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BRIEF REPORT

Eculizumab therapy in a child with hemolytic uremic syndrome and CFI mutation

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Abstract
Background Hemolytic uremic syndrome (HUS) is the most common cause of acute renal failure in childhood. It usually occurs after a prodromal episode of diarrhea and it leads to significant morbidity and mortality during the acute phase. However, cases that start as diarrhea-positive HUS whose renal function fail to recover should be screened for genetic disorders of the complement system, which is called atypical HUS (aHUS).
Case-Diagnosis/Treatment We herein report a 10-year-old girl, who initially came with bloody diarrhea and had features of HUS with delayed renal and hematological recovery despite plasma therapy. Eculizumab (600 mg/week) was initiated on day 15 for atypical presentation and later a complement factor I (*CFI*) mutation was detected. The girl recovered diuresis within 24 h and after the third eculizumab infusion, hemoglobin, platelet, and C3 levels normalized; renal function improved; and proteinuria completely disappeared in 2 weeks.
Conclusion It is our belief that eculizumab can be the treatment of choice in children who have plasma exchange-refractory HUS with defective regulation of the alternative complement pathway.

Introduction

Hemolytic uremic syndrome (HUS) is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury [1]. It usually occurs after a prodromal episode of diarrhea, frequently bloody [2]. Approximately 10% of HUS cases are in the "atypical" category and 50% of these are associated with an impairment in regulation of the alternative complement pathway [1]. Mutations in complement 3 (C3), factor H (FH), factor I (FI), factor B (FB), and membrane cofactor protein (MCP) genes are associated with atypical HUS, and the frequency of complement FI (CFI) mutations varies between 2 and 11.3% [3]. We describe a child, who initially came with bloody diarrhea, was diagnosed with plasma therapy-refractory HUS and *CFI* mutation, and was effectively treated with eculizumab.

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Case report

A 10-year-old previously healthy girl, born to nonconsanguineous parents, was referred to our emergency department with a history of fever, abdominal pain, vomiting, and bloody diarrhea of 3 days' duration. On admission, physical examination was normal. Initial blood count, complete blood chemistry, and urinalysis were normal. There were white blood cells (leukocytes) and amebic cysts under microscopic examination of the feces. Metronidazole therapy was started orally and she was followed as an outpatient.

One day later, the patient was admitted to hospital for the second time with severe bloody diarrhea and anuria. On clinical examination, the child's heart rate was 100/min, blood pressure was 103/57 mmHg and temperature was 37.5°C. Systemic examination showed abdominal tenderness. Laboratory investigations showed anemia with a hemoglobin level of 8.5 g/dl, total leukocyte count of 11,800/mm^3, platelet count of 54,000/mm^3, and corrected reticulocyte count of 6%. The peripheral blood smear demonstrated fragmented red blood

cells and thrombocytopenia. Coombs test was negative. Her blood level of urea was 102 mg/dl, creatinine was 2.48 mg/dl, lactate dehydrogenase (LDH) was 1,796 IU/l (normal <400 IU/l) ,and C3 level was 76 mg/dl (normal 83–177 mg/dl). We could not measure FI, FH, and factor B levels, and factor H autoantibodies. Stool analysis was negative for leukocytes, parasites, *Salmonella*, *Shigella*, and enterohemorrhagic *Escherichia coli* (EHEC). Because of severe bloody diarrhea, hemodialysis was commenced instead of peritoneal dialysis and transfusion of packed red blood cells was instigated. She continued to be oligo-anuric, thrombocytopenic, and anemic. Her renal failure progressed; creatinine rose to 8.5 mg/dl, and anemia became severe with a hemoglobin level of 7.3 g/dl. On the fourth day of admission, plasma exchange (PE) treatment with 150% plasma exchange volume was started because of low C3 levels, progression of renal failure, and anemia with the consideration of atypical HUS (aHUS). Mutational analysis was negative for *CFH*, *CFB*, and *MCP* genes. However, a heterozygous K434R mutation was found in exon 10 of the *CFI* gene (Fig. 1a).

