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Case History
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Plasmodium vivax Malaria: An Unusual Presentation of Atypical Hemolytic Uremic Syndrome

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Introduction

Atypical Hemolytic Uremic Syndrome (aHUS) is now a well-recognized entity associated with many diseases and settings. Historically this term was used to describe those with microangiopathic hemolytic anemia, thrombocytopenia and renal failure not associated with diarrhea. But now it is used to describe the complement mediated Thrombotic Microangiopathy (TMA) which does not have ADAMTS13 deficiency or documented shiga toxin as an etiological agent. aHUS is generally associated with genetic or acquired defect of regulation of complement on host cells. In aHUS, infections are usually considered as trigger and not the causes of disease [1]. Secondary HUS is associated with *Streptococcus pneumonia* and *influenza* virus, apart from transplantation, cancer, cytotoxic drugs, autoimmune diseases and pregnancy [1]. These infections are considered as causes of HUS and not just triggers.

In normal homeostasis, factor H and factor I are the regulatory molecules interacting with activated complement factors like C3b, thereby protecting red cells, platelets and endothelial cells from lysis [1]. If this fails, then the disbalance between activation and regulation may cause formation of membrane attack complexes on platelets and endothelial cells leading to platelet activation and endothelial damage respectively. This may trigger activation of coagulation system along with platelet aggregation leading to microthrombi formation within the vasculature. Thus aHUS can be perceived as severe complement dysregulation attacking red cells, platelets and endothelial cells in contact with plasma [1]. The typical clinical trial of Microangiopathic Hemolytic Anemia (MAHA), thrombocytopenia and organ damage in aHUS is a complement mediated process; hence it is logical that therapeutic complement inhibition may be effective in aHUS.

In Mumbai, malaria is rampant and endemic. We have a severe and rare not previously reported case of *P. vivax* induced aHUS.

Case History

An 18-year-old Indian male, presented to local facility for fever with chills and was treated as uncomplicated malarial fever. He was given chloroquine, amoxicillin clavulanate, and subsequently primaquine after confirming normal Glucose 6 Phosphate Dehydrogenase (G6PD) test. The patient was transferred to LTMGH hospital a week later for generalized weakness, persistent fever and oliguria. Physical examination showed blood pressure of 112/70 mmHg, subconjunctival hemorrhage, facial puffiness and mild icterus. His rapid malarial antigen test was positive, complete blood count revealed hemoglobin of 9.4 g/dl, WBC count 11500/µl, platelets of 47000/µl. Peripheral smear showed schistocytes, helmet cells, spherocytes, reticulocytosis, and low platelets (Figure 1). The laboratory investigation revealed Total bilirubin 5.2 mg/dL, indirect bilirubin 2.6 mg/dL, serum Aspartate Transaminase (AST) and serum Alanine Transaminase (ALT) were 93 units/L and 92 units/L respectively. Blood urea nitrogen was 48 mg/dL and creatinine 6.1 mg/dL. Serum Lactate Dehydrogenase (LDH) 1278 U/L (ref: 140-250 U/L). Investigation for iron deficiency anemia showed normal serum iron-78 mcg/dL (ref: 50-150), total iron binding capacity (TIBC)-345 mcg/dL (ref: 300-350). Prothrombin time was 11.2 sec (control <13) and International Normalized Ratio (INR) 1.0 (control <1.25), Activated Partial Thromboplastin Time (APTT) 28.6 sec (29-31), fibrinogen 337 mg/dL. Other serological tests for common coexistent infections like dengue and leptospirosis were negative. Urine routine microscopy showed Red blood cells 10-15/hpf, Epithelial cells 1-2/hpf, Pus cells 4-5/hpf. Ultrasonography showed normal sized kidneys. ADAMTS 13 levels were 114.21% normal (50% to 160%).

