CASE REPORTS

Dengue Fever Presenting with Concomitant Acute Coronary Syndrome (ACS) -   A Series of 5 Cases At A Tertiary Care Hospital In Dhaka

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Abstract:

Dengue fever may present with many cardiovascular manifestations contributing to death and disability. Acute Coronary Syndrome (ACS) during dengue is rare but poses important management dilemma. Here we present a series of 5 patients with dengue fever who developed different types of ACS during the ongoing dengue endemic in Bangladesh.

Five patients admitted with dengue fever and who developed ACS between 1st July to 30th September 2023 at Medicine Department of Uttara Adhunik Medical College, Dhaka, Bangladesh were studied. All the patients had some co-morbidity like diabetes, hypertension, or both. Treatment of ACS was tailored according to their CBC report, most importantly, platelet count, and hematocrit.

Four out of the 5 patients responded well to anti-ischemic therapy, even though anti-platelet and anti-coagulants could not be given in all cases.

There was 1 fatality, but that was due to ARDS consequent due to severe bilateral pneumonia. Management of ACS in dengue is challenging. Physicians should have appropriate preparedness to deal with these cases.

Key words: Dengue fever, Acute coronary syndrome, Unstable Angina, Non ST elevated myocardial infarction, Antiplatelet, Anticoagulant.

Introduction:

Dengue fever is an arboviral disease transmitted by the Aedes aegypti mosquito

Most people with dengue have no symptoms or only a mild self-limiting fever, but some may develop life threatening dengue hemorrhagic fever or dengue shock syndrome. A small proportion of patients may experience severe organ dysfunction affecting the liver, heart and nervous systems.[1] Increased pro-coagulant activity during dengue fever leading to thrombotic events is overlooked, but is an important complication which needs more awareness among clinicians. Thrombotic events of large veins including ileo-femoral deep vein thrombosis have been reported in Brazil representing 5.4% of all dengue in-patients. [3]Dengue associated cardiac involvement has varied incidence and presentation like Myocarditis, Pericarditis, functional abnormalities, arrhythmias, atrioventricular conduction disorders and nonspecific electrocardiographic (ECG) abnormalities are some of the cardiac problems observed in dengue patients. Acute coronary syndrome(ACS) could present in dengue fever but is not widely reported and management is also challenging due to unavailability of specific guidelines on management. Here we present a series of 5 cases of dengue fever with ACS and share the therapeutic challenges we faced while managing these patients.

The patients of this case series study were admitted in the Medicine Department of Uttara Adhunik Medical College and Hospital, Dhaka, Bangladesh between 1st July- 30th September 2023. Patients hospitalized with Dengue Fever who developed new-onset ECG changes consistent with ACS were selected, and Cardiac markers (Troponin I and CKMB), and Echocardiogram was done in each case.

Patients with pre-existing ECG changes and those with Dengue Myocarditis were not included in the case report.

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All of them were managed in the ICU with daily consultation by Cardiology Department. Their vitals, hydration status, urine output, CBC, glycemic control, ECG changes and cardiac markers were vigilantly followed. Evidence of other new-onset adverse events were also strictly monitored. Even though Total WBC Count, and Hematocrit play more important role in management of Dengue patient; we have focused more on mentioning about platelet count in this article, as that was directly related to our therapeutic approach.

Case Presentation:

Case 1:

A 62 year old man, previously known diabetic and hypertensive, presented with fever for 3 days associated with headache, nausea, and myalgia. Dengue NS1-Ag was positive, and he was given symptomatic treatment. Routine ECG revealed T inversion through leads V_1-V_5 on day 1. No earlier ECG was found for comparison, and he was given Tab Nitroglycerine, Trimetazidine, and Rosuvastatin. ECG was repeated after 6 hours and further deep T waves was found, along with new involvement of leads I, aVL, and V_6 as well.

He did not complain of any chest pain, chest tightness, or breathlessness and this could be explained by diabetic autonomic neuropathy. Troponin I was sent on 2 consecutive days, and both samples came out negative; So, he was diagnosed as a case of Unstable Angina and shifted to ICU. Echo showed regional wall motion abnormality in the lateral leads with an ejection fraction of 55%.

