

A case of Atypical Hemolytic Uremic Syndrome

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Abstract: Atypical hemolytic uremic syndrome (aHUS) is an extremely rare, life-threatening, progressive disease that frequently has a genetic component. In most cases, it is caused by chronic, uncontrolled activation of the complement system, a part of the body's immune system that destroys and removes foreign particles. About 33-40% of patients die or develop end-stage renal disease (ESRD) with the first clinical episode of aHUS even with the best supportive care. We report a case of atypical HUS with classical clinical & laboratory characteristics.

Keywords: Acute kidney injury, complement, thrombotic microangiopathy.

INTRODUCTION

Atypical hemolytic uremic syndrome (aHUS) is an extremely rare, life-threatening, progressive disease and is frequently associated with a genetic component [1]. In most cases it is caused by chronic, uncontrolled activation of complement system that destroys and removes foreign particles [2]. The disease affects both children and adults and is characterized by thrombotic microangiopathy (TMA), the formation of blood clots in small blood vessels throughout the body, which can lead to stroke, heart attack, kidney failure, and death [1, 3].

The complement system activation may be due to mutations in the complement regulatory proteins (factor H, factor I, or membrane cofactor protein) [4] or due to acquired neutralizing autoantibody inhibitors of these complement system components, for example anti-factor H antibodies [5].

About 33-40% of patients die or develop end-stage renal disease (ESRD) with the first clinical episode of aHUS even with the best supportive care. Including subsequent relapses, a total of approximately two-third (65%) of patients die, require dialysis, or have permanent renal damage within the first year after diagnosis despite plasma exchange or plasma infusion (PE/PI) [4].

CASE REPORT

A 2.5 year old male child was admitted with complaints of high grade fever for 15 days, yellowish discolouration of body and eyes for 10 days, one episode of seizure 8 days prior to admission, facial puffiness, decreased urine output, dark colored urine for 2 days. There was no history of dysentery.

Examination revealed severe pallor; facial puffiness and petechial spots all over the body. At the time of admission, blood pressure was 150/110 mmHg (> 99th percentile+5 mmHg). Systemic examination showed enlarged liver approx. 2 cm below costal margin with span 8 cm. & enlarged spleen 3 cm in splenic axis, rest of clinical examination being normal. Blood investigations done at the time of admission revealed anemia (haemoglobin-6.2gm/dl), low platelet counts (77000/uL), mildly elevated serum bilirubin (3.5mg/dl), raised serum lactate dehydrogenase (4634U/L), raised blood urea (127mg/dl) and raised serum creatinine (1.97mg/dl). Peripheral blood film showed schistocytes (fragmented red blood cells), helmet cells and a raised reticulocyte count of 5%. Urine examination revealed Hemoglobinuria. Ultrasound of the abdomen showed mild hepatosplenomegaly with increased kidney size. This laboratory finding were suggestive of intravascular hemolysis.

Anti nuclear antibody and Direct Coombs Test were negative. Stool culture was negative for shiga toxin producing *Esherichae coli*. Work up for parvovirus, hepatitis B,C and Scrub Typhus were negative.

Based on above clinical and lab findings, a presumptive diagnosis of atypical hemolytic uremic syndrome (aHUS) was considered. To confirm the diagnosis, anti FH antibody levels (anticomplement Factor H done at AIIMS Delhi) and C3 levels were done. Elevated Anti FH titres (1359 Au/ml) and low C3 level (51.35 mg/dl) supporting the diagnosis. As plasmapheresis immediately instituted to child, child was also administered Intravenous immunoglobulin

(1gm/kg/day for 2 days), steroids, antihypertensives (enalapril, amlodipine). Patient responded well to treatment (anti FH antibody level 240 Au/ml). Blood urea and serum creatinine came down to normal levels(0.63mg/dl) , blood pressure also came down to normal value (100/60 mmHg which is below 90th percentile).

DISCUSSION

Atypical HUS is a heterogeneous group presenting with renal dysfunction, neurological dysfunction, and hypertension. Lack of appropriate treatment in a timely fashion is associated with an abysmal prognosis, and leads to end stage renal disease in 31% of patients [6].

