Complicated Dengue Fever with diffuse Pulmonary Hemorrhage :

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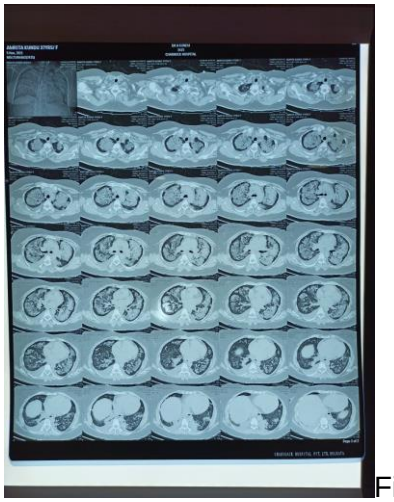
Introduction:

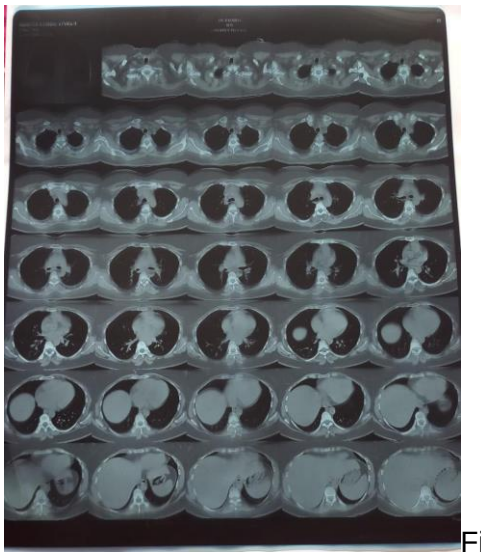
Dengue fever is an acute viral illness caused by dengue virus (type 1,2,3,4) . It is a mosquito-borne flavivirus that belongs to the family Flaviviridae, and consists of four distinct serotypes . Dengue virus causes disease in humans, including dengue fever, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) . The virus is transmitted to humans by the bite of infected female mosquitoes of the genus Aedes. Dengue disease has a wide spectrum of clinical signs and symptoms, ranging from asymptomatic infection to severe and lethal manifestations like thrombocytopenia and Hemorrhagic manifestation (DHF) and full blown shock syndrome also hepatitis, pancreatitis, serositis leading to ascites and pleural effusion, and . However, pulmonary hemorrhage and hemoptysis has been reported in 1.4% of dengue infections.

Case report:

A 37 years old normotensive, euglycemic, euthyroid lady presented in the ER with history of high grade intermittent fever for 5 days, along with nausea and vomiting for last 2 days and pain abdomen since 1 day. She had history of covid 19 infection 5 months back. She was admitted and all necessary investigations were sent. Initially, she had dehydration with BP : 100/60 mmHg (with postural drop of 10 mm hg in SBP) pulse : 82 beats / mins, SpO2 : 100%, with reduced air entry in right lung, with epigastric tenderness.
Her initial reports , showed positive for Dengue ns1 ag , and Dengue IgM , platelet count of 1.55 Lac, TC - 5100 , PCV - 34.4 , Hb- 10.9 gm/dal , raised liver enzyme - SGOT- 355 , SGPT - 749 (without hyper bilirubinaemia), low albumin, normal amylase , lipase levels and other fever profiles were negative. Chest xray showed B/L pleural effusion R>L .
Conservative therapy continued with IV fluid , hepato protective drugs, albumin transfusion etc . On day 7 of disease her livers enzymes increased (SGOT - 826, SGPT - 1592) , with drop in Hb (9.1) and PCV - (28.8), but platelet count increased to 1.7 lac. On day 9 of disease she developed sudden onset progressive hypoxia . She was put on oxygen support, later escalated to NIV support and then HFNC (since patient could not tolerate NIV) .
Her reports showed no thrombocytopenia (platelet - 1.95 lac) , but drop in Hb(7.1gm/dL) and pcv (24.9), with rise in INR (from 1.18 → 1.45). She was transfused with 1unit PRBC, along with inj Vitamine K .
HRCT Thorax was done . Scan(fig 1)

