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Case Report

A Fatal Clinical Case of Expanded Dengue Syndrome; Fortunately Saved

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Abstract

Dengue fever is still evolving to clinicians with changing and more challenging clinical and biochemical pattern even after more than two decades of epidemic. Most of cases being secondary infection showing increasing tendency to develop unusual and more severe form of disease. This case report is on a middle aged man who developed severe dengue in the form of Expanded Dengue Syndrome (EDS). Despite having severe Dengue hypovolemia was not a prominent feature. Along with broad spectrum of organ involvement he developed some very unusual features like Pneumonia, Hemophagocytic Lymphohistiocytosis (HLH), and most strikingly Haemolytic anaemia. Though Coombs test became negative, hemolysis was unexplainable other than autoimmune process. He was managed with broad spectrum antibiotics, methylprednisolone, transfusion of apheretic platelet, FFP and packed red blood cell. Prompt recognition and management saved the life of the patient.

Keywords: Expanded Dengue Syndrome (EDS); Hemophagocytic Lymphohistiocytosis (HLH); Haemolytic Anaemia

Introduction

As of 20 November 2022, a total of 52, 807 laboratory-confirmed dengue cases and 230 related deaths have been reported by the Ministry of Health and Family Welfare of Bangladesh since 1 January 2022 with a case fatality rate (CFR) of 0.44% [1]. Dengue has a wide spectrum of clinical signs and symptoms, ranging from asymptomatic infection to severe, lethal manifestations. Severe dengue is characterized by at least one of the following: severe plasma leakage leading to shock, with or without fluid accumulation with respiratory distress, and severe bleeding or severe involvement of organs (liver, central nervous system, heart, or other [2]. DF complications could involve several important organs such as the brain, liver, heart, lung, and kidney and have unusual and atypical clinical manifestations in each individual. Expanded Dengue Syndrome (EDS) is a new category from the WHO classification in 2012, namely, severe DF with unusual manifestations of other organ such as liver, kidneys, and other organs. Patients with comorbid, pregnancy, infants, elderly, and immune compromised are more prone to developing EDS conditions [3,4]. Hemolytic anemia is a rare complication of EDS where the mechanism of association has not been widely reported. Dengue virus needs to be investigated as an important triggering factor for Immune Associated Haemolysis syndrome (IAHS). The interrelationship between dengue and pneumonia is sporadically

reported in the literature. Along with co infection, the severe form of dengue might also prone to have pneumonia as complication and the pneumonia might be the cause of death in dengue patient [5]. Infection associated hemophagocytic lymphohistiocytosis (HLH) is another uncommon but potentially fatal complication in dengue fever. It would be important to differentially diagnose dengue-associated HLH from severe dengue hemorrhagic fever. Early recognition and initiation of steroid would be crucial for the successful treatment of dengue fever complicated by HLH. Here we discuss a case of a middle aged man who developed a severe form of dengue fever complicated with pneumonia, sepsis, AKI, HLH and haemolytic anaemia, those created a great management challenge.

Case Summary

Mr. Rokibul Islam, 35years, hypertensive, non-diabetic, non-smoker married male hailing from Rampura, Dhaka developed high grade continued fever on 16th October 2022. The highest recorded temperature was 104˚F. Initially, fever was not associated with any headache, body ache, joint pain, rash, respiratory and abdominal complain. His urine output and bowel habit were normal. The patient started cap cefixime on 2nd day of fever by himself. On 4th day of illness, he became afebrile but developed severe shortness of breath which was acute in onset and progressively increasing and was not associated with any cough, stridor, wheeze or chest pain or orthopnea. He was admitted to ICU for further management. On admission, patient was afebrile (temp was 98˚F), his blood pressure was 130/70 mmHg, pulse was 98 beats/min, respiratory rate was 20 breaths/min, oxygen saturation was 90% in room air, GCS score was 15/15, Tourniquet Test (TT) was negative. On respiratory system examination, there was coarse bilateral crepitation over almost whole lung fields along with features of mild pleural effusion on right side. Mild ascites was present on abdominal examination as evidenced by shifting dullness. A differential diagnosis of Dengue with pneumonia and covid 19 pneumonia were considered. IgM for dengue became positive. Initially, his O_2 demand was gradually increasing and he needed 25-30L O_2 per minute through high flow nasal cannula. On addition there was development of bilateral diminished breath sound on chest auscultation along with crepitation. Broad spectrum antibiotics Delafloxacin, Ticoplanin, and Polymyxin B were started. With treatment his respiratory symptoms were improving gradually and he started to maintain SPO_2 96% with10-12L O_2 per min through NRB mask. But eventually, the patient developed haematuria and large subcutaneous hemorrhage (echymosis) near venipuncture sites on mild trauma. Clinically he was gradually becoming anemic and icteric. Throughout his course of illness he was haemodynimcally stable without any significant feature of hypovolemia. On examination patient was moderately anaemic, icteric, there was large ecchymosis over both upper limbs. Features of pleural effusion and crepitation were much improved and there was no evidence of ascites or organomegaly. These scenario provoked strong suspicion of haemolysis which was confirmed after laboratory investigations. Patient also fulfilled the criteria for HLH. So our final diagnosis was Expanded dengue syndrome (pneumonia, sepsis, hepatitis, pancreatitis, Rhabdomyolysis, HLH, Hamolytic anaemia,). Along with fluid and electrolyte balance and broad spectrum antibiotics, the patent was treated with methylprednisolone. Fortunately patient responded well to treatment. Pneumonia resolved gradually, SpO_2 became 96% in room air, haemolysis ceased, regained normal kidney function and all his biochemical parameters settled down. Patent was discharged without any residual complication.

