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Case report

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A case presentation of a fatal dengue myocarditis showing evidence for dengue virus-induced lesion

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Abstract

Dengue is a prevalent arthropod-borne viral disease in tropical and subtropical areas of the globe. Dengue clinical manifestations include asymptomatic infections; undifferentiated fever; dengue fever, which is characterized by fever, headache, retroorbital pain, myalgia, and arthralgia; and a severe form of the disease denominated dengue haemorrhagic fever/dengue shock syndrome, characterized by haemoconcentration, thrombocytopenia, and bleeding tendency. However, atypical manifestations, such as liver, central nervous system, and cardiac involvement, have been increasingly reported. We report an atypical and rare presentation of dengue disease marked by a dramatic and fatal cardiogenic shock due to acute myocarditis. Histopathological analysis of heart tissue showed several multifocal areas of muscle necrosis and intense interstitial oedema associated with clusters of virus particles inside the cardiomyocytes and in the interstitial space, providing evidence of a possible direct action of dengue virus on myocardium.

Keywords

Acute heart failure, acute myocarditis, cardiogenic shock, dengue fever

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Introduction

Dengue, an arthropod-borne viral infection of humans, is endemic to tropical and subtropical regions of the world and represents an important public health problem. Dengue viruses are transmitted by the bite of the *Aedes aegypti* mosquito infected by the one of the four dengue virus serotypes: dengue-1, -2, -3, and -4. More recently, dengue disease has spread geographically to many previously unaffected areas and, as travelling around the world has become more accessible, physicians in temperate areas are more likely to see returning travellers with dengue infection.[1,12]

Clinical manifestations include fever, headache, retroorbital pain, rash, severe myalgia, and arthralgia. A more severe clinical presentation, dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS), is characterized by increased vascular permeability, thrombocytopenia (platelets <100,000), bleeding tendency, and, in a small percentage of patients, circulatory shock.[2–5]

In addition, especially during large outbreaks, atypical clinical manifestations have been described, such as encephalitis, Guillain-Barré syndrome, and fulminant hepatitis.[6,7]

Cardiac involvement in dengue has been reported in few studies, usually resulting in a benign and self-limited disease. Although reports of a more severe disease with progression to cardiogenic shock and death have been increasingly described,[8–10] the pathogenesis of myocardial lesions has not been elucidated. We present a rare case of a fulminant and fatal myocarditis caused by dengue virus and

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Table 1. Laboratory test results obtained during hospital admission.

Laboratory tests	Hospital admission	Normal range
Haemoglobin (g/dl)	12.3	13.5–17.5
Haematocrit (%)	40	39-50
Leukocytes	23,000	3,500–10,500
Platelets	106,000	150,000–450,000
Creatinine (mg/dl)	1.5	0.7–1.6
Troponin I (μg/l)	10.09	<0.01
CK-MB (U/l)	189	<25
Lactate (mmol/l)	18	<2.0
C-reactive protein (mg/l)	2.5	<5.0

provide more detailed histological evidence for a possible direct action of dengue virus on myocardial fibres.

Case report

A 37-year-old woman was admitted to the Emergency Department of the Clinical Hospital of the São Paulo University of Medical School at Ribeirão Preto with a history of progressive dyspnoea in the last 3 days that had recently evolved to dyspnoea at rest and orthopnoea, atypical chest pain, dizziness, and one episode of syncope. Eight days prior the admission, she complained of fever, headache, retro-orbital pain, arthralgia, and weakness. A dengue diagnosis was performed based on clinical and epidemiological grounds. Her past medical history was positive only for a diagnosis of Alport syndrome.

On clinical examination, she was in severe condition, agitated, with signs of poor peripheral perfusion, such as cold extremities and cyanosis. Heart rate was 145 bpm and blood pressure unrecordable. Cardiac and pulmonary auscultations were normal. Haemorrhagic suffusions or other skin lesions were absent. The 12-lead electrocardiogram detected atrial fibrillation, low voltage QRS, and diffuse ST-segment elevation.

Fluid resuscitation with 0.9% saline solution, infusion of sodium bicarbonate, and vasoactive drugs were promptly initiated. Dopamine was used in progressive doses up to 20 μg/kg/min, followed by increasing doses of norepinephrine up to 2 μg/kg/min, but haemodynamic stabilization was not achieved at any time.

Complementary exams are shown in Table 1. Emergency transthoracic echocardiography was performed at bedside and showed mild pericardial effusion, without signs of cardiac tamponade, and severe left ventricular dysfunction with diffuse hypokinesia of left ventricular wall.

