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CASE REPORT

Dengue myocarditis in Singapore: two case reports

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Abstract The authors report two cases of complicated dengue viral infection with acute myocarditis involving young male adults, of which one was fatal. The first case presented with typical signs of myocardial disease: chest pain and diaphoresis with myocardial depression in the electrocardiograph. The second case deteriorated rapidly and demised within the first day of admission. Histology of the heart muscles showed multiple small foci of myocyte necrosis surrounded by lymphocytes, in keeping with viral myocarditis. Both cases fulfilled the World Health Organization (WHO) diagnosis of probable dengue: the first case had positive dengue serology, both IgM and IgG at day six of illness, and the second case was polymerase chain reaction (PCR) positive for dengue and identified as serotype 2. Despite the severe outcome, both cases did not completely fulfil the criteria for dengue haemorrhagic fever (DHF). Although severe cardiac impairment is not commonly reported in dengue infection, it can be life threatening.

Keywords Dengue · Myocarditis · Singapore

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Introduction

Dengue is the most prevalent arthropod-borne viral disease, with an alarming global burden in tropical and subtropical regions and the potential for further geographic spread.

Dengue is hyperendemic in Singapore, with all four serotypes in co-circulation all year round. The dengue incidence rate was 98.1/100,000 population in 2010, with a case–fatality ratio of 0.08 % [1]. Although the incidence rate was not the highest in the Asia–Pacific region, the disease had high economic impact [2]. It was estimated that the average economic impact of dengue illness in Singapore over one 10-year period from 2000 to 2009 was between US$ 0.85 billion and US$ 1.15 billion [2].

The clinical features of dengue range from asymptomatic and subclinical infection to typical dengue fever, with a small proportion suffering from severe illness presenting with plasma leakage, bleeding or organ involvement. Dengue fatality is unusual, particularly among adults. Dengue fever classically comprises a febrile phase that spans 3–7 days, followed by a critical phase around the time of defervescence. This critical phase is when systemic vascular leakage may occur, which, in severe cases, may lead to shock and where haemorrhagic manifestations are most common. Subsequently, there is a recovery phase lasting several days, with normalisation of blood counts and haemodynamic parameters. Less common presentations such as encephalitis, liver failure, retinitis or myocarditis have been also reported. Although the cardiac complications of dengue are rare, asymptomatic myocardial involvement has been documented [3]. Acute myocarditis is the most common cardiac pathology described in cases that succumbed to dengue shock syndrome [4–6].

The authors report two cases of dengue complicated with acute myocarditis. One patient died after a sudden

onset of restlessness and acute myocarditis was diagnosed post mortem according to autopsy findings. As dengue management is challenging, often with an unpredictable clinical course and outcome, we aim to emphasise that atypical manifestations can occur and can be life threatening.

Case 1

A 20-year-old Chinese Singaporean male presented to the Emergency Department on January 12th, 2011, complaining of fever for the last 5 days, associated with occasional vomiting and nausea. He denied other complaints, including diarrhoea, cough, sore throat, rhinorrhoea, dyspnoea, headache, myalgia, arthralgia, abdominal pain and dysuria. However, he had noticed redness over bilateral thighs since that morning and denied any bleeding. He had a history of childhood asthma but no other significant past medical history, and did not have a history of drug, tobacco or alcohol abuse.

His tympanic temperature was 36.3 °C, pulse rate 116/min, respiratory rate 18/min, blood pressure 118/71 mmHg and a generalised petechial rash was found on physical examination. He was noted to be moderately obese (body mass index: 31.28 kg/m^2). An electrocardiogram (ECG) showed slight sinus tachycardia (102 bpm) (Fig. 1). Laboratory data revealed thrombocytopaenia (14×10^9/L; normal range 170–420 $\times$ 10^9/L), increased values of haematocrit (54.5 %; normal range 41–51 %) and haemoglobin (18.1 g/dL; normal range 13–17 g/dL), total leukocyte count (6.5×10^9/L; normal range 3.6–9.3 $\times$ 10^9/L), prolonged activated partial thromboplastin time (45.9 s; normal range 25–36 s) and an increased serum creatinine level of 124 μmol/L (normal range 60–105 μmol/L).

