocardial cell injury in dengue illness is not yet fully understood. Myocardial involvement in dengue may result either from direct DEN invasion of the cardiac muscles or a cytokine-mediated immunological response, or both.[28,29] The upsurge in serum tumor necrosis factor-α, interleukins 6, 13 and 18, and cytotoxic factors in patients with dengue illness lead to increased vascular permeability and shock;[30,31] whether these cytokines play a role in the development of myocardial cell injury is unknown. Of note, only DEN-2 and DEN-3 were reported to be the culprit viruses in dengue patients with cardiac complications where the DEN serotype was mentioned.[2–5] Further studies are needed to clarify the role that DEN serotype plays, if any, in cardiac complications in dengue-affected patients.

Our review shows that cardiac complications are not uncommon in dengue illness. Although it was self-limiting in our patient under supportive treatment, acute myocarditis in dengue may be clinically severe to such an extent that it has a fatal outcome.[19,23] Early recognition of myocardial involvement in dengue illness, prompt restoration of hemodynamic instability while avoiding fluid overload, and sparing unnecessary invasive management are important in treating dengue-affected patients with severe myocarditis.

Conflict of interest: No conflict of interest to declare.

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