INTRODUCTION

Dengue fever is caused by dengue virus, which is a single stranded ribonucleic acid (RNA) virus of the family Flaviviridae. It has four serotypes and transmitted by *Aedes* mosquitoes. Dengue infection can be asymptomatic or can be manifested as an undifferentiated fever, dengue fever, dengue haemorrhagic fever (DHF) or as dengue shock syndrome. The pathological features include thrombocytopaenia and increased vascular permeability leading to haemorrhagic complications with associated morbidity and mortality. Dengue infection could affect multiple organs like liver, heart, kidney, nervous system and lungs. Increased pro-coagulant activity during dengue fever leading to thrombotic events is overlooked, but an important complication which needs more awareness among clinicians. Thrombotic events of large veins including ileo-femoral deep vein thrombosis, pulmonary thrombo-embolism and mesenteric vein thrombosis have been reported in Brazil representing 5.4% of all dengue in-patients. Acute ST elevation myocardial infarction (STEMI) could present with dengue fever but not widely reported and management is challenging as no specific guidelines available regarding the management. We present two cases of Dengue fever complicated with acute STEMI and share the therapeutic challenges we encountered when managing the patients.
CASE PRESENTATION

Case 1
A 67-year-old Sri Lankan woman with type 2 diabetes mellitus presented with fever for two days which was associated with arthralgia, myalgia, nausea, and loss of appetite. Examination revealed a pulse rate of 112 bpm which was irregularly irregular, blood pressure was 120/70 mmHg without a postural drop. Auscultation of the precordium revealed evidence of mitral stenosis, as an incidental finding.

The electrocardiograph (ECG) demonstrated atrial fibrillation (AF) without ischaemic changes. The echocardiogram revealed the ejection fraction of 60% without regional wall motion anomalies and moderate mitral stenosis with dilated left atrium. The biochemical and haematological parameters are summarized in Table 1. The dengue specific rapid non-structural 1 (NS-1) antigen tested on the third day of the illness was negative. However, she was monitored and managed as dengue fever as she had decreasing pattern of platelet count and NS-1 antigen test could have false negative results. Valvular AF was managed with verapamil 40 mg twice daily for rate control, but anticoagulation was deferred as dengue was suspected.

She developed acute onset, tightening, central chest pain with autonomic symptoms and shortness of breath on the fifth day of the illness. Examination revealed an irregularly irregular pulse with an average rate of 100 bpm, blood pressure of 160/100 mmHg and 95% saturation on ambient air. The point of care ultrasonography did not show evidence of fluid leakage. The ECG showed elevation of ST segment in the chest leads V2 – V6 with T inversions in the inferior leads and previously detected atrial fibrillation with an adequate rate control. The biochemical and haematological parameters on the fifth day of the illness is illustrated in Table 1. Troponin I in six hours of onset of chest pain was positive at 18.66 ng/mL (Reference range < 0.5 ng/mL). Acute extensive anterior STEMI was diagnosed.

The primary percutaneous coronary intervention (PCI) was considered; however, patient did not give the consent for the procedure. Therefore, she was administered loading doses of aspirin, clopidogrel and atorvastatin. Furthermore, she was administered 5000 IU of intravenous unfractionated heparin (UFH), followed by 12 mg/kg/hour of infusion. Dual anti-platelet therapy was continued with heparin. The patient was monitored in a high dependency care unit with three hourly monitoring of packed cell volume and eight hourly monitoring with point of care ultrasonography for evidence of fluid leakage.

Intravenous UFH infusion was continued for four days while maintaining the activated partial thromboplastin time (APTT) two times the upper limit of normal. When the platelet count rose above 150 (188 x 10^3/UL), UFH was replaced with subcutaneous enoxaparin (60 mg twice daily) and six doses were given without developing any complications. Warfarin (5 mg daily) was initiated with enoxaparin and titrated to achieve an international normalized ratio (INR) for prothrombin time of 2.5 (range of 2-3).

The echocardiogram done after one week of the onset of acute coronary event, revealed the ejection fraction as 45% with hypokinesia in anterior, antero-septal, and apical walls. The ECG demonstrated Q waves in V2- V6 leads. Immunoglobulin M (IgM) antibodies to dengue virus done on day-10 of fever was positive, confirming dengue infection.