 Fig 1.

revealed extensive areas of consolidation with air bronchogram and ground glass opacities in both lungs suggestive of diffuse alveolar Hemorrhage. Pulse steroid therapy started (with inj methyl prednisolone at 40mg iv thrice daily dosage) and continued for 5 days, and later tappered over 1 week. Her oxygen requirement gradually reduced and she was discharged after 2 days after steroid therapy was completed. (With Hb - 10.5 , pcv - 29, platelet - 2.95 lac)
Repeat ct scan thorax was done after 1 month during OPD follow up which showed complete clearing of both lung parenchyma.

 Fig 2 .

Discussion:

This particular case talks about a relatively rare and potentially fatal complication of Dengue Fever.
Two most important prognostic marker of Dengue Fever, being thrombocytopenia, and hematocrit value , were gradually improving in this patient. Hence, a sudden onset respiratory distress and hypoxia should raise strong clinical suspicion to think of pulmonary Hemorrhage. Clinical suspicion was strengthened by drop in hemoglobin and hematocrit and was confirmed by timely done HRCT Thorax.

Most commonly, Hemorrhagic manifestations in DHF are associated with progressive thrombocytopenia and / or coaggulopathy (as marked by deranged PT, INR, aPTT values) . Though, in our case the hemorrhagic manifestation was not associated with thrombocytopenia (as platelet count was above 1 Lac) , though INR (1.45) and aPTT (44.5) were raised, indicating the presence of platelet dysfunction i.e qualitative fall in platelet count in Dengue viral infection.
It has been shown by various studies that thrombocytopenia and hypofibrinogenemia are the two most prominent hemostatic defects constantly discovered associated with Dengue fever. Increased intravascular clotting seemed to be one responsible factor, though not an outstanding one. This was evidenced by mildly and variably low factors II, V, VII, VIII, IX, X, and XII, and by mild to moderate increase of fibrin degradation products as well as low platelet counts and fibrinogen [1].
There are certain different hypotheses regarding the exact mechanism behind the platelet dysfunction leading to hemmoragic manifestation with or without thrombocytopenia and plasma leakage. A study by M Micheles et al showed that acute dengue was associated with platelet activation with an increased expression of the activated fibrinogen receptor (αIIbβ3), the lysosomal marker CD63 and the alpha-granule marker CD62P (P-selectin). Upon maximal platelet activation by TRAP(a platelet agonist) platelet function defects were observed with a significantly reduced maximal activated αIIbβ3 and CD63 expression and reduced platelet-monocyte and platelet-neutrophil complexes[2]. Studies have shown that DENV nonstructural protein 1 (NS1), which can be secreted into patients' blood, can stimulate immune cells via Toll-like receptor 4 (TLR4) and can cause endothelial leakage, it has also been showed that DENV could induce P-selectin expression and phosphatidylserine (PS) exposure in human platelets, Moreover, the activation of platelets by DENV NS1 promoted subthreshold concentrations of adenosine diphosphate (ADP)-induced platelet aggregation and enhanced platelet adhesion to endothelial cells and phagocytosis by macrophages [3] .

Thus we could conclude that bleeding manifestations can take place with or without thrombocytopenia due to ongoing platelet dysfunction and coaggulopathy, along with vast endothelial damage and plasma leakage. So a continuous clinical monitoring is required along with prompt response.

Reference :

1. **Hemostatic and platelet kinetic studies in dengue hemorrhagic fever** C Mitrakul et al. Am J Trop Med Hyg. 1977 Sep
2. **Platelet function alterations in dengue are associated with plasma leakage** M Michels et al. Thromb Haemost. 2014 Aug.
3. **Dengue virus nonstructural protein 1 activates platelets via Toll-like receptor 4, leading to thrombocytopenia and hemorrhage** Chiao-Hsuan Chao, Wei-Chueh Wu, Yen-Chung Lai, Pei-Jane Tsai, Guey-Chuen Perng, Yee-Shin Lin, Trai-Ming Yeh