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Case Report

A case of atypical hemolytic uremic syndrome with positive anti-factor H autoantibody

Yong-Hong Jian, Ding-Ping Yang, Hong-Yan Liu

Department of Nephrology, Renmin Hospital of Wuhan University, Wuhan, Hubei, China

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Abstract: Atypical hemolytic uremic syndrome (aHUS) is defined as HUS caused by dysregulation of the complement alternative pathway. Although the incidence rate of aHUS is less than 1/100,000, the prognosis is very poor. The main pathogenesis of aHUS is primarily the over-activation of the complement alternative pathway induced by the abnormalities of the Factor H protein family. aHUS associated with anti-Factor H autoantibodies accounted for approximately 10% of all aHUS cases. Herein is reported an adult with aHUS who exhibited positive anti-Factor H autoantibodies and homozygous deletion for complement Factor H-related protein 1 (CFHR1).

Keywords: Atypical hemolytic uremic syndrome, anti-factor H autoantibodies, complement factor H-related protein 1, plasma exchange

Introduction

Hemolytic uremic syndrome (HUS) is a disorder associated with Shiga toxin and clinically presents with thrombocytopenia, microangiopathic hemolytic anemia, and kidney injury. Atypical hemolytic uremic syndrome (aHUS), which is not related to Shiga toxin, is defined as HUS caused by dysregulation of the complement alternative pathway [1]. aHUS accounts for approximately 10% of all HUS cases, with a mortality rate as high as 25%, and 50% of aHUS cases eventually develop into end-stage renal disease [2]. Investigations have demonstrated that the underlying mechanism of aHUS is primarily the overactivation of the complement alternative pathway induced by the abnormalities of the Factor H protein family, such as Factor H mutation, non-allelic homologous recombination between Factor H and complement factor H-related protein1-5 (CFHR1-5), CFHR deficiency, and anti-Factor H antibodies. aHUS associated with anti-Factor H autoantibodies was first reported in 2005 by Dragon-Durey et al. [3]. In 2010, Moore et al. reported that this type of HUS accounted for approximately 10% of all aHUS cases [4].

Case report

A 17-year-old female was admitted to a local hospital due to nausea, vomiting, melena for 7 days, and oliguria for 5 days. Seven days before admission, after eating fast-food noodles, she started presenting with nausea and vomiting, melena, an abdominal burning sensation, umbilical pain, and facial and scleral jaundice. Two days later, oliguria (approximately 200 mL/24 h) occurred, with gross hematuria and lower extremity edema. Blood work showed Hb 47 g/L, PLT 46*10^9/L, AST 105 μmol/L, TBIL 133.4 μmol/L, DBIL 37.1 μmol/L, and Scr 575.9 μmol/L. A peripheral blood smear showed red blood cells of different sizes and a small amount of deformed red blood cells. Color Doppler ultrasound showed slightly enlarged collateral kidneys. The facial and scleral jaundice faded after measures such as hemodialysis, erythrocyte infusion, anti-infection, liver protection, and acid suppression. The patient was transferred to our hospital for further treatment on April 20, 2014. Physical examination on admission revealed BP 152/103 mmHg, facial and scleral jaundice, anemia complexion, umbilical tenderness (+), and moderate edema in the lower extremities, without a remarkable past history or family history. HUS was suspected. Further tests showed increased white blood cells, notably decreased hemoglobulin and platelets, abnormal renal and liver function, and low C3 (**Table 1**). The urinary erythrocyte morphology test showed an abnormal erythrocyte percentage > 75%. The peripheral blood smear displ-

Table 1. Laboratory findings of the patient: before and after plasma exchange

	A	B	C
Hb	70 g/L	78 g/L	59 g/L
PLT	21x10^9/L	119×10^9/L	52×10^9/L
ALT	95 U/L	9 U/L	-
AST	204 U/L	16 U/L	-
ALB	25.8 g/L	35.5 g/L	28.8 g/L
TBIL	82.7 μmol/L	32.5 μmol/L	17.7 μmol/L
DBIL	21.35 μmol/L	10.5 μmol/L	5.9 μmol/L
Cr	559.6 μmol/L	262 μmol/L	375 μml/L
LDH	20751 U/L	483 U/L	635 U/L
AMY	311 U/L	177.9 U/L	132.0 U/L
LIPA	1499.3 U/L	836.1 U/L	255.4 U/L
C3	0.41 g/L	0.24 g/L	
Peripheral schistocytes	> 2%	0-1%	1-2%

