Clinical Case Report

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Efficacy of rituximab and plasmapharesis in an adult patient with antifactor H autoantibody-associated hemolytic uremic syndrome

A case report and literature review

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Abstract

Antifactor H antibody (anti-CFHAb) is found in 6% to 25% cases of atypical hemolytic uremic syndrome (aHUS) in children, but has been only exceptionally reported in adults. There is no consensus about the best treatment for this type of aHUS. We report the case of an adult patient treated successfully with plasma exchange (PE), steroids, and rituximab.

A 27-year-old Caucasian male presented to hospital with anemia, thrombocytopenia, and acute renal failure. One week earlier, he had digestive problems with diarrhea. The diagnosis of anti-CFHAb-associated aHUS (82,000 AU/mL) without *CFHR* gene mutations was established.

He received Rituximab 375 mg/m^2 (4 pulses) with PE and steroids. This treatment achieved renal and hematological remission at day (D) 31 and negative anti-CFHAb at D45 (<100 AU/mL). At D76, a fifth rituximab pulse was performed while CD19 was higher than 10/mm^3. Steroids were stopped at month (M) 9. The patient has not relapsed during long-term follow-up (M39).

Rituximab therapy can be considered for anti-CFHAb-associated aHUS. Monitoring of anti-CFHAb titer may help to guide maintenance therapeutic strategies including Rituximab infusion.

Abbreviations: aHUS = atypical hemolytic uremic syndrome, Anti-CFHAb = antifactor H antibody, CFH = antigenic factor H, D = day, FB = factor B, ICU = intensive care unit, M = month, PE = plasma exchange, RTX = rituximab.

Keywords: adult, antifactor H autoantibody, case report, hemolytic uremic syndrome

1. Introduction

Atypical hemolytic uremic syndrome (aHUS) associated with antifactor H antibodies (anti-CFHAbs) typically occurs in children and teenagers. Anti-CFHAbs have been reported in 6% to 25% of patients in European cohorts[1,2] and in up to 56% of patients in India.[3] Only 9 adult cases have been documented.[4,5] Eculizumab is recommended in pediatrics aHUS as treatment of first intention.[6] In aHUS associated with anti-CFHAb, immunosuppressive regimens can also be used to achieve clinical remission and anti-CFHAb levels <1000 AU/mL.[6] However, given its rarity, the management of aHUS with anti-CFHAb remains debated and not consensual, particularly in adults. We report the case of an adult patient with anti-CFHAb-associated aHUS treated successfully with plasma exchange (PE), steroids, and rituximab (RTX).

2. Case report

A 27-year-old male without medical history was admitted to the intensive care unit (ICU) because of acute renal failure, thrombocytopenia, and anemia. One week earlier, he had experienced digestive problems with diarrhea. On ICU admission, he had hyperthermia (38.2 °C) and jaundice without hepatomegaly.

Laboratory findings showed microangiopathic hemolytic anemia (hemoglobin 7.3 g/dL; reference range 13.0–18.0 g/dL), hemolysis (haptoglobin < 0.08 g/dL; reference range 0.6–1.6 g/dL, lactacte deshydrogenase 2720 IU/L; reference range 87–241 IU/L), and numerous schizocytes on blood smear; thrombocytopenia (21,000 platelets/mm^3; reference range 150,000–450,000 platelets/mm^3), and acute renal failure (serum creatinine 242 μmol/L; reference range 59–104 μmol/L) with microscopic hematuria (21×10^3/mm^3) and nephrotic range proteinuria (6.2 g/d) consistent with probable glomerular injury. These elements are not suggestive of involvement of dehydration in

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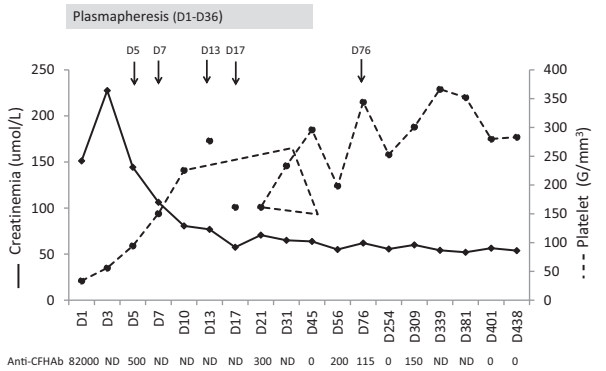

Figure 1. Biological course and treatment of an adult patient with antifactor H antibodies responsible for atypical hemolytic uremic syndrome. Anti-CFHAb = antifactor H antibody. Rituximab (375 mg/m^2) (back arrow).

renal failure. In patients with aHUS, renal biopsies are not recommended[7] owing to the risk of bleeding. We elected not to perform renal biopsy because of severe thrombocytopenia. Bone marrow aspiration was consistent with peripheral thrombocytopenia. Exploration of the complement system showed activation of the alternative pathway with C3 depletion (543 mg/L; reference range 660–1250 mg/L), normal C4 (332 mg/mL; reference range 93–280 mg/mL), low plasma levels of factor B (FB) (72 mg/L; reference range 90–320 mg/mL), and normal antigenic factor H (CFH) (77%; reference range 65%–140%). Anti-CFHAbs were positive with a titer of 82,000 AU/mL (reference range <100 AU/mL). Sequencing analyses evidenced no mutations in *C3*, *FB*, *CFH*, *CFI*, and *MCP* genes.[8] A disintegrin-like and metalloprotease with thrombospondin type I repeats-13 (ADAMTS13) was 53%.