Due to respiratory function deterioration, tracheal intubation and mechanical ventilation were initiated but she rapidly progressed to cardiopulmonary arrest with a pulseless electrical activity rhythm. Cardiopulmonary resuscitation was performed without success and the patient died 2 hours after hospital admission. Laboratory results obtained in the next days showed that real-time PCR results for *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and seasonal and H1N1 influenza virus were negative. Serology for dengue (IgG and IgM ELISA) was positive and confirmed dengue disease.

Necroscopic examination revealed a dilated and flabby heart. Histopathological study showed marked interstitial oedema with a diffuse inflammatory infiltrate mainly composed of lymphomononuclear cells and fibroblasts. Diffuse foci of myocytolytic necrosis where neutrophils could be identified in association with mononuclear cells. There were no atherothrombotic lesions of main coronary or intramyocardial coronary vessels. There was no evidence of bacterial or fungal infection in any organs. Electron microscopic study of the myocardium disclosed clusters of virus particles in diffuse foci of cardiomyocytes, presenting dissolution of myofilaments, and in the interstitial space (Figure 1).

Discussion

Dengue is a worldwide public health problem and causes innumerous deaths. More than 40% of the world's population lives in dengue endemic areas, and the World Health Organization estimates that about 2.5 billion people in 100 countries are at risk of infection and that as many as 100 million people are infected by dengue viruses every year. In the majority of infected people, dengue is an auto-limited disease that resolves in 5–7 days. However, approximately 500,000 people develop a severe form, leading to about 20,000 deaths annually. Consequently, approximately 0.5% of dengue patients develops a severe form and requires a specialized treatment.[11,12]

There are few reports of adult patients with acute heart failure during dengue virus infection, and, in two of them, this complication was considered to be the cause of death.[6,13,14] We report a rare case of a 37-year-old woman with dengue that developed a fulminant and fatal cardiogenic shock 8 days after disease onset and provided detailed histological evidence that support the hypothesis of a possible direct viral lesion on myocardial fibres.

The presence of IgM and IgG antibodies on the 8th day of disease and the absence of a medical appointment in any of the city health centres in the last 8 months indicate that this patient might have experienced a secondary dengue infection. The observation that complications are more frequent during secondary infection is well known.

Cardiac involvement in dengue and its pathogeneses have been seldom described and poorly investigated. In one study in Sri Lanka, 25% of dengue patients presented with one or more elevated markers of myocardial injury, such as increase in myoglobin, CK-MB, troponin T, N-terminal type B peptide, and/or heart-type fatty acid binding protein levels.[15]