He was given intravenous hydration while under the Infectious Diseases service, with the presumptive diagnosis of dengue. Dengue IgM and IgG were positive on serum collected at the sixth day of illness. He was haemodynamically stable from admission, but on the third day of admission (seventh day of illness), he complained of central chest pain, nausea, vomiting and diaphoresis of sudden onset. No signs of bleeding or hypotension were noted and his pulse rate was 98/min. His platelet count had risen to 36×10^9/L and haematocrit decreased to 46.8 %. Troponin I serum level was 3.06 μg/L (normal range 0.0–0.5 μg/L) and his hepatic and renal functions were normal. Chest radiography showed no signs of fluid overload or pulmonary consolidations, and his cardiothoracic ratio was normal. ECG disclosed widespread ST-segment elevations and T-wave inversions (Fig. 2). Transthoracic echocardiography revealed a left ventricular systolic dysfunction with mild hypokinesia and an ejection fraction of 45 %. Treatment under close monitoring in the High Dependency Unit included a single dose of 300 mg acetylsalicylic acid, bisoprolol 2.5 mg OD and enalapril 1.25 mg BD.

The patient's clinical status improved subsequently, with ST-segment normalisation (Fig. 3). He was discharged after five inpatient days with full resolution of

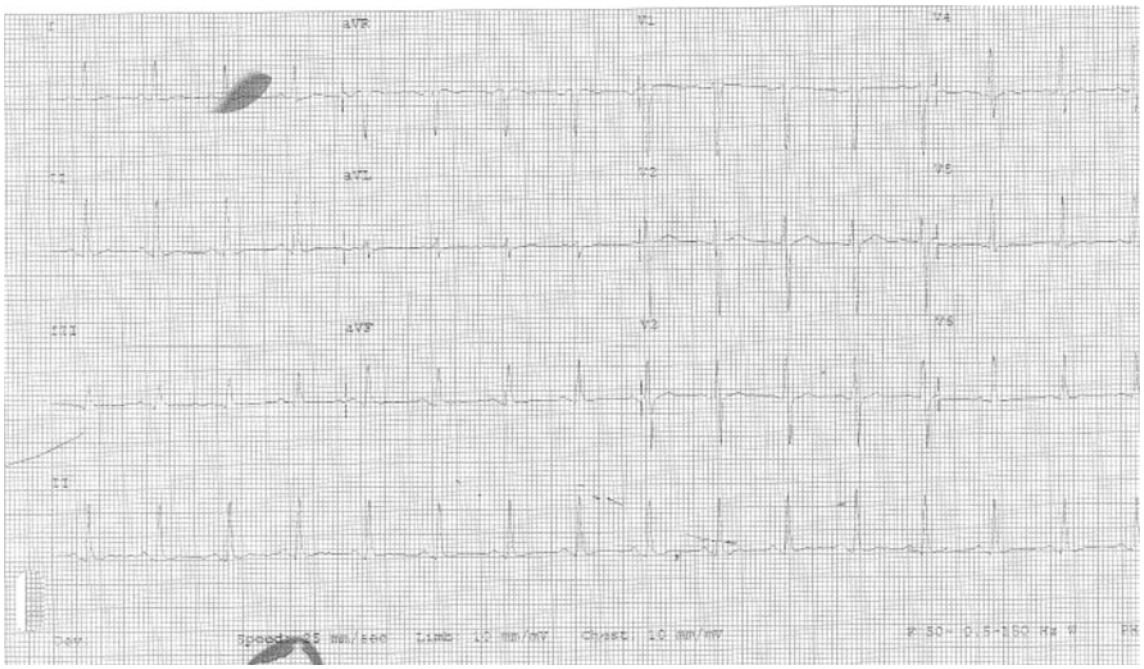

Fig. 1 Slight sinus tachycardia

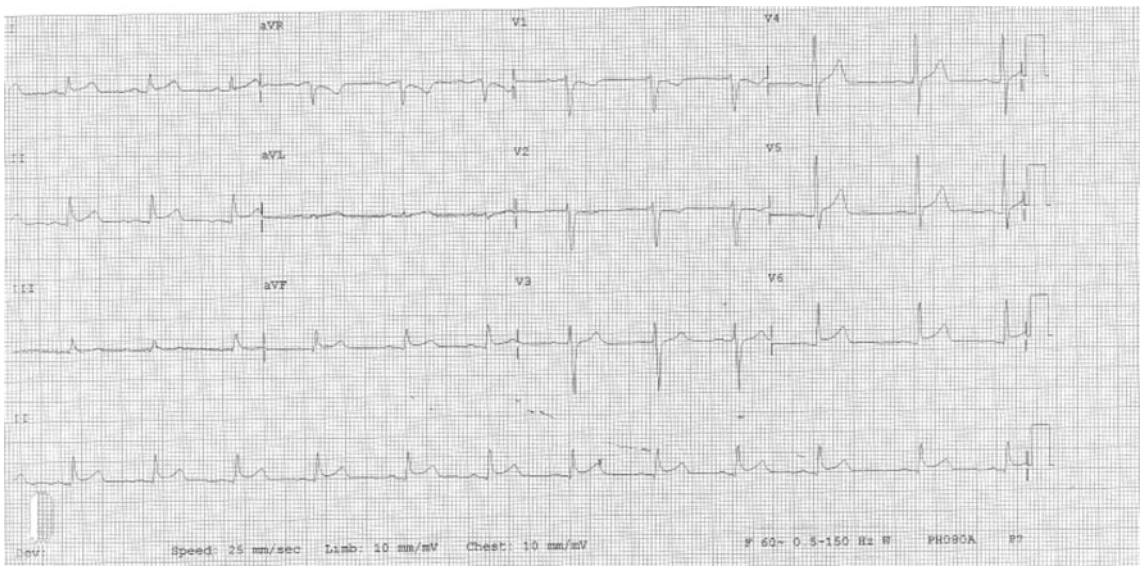

Fig. 2 ST-segment elevation

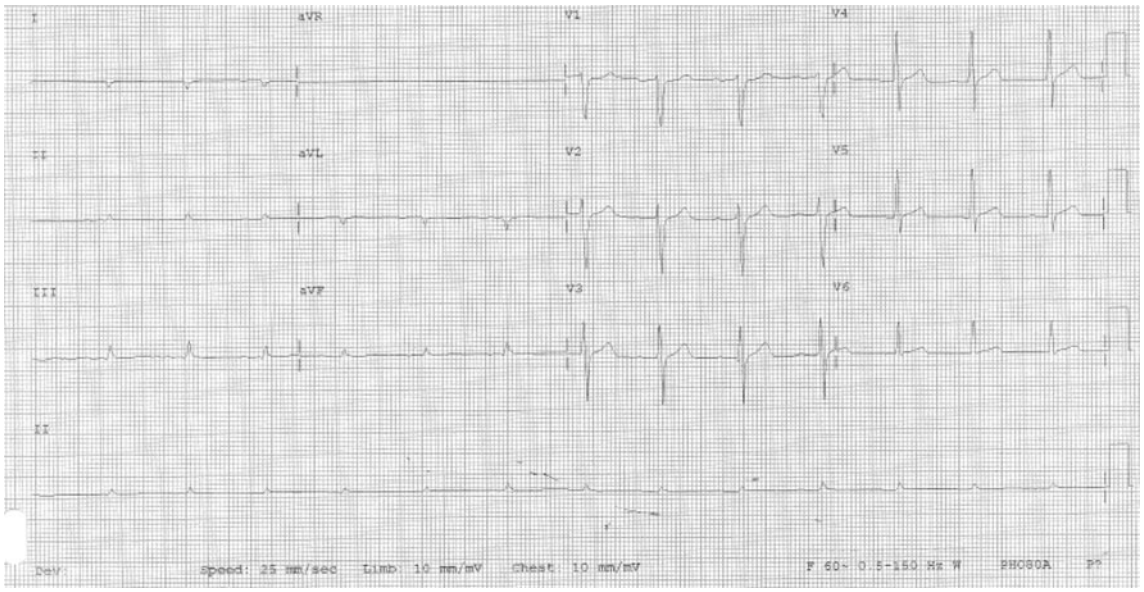

Fig. 3 ST-segment normalisation

symptoms, platelet count of 122 $\times$ 10^9/L and haematocrit of 48.7 %. He was well at clinic review a month later.