Daily PE with fresh frozen plasma (60 mL/kg) was initiated on day (D) 1 of hospitalization and continued until D36. After diagnosis of anti-CFHAb-associated aHUS (D5), immunosuppressive drugs were introduced: steroids (1 mg/kg/d) and 4 RTX infusions (375 mg/m^2) at days 5, 7, 13, and 17 of hospitalization (Fig. 1).

PE associated with immunosuppression achieved negative anti-CFHAb (<100 AU/mL at D45) along with undetectable peripheral B cells, improvement of hematological parameters (at D31 hemoglobin levels had increased to 11.4 g/dL and 140,000 platelets/mm^3), and improvement in renal function (serum creatinine had decreased to 113 μmol/L at D31). Anti-CFHAb increased further to 200 AU/mL following acute viral gastroenteritis at D56 (Fig. 1). At D76, a single RTX infusion (375 mg/m^2) was performed because peripheral B lymphocytes were >10/mm^3. Steroids were stopped at M9. At M10, there was a rebound of anti-CFHAb followed by spontaneous disappearance a month later, without medical intervention (Fig. 1). Laboratory findings showed no hemolysis (haptoglobin 1.04 g/dL, 229,000 platelets/mm^3, hemoglobin 15.3 g/dL, no schizocyte on blood smear) and normal serum creatinine at 87 μmol/L. At M39, the patient is in complete remission with normal renal function. No complication was observed during follow-up.

3. Discussion

CFH is the main inhibitor of the complement alternative pathway.[2] CFH leads to inactivation of the surface-bound C3b cells and inhibits the generation of C3 convertase. Anti-CFHAbs[9] are responsible for acquired functional CFH deficiency and promote complement alternative pathway activation (low C3 and FB plasma levels). Homozygous deletions in complement factor H-related protein 1 (a protein-coding gene) with or without homozygous complement factor H-related protein 3[10] deletion have been observed in 60% to 82.4% of patients with anti-CFHAb-associated aHUS.[1,3] These patients can have normal plasma C3 levels in more than 1/3 of cases.[3,5]

Anti-CFHAb-related aHUS has been reported in only 9 adults, 8 males, and 1 female.[4,5,11] The characteristics of adults and children with anti-CFH antibody-associated aHUS are different. In children, the mean age is 8.2 years (0.7–11.4) with a predominance of female (F/M = 6/4). In the adults, the mean age is 31.5 years (21–45) with a predominance of male (F/M = 1/3). The prognosis is more severe in children who have a higher risk of relapse.[12] At disease onset, renal disease is often severe with hypertension, oligo-anuria, and dialysis requirement in 30% of cases.[3,5] In a French cohort,[5] extrarenal manifestations were frequently observed[3,5] such as fever, digestive problems, pancreatitis, hepatitis, seizure, and more rarely cardiac complications.[5]

In France, it has been recommended that all adult patients with aHUS receive daily PE with exchange of 1.5 plasma volume (60 mL/kg) as early as possible until the results of ADAMTS 13 and complement investigation.[13,14] Recent pediatric guidelines[6] recommend that eculizumab be started within the first 24 to 48 hours in aHUS or PE if eculizumab is not available immediately. However, results of treatment of anti-CFHAb-related aHUS by eculizumab are scarce (Table 1). The high cost of eculizumab and the absence of data on the processing time limit its use.[15]

