

Atypical haemolytic uraemic syndrome and its treatment: A case report

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Abstract

Atypical Haemolytic Uraemic Syndrome (aHUS) is considered an uncommon pathology that usually affects young adults and causes acute kidney injury which can further lead to End Stage Renal Disease (ESRD). Here we present the case of a previously healthy young boy who was diagnosed as a case of atypical HUS on renal biopsy in Sheikh Zayed Hospital Lahore. His C3 was low, while ANA and C-ANCA P-ANCA were in normal range; multiple sessions of plasmapheresis were conducted, whereas IV Methylprednisolone was also given during both admissions (the patient had to be readmitted six months later after having been discharged on improvement). After that, his GFR improved along with other laboratory parameters. Rituximab was also offered but the family refused due to affordability issue.

Keywords: Atypical HUS (aHUS), End Stage Kidney Disease, Complement Alternative Pathway.

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Introduction

Haemolytic uraemic syndrome (HUS) is an uncommon state of thrombotic microangiopathy (TMAs). The presentation of TMAs includes thrombocytopenia, microangiopathic haemolytic anaemia and thrombi in small blood vessels that subsequently leads to end-organ dysfunction. The most common TMAs are Shiga Toxin-producing *Escherichia Coli* (STEC-HUS) associated HUS and thrombotic thrombocytopenic purpura (TTP) than atypical HUS (aHUS) and secondary HUS after the associated pathology. AHUS did not have a good prognosis previously but with the advent of Eculizumab, anti C5, progression to End Stage Renal Disease can be prevented. AHUS usually occurs due to abnormality of alternative complement pathways but can also present without complement dysregulation. Triggering factors include autoimmune disease, transplant, pregnancy and infections. Extra renal manifestations have been reported in almost 20 percent of the cases. Low C3 levels can also be seen in acute cases of Shiga toxin-associated HUS (STEC-HUS). Genetic variants have also been reported in aHUS that can guide towards treatment but therapy

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should not be delayed while waiting for the result of genetic variants.

All patients with primary aHUS should get Eculizumab, which if unavailable, the second option is plasma exchange therapy. The patient should ensure vaccination against meningococcal infection before starting Eculizumab, while antibiotic prophylaxis should also be given initially for two weeks. Kidney transplantation is the ultimate option but in case of a living related kidney donor, the potential donor carries a risk of genetic disease that must be excluded before transplant.

Case Report

A 15-year-old boy presented in the emergency room of Sheikh Zayed Hospital Lahore in January 15, 2019, with complaints of fever, nausea and bilious vomiting for the past one week, while there was no history of diarrhoea or abdominal pain. He had also noticed decreased urine output in the preceding week.

At presentation, he was pale, hypertensive (150/100mm Hg) and tachypnoeic. He was admitted to intensive care unit where his initial investigations showed normochromic normocytic anaemia with Hb 8g/dl (12-16), platelet count 120 (150-450), renal impairment creatinine 6.0 mg/dl (1.0-1.2mg/dl), BUN 75 mg/dl (7-18mg/dl), high lactate dehydrogenase LDH 1200U/L (81-234U/L) along with proteinuria 2+ and microscopic haematuria (RBCs 10-12) on urinalysis. Arterial blood gases reflected the picture of metabolic acidosis with pH 7.29 (7.40) and bicarbonate of 17 meq/L (24.0).

Further anaemia study revealed haemolysis; fragmented RBCs in peripheral blood smear and liver function tests (LFTs) showed high indirect bilirubin of 7mg/dl (0.0-1.0mg/dl). The Coombs test was negative and fibrin degradation products (FDP) were normal along with the coagulation profile. On the preliminary findings of TMA, the patient was initiated with daily plasma exchanges (1.5 litre) and total 13 sessions were carried out with gradual recovery of renal functions, platelet count and LDH levels (normalised to 275 U/L). During the course of the treatment, IV Methylprednisolone 1.5g was also instituted.

Further serology workup revealed low C3 level 28 (90-180mg/dl); ANA and ASO titre were also normal. C-ANCA

and P-ANCA were negative. ADAMTS-13 activity was within normal range. The patient had refused renal biopsy despite counselling. His condition improved and he was discharged in February 2019, with creatinine level of 1.4 mg/dl, on Prednisone 0.5mg/kg/day and antihypertensive drugs.

