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Case Report

Dengue Hemorrhagic Fever and Non Immune Hemolytic Anemia: Two Recherché in Alliance

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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, retro orbital pain, myalgia, and arthralgia; and a severe form of the disease denominated dengue hemorrhagic fever/dengue shock syndrome, characterized by hemoconcentration, thrombocytopenia, and bleeding tendency. However, atypical manifestations, such as liver, central nervous system, and cardiac involvement, have been increasingly reported called expanded dengue syndrome. We report a 42 years old lady with atypical and rare presentation of dengue disease marked by non immune hemolysis following the critical phase of infection. Condition improved after conservative treatment. Hematological complications in dengue are now increasingly observed with the most common case is cytopenias and bleeding. Non immune hemolytic anemia in dengue is self-limiting in almost all cases. The main mechanism of hemolysis is still unknown though both direct viral infection and immune mediated damage have been suggested to be the cause. To avoid otherwise preventable morbidity and mortality, physicians should have a high index of suspicion for hematological complications in patients with dengue illness and should manage this accordingly.

Keywords: Non immune hemolysis; Thrombocytopenia; Expanded dengue syndrome; Dengue fever

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 travelers with dengue infection [1,2].

World Health Organization (WHO) classification of symptomatic dengue infection, continuously evolved, first in 1997 it divided into dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). In 2009 it improved into dengue with or without warning signs and severe dengue [3]. However, in 2011, WHO Regional Office for South East Asia (SEARO) revised and further improving the classification, divided into DF, DHF without shock or with shock (DSS) characterized by increased vascular permeability, thrombocytopenia (platelets <100,000), bleeding tendency, and, in a small percentage of patients, circulatory shock [4-7] and expanded dengue syndrome [8].

Expanded dengue syndrome is a new entity added to the classification system to incorporate a wide spectrum of unusual manifestations of dengue infection affecting various organ systems that had been reported including gastrointestinal, hepatic, neurological, cardiac, pulmonary and renal systems [8]. Patients with comorbid, pregnancy, infants, elderly, and immunocompromised are more prone to developing EDS conditions [9,10]. Hemolytic anemia is a rare complication of EDS where the mechanism of association has not been widely reported.

Unlike other viral infections, non immune hemolysis determined by dengue infection is a rare complication. We describe a 42 years old Bangladeshi lady diagnosed with non immune hemolysis caused by oligosymptomatic dengue infection.

Case Presentation

A 42 years old pleasant lady, from Dhaka, Bangladesh, not known to have any diabetes mellitus, hypertension, bronchial asthma or epilepsy presented to us with the history of high grade, intermittent fever, severe headache, body ache and retro orbital pain for 4 days, vomiting for several times for the same duration. Previously, she went to the primary care facility and was given antibiotics (Azithromycin) and acetaminophen. The patient had no history of dengue fever. She denied any cough, chest pain, palpitation, shortness of breath, abdominal pain or distension, burning micturition, joint pain. She had no recent history of travel of late. She lives in 2nd floor of her apartment and have hobby of gardening. His elder brother just recovered from dengue 1 week prior his illness. On examination, she was compos mentis (GCS 15), febrile (temperature 103°F), with pulse 110beats/min, with normal rhythm and volume, blood pressure was 90/70 mm of Hg. There was diffuse blanching erythema, more prominent over trunk but there were no other signs of active bleeding. Other systematic examination revealed no abnormalities.

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Table 1:

Test names (Reference range)	Day 1	Day 3	Day 5	Day 6	Day 8
Hb (12-16 gm/dl)	12	12.8	6.9	11.8	11.9
MCV	82.3	82.6	84.5	81.6	81.8
MCH	29.1	29.3	29.7	28.8	30
TC WBC (3500-11000/mm^3)	3700	3150	4320	4600	5100
Platelet (150000-450000/mm^3)	36000	40000	79000	97000	178000
Hct (35-47%)	37.1	40	19.6	35.6	36.5
SGOT (10-45 U/L)	729	404	458		96
SGPT (10-50 U/L)	1218	887	412		69
S. Creatinine (0.6-1.2 mg/dl)	1.1	0.8	1.1		1
S. Sodium (135-145 mmol/L)	130	141	136		140
S. Potassium (3.555mmol/L)	4.2	4.1	3.7		4.3
S. Albumin (3.5-5.0 g/dl)			3.3		3.8
Blood glucose (<7.8mmol/L)	7	5.7	6.9		5.9
Non fasting cholesterol (mg/dl)			96		
C-reactive protein (<6mg/L)		18			5
S. LDH (140-280 U/L)			2205		247
ICT for malaria	Negative				
Blood film for malarial parasite	Negative				
Blood Culture	No growth				
Dengue NS1 antigen	Positive				
PT			Pt: 12sec, control 13sec, INR:1.06		
aPTT			Pt: 35sec, control 36sec		
Reticulocyte count (0.5-1%)			7.20%		1.50%
Serum Bilirubin (0.2-1.2 mg/dl)			6.19		1.16
Direct (<0.2mg/dl)			3.12		0.8
Indirect (0.2-0.8 mg/dl)			3.07		0.36
Coombs test (direct and indirect)			Negative		
Peripheral blood film			Anisopoikilocytosis, fair no of poly chormatic cells with scattered nucleated RBC, normal white cells, thrombocytopenia		
Day count is as per hospital stay					