After ten sessions of daily PE, her urinary output was 200 ml/day with estimated glomerular filtration rate (eGFR) of 16 ml/min/1.73 m^2 and proteinuria 126 mg/m^2/h. She developed persistent low platelet and hemoglobin levels and renal failure under PE (Fig. 1b). Given the devastating renal prognosis in HUS despite PE, eculizumab (600 mg/week) was administered on the 15th day of admission. The girl recovered diuresis within 24 h, which allowed discontinuation of hemodialysis. After the third eculizumab (600 mg/week) infusion, hemoglobin (11.4 g/dl), platelets (254,000/mm^3) (Fig. 1b), and C3 levels normalized, renal function improved (creatinine level was 0.5 mg/dl and eGFR rose to 108 ml/min/1.73 m^2), and proteinuria completely disappeared within 2 weeks.

Eculizumab was well tolerated with no infusion-related or infectious complications. It was discontinued after the third infusion and the patient was discharged. The patient has remained in full remission for the past 4 months (Fig. 1b).

Discussion

Hemolytic uremic syndrome is a common cause of acute kidney injury in children [4]. It can be classified as diarrheal associated HUS (D+HUS) and nondiarrheal/atypical HUS (aHUS). D+HUS is the most common form and is due to gastrointestinal infection triggered by Shiga-toxin producing *Escherichia coli* (STEC), *Shigella*, and rarely by *Entamoeba histolytica* [4, 5]. The atypical form has been associated with complement dysregulation and occurs in 10% of cases [1]. In many aHUS patients, an infectious