A: at admission; B: after 6 sessions of plasma exchange; C: 10 days after plasma exchange discontinued; "-": not checked.

ayed a schistocyte percentage > 2%, EBV-DNA (+), and free hemoglobin 256 mg/L. Respiratory pathogen antibodies, acidified serum hemolysis test, anti-human globulin test, sucrose hemolysis test, anti-cyclic citrullinated peptide, haptoglobin, human cytomegalovirus, ASO, RF, ANCA+ENA complete set, anti-platelet antibody IgG, erythrocyte osmotic fragility test, Shigella and Salmonella fecal culture, and fecal Escherichia coli O-157 were all negative. The white blood cell count was normalized gradually by anti-infection therapy. Intermittent perfusion of washed red blood cells and platelets and 6 sessions of plasma exchange led to a significant increase and stabilization of hemoglobulin and platelets and liver function recovery and notable improvement of renal function and peripheral blood schistocytes (**Table 1**). The patient discontinued plasma exchange due to financial difficulties and continued taking oral drugs and enemas with Chinese medicine for renal protection and detoxification. The patient's condition deteriorated again after May 20, 2014; specifically, the urine volume decreased, hemoglobulin and platelets decreased again, and blood creatinine and peripheral blood schistocytes were elevated. The patient was transferred to institutes at her original residence for further treatment due to financial reasons. The diagnosis at discharge at our hospital was aHUS (based on the Nephrology, 3rd Edition). Before discharge, with the consent of the patient and her parents, blood samples collected from the patient and her parents were sent to Peking University First Hospital for Factor H test. The patient's results were Factor H 24 μg/mL (reference 300-800 μg/mL), homozygous deletion for complement Factor H-related protein 1 (CFHR1), and anti-Factor H IgG antibody (+). The results of her parents were all normal. At the one-month follow-up, the patient was undergoing maintenance peritoneal dialysis due to renal failure.

Discussion

Statistics show that the incidence of aHUS is 0.2/100,000 in adults and 0.33/100,000 in individuals under 18 years of age [5]. For 70% of aHUS patients, the age of onset is under 2 [6]. The patient in this case report had a late onset. Studies have demonstrated that the development of aHUS is due to the lack or deficiency of complement alternative pathway regulators such as Factor H, membrane co-factor protein (MCP or CD46), and Factor I [7], among which Factor H is the most important. The Factor H family, consisting of Factor H, complement Factor H-like protein 1 (CFHL-1) and complement Factor H-related protein 1-5 (CFHR1-5), plays a key role in the regulation of the complement alternative pathway. In 2005, Dragon-Durey et al. discovered for the first time the presence of anti-Factor H IgG antibodies in the serum of 3 patients with relapsing aHUS and proposed that the Factor H deficiency acquired by the development of anti-Factor H autoantibodies was the main mechanism of aHUS. Anti-Factor H antibodies bind to the SCR 19-20 region of Factor H and thereby inhibit the binding of Factor H to the C3b and influence regulation of the complement alternative pathway at the cellular surface [8]. Studies have shown that production of anti-Factor H antibodies is associated with the CFHR defect, and that homozygous deletion of CFHR1 is the primary precursor to the production of anti-Factor H antibodies [9]. However, the underlying mechanism is still unclear. CFHR1 is composed of 5 SCR domains, and the amino acid sequence of the C-terminal SCR3-5 is almost identical to the SCR18-20 of CFH. CFHR1 can inhibit the formation of C5 convertase and membrane attack

complexes and is complementary to CFH in the regulatory activities of the complement alternative pathway [10].