His initial platelet count was 2,40,000/mm^3 and he was given a loading dose of Aspirin and Clopidogrel, along with Enoxaparin. Potential platelet donors were kept ready in case there was a drastic fall in Platelet counts. On day 3 of therapy, his platelet count dropped to below 100,000/mm^3 and continued to fall thereafter, so LMWH and anti-platelets were stopped, he was continued on anti-ischemic drugs. His platelet continued to fall and reached 8000 after 3 days; he was given 1 unit of apheretic platelet. Platelet count didn't fall any further, and continued to rise. He was discharged after 10 days of admission with resolved ECG changes and platelet count was 1, 20,000/mm^3. He followed up with repeat Echocardiogram after 1 month, and then Left ventricular ejection fraction was 60%.

Case 2:

A 56 year old diabetic and hypertensive gentleman, previously on anti-anginal therapy for chronic stable angina was admitted with history of fever fever for five days back, which subsided 2 days ago. He complained of extreme weakness, and exertional chest discomfort while walking to the bathroom. Anti- dengue IgM antibody was positive, platelet count was 90,000/mm^3 on Day 1, and ECG showed horizontal ST depression > 3 mm in leads V_1 through V_6. Troponin I was raised (2.48ng/mL), and he was shifted to ICU with a diagnosis of NSTEMI. As his platelet count continued to fall, LMWH and anti-platelets could not be given. Moreover the aspirin he was previously getting had to be stopped. His Echocardiograph showed regional wall motion abnormality in the anterior leads, with ejection fraction of 46%. He also showing evidence of plasma leakage.

As his vitals were stable, he was given Furosemide infusion and injectable nitroglycerine for 2 days, along with Trimetazidine, and statins. Fortunately, his chest pain and breathlessness, lung findings, ECG changes, platelet counts, NT-pro BNP levels, and Troponin I samples improved, and he was discharged after 12 days of hospital stay and follow-up after 3 days. LVEF was 52% in echocardiography after 1 month.

Case 3:.

A 72 year old lady not previously known to be diabetic or hypertensive was admitted with fever for 4 days with vomiting and loose motion. On examination she was dehydrated, febrile, Temp-102^0 F, Pulse-110/min, BP- 90/70 mm Hg , RBS- 18.3 mmol/L and the ECG was normal. Dengue NS1-Ag on 2nd day of fever was positive. She was treated conservatively, and gradually improved.

On day 4, she complained of chest tightness, and urgent ECG revealed ST depression and T inversion in anterolateral leads (leads I, aVL, V_4-V_6). Two consecutive samples of Troponin I came out negative and she was labelled as a case of Unstable Angina. Her platelet count at that time was 40,000 cumm and falling; and she was not given antiplatelet and anticoagulant.

Despite her age and newly detected diabetes, she responded well to therapy and didn't develop any acute cardiovascular complication, like cardiogenic shock, or heart failure. Echocardiogram didn't show any regional wall motion abnormality, and her ejection fraction was 62%. She was discharged with advice to follow up after 1 month.

Case 4:

A 46 year old diabetic man presented to a private chamber outside with fever, vertigo, and breathlessness for 2 days. His dengue NS1 Ag test was positive, and he was found to be hemodynamically unstable with significant ST depression in leads II, III, aVF, and V2-V4. He was admitted in CCU. First sample of Troponin I was raised (14.6 ng/mL), initial platelet count was 70,000/cumm and he was given LMWH, and loading dose of anti-platelets. Platelet counts continued to decline; the above treatment was stopped, and he was shifted under Medicine at ICU. His condition was unstable from the outset and no improvement was noticed. Apart from grossly uncontrolled diabetes, he had clinical, biochemical and radiological evidence of acute LVF, bilateral pneumonia with severe metabolic acidosis, cardiogenic/septic shock, as well as acute ischemic stroke. He was treated with Infusion furosemide, infusion noradrenaline, injectable Meropenem and injection Moxifloxacin, insulin infusion. He subsequently had respiratory arrest and ventilated. He also developed ARDS, and was given methylprednisolone rescue therapy, but unfortunately he succumbed and died.

