Introduction

Approximately, 10% of all hemolytic uremic syndrome (HUS) is atypical, caused by neither shigatoxin-producing bacteria nor streptococci. Atypical HUS (aHUS) is usually associated with perturbations in alternate complement cascade and has poor prognosis, with mortality as high as 25% and progression to end-stage kidney disease (ESKD) in 50% cases.[1] Complement factor B (CFB) is an essential component for activation of alternate complement pathway. Its active subunit combines with C3b to form C3 convertase (C3bBb), the chief driver of the activation of complement cascade. Gain of function mutations in CFB is described to cause chronic alternative complement pathway activation and is a rare cause of aHUS, implicated in only 1–2% of all cases of aHUS.[2]

Case Report

A 47-year-old male without previous comorbidities presented with complain of pedal edema, facial puffiness, and decreased urine output for 2 days. On examination, he had pallor, pedal edema, and blood pressure of 168/94 mm Hg. Rest of the physical examination was within normal limits. Laboratory parameters revealed hemoglobin 8.5 g/dl, total leukocyte count 11500/µL, platelet count 83000/µL, serum creatinine 7.4 mg/dl, serum lactate dehydrogenase 1565 U/L, peripheral blood film showing schistocytes, slightly raised total, and indirect bilirubin, normal kidney sizes on ultrasonography, no active urinary sediments, complement C3 level 46 mg/dl (normal level 90–180 mg/dl) and negative ANA; there was no evidence of G6PD deficiency. The patient received seven sessions of plasma exchanges along with three sessions of hemodialysis, following which he achieved hematological remission and became dialysis independent. Renal biopsy was done which revealed evidence of thrombotic microangiopathy (TMA). Antibodies to complement factor H were not sent for. Whole exome sequencing revealed novel heterozygous variation in exon 8 of the gene encoding complement factor B (CFB), at c.1106C>T (p.Pro369Leu) that was classified as variant of uncertain significance using the 2015 criteria of the American College of Medical Genetics and Genomics. The disease relapsed once 1 month after hematological remission, with platelet count dropping to 75000/µL and mildly elevated LDH (437 U/L). The relapse responded promptly to plasma infusions, administered at 20 ml/kg/day for 3 days, with platelet count and LDH returning to normal. However, C3 level remained low (52 mg/dl) and serum creatinine was 3.5 mg/dl on last follow-up.

Discussion

Hemolytic uremic syndrome is characterized by a triad of microangiopathic...
hemolytic anemia, thrombocytopenia, and acute kidney injury. Shigatoxin (Stx)-producing *Escherichia coli* O157:H7 is the most common type of HUS. HUS not caused by Stx is termed atypical HUS and is primarily caused by complement dysregulation. Besides these, HUS might also be secondary to other infections, metabolic condition, drugs, pregnancy, autoimmune disease, or following transplantation.[1,3] Atypical HUS represents approximately 5–10% of all HUS in children and majority of cases in adult. aHUS is an uncommon disease, affecting two per million population. Almost 20% of cases of aHUS are familial.[4]

Deficiencies in the alternative complement pathway proteins include inactivating mutations of genes coding regulators of the alternative complement pathway, such as complement factor I (*CFI*), factor H (*CFH*), membrane cofactor protein (*MCP*), and thrombomodulin (*THBD*); gain of function mutations in genes encoding factor B (*CBF*) and C3 (*C3*), and, chiefly in children, antibodies to CFH associated with homozygous *CFHR1* deletion. Additionally, single nucleotide polymorphisms or haplotypes in *CFHR1*, *CFH*, and *MCP* increase susceptibility to aHUS.[5] Mutations in *CFH* are most common (20–30% of aHUS), followed by *MCP* (10-15%), *C3* (5-10%), *CFI* (4-10%), and *THBD* (5%); of these, gain-of-function mutations in *CFB* are the rarest, seen only in 1 to 2% of patients with aHUS.[3] Table 1 summarizes the handful of cases with CFB mutation reported worldwide. The first such report was of two mutations from the Spanish aHUS cohort in 2007.[2]

Outcomes of aHUS vary depending upon the underlying complement factor deficiency. Around 60–70% of aHUS patients with *CFI*, *CFH*, and *C3* mutations, and 30% of those with anti-CFH autoantibodies die during the acute episode or go into end-stage kidney disease after relapses. Mutations in *CFB* are commonly associated with adverse renal outcomes, with loss of renal function in 88% of patients.[2]

Eculizumab is considered as the first-line therapy for all forms of primary aHUS, since this treatment improves renal function when started early during presentation with aHUS.[13] The duration of treatment remains unclear; whereas there is no evidence to support lifelong therapy in all types of aHUS, relapses occur after therapy discontinuation in 60-70% patients with *CFH* mutations, 50% with *MCP* mutations and 43% in *C3* mutations.[14] Hence, long-term therapy is recommended. In our case, eculizumab was indicated but could not be started due to unavailability. Plasma therapy in the form of plasma exchange or plasma infusion may be the only therapy available, especially in developing countries such as in our case. The therapy should be started as soon as aHUS is suspected, ideally within 24 hours of presentation, and continued until normalization of platelet count and serum LDH. Plasma exchange is gradually tapered and