Dragon-Durey et al. used plasma exchange and immunosuppressive therapy in 3 patients with positive anti-Factor H IgG and achieved remission and non-recurrence at one year, which confirmed the efficacy of plasma exchange and immunosuppressive therapy [3]. Current treatments for aHUS include plasma therapy (plasma exchange, plasma infusion), immunosuppressants (e.g., glucocorticoids, mycophenolate mofetil, azathioprine, cyclophosphamide), and rituximab. Plasma therapy has been regarded as the first-line regimen to treat aHUS [2]. However, its application is limited by insufficient plasma sources, equipment requirements, and high costs. In a small number of studies, immunosuppressants (glucocorticoids combined with cyclophosphamide or mycophenolate mofetil) were applied to treat aHUS with success [11, 12]. However, due to the small sample size and lack of evidence-based verification, this treatment method was not suitable for widespread clinical adoption. In 2009, Gruppo et al. proposed that eculizumab, a new immunosuppressant, could effectively reverse the renal injury in aHUS [13]. Eculizumab is a recombinant human anti-C5 monoclonal antibody that can effectively inhibit C5 cleavage to form C5a and C5b, thereby inhibiting the formation of membrane attack complexes and reducing the abnormal activation of the complement system. In 2011, eculizumab was approved by the FDA to treat aHUS. A 2-year follow-up study in 2015 confirmed the safety and efficacy of eculizumab to treat aHUS and found that the clinical effects of early application were maintained after 2 years [14]. The latest international consensus highlights the benefits of early application of anti-complement agents, such as the use of eculizumab in children with aHUS, especially those with complement gene defects. In the same consensus, plasma therapy is considered to have limited effects on the prognosis of kidney injury and to be associated with a high incidence of complications, such as infection, thrombosis and allergies [15]. For the case reported in this study, laboratory indicators of the patient were improved remarkably after 6 sessions of plasma exchange, but after plasma exchange was discontinued the illness recurred very soon with a progressive decline in renal function. Recently, some researchers proposed simple supplementation of Factor H as an effective way to treat aHUS. However, preliminary studies demonstrated that artificial synthesis of Factor H was very difficult, and the synthesized materials may not display complete complement regulatory activity [16]. Further research is needed to validate this proposed treatment method.

Although the incidence rate of aHUS is low, the poor prognosis signifies the importance of early diagnosis and effective treatment. Reviewing and studying aHUS cases can improve clinicians' skills in recognizing and managing the disease. Currently, the available treatments for aHUS are limited and usually expensive, which restricts their widespread clinical adoption. Thus, further investigation of the aHUS mechanism and development of more effective and affordable therapy methods are of great significance.

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Disclosure of conflict of interest

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Address correspondence to: Hong-Yan Liu, Department of Nephrology, Renmin Hospital of Wuhan University, No. 238 Jiefang Road, Wuchang District, Wuhan 430060, Hubei, China. Tel: 0086-027-88041911-81396; Fax: 0086-027-88041911-81396; E-mail: hongyan_liu202@aliyun.com

References

[1] Franchini M. Atypical hemolytic uremic syndrome: from diagnosis to treatment. Clin Chem Lab Med 2015; 53: 1679-1688.

[2] Noris M and Remuzzi G. Atypical hemolytic-uremic syndrome. N Engl J Med 2009; 361: 1676-1687.

[3] Dragon-Durey MA, Loirat C, Cloarec S, Macher MA, Blouin J, Nivet H, Weiss L, Fridman WH and Fremeaux-Bacchi V. Anti-Factor H autoantibodies associated with atypical hemolytic uremic syndrome. J Am Soc Nephrol 2005; 16: 555-563.

[4] Moore I, Strain L, Pappworth I, Kavanagh D, Barlow PN, Herbert AP, Schmidt CQ, Staniforth SJ, Holmes LV, Ward R, Morgan L, Goodship TH

and Marchbank KJ. Association of factor H autoantibodies with deletions of CFHR1, CFHR3, CFHR4, and with mutations in CFH, CFI, CD46, and C3 in patients with atypical hemolytic uremic syndrome. Blood 2010; 115: 379-387.