Case 5:

A 68-year old man with hypertension was admitted with fever, abdominal pain and vomiting for 2 days. Dengue

Table-I

Haematological and Biochemical Parameters

Case	Age	Sex	Comorbidity	Platelet Count At Diagnosis (Per mm^3)	Lowest Platelet Count Reported (Per mm^3)	Sgpt (U/L)	Antiplatelet/ LMWH Given
1	62 Y	Male	DM, Hypertension	2,40,000	8000	125	Yes, 4 days
2	56 Y	Male	Hypertension, IHD	90,000	15000	86	No
3	72 Y	Female	Diabetes, newly detected	1,60,000	20,000	92	No
4	46	Male	DM	70,000	6000	345	Yes, 1 day
5	68	Male	Hypertension	2,20,000	35,000	43	Yes, 5 days

Table-II

Cardiac parameters, Management and Clinical outcome

Case	Ecg	Troponin I	Echo	Cardiac Complications	Other Complications	Platelet Transfused	Outcome
1.	New Ischemic changes I, avL, V1-V6	Negative	RWMA present (EF- 55%)	Nil	Nil	Yes, 1 unit	Improved and discharged
2.	ST depression in V1-V6	Positive	RWMA (EF- 46-48%)	Developed HF	Nil	No	Improved and discharged
3.	Ischemic changes in I, avL, V1-V6	Negative	Normal (EF- 62%)	Nil	AKI (resolved)	No	Improved and discharged
4.	Significant ST depression in antero-lateral and inferior leads	Strongly positive	RWMA (LVEF-36%)	HF, Cardiogenic shock	Severe pneumonia, severe metabolic acidosis, ARDS	Yes, platelet, whole blood under diuretic coverage	Died on day 14
5.	T inversion in inferior leads	Negative	Normal (EF- 62%)	Nil	Nil	No	Improved and discharged

NS1 Ag was positive, S. lipase was normal and initial CBC showed mild hemoconcentration with normal platelet count and haemoglobin. He was treated conservatively, and his symptoms improved. He complained of chest tightness on the 3rd day and ECG showed T inversion in the inferior leads, with 2 consecutive Troponin I samples being normal.

He was diagnosed as Unstable Angina and was shifted to ICU. LMWH and anti-platelets were started and continued for 5 days. They had to be discontinued from the 6th day onwards due to fall of platelet count to 53000/mm^3. He was hemodynamically stable with anti-ischemic therapy only, and did not need any platelet infusion. He was discharged on the 10th day with all normal parameters and was asked for follow up after 1 week with CBC and ECG, and after 1 month with Echocardiogram.

Discussion:

We reported five cases of dengue fever complicated with acute coronary syndrome and discussed the therapeutic challenges associated with their management. These patients had clinical and serological evidence of dengue infection with development of Unstable Angina, and Non ST elevated MI during hospital admission.

Cardiac involvement in dengue is well known. Of the dengue serotypes, cardiac involvement has been described in infections with DENV-2 and DENV-3 [5,6] serotypes. Reported cardiac complications of dengue include; conduction abnormalities, hypotension, arrhythmias, myocarditis, heart failure, pericarditis and cardiomyopathy.[7] The cytokine storm occurring in dengue fever is implicated in the pathogenesis of myocarditis and occurrence of arrhythmias.[8]

Dengue myocarditis can sometimes masquerade myocardial infarction.[9,10] However, dengue fever complicated with true myocardial infarction is reported in only a few case reports. [11,12,13]

Older age, presence of type 2 diabetes and hypertension as risk factors favors preexisting coronary atherosclerosis in these patients. Development of acute ischemic type chest pain ST segment elevation in anterior chest leads with reciprocal changes in inferior leads and evolution of Q waves favour Myocardial Infarction over Myocarditis and Pericarditis. Furthermore, the presence of regional wall motion abnormalities on echocardiography also provides evidence of ischemia-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.[14] Endothelium loses it's non-thrombogenic protective properties (maintained by expression of tissue factor, plasminogen activator inhibitor-1 and von Willebrand factor) due to endothelial damage by dengue virus, cytokines and antibodies.[14]

Dengue virus downregulates the thrombomodulin-thrombin-protein C complex formation at the endothelial surface, with a reduction in activated protein C level.[15] Plasma levels of anticoagulant proteins C, S and anti-thrombin III have been reduced and levels of pro-coagulant tissue factor and antifibrinolytic plasminogen activator inhibitor- 1 have been increased during the course dengue fever.[16] Increased lupus anticoagulant activity has been demonstrated in a patient with cerebral ischaemia.[17] 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,[18], pulmonary thrombo-embolism , mesenteric vein thrombosis4and central retinal vein occlusion[19] 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, thrombocytopenia, 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. Here we will discuss the management of Unstable Angina and NSTEMI in five patients presented with both complicated and uncomplicated Dengue Fever.