He was lost to follow up and almost six months later in July 2019, he again presented with shortness of breath with blood pressure at 200/100mmHg, along with features of fluid overload. He had severe metabolic acidosis and acute kidney injury reflecting creatinine at 10mg/dl and urea 88mg/dl. He was stabilised after two sessions of haemodialysis on consecutive days. Laboratory investigations revealed thrombocytopenia and haemolytic anaemia with the presence of markedly raised LDH and fragmented red blood cells (RBCs) in peripheral blood film. Considering the diagnosis of thrombotic microangiopathy again, he was started on Solumedrol pulse 3gm in combination of plasmapheresis and seven sessions were carried out on a daily basis. He showed significant clinical and biochemical improvement and subsequently renal biopsy was performed which showed the histopathological features of thrombotic microangiopathy. He was diagnosed as a case of atypical HUS on the basis of atypical presentation with low C3 level and normal ADAMTS-13 activity along with striking findings on renal biopsy. The limitations were availability of genetic testing and barriers to treatment were availability of Eculizumab in developing countries like ours, whereas Rituximab couldn't be administered due to financial problems of the family. Currently the patient is free of dialysis with creatinine at 3.1mg/dl (eGFR 41ml/min) and adequate urine output as per last follow up in Sheikh Zayed Hospital Lahore on December 13, 2019.

Discussion

Haemolytic uraemic syndrome (HUS) comes under the category of thrombotic microangiopathies (TMAs). The common features of TMAs are haemolysis, thrombocytopenia, and thrombus in small blood vessels that leads to end organ damage. Clinically TMAs in order of frequency are HUS related Shiga toxin-producing *Escherichia coli* infection (STEC-HUS) and thrombotic thrombocytopenic purpura (TTP), followed by atypical HUS (aHUS) and HUS associated with other diseases (called secondary HUS).¹

Atypical HUS is a complement-mediated disorder that is controlled by many genes.² Many patients have urinary tract or gastrointestinal infection before the clinical trio and develop to aHUS.³ In complement mediated HUS,

mutation of complement factor H (CFH) gene has been commonly seen that is necessary for regulatory proteins. Alterations in Plasminogen, Diacylglycerol Kinase E and Factor X11 have also been seen that are linked directly to the complement system.⁴

Complement is the main defence mechanism to combat against virulent organism. There are three pathways for its activation namely: classical, lectin and alternate pathway.⁵ All three pathways meet at the point where C3 starts to divide. The first two pathways (classical and lectin) get activated by combining with antigen-antibody complexes or microorganisms respectively while an alternate pathway remains continuously operational that subsequently produces C3b that further stick with pathogens and host cells without any difference. C3b meet CFB, that breaks down by Factor D which further make C3 convertase C3bBb. C5 breakdown occurs to form the membrane attack complex (MAC or C5b-9) causing further cell lysis. Alternative pathway can lead to formation of C3b spontaneously that leads to phagocytosis which can also initiate self-inflicting response.

Complement factor H (CFH) usually regulates the alternative pathway that can dissociate C3 convertase and can overcome the destructing process. Another regulatory protein is membrane cofactor protein (MCP) that is expressed on all cells except erythrocytes. The CFI is a serine protease that regulates three different complement pathways in the presence of cofactor proteins. Complement factor B and C3 mutation has been observed in 8% of patients; it causes a hyperactive C3 convertase resistant to dissociation. Mutation of thrombomodulin, an endothelial surface anticoagulant protein that also modulates complement on cell surface, is usually seen in 3 to 4% of aHUS cases. Diacylglycerol E mutation is associated with infantile recessive aHUS.

In our patient no secondary cause of aHUS was present, while renal biopsy confirmed the features of TMA along with low C3 level in labs. The patient's condition improved after plasmapheresis sessions. He can have a genetic variant of this disease as he was quite young in age but due to non-availability of genetic test in our country this variety could not be ruled out.

Management

Plasma therapy was the first line of treatment till 2010, referring to various clinical trials.⁶ Plasma therapy prevents relapse and end stage renal disease (ESRD) in CFH mutation which has been noted in 12 different observations.⁷ In a study, 10 out of 12 patients' kidney functions were preserved after review in one to six years

with plasma therapy, only two developed ESRD after four years and seven years respectively,⁸ which showed doubtful effect of plasma therapy for long-term usage. In another review, patients who were treated with plasma therapy during acute stage had expired or developed ESRD during one year.⁹

Almost 25% patients responded to plasma therapy while 75% progressed to ESRD or died due to CFI mutation in an Italian Registry.¹⁰

No appreciated results of renal transplant have been seen in aHUS with recurrence in 60-80% of transplanted patients while graft failure has been observed in 80-90% cases.

Conclusion

The diagnosis of aHUS is a challenging task due to limited availability of genetic screening and antibodies to complement proteins, especially in the Third World countries. Generally, the prognosis of aHUS is poor in this patient despite the available option of plasma exchange and Eculizumab.

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