[5] Mele C, Remuzzi G and Noris M. Hemolytic uremic syndrome. Semin Immunopathol 2014; 36: 399-420.

[6] Sellier-Leclerc AL, Fremeaux-Bacchi V, Dragon-Durey MA, Macher MA, Niaudet P, Guest G, Boudailliez B, Bouissou F, Deschenes G, Gie S, Tsimaratos M, Fischbach M, Morin D, Nivet H, Alberti C, Loirat C; French Society of Pediatric Nephrology. Differential impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. J Am Soc Nephrol 2007; 18: 2392-2400.

[7] Kavanagh D, Richards A, Fremeaux-Bacchi V, Noris M, Goodship T, Remuzzi G and Atkinson JP. Screening for complement system abnormalities in patients with atypical hemolytic uremic syndrome. Clin J Am Soc Nephrol 2007; 2: 591-596.

[8] Loirat C and Fremeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis 2011; 6: 60.

[9] Brocklebank V, Johnson S, Sheerin TP, Marks SD, Gilbert RD, Tyerman K, Kinoshita M, Awan A, Kaur A, Webb N, Hegde S, Finlay E, Fitzpatrick M, Walsh PR, Wong EKS, Booth C, Kerecuk L, Salama AD, Almond M, Inward C, Goodship TH, Sheerin NS, Marchbank KJ and Kavanagh D. Factor H autoantibody is associated with atypical hemolytic uremic syndrome in children in the United Kingdom and Ireland. Kidney Int 2017; 92: 1261-1271.

[10] Heinen S, Hartmann A, Lauer N, Wiehl U, Dahse HM, Schirmer S, Gropp K, Enghardt T, Wallich R, Halbich S, Mihlan M, Schlotzer-Schrehardt U, Zipfel PF and Skerka C. Factor H-related protein 1 (CFHR-1) inhibits complement C5 convertase activity and terminal complex formation. Blood 2009; 114: 2439-2447.

[11] Dragon-Durey MA, Sethi SK, Bagga A, Blanc C, Blouin J, Ranchin B, Andre JL, Takagi N, Cheong HI, Hari P, Le Quintrec M, Niaudet P, Loirat C, Fridman WH and Fremeaux-Bacchi V. Clinical features of anti-factor H autoantibody-associated hemolytic uremic syndrome. J Am Soc Nephrol 2010; 21: 2180-2187.

[12] Guan N, Liu X, Yao Y, Yang J, Wang F, Xiao H, Ding J, Zhao M, Yu F and Wang F. Clinical characteristies of atypical hemolytie uremic syndrome associated with H factor antibody in children. Zhonghua Er Ke Za Zhi 2014; 52: 223-226.

[13] Gruppo RA and Rother RP. Eculizumab for congenital atypical hemolytic-uremic syndrome. N Engl J Med 2009; 360: 544-546.

[14] Licht C, Greenbaum LA, Muus P, Babu S, Bedrosian CL, Cohen DJ, Delmas Y, Douglas K, Furman RR, Gaber OA, Goodship T, Herthelius M, Hourmant M, Legendre CM, Remuzzi G, Sheerin N, Trivelli A and Loirat C. Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies. Kidney Int 2015; 87: 1061-1073.

[15] Loirat C, Fakhouri F, Ariceta G, Besbas N, Bitzan M, Bjerre A, Coppo R, Emma F, Johnson S, Karpman D, Landau D, Langman CB, Lapeyraque AL, Licht C, Nester C, Pecoraro C, Riedl M, van de Kar NC, Van de Walle J, Vivarelli M, Fremeaux-Bacchi V; HUS International. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. Pediatr Nephrol 2016; 31: 15-39.

[16] Buttner-Mainik A, Parsons J, Jerome H, Hartmann A, Lamer S, Schaaf A, Schlosser A, Zipfel PF, Reski R and Decker EL. Production of biologically active recombinant human factor H in physcomitrella. Plant Biotechnol J 2011; 9: 373-383.