PCI or thrombolysis or both involve anti-platelets and anticoagulants with high risk of bleeding. Thrombocytopaenia and coagulopathy in dengue further worsen the risk. There is no clear guideline on management of such patients in this situation.

Our first patient developed NSTEMI on the 3rd day of febrile ill-ness at a platelet count 2,40,000/cm3 , then we started anti-platelet LMWH after considering the risk and benefits and which was withheld after 3 days when platelet had fallen below 70,000/cm3 and was treated conservatively with anti-ischemic with close monitoring of new cardiac events. He was given 1 unit apheretic platelet. He was discharged after 10 days of admission with resolved ECG changes and improved Ejection Fraction and Platelet count 1, 20,000 with anti-platelet drugs .

In our second case only conservative treatment was given. Patient had NSTEMI and LVF which was eveident by Ejection Fraction 46-48% and raised NT-pro BNP (1500 pg/mL), he was given Furosemide Infusion and injectable nitroglycerine for 2 days, along with Trimetazidine, and statins. Fortunately, his chest pain and breathlessness, lung findings, ECG changes, platelet counts, NT-pro BNP levels, and Troponin I samples improved.

In Our third and fifth case one was a 72 years old non diabetic and normotensive lady and the other was a 68 years old Hypertensive old man who came with Dengue NS1Ag positive. ECG revealed ST depression and T inversion in anterolateral leads (leads I, avL, V4-V6). 2 consecutive samples of Troponin I came out negative and was labelled as a case of Unstable Angina. Third was not treated with anti-platelet or anti-ischemic agents due to Dengue Fever but improved symptomatically after the course of ill-ness and the fifth one was transferred to ICU and was given anti-platelet along with LMWH upto platelet count 50,000/cm3 and was stopped on 4th day of antiplatelet treatment. He was hemodynamically stable with anti-ischemic therapy only, and did not need any platelet infusion. He was discharged on the 10th day with all normal parameters and asked to follow up after 1 week with CBC and ECG, and after 1 month with Echocardiogram.

Unfortunately the outcome of our 4th case was different the patient subsequently went into respiratory arrest and had to be ventilated. He also developed ARDS and MODS, and was given methylprednisolone rescue therapy but unfortunately he succumbed and died.

Nonetheless, in patients presenting with acute coronary syndrome with thrombocytopaenia due to non- dengue related causes there have been successful attempts at

PCI and antiplatelet 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. [20] Further studies are required to determine whether this approach is beneficial in the case of dengue related thrombocytopaenia. However, it is pleasing to note that conservative management has also led to fair outcomes

Conclusion :
All 5 cases presented therapeutic challenge due to our inability to use antiplatelet and anticoagulant due to thrombocytopenia, and fortunately 4 out of the 5 patients discussed were discharged without any adverse event.

The unfortunate patient who had died presented after developing NSTEMI, and had other adverse features like Heart failure, Ischemic stroke, and ARDS.

Strict monitoring of vitals, hematological and cardiac parameters and good glycemic control, along with proper fluid management resulted in less morbidity despite high risk and inability to use proper drugs.

References:
1. Guzman MG and Harris E. Dengue. Lancet 2015; 385(9966): 453–465.

2. Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. Nature 2013; 496(7446): 504–507.

3. da Costa PSG, Ribeiro GM, Junior CS and da Costa Campos L. Severe thrombotic events associated with dengue fever, Brazil. Am J Trop Med Hyg. 2012;87(4):741-742. https://doi.org/10.4269/ajtmh.2012.11-0692

4. Yacoub S, Wertheim H, Simmons CP, et al. Cardiovascular manifestations of the emerging dengue pandemic. Nat Rev Cardiol 2014; 11(6): 335–345.