Table 1: Haematological and biochemical parameters of the first patient

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Reference range</th>
<th>2nd day of the illness</th>
<th>5th day of the illness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haematology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total white cell count (cells/µL)</td>
<td>4,000–11,000</td>
<td>6,670</td>
<td>6,000</td>
</tr>
<tr>
<td>Neutrophil count (cells/µL)</td>
<td>1,500–8,000</td>
<td>3,630</td>
<td>1,990</td>
</tr>
<tr>
<td>Lymphocyte count (cells/µL)</td>
<td>1,000–4,800</td>
<td>2,040</td>
<td>3,440</td>
</tr>
<tr>
<td>Haemoglobin level (g/dL)</td>
<td>12.0–15.5</td>
<td>11.6</td>
<td>11.3</td>
</tr>
<tr>
<td>Packed cell volume (%)</td>
<td>36–46.5</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>Platelet count (platelets/µL)</td>
<td>150,000–450,000</td>
<td>114,000</td>
<td>87,000</td>
</tr>
<tr>
<td>Prothrombin time (seconds)</td>
<td>11–14</td>
<td>12.2</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>0.8–1.2</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>APTT (seconds)</td>
<td>24–38</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td><strong>Biochemistry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C- reactive protein (mg/L)</td>
<td>&lt; 6</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>60–110</td>
<td>80</td>
<td>71</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>3.5–5.1</td>
<td>3.6</td>
<td>4.5</td>
</tr>
<tr>
<td>Serum sodium (mmol/L)</td>
<td>135–148</td>
<td>136</td>
<td>131</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/L)</td>
<td>10–35</td>
<td>99</td>
<td>108</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>10–40</td>
<td>35</td>
<td>46</td>
</tr>
</tbody>
</table>
She was discharged on the 14\textsuperscript{th} day of the illness after successful recovery. HAS-BLED score for risk of bleeding was two. She was prescribed warfarin, aspirin and clopidogrel for one month, with a plan to review in medical clinic for further care.

**Case 2**

An 83-year-old Sri Lankan woman presented with high grade fever with chills for 2 days. She had associated arthralgia, myalgia, and a few episodes of loose stools. She had hypertension for 10 years and a prior ischaemic stroke. On admission she was febrile, pulse rate was 80/min with a blood pressure of 140/90mmHg. Rest of the systemic examination was unremarkable. Full blood count showed a white cell count of 5.94 (10\textsuperscript{3}/UL), with low platelets of 40 (10\textsuperscript{3}/UL). Dengue NS1 antigen was positive. On the third day of her febrile illness, she complained of epigastric pain and had reduced urine output < 0.5 mL kg/h and melena. She was found to be tachycardic with a blood pressure of 90/70 mmHg. Ultrasonography revealed fluid in the hepatorenal pouch proving fluid leak and critical phase of dengue. Despite clinical and radiological evidence of fluid leak there was a drop in the packed cell volume (PCV) from 46% to 42%. A diagnosis of DHF with bleeding was made and she received appropriate intravenous fluid resuscitation including transfusion of one unit of blood. A summary of relevant investigation results is shown in Table 2.

On the 4\textsuperscript{th} day of fever, she complained of chest tightness and shortness of breath associated with profuse sweating. Her pulse rate was 96 bpm and blood pressure was 100/60 mmHg with an oxygen saturation of 97 % on room air. The ECG showed ST elevation in leads V1-V4 with T-wave inversion in leads II, III, and aVF. Troponin I was strongly positive at 20.45 ng/ml (control - <0.5 ng/ml).

Echocardiogram revealed a compromised ejection fraction of 35-40% with anterior, antero-septal, and apical hypokinesia. The platelet count at this point was 16 (10\textsuperscript{3}/UL). Anterior STEMI with acute heart failure was diagnosed. Neither thrombolysis nor the anticoagulation was offered due to severe thrombocytopaenia and the presence of active bleeding.

Primary PCI was also not possible as definitive dual anti-platelets and heparin would be required post-procedure to prevent stent thrombosis. Statins were deferred due to hepatitis associated with dengue (AST- 664 U/L, ALT- 317 U/L). Thus, the STEMI was managed conservatively. Her platelet count started to rise during hospital stay and her vital parameters improved with appropriate fluid management. Serial ECGs revealed Q wave formation. Both immunoglobulins M (IGM) and G (IgG) for dengue (done on day 7 of fever) were positive. Single antiplatelet (aspirin) was started once the platelet count rose above 50 (10\textsuperscript{3}/UL) with a plan to commence dual antiplatelet therapy when it rises above 100 (10\textsuperscript{3}/UL). Coronary angiogram was planned with cardiology review as outpatient.

**DISCUSSION**

We report two cases of dengue fever complicated with acute STEMI and discuss the therapeutic challenges associated with their management. Both patients had clinical and serological evidence of dengue infection with development of STEMI during the critical phase. Cardiac involvement in dengue is well known. Of the dengue serotypes, cardiac involvement has been described in infections with DENV2 and DENV3.\textsuperscript{5,6} Reported cardiac complications of dengue include; conduction abnormalities, hypotension, arrhythmias, myocarditis, and acute heart failure. A summary of relevant investigation results is shown in Table 2.

