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AN UNUSUAL PRESENTATION OF DENGUE FEVER - DENGUE FEVER WITH THROMBOTIC MICROANGIOPATHY

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ABSTRACT

BACKGROUND

Dengue fever is a tropical, vector-borne infection caused by Flaviviridae, transmitted by the bite of Aedes mosquito. Dengue fever is predominantly asymptomatic but common clinical manifestations include fever with thrombocytopenia induced bleeding tendency, myalgia, arthralgia. Renal involvement in dengue is attributed to pre-renal Acute Kidney Injury. Dengue fever induced thrombotic microangiopathy is very rare. We present a case of Dengue fever induced Thrombotic microangiopathy.

INTRODUCTION

Various presentations of Dengue fever represent a spectrum ranging from asymptomatic cases to undifferentiated fever to severe Dengue with or without organ involvement. [1] Organ involvement can occur in the form of asymptomatic transaminitis, fulminant hepatic failure, myocarditis, pulmonary hemorrhage, spontaneous splenic rupture, lymph node infarcts, polyneuropathy. [1]

Dengue fever presents with typical as well as atypical symptoms, one of the atypical presentations being Acute Kidney Injury of the pre-renal type, secondary to dehydration. [2] Incidence of renal involvement in Dengue fever ranges from 0.3% to 13.3%.[3] A recent study from India reported Acute Kidney Injury in 10.8% of patients with Dengue fever. [1] Besides pre-renal AKI, other renal involvements seen in Dengue include Acute Tubular Necrosis, rhabdomyolysis, sepsis related Hemolytic Uremic Syndrome. [2] Thrombotic microangiopathy occurs very rarely in association with Dengue fever due to activation of complement pathway. [1]

CASE PRESENTATION

A 31-year-old male with no previous medical comorbidities presented to the emergency room with history of high-grade fever and low back ache for a duration of 3 days. On admission, his vital signs were stable and systemic examination was unremarkable. Arterial Blood Gas revealed severe metabolic acidosis with high lactate and low bicarbonate levels. Patient was admitted to the ICU. Baseline blood investigations showed elevated total count and thrombocytopenia, deranged RFT and deranged LFT in the form of indirect hyperbilirubinemia with severe transaminitis. Inflammatory markers were elevated. Patient also had coagulopathy with elevated D-dimer levels and reduced serum fibrinogen. Serum procalcitonin was mildly elevated. Peripheral smear showed presence of schistocytes, polychromatophillic cells and microspherocytes and reticulocyte count was 7.9%. Fever profile was sent, and patient tested positive for Dengue NS1 and IgG.

With the above clinical picture of Microangiopathic Hemolytic Anemia, ANA profile was done to rule out autoimmune disease and was negative. Serum complement levels were low, presumably secondary to liver dysfunction. On day 2 of hospital stay, patient was intubated in view of respiratory distress. In view of anuria and worsening renal function, hemodialysis was initiated, and 6 cycles were completed. Three cycles of High-flow plasmapheresis were carried out and patient was

extubated. Repeat complement levels improved concurrently with improving liver function and coagulopathy. Gradual improvement in renal function and urine output occurred and patient was discharged.

DISCUSSION

Microangiopathic Hemolytic Anaemia is a broad terminology used to describe any hemolytic anaemia due to red cell fragmentation occurring in association with small vessel disease. [4] Characteristic features that aid in diagnosis include, evidence of fragmented red cells on peripheral smear, thrombocytopenia and microthrombi in the vasculature causing ischemic tissue necrosis. Red cell destruction within the microvasculature causes hemolysis and fragmentation of RBCs, whereas thrombocytopenia results from platelet activation and consumption.

Clinical spectrum of Microangiopathic Hemolytic Anaemia ranges from Disseminated Intravascular Coagulation, Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura, all three being clinicopathological diagnoses. Depending on whether renal or neurological symptoms prevail, Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura can be described as two pathologically indistinguishable but clinically different entities. [5]

Disseminated Intravascular Coagulation is a widespread hypercoagulability state causing both micro and macrovascular thrombi, leading to multiorgan dysfunction. As a part of the process of thrombosis, there is consumption of clotting factors and platelets, resulting in life threatening hemorrhage. Hence, it is otherwise called ‘consumptive coagulopathy’. It commonly occurs in critically ill patients such as those with severe sepsis, trauma, malignancy, placental abruption. Vascular endothelial damage appears to be the inciting factor that results in an imbalance between coagulation and bleeding, forming clots in the circulation and concurrent consumption of coagulation factors and platelets, causing bleeding elsewhere. Diagnosis is based on a prolonged Prothrombin time and Partial Thromboplastin Time, decreased serum fibrinogen, hematocrit and platelet count, increased D-dimer. Treatment is mainly supportive with platelet and plasma transfusion and IV anticoagulant is needed. [6]

Hemolytic Uremic Syndrome presents with non-immune hemolytic anaemia of the microangiopathic type, thrombocytopenia and renal impairment. Of the two forms, the typical form occurs in children, commonly triggered by Shiga-toxin producing E.coli infection and manifests as bloody diarrhoea. [7] The atypical form can occur at any age and is the less common type. Multiple triggers including non-enteric bacterial infections, viral infections, drugs, malignancies, autoimmune diseases can precipitate the disease. Complement activation and consumption as evidenced by reduced levels of serum C3 and its deposit in the glomeruli and renal microvasculature is a hallmark of the disease. In contrast, serum C4 levels are found to be normal - reflecting the activation of the alternative complement pathway. Treatment is supportive with hemodialysis and definitive with plasma exchange. [7]

The third entity of the spectrum, Thrombotic Thrombocytopenic Purpura is characterised by the pentad of hemolytic anaemia, thrombocytopenia, fever, renal and neurological dysfunction. It results from congenital or acquired deficiency of ADAMTS13, a vonWillebrand factor cleaving protease. Low levels of ADAMTS13 activity leads to accumulation of large multimers of vWF that bind platelets and initiate thrombosis and organ ischemia, as evidenced by renal and neurological dysfunction. Congenital TTP results from decrease or absence of ADAMTS13 enzyme whereas the

acquired form results from autoantibodies targeting ADAMTS13. Plasmapheresis with high dose corticosteroid therapy appears to be the mainstay of treatment. [3]

Microangiopathic hemolytic anaemia occurring secondary to Dengue fever is an uncommon association. Our patient had features of both Disseminated Intravascular Coagulation and atypical Hemolytic Uremic Syndrome. With early institution of plasmapheresis alongside hemodialysis support, patient's liver function improved concurrently with serum complement levels and coagulopathy. Renal function and anuria gradually improved, and patient was discharged on day 32 of hospital stay with normal renal parameters and no further hemodialysis support.

CONCLUSION

Dengue fever causing Microangiopathic Hemolytic Anaemia is an uncommon entity and a strong index of clinical suspicion is required for the diagnosis. With rising incidence of Dengue fever and better understanding of the disease, atypical manifestations are being increasingly recognised. Lack of awareness of atypical manifestations can lead to increased mortality from a potentially treatable disease.

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