She was started treatment with intravenous fluids, anti-emetics, anti-pyretic. He became afebrile the next day but considering her newly developed abdominal discomfort, USG of whole abdomen was done which revealed thickened edematous gall bladder, moderate ascites and bilateral pleural effusion suggestive of dengue hemorrhagic fever. Serial blood count monitoring was done which showed progressive improvement of her white cell and platelet counts and volume replacement was done accordingly. With conservative management he showed dramatic improvement in following 4 days with reduced headache, vomiting and general well being. But she complained of worsening weakness. Repeat clinical examination showed severe pallor and icterus. As there was no bleeding with stable hemodynamic and presence of jaundice, work up for hemolytic anemia was undertaken and she was found to have non immune hemolytic anemia. No active management was given apart from regular close monitoring of her blood counts and vital signs. She was discharged on the eleventh day of illness with complete recovery and was found to be well on follow-up after 1-week.

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 [2,11].

Dengue virus infection is a disease that found in children and adults with the main symptoms of fever, muscle and joint pain that usually worsens after the first three days. This disease is an acute febrile illness accompanied by bleeding manifestations with potential shocking and can lead to death in children <15 years, but not likely to attack adults [12]. Signs of this disease are sudden high fever 2 to 7 days with no obvious cause, weakness, lethargy, anxiety, heartburn, accompanied by signs of bleeding in the skin (petechiae), bruising (ecchymosis) or rash (purpura). Sometimes there are other spontaneous bleeding manifestations such as nosebleeds, bleeding gums to dysentery. Severe symptoms can lead to decreased awareness or shock [13].

Laboratory results in dengue fever are found in thrombocytopenia (20% of the baseline on dengue hemorrhagic fever is a sign of plasma. Serological tests results in dengue are influenced by the type of dengue infection, whether it is the primary/first, or secondary/reinfection. IgM antibodies are detectable by days 3-5 after the onset of illness, rise quickly in two weeks and decline to undetectable levels after 2-3 months, because this late appearance, the first five days of clinical illness are usually negative of IgM. In dengue secondary infection, the rise of IgM is not as high as primary infection, and sometimes absent / undetectable completely [14].

IgG antibodies in primary infection, evolves relatively slow, with low titers 8-10 days after fever onset, increase subsequently and remain for many years, whereas in secondary infection it evolves rapidly, with high titers soon after fever onset and persist to a lifelong period. Hence, a ratio of IgM/IgG is commonly used to differentiate between primary and secondary dengue infections. Ratio of IgM/IgG titer less than 1.2 is considered a secondary dengue infection. But to be noted, titer ratio only could be validly use as a data if the IgG/IgM serological test is using pure quantitative means, not by qualitative or semi-quantitative [15].

NS1 antigen detection is widely used and cost-effective, NS1 could be detected from day 1-8 of fever onset, unaffected by a primary or secondary dengue infection. In conclusion, by combining

the serological (IgG and IgM) and NS1 tests, clinicians could rapidly assess the dengue diagnosis with its types (primary or secondary infection) and applies the best treatment [16].

In 2011, based on many reports of cases with dengue-related unusual manifestations and organ complications, WHO-SEARO further improved and revised 2009 WHO guidelines by adding a new entity, that is expanded dengue syndrome (unusual/atypical manifestation of dengue), these include neurological, hepatic, renal, cardiac and other isolated organ involvement, that could be explained as complications of severe, profound shock or associated with underlying host conditions/diseases or co infections [8].

