Case Report

Atypical hemolytic uremia syndrome in a young adult male

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ABSTRACT

Atypical hemolytic uremia syndrome (aHUS) is a rare and life-threatening disease, characterized by the same triad of hemolytic anemia, thrombocytopenia, and renal failure as seen in HUS. It differs in its etiology, being caused by a dysregulation of the complement pathway rather than Shiga-like toxin-producing *Escherichia coli*. Prognosis is poor, with 50% of cases progressing to end-stage renal disease (ESRD) and 25% succumbing in the acute phase. The treatment of choice is therapeutic plasma exchange which can lower mortality. Monoclonal antibody drugs such as eculizumab, which suppress the dysregulated complement pathway, help to prevent complement-mediated kidney injury. We report the case of a young adult male who presented with thrombocytopenia and worsening acute kidney injury and was diagnosed with aHUS based on high lactic dehydrogenase, low complement C3, and haptoglobin, as well as renal biopsy showing thrombotic microangiopathy.

Key words: Atypical HUS, Hemolytic uremia syndrome, Thrombotic microangiopathy, Renal biopsy

Hemolytic uremia syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are frequently occurring thrombotic microangiopathies that have common manifestations including thrombocytopenia, microangiopathic hemolysis hemolytic anemia, and end-organ damage caused by microthrombi [1,2]. The less common thrombotic microangiopathies include those which are usually caused by uncontrolled complement activation, or as secondary HUS with the coexisting disease [3].

CASE REPORT

A 44-year-old male patient was admitted to our hospital with complaints of dry cough, generalized weakness, reduced appetite, insomnia, 2–3 episodes of diarrhea for 2 days, and breathlessness on exertion for 1 day. He had a complex medical history comprising deep vein thrombosis, anti-phospholipid antibody syndrome, pulmonary thromboembolism (for which he underwent pulmonary thromboendarterectomy), and Evan's syndrome (autoimmune hemolytic anemia with refractory idiopathic TTP) along with multiple hospital admissions. He was presently on treatment for hepatitis C with velpatasvir and sofosbuvir.

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On arrival, he was febrile and tachypneic with low oxygen saturation on room air of 86%. Chest roentgenogram revealed left lower lobe pneumonia with bilateral mild pleural effusion. He was admitted to the intensive care unit and empirically initiated on ceftriaxone and azithromycin for community-acquired pneumonia.

Laboratory tests showed serum creatinine of 4.05 mg/dl, hemoglobin (Hb) of 10.2 g/dl, total leukocyte count of 6000 cells/mm^3, platelet count of 32000 cells/mm^3, and lactate dehydrogenase (LDH) of 414 IU/L. His breathlessness worsened the next day and creatinine levels increased further to 6.01 mg/dl, necessitating renal replacement therapy. Further tests showed normal d-dimer level, negative anti-nuclear antibody profile, low haptoglobin (0.08 mg/dl, normal range 41–165 mg/dL), low complement C3 (0.2 mg/dl, normal range 88–201 mg/dL), elevated ADAMTS-13 activity (60.7%), and factor H antibody assay of 132.7 mg/ml (normal range 0.3–0.5 mg/ml). Stool culture and multiplex polymerase chain reaction test on nasopharyngeal swab was negative while blood culture grew *Enterococcus fecalis* for which he was initiated on vancomycin 1 g every 48 h. Peripheral smear showed normocytic normochromic erythrocytes, many polychromatophils, leukocytosis with relative neutrophilia, and thrombocytopenia with giant platelets. Ultrasound abdomen showed moderate splenomegaly. A high-resolution computed tomography of the chest was suggestive of bilateral interstitial edema with minimal right-sided effusion and fibrotic bands,

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suggestive of old infection. Doppler's study of abdominal vessels was normal. The differentials pursued on this background of thrombocytopenia with worsening renal parameters were relapse of ITP and Atypical HUS (aHUS).

The patient was treated with oral prednisolone 60 mg once daily and eight sessions of plasmapheresis, with the plasma of 40 ml/kg in each session. Following this, his platelet counts increased to 113,000 cells/mm^3. His general condition improved, but since he remained on renal replacement therapy, he underwent a renal biopsy. Histopathology showed features of thrombotic microangiopathy and intraluminal thrombi in renal tubules, while immunofluorescence studies showed IgM and complement deposition (Fig. 1), which were conclusive for aHUS. The patient was discharged after 18 days, with a platelet count of 90,000 cells/mm^3 and Hb of 9.3 g/dl. At present, the patient remains on regular thrice weekly hemodialysis and on oral prednisolone 5 mg and warfarin 5 mg, on alternate days.

DISCUSSION

aHUS previously referred to as diarrhea-negative HUS presents with the same triad of microangiopathic hemolytic anemia, renal insufficiency, and thrombocytopenia, as seen in HUS [2]. The annual incidence in the age group up to 20 years ranges from 0.26 to 0.75 per million population, and for all ages, from 0.23 to 1.9 per million population [4]. It is a diagnosis of exclusion after ruling out Shiga toxin-producing *Escherichia coli* which accounts for 90% of cases of HUS, and also TTP, which presents with similar findings [3]. Prognosis is poor with up to 50% of cases progressing to end-stage renal disease (ESRD) needing long-term renal replacement therapy, or irreversible brain damage, and mortality of 25% [3]. Delay in recognition and treatment is known to cause poor outcomes.

aHUS is essentially caused by a dysregulated activation of the alternative complement pathway, as a result of mutations in complement regulatory proteins such as factor H, membrane cofactor protein, and factor I which results in reduced serum levels of complement C3 [5,6]. Deficiency of factor H, as well as an increase in anti-complement factor H (CFH) antibodies titers, can both predispose to the development of atypical HUS. The result is damage to endothelial cells by the formation of membrane attack complexes on them, as well as complement-mediated platelet activation, resulting in thrombocytopenia and platelet-rich microvascular thrombi. This form of HUS caused by genetic alterations is also referred to as familial HUS. Infections can precipitate the acute event in 60% of such patients. Hence, patients suspected to have atypical HUS should be tested for low serum C3 concentrations, although normal C3 levels may not exclude a complement dysfunction. The patient in the present case showed both low C3 and high CFH levels.