5. Kularatne SAM, Pathirage MMK, Medagama UAB, Gunasena S and Gunasekara MB. Myocarditis in three patients with dengue virus type DEN 3 infection.Ceylon Medical Journal. 2006; 51(2): 75-76. https://doi.org/10.4038/cmj.v51i2.1362

6. Neeraja M, Lakshmi V, Teja VD, Lavanya V, Priyanka EN, Subhada K, et al. Unusual and rare manifestations of dengue during a dengue outbreak in a tertiary care hospital in South India. Arch Virol. 2014;159(7):1567-1573. https://doi.org/10.1007/s00705-014-2010-x

7. Shivanthan MC, Navinan MR, Constantine GR and Rajapakse S. Cardiac involvement in dengue infection. J Infect Dev Ctries. 2015;9(4):338-346. https://doi.org/10.3855/jidc.6200

8. Wali JP, Biswas A, Chandra S, Malhotra A, Aggarwal P, Handa R, et al. Cardiac involvement in Dengue Haemorrhagic Fever. Int J Cardiol. 1998;64(1):31–36. https://doi.org/10.1016/S0167-5273(98)00008-4

9. Deshwal R. Dengue Myocarditis Presenting as ST Segment Elevation MI. J Assoc Physicians India. 2019;67(3):91–92.

10. Patra S, Bhardwaj G, Manohar JS, Srinivasa KH, Kharge J and Manjunath CN. Acute myocardial infarction being the presentation of dengue myocarditis. J Cardiovasc Dis Res. 2013;4(2):159–161.   https://doi.org/10.1016/j.jcdr.2013.03.001

11. Umakanth M. Dengue fever complicated with Non-STEMI. Saudi J. Med. Pharm.Sci. 2017;3:704-706.

12. Lin SC, Huang CH, Lin CY, Lee WH, Su HM, Lin TH, et al. Dengue virus infection complicated with simultaneous multivessel ST elevation myocardial infarction. J Microbiol Immunol Infect. 2016;49(4):619-620. https://doi.org/10.1016/j.jmii.2015.05.023 13. Gopalakrishnan M. Acute St Elevation Awmi with Severe Thrombocytopenia in Dengue Fever is rare - Case Report. JMSCR. 2016;04(05):10635–10636. https://doi.org/10.18535/jmscr/v4i5.40

13. Gopalakrishnan M. Acute St Elevation Awmi with Severe Thrombocytopenia in Dengue Fever is rare - Case Report. JMSCR. 2016;04(05):10635–10636. https://doi.org/10.18535/jmscr/v4i5.40

14. Mairuhu ATA, Mac Gillavry MR, Setiati TE, Soemantri A, ten Cate H, Brandjes DPM, et al. Is clinical outcome of dengue-virus infections influenced by coagulation and fibrinolysis? A critical review of the evidence. Lancet Infect Dis. 2003;3(1):33–41. https://doi.org/10.1016/S1473-3099(03)00487-0

15. Cabello-Gutierrez C, Manjarrez-Zavala ME, Huerta-Zepeda A, Cime-Castillo J, Monroy-Martinez V, Correa BB-, et al. Modification of the cytoprotective protein C pathway during Dengue virus infection of human endothelial vascular cells. Thromb Haemost. 2009;101(5):916–928.

16. Wills BA, Oragui EE, Stephens AC, Daramola OA, Dung NM, Loan HT, et al. Coagulation abnormalities in dengue hemorrhagic Fever: serial investigations in 167 Vietnamese children with Dengue shock syndrome. Clin Infect Dis. 2002;35(3):277–285. https://doi.org/10.1086/341410

17. Chen WH. An unusual transitory increase of lupus anticoagulant in dengue virus infection complicated with cerebral ischaemia. J Infect. 2006;52(3):e87-e91. https://doi.org/10.1016/j.jinf.2005.06.003

18. Samarasekara K and Munasinghe J. Dengue shock syndrome complicated with acute liver failure and   kidney injury, infective endocarditis, and deep vein thrombosis: a case report. J Med Case Reports. 2018;12:321. https://doi.org/10.1186/s13256-018-1862-1

19. Velaitham P and Vijayasingham N. Central retinal vein occlusion concomitant with dengue fever. Int J Retina Vitreous. 2016;2:1. https://doi.org/10.1186/s40942-016-0027-x

20. . Neskovic AN, Stankovic I, Milicevic P, Aleksic A, Vlahovicstipac A, Calija B, et al. Primary PCI for Acute Myocardial Infarction in a Patient with Idiopathic Thrombocytopenic Purpura, A Case Report and Review of the Literature. Herz. 2010;35(1):43–49. https://doi.org/10.1007/s00059-010-3262-1