There are multiple etiologies of atypical HUS and some include primary causes such as complement dysregulation, and secondary causes such as infections like streptococcus pneumoniae and human immunodeficiency viral infection, drug toxicity, or autoimmune disorders like SLE [7]. Complement activation and dysregulation is central to the pathophysiology of aHUS but normal C3 and/or C4 levels do not rule it out [8]. In the pathogenesis of aHUS alternative pathway is involved which is continuously activated by hydrolysis of C3 (does not require initiators) and regulated by complement factors I, H, thrombomodulin and membrane cofactor protein [9].

aHUS is associated with heterozygous mutations of following:-

1.complement factor H (CFH) [10-12], 2.membrane cofactor protein (MCP, CD46) [13], 3.factor I (CFI) [11, 14, 15] 4. Gain-of-function mutations in C3 and complement factor B (complement activating factors) [9]. ** Autoantibodies to factor H is the most common mutation seen (5-10%) [16, 17]. Around 35–40% of patients with aHUS will not have genetic mutation identified [18].

Atypical hemolytic-uremic syndrome should be distinguished from a more common condition called typical hemolytic-uremic syndrome. Unlike the atypical form, the typical form is caused by infection with certain strains of Esherichae coli and shigella dysenteria type-1 that produce shiga-like toxins. The typical form is characterized by severe diarrhea and most often affects children younger than 10. The typical form is less likely than the atypical form to involve recurrent attacks of kidney damage that lead to end stage renal disease.

The neurological and kidney-related signs and symptoms of aHUS overlap with those of thrombotic thrombocytopenic purpura (TTP). However, unlike aHUS, TTP is primarily an autoimmune disorder in which the presence of an inhibitory autoantibody results in severe deficiency of ADAMTS13, an enzyme that

cleaves von Willebrand factor (vWf), a large protein involved in blood clotting into smaller pieces.

As per the Joint Committee of the Japanese Society of Nephrology and the Japan Pediatric Society (JSN/JPS), a definitive diagnosis of aHUS is made when there is a triad of thrombocytopenia (platelets less than 1,50 000/uL), microangiopathic hemolytic anemia (hemoglobin of <10g/dL with increased LDH, decreased haptoglobin and presence of fragmented red cells in peripheral smear), and acute kidney injury (defined by the international guidelines group, the Kidney Disease: Improving Global Outcomes) with no association with Shiga toxins. TTP should also be excluded, in which ADAMTS13 activity has great value [9].

Treatment for aHUS is a combination of supportive care and measures to correct the underlying cause, the abnormality in the alternative pathway of complement. Supportive care consists of blood transfusions and management of kidney dysfunction, including antihypertensives, fluid management, and dialysis when necessary. Patients may require supportive care for dysfunction in other organs, such as insulin for pancreatic dysfunction. Platelets are given only if the patient is actively bleeding or having a procedure.

Since 1980, plasma exchange therapy has been the validated therapy for aHUS. Registry data reports effectiveness of this therapy in at least 70% of cases in which hematologic remission was achieved while renal response is less certain [18].

Eculizumab is a new therapeutic approach for aHUS. It is a humanized recombinant immunoglobulin G2/4 monoclonal antibody against complement factor C5. It inhibits the generation of C5b-9 (membrane attack complex) and hence inhibits the complement system. Eculizumab was approved by the Food & Drug Administration (FDA) in 2011 for the management of aHUS and cases have been reported to have favourable outcome with this therapy [19].

CONCLUSION

Our case provides a very good insight into the approach to the diagnosis and management of atypical hemolytic uremic syndrome . Quality of life is very poor for patients with aHUS, who are burdened with fatigue, renal complications, hypertension, neurological impairment, gastrointestinal distress, clotting at the site of venous access, and ultimately death. The main strategy remains to continue research towards better treatment options and therapeutic regimens in patients with aHUS to prevent irreversible renal dysfunction, thereby improving quality of life.

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