Figure 1

Investigation profile

Discussion

DF, DHF, and DSS are all names given to different symptomatically distinct dengue manifestations. The World Health Organization, in 2012, coined the term “expanded dengue syndrome” to describe patients that do not fit into either DHF or DSS but show atypical symptoms in vital organs systems such as the cardiovascular system, neurological system, kidneys, gut, and hematological

Investigations	20.10.22	21.10	22.10	23.10	25.10	26.10	27.10	28.10
CBC								
Hb%	18.1	11.5	10.5	8.7	8.0	8.2	8.4	8.4
WBC K/µL	6.4	8.3	27.1	20.5	22.6	22.9	20.79	17.36
Neutrophil	58	65	77	80	85	90	95	90
Platelet	14	16	65	100	120	100	93	95
HCT	50.9%	32.5%	30.2%	27.1%	26.6%	26.9%	27.1%	27.4%
ESR mm in 1st hour	14	11	19	28	34	42	39	39
Ns1 antigen	Negative							
IgG for dengue	Positive							
IgM for dengue	Weakly positive							
RT-PCR for Covid 19	negative							
Na+ mmol/L	125		136					
K+ mmol/L	3.5		3.6					
SGPT U/L	2149	1633	350	121	73			
SGOT U/L	9102	4836	1170	109	65			
S lipase U/L		1728			163			
S. albumin gm/dl	3.34		3.35	3.21				
S. bilirubin mg/dl			4.7	5.3	5.8. Direct-1.8 Indirect 3.99			
Urine R/M/E								
Albumin	++	+++	++					
RBC/HPF	4-6	Plenty	30-40					
Pus cell/ HPF	1-3	4-6	2-4					
S cr mg/dl	2.54	1.97	1.37	1.22	1.1			
S urea mg/dl	40				93			
S ferritin(20-300 ng/mL)	75,500	105,435	65,208	26,268	15,396			6262
CRP mg/L			22	59	21		18	10
Reticulocyte count %				2.71	5.62		10.26	6.30
Coombs test Direct and indirect					Negative			
LDH IU/L					3390			
PT in sec								
APTT n sec	20		32	18		16		
INR	1.72		2.7	1.55		1.39		
Fibrinogen mg/dl				170				
D-dimer **µg/mL**			20.69				32.9	35

S. procalcitonin	1.03		13.10		1.08		3.32	
CPK U/L			8476	5663				
Blood C/S	No growth							
Urine C/S	No growth							
S.TG mg/dl						300		
NT pro BNP pg/ml			1517.6			3328		
USG of W/A	Right sided pleural effusion Moderate ascites Thick walled GB with pericholecystic collection							
ECG	Normal							