In a recent retrospective study in 138 children with anti-CFHAb-related aHUS,[3] renal survival at M12 in the group treated with PE and induction immunosuppression (steroids and cyclophosphamide or RTX) was better than in the group treated with PE alone, 75.6% and 41.5%, respectively[3] (Table 1). RTX therapy has been described in case series with good results. In the French cohort, RTX allowed PE weaning in 1 patient and was used in the prevention of (aHUS) relapse after renal transplantation in 3 others became redundant.[5] In a retrospective case series[16] of 45 children treated for anti-CFHAb-related aHUS, RTX infusion (n = 14) or cyclophosphamide (n = 31) led to renal remission in 13 (92%) and 29 (93%) cases, respectively. The relapse rates for RTX and cyclophosphamide were 4/13 (31%) and 3/29 (10.5%), respectively. Cyclophosphamide can give good results[17] in patients resistant to induction therapy with PE, steroids, and RTX. Hence, PE and steroids associated with immunosuppressive therapy (cyclophosphamide pulses or rituximab) have been proposed as first-line therapy for induction in patients with anti-CFHAb-related aHUS.[18] Plasma exchange removes circulating antibodies. We used RTX rather than cyclophosphamide because RTX leads to specific and rapid (24–72 hours) depletion of peripheral B cells, with the exception of plasma cells. In patients with anti-CFHAb-related aHUS treated with RTX, there is a link between peripheral B-cell depletions, decrease in anti-CFHAb rate, and clinical remission.[19] Thus, the main mechanism of action of RTX could be the depletion of B cells leading to short-lived plasmocytes that secrete anti-CFHAb (lifespan 10–20 days).[20] This would explain why the action of rituximab occurred after 10 to 21 days.[21] Cyclophosphamide targets on all cell lines producing antibodies (LcB, LcT, and plamocytes).[22] In addition, RTX is generally well tolerated in autoimmune hematologic diseases. Most frequent side effects include infusional symptoms, serum sickness, and an increased risk of severe infections particularly pyogenic or herpes

Table 1

aHUS outcomes according to treatments.

Study design, reference	Treatments (dosage)	Last follow-up/control signs of activity UHSa					
		Anti-FHAb <100 AU/mL	HCR	RCR	Kidney survival	Patient survival	Relapse
Plasmapheresis							
Dragon-Durey et al[5]; 15 patients	PE (dosage unspecified)a	ND	ND	ND	14/15 (40)	14/15 (93)	6/15 (40)
Plasmapheresis + cyclophosphamide pulse							
Sana et al[17]; 4 children	CP (0.5–1 g/1.73 m^2, n = 2–5); PE (60 mL/kg; n = 2–11); Steroids (0.5–2 mg/kg/d while 4–24 mo); IVIg	1/4 (25)	4/4 (100)	4/4 (100)	ND	ND	1/4 (25)
Khandelwal et al[16]; 31 children	CP (500 mg/m^2; n = 5); PE (60 mL/kg); Steroids (1 mg/kg/d)	0/31 (0)	ND	29/31 (93)	ND	ND	3/31 (9.6)
Plasmapheresis + rituximab							
Lionet et al[4]; 1 adult; After second relapse	PE (35 mL/kg) (NB: EP stopped after second RTX); Steroids (1 mg/kg/d); RTX (375 mg/m^2/week for 4 weeks)	1/1 (100)	1/1 (100)	1/1 (100)	ND	ND	0/1
Dragon-Durey et al[5]; 5 patients: 1 adult and 4 children	PE; RTX	2/5 (40)	ND	ND	5/5 (100)	ND	ND
Khandelwal et al[16]; 14 children	RTX (375 mg/m^2; n = 2); PE (60 mL/kg); Steroids (1 mg/kg/d)	0/14 (0)	ND	13/14 (92)	ND	ND	4/14 (28)
Eculizumab							
Ito et al[23]; 2 children	EP; Eculizumab	ND	2/2 (100)	2/2 (100)	ND	ND	0/2 (0)
Fakhouri et al[24]; 1 child	RTX (375 mg/m^2; n = 4) + steroids; Eculizumab (600 mg/wk for 2 wk and 900 mg/wk for 2 wk)	ND	1/1	0/1	1/1 (100)	1/1 (100)	ND

CFHa = factor H antibody, CP = cyclophosphamide pulse, DX = X days, Ec = eculizumab, HCR = hematologic complete remission, IVIg = intravenous immunoglobulin, MX = X months, ND = no data, PE = plasmapheresis exchange, RCR = renal complete remission, RTX = rituximab, Tx = transplantation, wk = week, YX = X years.

virus infections, and pneumonitis caused by *Pneumocystis jiroveci*.[22] Using Cyclophosphamide in young patients may thus induce digestive problems, alopecia, medullar toxicity, and secondary malignancies.

The pediatric guidelines[6] recommend maintenance treatment with MMF and steroids with an anti-CFHAb target rate <1000 AU/mL to avoid relapse. In a retrospective study,[3] the relapse-free survival rate was 92.3% with maintenance therapy and 69.1% without treatment at M12.[3] New RTX infusions can be used as maintenance therapy when anti-CFHAb are >1000 AU/mL, because the rate rises before clinical symptoms.[18] For patients who are in complete remission after 1 year and have anti-CFH antibody titers <1000 AU/mL and normal C3 rate, it can be envisaged to discontinue treatment.[6]

4. Conclusion

In summary, this observation demonstrates the need for rapid detection of anti-CFH antibody in the management of aHUS even when C3 levels are normal and/or there are digestive symptoms in adult patients. Treatment of this form of aHUS with RTX may be beneficial with good outcomes for renal function and platelet levels without long-term relapse. A rituximab preemptive therapy using a monitoring of anti-CFHAb could be considered for anti-CFHAb-associated aHUS.

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