Case 2

A 41-year-old Chinese male presented to the Emergency Department on March 21st, 2011, with a two-day history of fever, chills, generalised myalgia and arthralgia. He denied other complaints, including cough, sore throat, rhinorrhoea, dyspnoea, nausea, vomiting, diarrhoea, headaches, chest pain, abdominal pain, dysuria and bleeding. He had undergone cholecystectomy 10 years prior. He was born in the People's Republic of China, worked in Singapore for the previous 2 years as a construction worker and his last travel was to China (Jiangsu province) two months prior to presentation. He denied drug, tobacco and alcohol abuse, as well as any high-risk sexual contact.

Apart from pyrexia (38.6 °C), his physical examination was unremarkable. He was sent home on antipyretics. Two days later, his full blood count, ordered by a private primary care physician, showed leukopaenia (1.3 $\times$ 10^9/L; normal range 4.0–11.0 $\times$ 10^9/L), thrombocytopaenia (75 $\times$ 10^9/L; normal range 150–400 $\times$ 10^9/L) and normal

values of haemoglobin (15.4 g/dL; normal range 13.5–18.0 g/dL) and haematocrit (46.3 %; normal range 38–52 %). On the sixth day of illness, he was admitted under the Infectious Diseases service due to loss of appetite, severe vomiting, nausea, malaise, mild headaches and dizziness. Upon physical examination, a generalised maculopapular rash was noted, with petechiae over his lower limbs; he was alert with a tympanic temperature of 37.3 °C; heart rate 109 bpm; respiratory rate 20/min; supine blood pressure 107/68 mmHg and sitting blood pressure 107/73 mmHg. Signs of meningeal irritation were absent. Laboratory data of relevance included thrombocytopaenia (27×10^9/L; normal range 170–420 $\times 10^9$/L), haematocrit value of 50 % (normal range 41–51 %), haemoglobin level of 16.9 g/dL (normal range 13–17 g/dL), normal leukocyte count (4.5×10^9/L; normal range 3.6–9.3 $\times 10^9$/L), increased serum creatinine level of 115 μmol/L (normal range 60–105 μmol/L) and elevation of aminotransferases [alanine aminotransferase: 115 U/L (normal range 17–63 U/L); aspartate aminotransferase: 64 U/L (normal range 15–41 U/L)]. His coagulation profile was normal. Chest radiography showed neither pulmonary consolidations nor pleural effusions. Intravenous hydration with 0.9 % normal saline solution (1,500 mL at 62.5 mL/h) was started. Less than 12 h following admission, the patient was reported to be restless and collapsed and died. The autopsy report revealed, as the final cause of death, acute myocarditis complicating dengue infection based on the presence of multiple areas of myocardial necrosis surrounded by inflammatory cellular infiltrate. DENV-2 was detected by reverse transcriptase polymerase chain reaction (RT-PCR). Positive dengue serology was also found. Other viral infections were excluded, including Chikungunya (serum PCR), common enteroviruses (brain and heart tissue cultures), common respiratory viruses (lung tissue culture and immunofluorescence), mumps (brain tissue culture), measles (brain tissue culture) and herpes simplex virus (brain tissue culture and serology). Additionally, serologic tests also excluded the following infections: human immunodeficiency virus, viral hepatitis (A, B and C), Epstein–Barr virus and cytomegalovirus. Blood cultures yielded no bacterial growth.

Discussion

Using the current World Health Organization (WHO) dengue classification of 2009, both cases are classified as severe dengue due to major organ involvement (heart). Both patients had warning signs at admission, essentially, severe thrombocytopaenia simultaneous with increased haematocrit in the first case and persistent vomiting in the second. Dengue haemorrhagic fever (DHF) criteria, as outlined by the previous dengue classification (WHO, 1997), were not fulfilled in either of the cases, as significant recorded haemoconcentration (>20 %) or evidence of plasma leakage was lacking. However, in the first case, some doubts may arise as the baseline haematocrit value was unknown and with mild elevation at presentation but without documentation of a 20 % or higher rise. The strict criteria for DHF in the WHO 1997 classification may miss certain cases of severe dengue disease [7]. This has been addressed in the WHO 2009 guidelines with specific inclusion of severe bleeding and severe organ involvement as separate categories of severe dengue disease, as well as in a regional update to the 1997 guidelines, which covers unusual or atypical manifestations under the category of Expanded Dengue Syndrome independent of DHF status [8].