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Reference range</th>
<th>Day 2 of illness</th>
<th>Day 4 of illness</th>
<th>Day 10 of illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total white cell count (cells/µL)</td>
<td>4,000–11,000</td>
<td>5,940</td>
<td>8,580</td>
<td>5,740</td>
</tr>
<tr>
<td>Neutrophil count (cells/ µL)</td>
<td>1,500–8,000</td>
<td>3,690</td>
<td>6,380</td>
<td>3,450</td>
</tr>
<tr>
<td>Lymphocyte count (cells/ µL)</td>
<td>1,000–4,800</td>
<td>1,920</td>
<td>1,450</td>
<td>1,530</td>
</tr>
<tr>
<td>Haemoglobin level (g/dL)</td>
<td>12.0–15.5</td>
<td>16.3</td>
<td>15.9</td>
<td>11.0</td>
</tr>
<tr>
<td>Packed cell volume (%)</td>
<td>36–46.5</td>
<td>49.3%</td>
<td>48%</td>
<td>33.5%</td>
</tr>
<tr>
<td>Platelet count (platelets/ µL)</td>
<td>150,000–450,000</td>
<td>40,000</td>
<td>16,000</td>
<td>51,000</td>
</tr>
<tr>
<td>Prothrombin time (seconds)</td>
<td>11–14</td>
<td>14.7</td>
<td>12.5</td>
<td>15.4</td>
</tr>
<tr>
<td>INR</td>
<td>0.8–1.2</td>
<td>0.89</td>
<td>0.89</td>
<td>1.11</td>
</tr>
<tr>
<td>APTT (seconds)</td>
<td>24–38</td>
<td>36.5</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Biochemistry</td>
<td></td>
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<td>C- reactive protein (mg/L)</td>
<td>&lt; 6</td>
<td>65</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>60–110</td>
<td>2.27</td>
<td>1.02</td>
<td>0.69</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>3.5–5.1</td>
<td>3.6</td>
<td>3.9</td>
<td>3.3</td>
</tr>
<tr>
<td>Serum sodium (mmol/L)</td>
<td>135–148</td>
<td>147</td>
<td>140</td>
<td>144</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/L)</td>
<td>10–35</td>
<td>989</td>
<td>664</td>
<td>135</td>
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<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>10–40</td>
<td>256</td>
<td>317</td>
<td>65</td>
</tr>
</tbody>
</table>
heart failure, pericarditis and cardiomyopathy. The cytokine storm occur in dengue fever is implicated in the pathogenesis of myocarditis and occurrence of arrhythmias. Dengue myocarditis can sometimes masquerade as myocardial infarction. However, dengue fever complicated with myocardial infarction is reported in only a few case reports.

The older age, presence of type 2 diabetes and hypertension as risk factors favors preexisting coronary atherosclerosis in these patients. The development of acute ischaemic type chest pain, ST segment elevation in anterior chest leads with reciprocal changes in inferior leads and evolution of Q waves favor myocardial infarction over myocarditis or pericarditis. Furthermore, the presence of regional wall abnormalities on echocardiography also provide evidence of ischaemia induced injury in a defined territory of a coronary artery.

Even though bleeding manifestations are common, increased pro-coagulant activity during dengue fever has been described due to various pathological mechanisms. Endothelium loses its' non-thrombogenic protective properties (maintained by expression of tissue factor, plasminogen activator inhibitor-I and von Willebrand factor) due to endothelial damage by dengue virus, cytokines and antibodies. Dengue virus down regulates the thrombomodulin-thrombin-protein C complex formation at the endothelial surface, with a reduction in activated protein C level. Plasma levels of anticoagulant proteins C, S and anti-thrombin III have been reduced and levels of pro-coagulant tissue factor and anti-fibrinolytic plasminogen activator inhibitor-1 have been increased during the course dengue fever. Increased lupus anticoagulant activity has been demonstrated in a patient with cerebral ischaemia. Consequently, clinically significant major thrombotic events are described in the literature. In a Brazilian case series, 5.4% of all thrombotic events were reported in patients without dengue shock syndrome or dengue hemorrhagic fever. Deep vein thrombosis, pulmonary thromboembolism, mesenteric vein thrombosis and central retinal vein occlusion are among the reported thrombotic events in dengue fever.

Dengue complicating other medical conditions create complexities difficult in managing. Most difficulties are due to fluid leakage, thromboembolism, hepatitis and bleeding associated with dengue. The unpredictability of behavior of each case make it difficult to layout a general guide for the management. Therefore, one should carry out a tailor-made management with frequent monitoring. Acute coronary syndrome complicating dengue is one such situation. We discussed the management of STEMI in two complex patients presented with uncomplicated dengue and dengue complicated with DHF and bleeding.