On day four of his admission, creatinine increased to 7.9 mg/dl and blood urea nitrogen to

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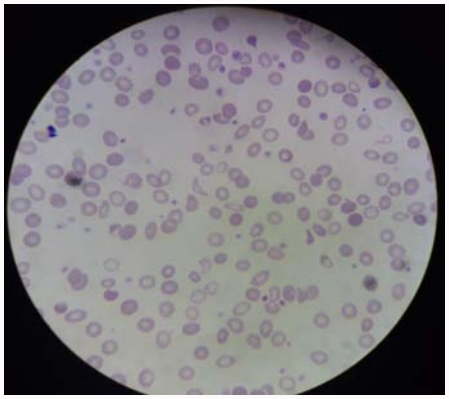

Figure 1: Peripheral smear showed schistocytes, helmet cells, spherocytes, reticulocytosis, and low platelets.

120 mg/dL, and he developed oligoanuria with respiratory distress. Patient was intubated and put on ventilatory support. Hemodialysis was initiated and patient was given alternate day hemodialysis and received packed red cells transfusion in view of persistent hemolysis and resultant low hemoglobin. He was given Inj. artesunate 2.4 mg/kg loading dose, followed by 1.2 mg/kg for 7 days, inj. ceftriaxone 1 g, antiemetics, antipyretics, and supportive care in ICU. Initially there was no response to hemodialysis with persistent oliguria. He required mechanical ventilation for seven days. After nine days of initiation of hemodialysis, urine output began to improve and creatinine reduced to 3.5 mg/dl and urinary output increased to 2500 ml/24 h on day 13 of admission. He was discharged on day 20 with Hemoglobin of 9.9 g/dl, creatinine 1.1 mg/dl and absent schistocytes in peripheral smear.

Discussion

Microangiopathy is now seen not only in hematology but also in rheumatology and infectious diseases. Malaria which is well known for hemolysis has not yet been described to cause AHUS.

According to world malaria report of 2017, number of malaria cases reported from India is 1.3 million and deaths at 23,990 [2]. The incidence of acute renal failure due to malaria in India is around 4% to 17.2% [3]. Renal manifestations range from mild proteinuria and urinary sediment abnormalities, acute tubular necrosis, glomerulonephritis and acute interstitial nephritis, all leading to acute kidney injury. The mechanisms for renal involvement are many including microcirculation blockade by parasitized RBC leading to acute renal insufficiency, immune system activation leading to complement activation causing immune complex deposition and glomerulonephritis as well as a secondary hemolytic uremic syndrome. Cortical necrosis has also been described in malaria [4].

Complement activation is central in aHUS; release of C5 a along with increased activity of tissue factor produces a procoagulant state of endothelium. ADAMTS13 is zinc containing metalloproteinase enzyme acting as von Wille Brand (vWF) factor cleaving protease. This helps to keep in check vWF polymers in plasma. Low ADAMTS13 levels would be seen in congenital or acquired Thrombotic Thrombocytopenic Purpura (TTP) which would be close differential. This patient had classical microangiopathy, severe renal failure and a normal ADAMTS13 fulfilling the criteria for aHUS. This hospital is a 1500 bedded Municipal General Hospital in Mumbai in the state of Maharashtra. There is frequently an inability to procure a medication, because sometimes it's not licensed or unavailable for this institution. The use of eculizumab to reverse the complement mediated disease has been well described for aHUS, paroxysmal nocturnal hemoglobinuria, and generalized myasthenia gravis and even in other disorders like Guillain Barre Syndrome where complement mediated demyelination is implicated [5]. The occurrence of TMA in this case of complicated malaria attributed to aHUS brings the important role of complement system in picture. Eculizumab is a humanized monoclonal antibody that blocks terminal complement by binding to C5. Early use of eculizumab in such patient can help in recovery from renal failure, prevent the need of hemodialysis and also reduce the mortality inherently associated with such illness. If eculizumab was available we would have used it even without our ability to be secure that this was a complement mediated aHUS (by demonstration of reduced factor H and I activity). Therefore, dialysis was the only option along with supportive therapy as eculizumab was not available for a therapeutic intervention. Fortunately this patient recovered from his renal failure. As malaria is a common entity in India, one has to be aware of AHUS as a rare and dreaded complication of malaria. Eculizumab, if and when available would be the drug of choice.

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