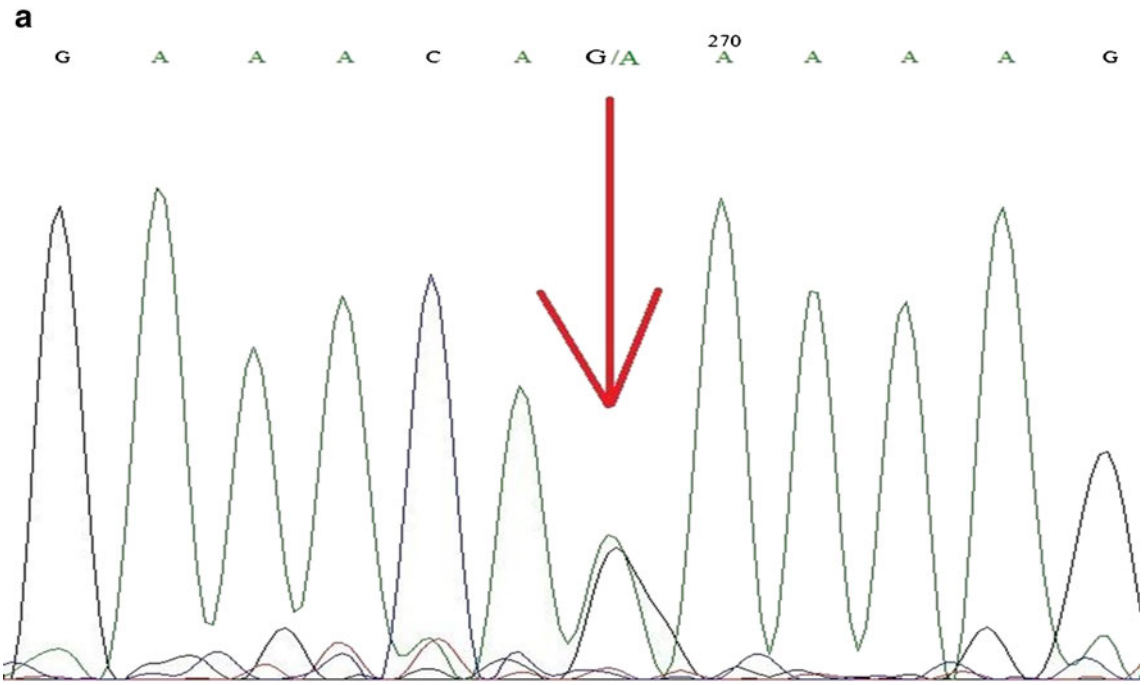

Fig. 1 **a** K434R heterozygous mutation in the *CFI* gene. **b** Summary of laboratory values of this patient with hemolytic uremic syndrome before and after eculizumab administration: Eculizumab was initiated at a dose of 600mg/week on the 15th day of admission after the patient failed to respond to daily therapeutic plasma exchange. It was discontinued after the third infusion. The hemoglobin levels remained stable (13.9 gr/dl) with normal platelet counts (230,000/mm^3), the renal function progressively improved (creatinine: 0.5 mg/dl) for the past 4 months

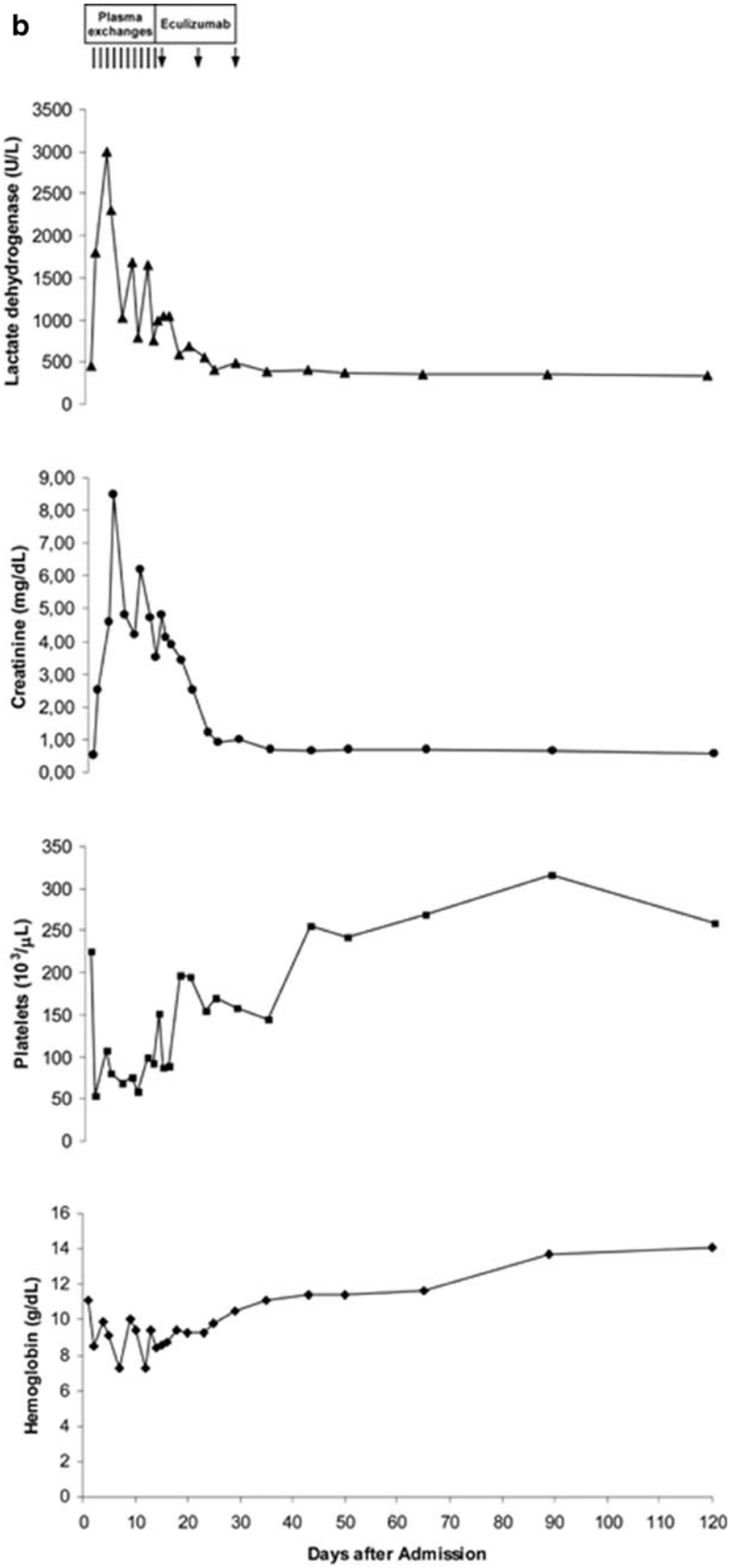

Fig. 1 (continued)