PCI or thrombolysis or both involve anti-platelets and anticoagulants with high risk of bleeding. Thrombocytopenia and coagulopathy in dengue further worsen the risk. There is no clear guide on management of such patients in this situation. The first patient developed STEMI on the fifth day of the febrile illness at a platelet count of 87 (10^3/UL). Primary PCI was not performed as the patient did not give consent after considering the risks and benefits. Thrombolysis was not considered due to associated high bleeding tendency. UFH was administered as the platelet count was more than 50 (10^3/UL). It was chosen over low molecular weight heparin (LMWH) as the UFH has a relatively shorter half-life (1 hour vs. 4 hours) and as its' action can be reversed completely by the antidote, protamine sulphate, compared to reversal of only 60% of action of LMWH. Anti-platelets were also administered cautiously and patient was monitored for any adverse complication.

In a similar reported case, primary PCI was performed and standard treatment for STEMI was administered as the initial platelet count was 155 (10^3/UL) with the nadir platelet count of 95 (10^3/UL) without bleeding manifestations. Furthermore, withholding warfarin in a patient with DHF and severe thrombocytopenia who was on mandatory anticoagulation for mechanical mitral valve replacement, has been described, where the warfarin was re-commenced when platelet count rose above 50 (10^3/UL).

In contrast, our second patient with DHF and bleeding developed STEMI when her platelet count was 16 (10^3/UL). In platelet counts below 30 x 10^3/µl antiplatelet therapy and anticoagulants are contraindicated. Thus, we were unable to administer any specific treatment for acute coronary syndrome at the time of presentation. This is also the case in previously reported cases of dengue and acute coronary syndrome with severe thrombocytopenia. Nonetheless, in patients presenting with acute coronary syndrome with thrombocytopenia due to non-dengue related causes there have been successful attempts at PCI and anti-platelet therapy after raising the platelet count with platelet transfusions, intravenous immunoglobulins and danazol. Newer anticoagulants such as fondaparinux have also been used in such situations as they carry a lower bleeding risk compared to heparin. Further studies are required to determine whether this approach is beneficial in the case of dengue related thrombocytopenia. However, it is heartening to note that conservative management has also led to fair outcomes.
CONCLUSIONS

Cardiac complications in dengue fever may be related or unrelated to the illness itself. Disease related complications are of a wide spectrum and range in severity from asymptomatic to life threatening. Both bleeding manifestations and thrombotic events occur complicating dengue fever. Acute coronary syndrome presenting in a background of dengue fever must be differentiated from acute myocarditis. Management of myocardial infarction in this situation should be individualized and relies primarily on the degree of thrombocytopaenia and bleeding risk. Despite conservative management, such patients have demonstrated good clinical recovery. Further investigation and meta-analyses are required to include safe administration of dual anti-platelet and anti-coagulants into dengue practice guidelines with regard to the management of acute coronary syndrome.

List of abbreviations

- DNA: Ribonucleic acid
- DHF: Dengue haemorrhagic fever
- ECG: Electrocardiograph
- NS-1: Non-structural 1
- PCI: Percutaneous coronary intervention
- PCV: Packed cell volume
- INR: International normalized ratio
- LMWH: Low molecular weight heparin

DECLARATIONS

Ethical approval and consent to participate

Not applicable

Consent for publication

Informed written consent was obtained from the two patients for publication purposes.

Availability of data and material

All necessary data and material are provided.

ACKNOWLEDGEMENT

We thank the institute of Cardiology, National Hospital of Sri Lanka who extended their support in managing the two patients.

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Wijayabandara, et al.: Dengue fever complicated with acute ST elevation myocardial infarction - a therapeutic conundrum

https://doi.org/10.1160/TH08-04-0271


Author’s Contribution:
MW, CG, PK, SF and SJ- Contributed for the management of the first patient; DW, CG, PK and SJ - Contributed for the management of the second patient. All authors contributed to the drafting of the manuscript. All authors read and approved the final manuscript.

Work attributed to:
University Medical Unit, National Hospital of Sri Lanka, Colombo, Sri Lanka.

Orcid ID:
Dr. Maheshi Wijayabandara- https://orcid.org/0000-0003-3350-7011
Dr. Devasmitha Wijesundara- https://orcid.org/0000-0002-2503-3955
Dr. Champika Gamakaranage- https://orcid.org/0000-0001-6040-5649
Dr. Panduka Karunanayake- https://orcid.org/0000-0002-8102-6952
Prof. Saroj Jayasinghe- https://orcid.org/0000-0003-1460-6073

Source of Funding: No funding source for this case report. Conflict of Interest: Authors declare that they have no competing interests.