In our patient there was hepatotoxicity. Both direct and indirect bilirubin was high suggesting hemolysis. High LDH cannot be used as sole indicator of hemolysis since significant elevations of LDH and AST are usual findings in severe dengue cases due to ischemic tissue injury [17]. Our case of severe dengue fever developed hemolysis, as manifested by sudden drop of hemoglobin, reticulocytosis, no blood loss and normal coagulation studies. Hemolytic anemia alone in dengue fever is considered rare and has been described in case reports in Sri Lanka [18] and in India as cold agglutinin induced hemolytic anemia in a dengue patient [19].

With the sudden anemia, disseminated intravascular coagulopathy was considered, but ultimately thought unlikely as the peripheral blood film lacked microangiopathic features, and PT APTT were normal. This patient had a self-limiting hemolytic anemia following dengue fever. An extensive literature survey did not reveal much previous reports of such an association. We have excluded, as far as possible, other likely causes of hemolysis. G6PD deficiency could induce oxidative hemolysis secondary to dengue fever. The mechanism of the hemolytic anemia is not clear.

Hemolytic anemia is a rare complication of EDS and the mechanism remains unclear. Physical examination and patient previous history could be important clues to diagnose haemolytic anemia [20]. In our case, haemolytic anemia was confirmed on the eighth day of disease. Peripheral blood examination showed normocytic normochromic erythrocytes with cell polychromasia (+) and normoblast (+) and increased reticulocytes, which corresponds to the criteria for hemolytic anemia [21]. In the case of acquired hemolytic anemia characterized by an increase in absolute reticulocyte indicating an increase in erythropoiesis [22]. The destruction of RBC is characterized by increased bilirubin, as well as LDH. However, in our case, LDH levels were increased. Increased bilirubin occurs in hemolytic anemia due to increased hemoglobin catabolism in the RES resulting in unconjugated bilirubin formation [23] and LDH as well as hemoglobin enters the bloodstream when red blood cells are destroyed [24].

It is known that high hemoglobin and hematocrit in DHF patients are caused by plasma leakage due to cross-reactions between pro-inflammatory mediators such as tumor necrosis factor (TNF)-alpha and anti-NS1 antibodies with proteins on the surface of endothelial cells, causing apoptosis of these cells. When the patient is rehydrated, hemoglobin will return to its original state [22]. This is one of the reasons that often cause a delay in diagnosis and treatment. The mechanism of hemolytic anemia associated with dengue virus infection remains unclear. A predictable possibility is the presence of cold-type autoimmune hemolytic anemia, which is caused by complications of several infections that are characterized by the destruction of antibody-coated red blood cells. However, the initiation of the production of the autoantibodies remains unclear. The key that plays a role in this process is the regulation of cytokines that trigger the activation of T lymphocyte immune regulatory activity in dengue infection hemolytic anemia [18].

In this study, the Coomb test was negative. Hemolytic anemia with a negative Coombs test is known to be related to the hemolysis process that is based on IgA antibodies [25]. Antibody examination was not done in our study due to limited resources in our facility. This is similar to Medagoda et al.'s study on negative coomb test in Dengue Shock Syndrome patients [26], but in contrast to the study of Ayeetal and Nurul et al. that showed positive indirect coomb's test in dengue patients [27,28]. Cold agglutinin is an antibody contained in the structure of the carbohydrate antigen of erythrocytes, which will be active at low temperatures (<37°C) with most consist of IgM antibodies [26]. Polyclonal IgM is usually acquired after infection-causing generalized hemolysis and is self-limiting, but requires transfusion in some cases. There is no previous evidence regarding the association of cold agglutinin hemolytic anemia with dengue virus infection, in which bleeding manifestations are one of the characteristic features of increased vascular permeability, thrombocytopenia, and hemoconcentration [29].

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 [30]. 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 [21]. The recovery process from dengue infection will also result in there solution of a hemolysis [31].

Conclusion

In view of the rising incidence of dengue fever and a greater understanding of the disease, atypical manifestations of dengue fever are increasingly being diagnosed. 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. Our case implies that immune hemolytic anemia might be a potential clinical feature of severe dengue. It alerts clinicians to consider hemolysis as a cause of anemia other than blood loss due to gastrointestinal bleeding, in dengue. It also implies that dengue virus infection might be included in the list of the infective causes of immune hemolytic anemia in addition to Mycoplasma pneumoniae and others. Moreover, recovery from dengue fever results in the resolution of hemolysis.

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