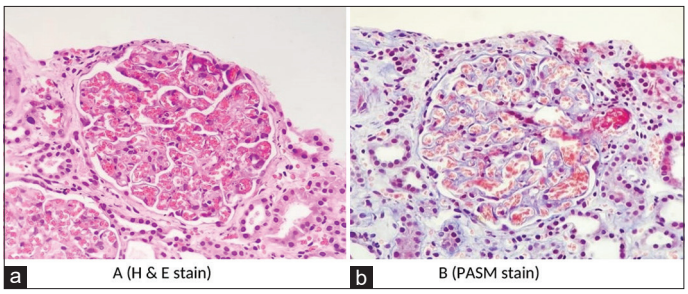

Figure 1: Renal biopsy histopathology slides using H and E (a) and PASM stain (b) showing thrombotic microangiopathy with diffuse mesangiolysis in most glomeruli and suffusion of fragmented RBCs in the mesangial region. Tubules show severe degree of acute tubular injury with interstitial hemorrhage and RBC casts in the lumen

aHUS must be distinguished from secondary HUS, also known as sporadic HUS, which occurs as a complication of a coexisting disorder or disease, most commonly *Streptococcus pneumoniae* infection. Other causes include autoimmune disorders (e.g., scleroderma, lupus, and antiphospholipid syndrome), postpartum HUS, bone marrow or solid organ transplantation, malignancy, and other infections such as *E. coli, Shigella dysenteriae*, and human immunodeficiency virus, even normal pregnancy, or use of certain drugs such as chemotherapy agents (mitomycin, cisplatin, and bleomycin), immunotherapeutic agents (cyclosporine and tacrolimus), and antiplatelet agents (ticlopidine and clopidogrel).

Central nervous system manifestations such as confusion, seizures, acute infarcts, and coma are the most common extrarenal manifestation of aHUS. Patients with ESRD requiring regular hemodialysis have a poor outcome [1]. Although this patient required regular dialysis, his renal function parameters improved during the course of hospitalization, and he had no neurological manifestations.

The Joint Committee of the Japanese Society of Nephrology and the Japan Pediatric Society has developed diagnostic criteria for aHUS [7]. A definitive diagnosis requires the findings of thrombocytopenia (platelets count <1,50,000/μL), acute renal failure (as per Kidney Disease: Improving Global Outcomes guidelines), and microangiopathic hemolytic anemia (Hb <10 g/dL along with either increased LDH or decreased haptoglobin or schistocytes on peripheral smear). Along with this, Shiga toxin should be ruled out by stool culture and TTP should be excluded from the study. The patient in this report fulfilled all these criteria. He underwent a renal biopsy in view of persistent renal failure, which was reported as acute thrombotic microangiopathy. The findings included diffuse mesangiolysis in most glomeruli, with a suffusion of fragmented RBCs in the mesangial region, diffuse capillary fibrin thrombi, acute tubular injury with RBC casts in the tubular lumen, and thrombosis in preglomerular arterioles. An immunofluorescence study showed the trapping of IgM and C3 in the glomerular tufts. Based on these findings, as well as high CFH antibody titer and LDH, low C3, and haptoglobin, the patient was diagnosed with aHUS.

Plasma exchange which removes complements and immune deposits from the circulation may lower the mortality rate in atypical HUS. This is indicated as a first-choice therapy in patients with a fluid restriction such as renal or heart failure. It should be initiated within 24 h of presentation, at a rate of one plasma volume (40 ml/kg) per session, and has been shown to benefit at least 70% of cases, with remission of hemolysis and improvement in platelet

counts. An alternative to plasma exchange is plasma transfusion, at the rate of 30–40 ml/kg on the 1st day followed by 10–20 ml/kg/day. Whichever modality is chosen should be continued for at least 2 days after remission, which typically occurs in 7–10 days after initiation of plasma therapy [8]. Patients who are refractory to plasma therapy may respond to bilateral nephrectomy. Other treatments such as intravenous immunoglobulins, steroids, heparin, and fibrinolytic agents have not proven beneficial.

The underlying dysregulated complement activation presents a therapeutic target for two monoclonal antibodies, pexelizumab, and eculizumab, which are directed against complement C5, thus preventing complement-mediated kidney damage in both acute episodes and recurrent disease. Eculizumab has been shown to reduce the occurrence of ESRD in many individuals [6,9]. Patients should receive the meningococcal vaccine before initiation of eculizumab as the risk of encapsulated bacterial infections increases with eculizumab therapy. However, the prohibitive cost of this drug has precluded its wider usage. Cyclophosphamide pulse doses in combination with prednisone and plasma exchange can be used in refractory cases to decrease CFH antibody levels and prevent relapse [10].

CONCLUSION

Atypical HUS is a rare disorder that requires a high index of suspicion, as early diagnosis and initiation of plasma exchange can be life-saving, while delay may result in ESRD or death. Renal biopsy is invaluable in confirmation of diagnosis and should be resorted to when clinical findings and other tests for aHUS have been inconclusive.

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