process such as diarrhea is identified 1–2 weeks before HUS onset. On the other hand, a genetic component may also contribute to some D+HUS cases [6]. It is important to note that low levels of C3 may indicate complement dysregulation and patients who start as D+HUS, but whose renal function fails to recover, should be evaluated further for the possibility of aHUS [7, 8].

In our patient, bloody diarrhea was evident on admission, but stool analysis was negative for leukocytes, parasites, *Salmonella*, *Shigella*, and enterohemorrhagic *Escherichia coli* (EHEC). Hemodialysis was started as soon as possible, but renal failure progressed and the C3 levels were found to be low. The delay in recovery suggested the possibility of aHUS and we undertook mutational analysis of complement factor genes.

Most cases of aHUS (50%) are strongly associated with mutations in genes encoding CFH, CFI, and MCP [9], and approximately 10% of children with aHUS have anti-CFH autoantibodies. Our patient was found to be heterozygous for a *CFI* mutation (ensemble accession number ENST00000512148 was used for K434R mutation; NT_016354.17 accession number was used for determination of the same mutation, but named K441R [rs41278047] in the NCBI database), but negative for *CFH* and *MCP* mutations. CFH autoantibodies could not be investigated.

Most patients with HUS and *CFI* mutations are heterozygous, and to date 40 case reports with *CFI* mutations related to clinical descriptions of HUS have been published [3]. The heterozygous mutation we found has to our knowledge not been described in HUS patients before. HUS onset in patients with *CFI* mutations following an infectious episode, such as diarrhea or upper respiratory tract infection, has been noted in 63% of patients [3]. In our patient we hypothesize that the dysentery predisposed the child, who was sensitive because of the *CFI* mutation, to develop HUS.

In FI-associated aHUS the overall prognosis is poor and more than 50% develop end stage renal disease (ESRD) or die during the first episode or within 1 year after the onset [3]. Plasma exchange is recommended for the management of HUS [3, 10, 11]. However, this invasive procedure, which requires a central venous catheter, can cause frequent allergic reactions and other complications. In our patient PE was initially thought to be effective, but despite 10 sessions of PE, hemoglobin and platelet levels were low, and renal failure continued, which was a cause for concern and indicated the possibility of aHUS.

New treatment agents like eculizumab, the monoclonal C5 antibody against terminal complement protein C5, have recently been reported in the treatment of aHUS and severe neurological or cardiovascular involvement D+HUS [12–15]. To date no severe side effects of eculizumab have been documented in the reported cases of aHUS. However, this treatment increases the risk of infection by encapsulated organisms, such as *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*. Vaccination against these pathogens is necessary at least 2 weeks prior to initiation of eculizumab [13–15]. The optimal duration of eculizumab treatment in children with HUS remains unclear and there are currently no clear recommendations available. Most authors suggest giving eculizumab every 2 weeks because of the possibility of relapse [13–15]. However, this is a new therapy and eculizumab may cause long-term side effects when used for a long time. Given these concerns regarding side effects, we only gave eculizumab three times and followed up the patient closely (weekly) for relapse of HUS. Our patient has remained in full remission for the past 4 months with serum creatinine 0.56 mg/dl.

To our knowledge, there is only one reported adult patient with a *CFI* mutation associated with aHUS who was treated with eculizumab. In that case, eculizumab was given four times weekly, continued every 2 weeks, and her last creatinine was 2.7 mg/dl [15].