Table 1

Figure 2

system. Since last few years clinicians are observing significant changes in clinical and biochemical pattern of dengue fever [6]. EDS is now being increasingly used in literature around the world, as it encompasses the rare atypical and uncommon symptoms of dengue, which we are seeing in recent times since the severity and spectrum of disease in DF has broadened [7,8]. Our patient was a case of secondary dengue infection as evidenced by positive IgG and IgM for dengue. NS1 was negative but is not unlikely finding on 5th day of fever. Eventually he developed severe form of disease with multi organ involvement and some uncommon features like Pneumonia, Hemophagocytic Lymphohistiocytosis (HLH) and most interestingly Haemolytic Anaemia. The presenting feature of the patient was pneumonia. Pulmonary complications are less common in dengue and can present as pleural effusion, pneumonitis, non cardiogenic pulmonary edema, acute respiratory distress syndrome (ARDS), and pulmonary hemorrhage. Such complications coincide with capillary leak syndrome and thrombocytopenia. Dyspnea may occur due to pleural effusion (most frequently), ARDS, pulmonary hemorrhage, pneumonia, or shock [9,10]. In general dengue does not cause pneumonia. Finding of pneumonia in dengue case is possible and usually implies superimposed bacterial infection. The Staphylococcus pneumonia is an important concomitant problem seen in dengue patient [11]. The co-infection between dengue and influenza can result in exacerbation of pneumonia [12]. Without co-infection, the severe form of dengue might also prone to have pneumonia as complication and the pneumonia might be the cause of death in dengue patient [5], In our patient cause of Pneumonia could not be specified as sputum and blood culture yielded no growth. We treated the case as secondary pneumonia and patient responded well with broad spectrum antibiotic. Most strikingly our patent developed haemolytic anaemia. Hemolytic anemia is a rare complication of EDS and the mechanism remains unclear. In our case, haemolytic anemia was suspected when the patent became anaemic without any obvious bleeding. He also developed jaundice most likely from combined haemolysis and hepatitis as his SGPT level was also very high. Blood examination showed normocytic normochromic erythrocytes and increased reticulocytes which corresponds to the criteria for hemolytic anemia [13]. The destruction of RBC was also characterized by increased indirect bilirubin, as well as raised LDH. The mechanism of hemolytic anemia associated with dengue virus infection remains unclear. A predictable possibility is the presence of cold-type autoimmune haemolytic anemia, which is caused by complications of several infections that are characterized by the destruction of antibody-coated red blood cells. The key that plays a role in activation of antibody is the regulation of cytokines that trigger the activation of T lymphocyte immune regulatory activity in dengue infection haemolytic anemia [14]. In this case, the Coombs test was negative. 5-10% of all cases of AIHA are Coombs negative [15]. Hemolytic anemia with a negative Coombs test is known to be related to the hemolysis process that is based on Ig A antibodies [16]. Antibody examination was not done in our study due to limited resources in our facility. This is similar to Medagodaetal's study on negative coombs test in Dengue Shock Syndrome patients [17]. The cause of hemolytic anemia in dengue virus infection is the result of transient depression of the bone marrow and a form of bleeding complications that occur [18]. Atypical manifestations of dengue infection have increased in diagnosis, in line with the ability to form transient polyclonal antibodies directly against erythrocytes antigens which in turn result in complement-mediated hemolysis [19]. Non immune haemolysis from sepsis induced disseminated intravascular coagulation was a possibility but patients APTT was normal.. Renal function examination showed an increase in creatinine parameters, AKI seems to be a frequent complication of severe dengue that increases the morbidity and mortality of the affected patients. Its etiopathogenesis is probably multifactorial, caused by intense systemic inflammation, hemodynamic instability, hemolysis, rhabdomyolysis and acute glomerulitis [20]. HLH in dengue infection remains a diagnostic challenge and can be misdiagnosed as sepsis because of the nonspecific, overlapping clinical features. The diagnosis of HLH requires fulfillment of at least 5 of the 8 criteria as listed: fever, splenomegaly, cytopenia affecting at least 2 of 3 lineages in peripheral blood, ferritin ≥ 500 μg/L, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in bone marrow or spleen or lymph nodes, low or absent NK-cell activity, and high level of soluble CD25 [20]. Markedly raised serum ferritin level is strongly associated with HLH, and a cutoff value of > 10,000 mcg/L was 90% sensitive and 96% specific for HLH [22]. Early recognition of this condition and use of corticosteroids is a major contributing factor in improving clinical outcome. Very high ferritin level provoked the suspicion of HLH in our patient and it was confirmed as he fulfilled the following criteria: fever, cytopenia (anemia and thrombocytopenia), increased Ferritin, increased Triglycerides, increased D-dimer, decreased Fibrinogen. We immediately started methylprednisolone to combat HLS and hemolysis and the

outcome was excellent. Our patient developed severe inflammatory complications but hemodynamic instability was not a prominent feature in this case. There was features of plasma leakage but his TT was repeatedly negative. Considering the whole scenario it was totally an atypical case of Dengue with diagnostic and management challenges.

Conclusion

Though we are dealing with dengue for several years, clinicians still observe changing and more challenging pattern of Dengue. The involvement of EDS with damage to various specific organs is still an important matter for further study. In anemia where there is no bleeding, it is necessary to suspect a hemolysis process that may occur due to an autoimmune process or direct infection of a virus. In case of very high level of acute phase reactant ferritin, other criteria of HLH should be sort out. As practitioners in both hospital and primary health care, early diagnosis of life threating conditions like haemolytic anemia and HLH is important to save life of the patients.

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