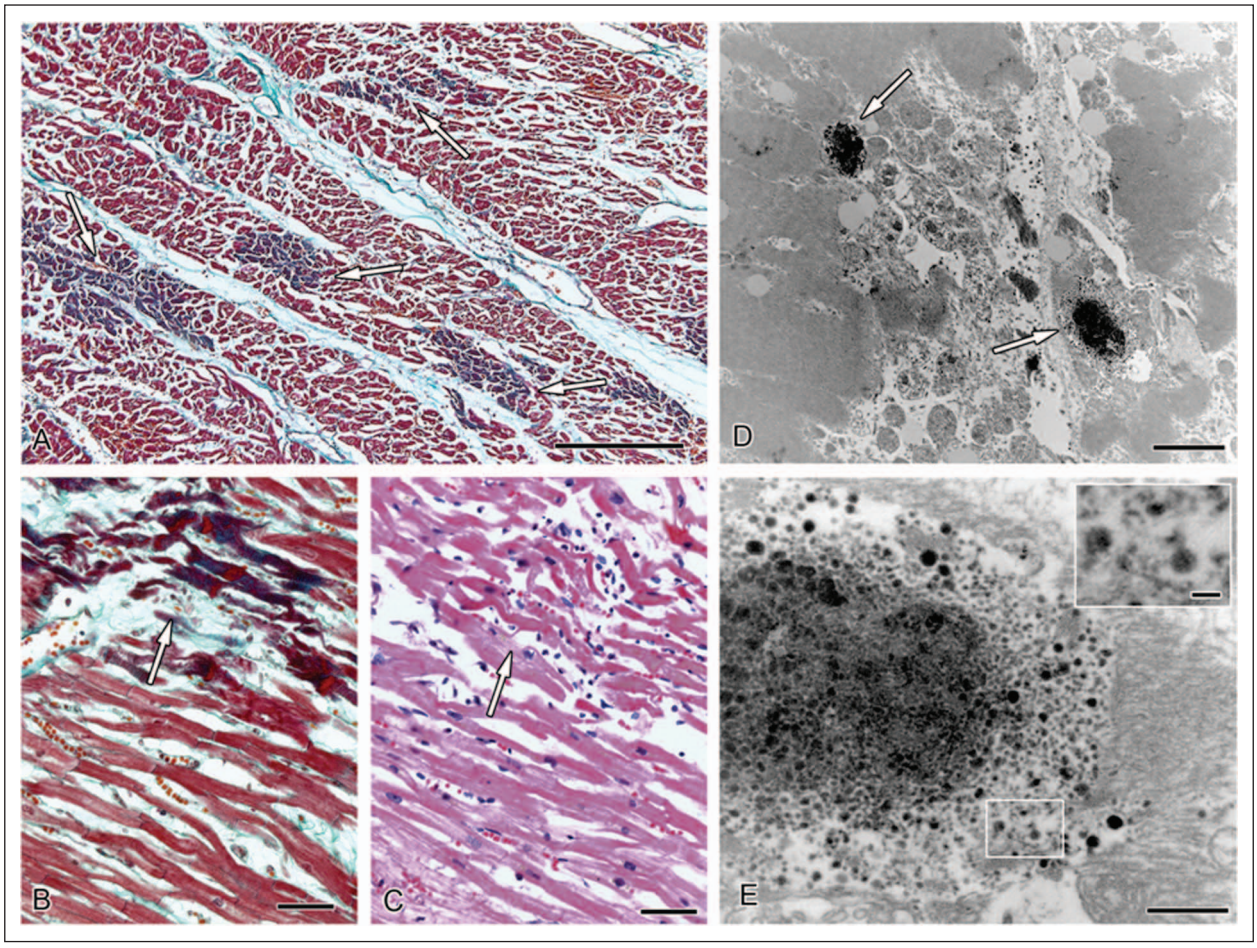

Figure 1. (A) Representative image of the myocardium showing diffuse foci of myocytolytic necrosis stained in blue (Masson's trichrome stain, bar 100 μm). (B and C) Detail of a focus of myocytolytic necrosis as seen with Masson's trichrome staining (B) and haematoxylin and eosin staining (C). In C, the presence of neutrophils can be clearly disclosed beside mononuclear cell (bars 50 μm). (D) Representative image of electron microscopic findings showing cluster of dengue-like virus particle inside the cells and in the interstitial space. The dissolution of myofilaments is a prominent feature in cardiomyocytes (bar 2 μm). (E) Higher magnification showing a cluster of dengue-like virus particles (bar 500 nm) and dengue-like virus particles in detail (inset, bar 100 nm). The loss of virus particles depends on the fact that the myocardial tissue was first fixed in formaldehyde and processed for light microscope and reprocessed for electron microscopy.

In another report of 102 children with DHF, 10 patients had acute myocarditis requiring use of inotropic drugs and one child died.[16] Studying 17 DHF/DSS patients with radionuclide ventriculography, Wali et al.[17] showed that seven patients had ejection fraction less than 40%, 12 had global hipokinesia, and, after 3 weeks of follow up, all alterations had returned to normal. Weerakoon et al.[18] performed autopsies on five patients who died due to dengue complications and showed histopathological evidence of myocarditis.

Cardiac arrhythmias are other clinical manifestations of myocarditis. Various arrhythmias have been described during dengue virus infection such as atrial fibrillation, ventricular tachycardia and even atrioventricular blocks. These arrhythmias are associated to syncope and even sudden death.[13,14,19–21] Our patient presented with atrial fibrillation at admission, which could have contributed to the cardiogenic shock and death.

The mechanism of myocardial damage in dengue could be the release of inflammatory mediators and/or the direct action of the virus on cardiomyocytes, as seen in acute myocarditis caused by other viruses.[22] Salgado et al.,[23] using immunofluorescence confocal microscopy in heart tissue, reported that myotubes were infected by dengue virus in one child with fatal DHF, although the myocardium sections appeared morphologically normal, with minimal cellular infiltrates. Moreover, clinical characterization of myocarditis in this case was not complete.

We have demonstrated that the fulminant course of clinical dengue myocarditis was associated with intense

interstitial oedema, several multifocal areas of necrosis, and diffuse inflammatory infiltration. Interestingly, the myocytolitic necrotic areas were replete with virus particles, therefore providing detailed histological evidence of a possible dengue direct action in cardiomyocytes. Further clinical and experimental studies are necessary to better understand the molecular mechanism of dengue virus-induced lesions on the myocardium.

Other pathogens occurring simultaneously or following dengue infection have been described.[24,25] In this case, infection by other pathogens were ruled out clinically and with laboratorial and histopathological data. We did not objectively exclude coxsackie B and other virus infections, but the temporal association with a dengue-like disease and the positive serology for dengue confirm dengue virus as the more probable causative agent in this patient.

Conclusions

Dengue virus can produce atypical manifestations as acute myocarditis leading to cardiogenic shock and death by a possible direct virus action on cardiomyocytes. Physicians taking care of dengue patients should be aware of this possible complication.

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Conflict of interest

None.

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