In conclusion, to the best of our knowledge, our case is the first reported child with a heterozygous *CFI* mutation and HUS to be treated with eculizumab. We achieved a high and sustained response. Eculizumab should be considered as a first-line therapy for children if they have identified complement regulatory factor mutations and PE-refractory HUS. Future clinical trials in children with HUS are necessary to determine if successfully treated patients will require prophylactic therapy, and to demonstrate the safety of eculizumab.

References

1. Waters AM, Licht C (2011) aHUS caused by complement dysregulation: new therapies on horizon. Pediatr Nephrol 26:41–57
2. Besbas N, Karpman D, Landau D, Loirat C, Proesmans W, Remuzzi G, Rizzoni G, Taylor CM, Van de Kar N, Zimmerhackl LB, European Paediatric Research Group for HUS (2006) A classification of hemolytic uremic syndrome and thrombotic thrombocytopenic purpura and related disorders. Kidney Int 70:423–431
3. Nilsson SC, Sim RB, Lea SM, Fremeaux-Bacchi V, Blom AM (2011) Complement factor I in health and disease. Mol Immunol 48:1611–1620
4. Boyer O, Niaudet P (2011) Hemolytic uremic syndrome: new developments in pathogenesis and treatment. Int J Nephrol 2011:908407
5. Cavagnaro F, Guzman C, Harris P (2006) Hemolytic uremic syndrome associated with Entamoeba histolytica intestinal infection. Pediatr Nephrol 21:126–128
6. Sánchez-Corral P, Melgosa M (2010) Advances in understanding the aetiology of atypical Haemolytic Uraemic Syndrome. Br J Haematol 150:529–542
7. Sethi SK, Marie-Agnes DD, Thaker N, Hari P, Bagga A (2009) Hemolytic uremic syndrome due to homozygous factor H deficiency. Clin Exp Nephrol 13:526–530
8. Gupta A, Khaira A, Rathi OP, Mahajan S, Bhowmik D, Agarwal SK, Tiwari SC (2011) Diarrhea-related hemolytic uremic syndrome: unmasking antifactor H antibodies. Saudi J Kidney Dis Transpl 22:1017–1018
9. Mache CJ, Acham-Roschitz B, Frémeaux-Bacchi V, Kirschfink M, Zipfel PF, Roedl S, Vester U, Ring E (2009) Complement inhibitor

eculizumab in atypical hemolytic uremic syndrome. Clin J Am Soc Nephrol 4:1312–1316
10. Johnson S, Taylor CM (2008) What's new in haemolytic uraemic syndrome? Eur J Pediatr 167:965–971
11. Ariceta G, Besbas N, Johnson S, Karpman D, Landau D, Licht C, Loirat C, Pecoraro C, Taylor CM, Van de Kar N, Vandewalle J, Zimmerhackl LB, European Paediatric Study Group for HUS (2009) Guideline for the investigation and initial therapy of diarrhea-negative hemolytic uremic syndrome. Pediatr Nephrol 24:687–696
12. Tschumi S, Gugger M, Bucher BS, Riedl M, Simonetti GD (2011) Eculizumab in atypical hemolytic uremic syndrome: long-term clinical course and histological findings. Pediatr Nephrol 26:2085–2088
13. Ariceta G, Arrizabalaga B, Aguirre M, Morteruel E, Lopez-Trascasa M (2012) Eculizumab in the treatment of atypical hemolytic uremic syndrome in infants. Am J Kidney Dis 59:707–710
14. Prescott HC, Wu HM, Cataland SR, Baiocchi RA (2010) Eculizumab therapy in an adult with plasma exchange-refractory atypical hemolytic uremic syndrome. Am J Hematol 85:976–977
15. Lapeyraque AL, Malina M, Fremeaux-Bacchi V, Boppel T, Kirschfink M, Oualha M, Proulx F, Clermont MJ, Le Deist F, Niaudet P, Schaefer F (2011) Eculizumab in severe Shiga-toxin-associated HUS. N Engl J Med 364:2561–2563