A recent dengue secondary infection cannot be excluded in both cases due to the presence of positive IgM and IgG serology collected in the acute phase (sixth day of illness) [9]. The identification of DENV-2 in the second case is consistent with DENV-2 as the most prevalent dengue serotype circulating in Singapore, responsible for around 70 % of cases [1]. To date, three DENV serotypes have been reported as causing acute myocarditis, specifically: DENV-2 documented in 17 Indian children with DHF and/or dengue shock syndrome (DSS) during the 1996 outbreak in the Delhi region; DENV-3 in three Sri Lankan adult patients with myocarditis detected in the early phase of infection during an outbreak in Kandy district in 2005 and DENV-1 in a Colombian child with DHF and fulminant myocarditis in the 2004 outbreak in Neiva city [5, 10, 11]. Notwithstanding that cardiac involvement during dengue infection has been occasionally reported since the 1940s supported by immunohistochemistry and histopathological studies, its impact on morbidity and mortality remains unclear, probably denoting the lack of notification and/or diagnosis [6, 12, 13].

The two cases reported here are not unique; however, they exemplify the spectrum of myocarditis presentation, severity and outcome. There have been reports of acute myocarditis, as well as myopericarditis, pericarditis, asymptomatic myocardial dysfunction and cardiac rhythm disturbances, such as atrioventricular blocks, sinus node dysfunction, ventricular ectopic beats, atrial fibrillation, ST-segment and T-wave changes, tachycardia and bradycardia [3, 14–19]. Electrocardiogram abnormalities have been reported during the entire course of dengue. A Vietnamese observational study reported 35 % cardiac involvement in early dengue, compared with 62.5 % (75/120) during an outbreak in Sri Lanka [17, 20]. Relative bradycardia in dengue patients has been reported in Singapore [21]. In some occurrences, as documented in the first report, the cardiac impairment is clinically transient and occurs during the critical phase, when patients are

prone to be haemodynamically unstable. In other situations, such as in the second report, the evolution can be fulminant [22]. Therefore, the clinical spectrum of myocarditis is far from homogeneous. It has been demonstrated that patients with DSS are more prone to myocardial depression with reduction of the left and/or right ventricular function. One study performed in Thailand involving 99 paediatric patients revealed that approximately one-third (9/25) of DSS patients had a ventricular ejection fraction less than 50 % at the critical stage [23]. On the other hand, myocarditis can be completely asymptomatic, as shown by a study conducted in Sri Lanka, revealing 24 % (44/85) of dengue patients with echocardiographic evidence of myocarditis, without any cardiac complaints and with complete resolution during convalescence [3]. Nevertheless, symptomatic myocarditis had a substantial impact, around 12.4 % (13/105) in paediatric DHF patients during an outbreak in Colombia (Neiva city, 2004) [24].

The cardiac involvement was confirmed by histology in the second case and by the ECG and echocardiogram in the first case. Serum biomarkers of myocardial injury, namely, increased troponin I, were helpful to confirm diagnosis. However, most myocarditis patients do not have elevated levels of cardiac biomarkers [25].

Recent expert opinions highlighted the detrimental effect of obesity in fluid management and a more severe outcome in dengue due to the complications of capillary leakage. The first patient was moderately obese; however, this anecdotal case cannot determine the effect of obesity on dengue severity. Regarding this issue, published studies are scarce and the literature focused on the paediatric population, but obesity was found to be a major risk factor for acute kidney injury in Thai children with DHF, as well as a risk for unusual presentations or shock [26, 27].

Conclusions

Myocardial injury secondary to dengue can lead to fatal outcome. Ventricular function may be temporarily compromised during dengue infection. Echocardiography is an important tool to assess and rule out other causes of heart failure.

Dengue myocarditis is generally reversible, with a favourable outcome if diagnosed and treated early. Furthermore, in order to provide adequate and efficient supportive therapy avoiding major organ impairment, it is crucial to diagnose dengue as early as possible, using either laboratory methods such as reverse transcriptase polymerase chain reaction (RT-PCR) and dengue-specific antigen and antibody enzyme-linked immunosorbent assays (ELISAs) where available, or lateral-flow-based immunochromatographic rapid diagnostics tests.

Conflict of interest None.

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