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Table 1: Comparision of CFB gene mutation of various cohorts and case reports

| Cohort/case report | Patient (n) | Genotype | Nucleotide | Amino acid change | Domain |
|--------------------|------------|----------|------------|------------------|--------|
| de Jorge et al., 2007[^5] | 1          | Heterozygous | c.858C>G   | F286L            | VWA    |
|                     | 1          |          | c.967A>G   | K323E            | VWA    |
| Fremeaux-Bacchi et al., 2013[^5] | 1          |          |           | D279G            | -      |
|                     | 1          | -        |           | K350D            | -      |
|                     | 1          | -        |           | P369L            | -      |
|                     | 1          | -        |           | V455I            | -      |
| Maga et al., 2010[^6] | 1          |          | c.497C>T   | p. 166P          | SCR3   |
|                     | 1          | c.608G>A | p.R203Q    | SCR3             |
|                     | 1          | c.724A>C | p.I242L    | -                |
|                     | 1          | c.967A>C | p.K323Q    | VWA              |
|                     | 1          | c.1365C>T| p.M458I    | VWA              |
|                     | 1          | c.1598A>G| p.K333R    | SP               |
|                     | 1          | c.1807T>G| p.F603V    | MG6b             |
|                     | 1          | c.3125G>T| p.R1042L   | TED              |
|                     | 1          | c.608G>A | p.R203Q    | SCR3             |
| Tawadrous et al., 2010[^7] | 1          | -        | c.1598A>G  | p.Lys533Arg      | -      |
| Funato et al., 2014[^8]  | 1          | Heterozygous | c.1050G>C  | p.Lys530Asn      | -      |
| Geerdink et al., 2012[^9] | 2          | -        | c.967A>G   | p.Lys323Glu      | -      |
| Roumenina et al., 2009[^10] | 1          | Heterozygous | c.1050G>C  | p.Lys530Asn      | VWA    |
|                     | 1          | c.837A>C | p.Asp279Gly| VWA              |
| Alfakeeh et al., 2016[^11] | 1          | Heterozygous | c.1697A>C  | p.Glu566Arg      | -      |
| Zhang et al., 2016[^12]  | 1          | Heterozygous | c.1598A>G  | p.Lys533Arg      | SP     |
|                     | 1          | Heterozygous | c.221G>A   | Arg74His         | SCR1   |
|                     | 1          | Heterozygous | c.2008A>G  | Lys670Glu        | SP     |
withdrawn after achieving remission. Although there is limited evidence to establish the superiority of plasma exchange over plasma infusion, most experts recommend exchanges in view of the volume of plasma replaced. Overall, the choice is based on available resources, local expertise, and individual tolerance.[15] During plasma exchange, 1–2 plasma volumes (40–80 mL/kg per in adults and 50–100 mL/kg in children) are replaced in each session, with exchange frequency and duration decided based on the clinical response. Plasma infusions are an option when eculizumab or plasma exchange are not available and are administered initially at 30–40 mL/kg, followed by 10–20 mL/kg/day. Plasma infusion are also used to prevent or treat recurrence of aHUS when eculizumab is not accessible, as in our patient, and should be continued until normalization of platelet count and serum LDH.[16] Recently published HUS guidelines on managing aHUS in developing countries recommended long-term plasma infusion and consideration of eculizumab in patients with aHUS with mutations in \( \text{CFB}, \text{CFI}, \text{C3}, \text{CFH}, \text{or} \; \text{THBD}.[17] \)

Data are limited on response to plasma therapy in patients with CFB mutations. Remission following plasma therapy was reported in five cases[2,7,8,10] and in 30% patients with CFB mutation in another series.[1] In our patient, seven sessions of plasma exchanges led to hematological remission and discontinuation of dialysis, although renal function remained deranged. Family screening was offered after genetic counseling but could not be conducted due to financial constraints. The novel variation in CFB in our index patient while classified as variation of unknown significance using standard criteria, is uncommon, reported in 0.1%, and 0.05% cases in the 1000 Genome Project and Exome Aggregation Consortium databases, respectively. Its functional significance as a gain-in-function variation requires testing in animal and \textit{in vitro} models.

**Conclusion**

We describe, in an adult patient with aHUS, a novel heterozygous variation in \( \text{CFB} \) in exon 8 leading to amino acid substitution of leucine for proline at codon 369 (c.1106C>T; p.Pro369Leu). The functional significance and pathogenicity of the reported change requires confirmation in \textit{in vitro} and animal models and/or reporting in more patients with aHUS.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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