Efficacy of Eculizumab Therapy for Atypical Hemolytic Uremic Syndrome Recurrence and Antibody-Mediated Rejection Progress After Renal Transplantation With Preformed Donor-Specific Antibodies: Case Report

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ABSTRACT

Atypical hemolytic uremic syndrome (aHUS) develops as the result of unregulated complement progression and precipitates de novo thrombotic microangiopathy. Plasma therapy is used to control the progression of the complement cascade, but that therapy is not effective in all patients and is accompanied by risk of infection and/or allergy. Eculizumab has been reported as an efficient therapy for aHUS. We report the case of a 35-year old woman who underwent effective eculizumab therapy for aHUS recurrence and antibody-mediated rejection (AMR) progress after renal transplantation with preformed donor-specific antibodies (DSA). She developed end-stage renal disease due to suspicious IgA nephropathy at age 33 years. Kidney transplantation was performed at age 35 years, and aHUS recurred 2 weeks later, leading to the progressive hemolytic anemia and renal dysfunction. Therefore, she underwent plasma therapy several times. Because it was difficult to continue to plasma therapy for severe allergy, eculizumab was proposed as an alternate therapy. Treatment with eculizumab was initiated 36 days after renal transplantation. After 3 years of eculizumab treatment, and without plasma therapy, schistocytes decreased, haptoglobin increased to within normal limits, creatinine levels stabilized, and no further episodes of diarrhea were reported. At protocol biopsy 1 year after transplantation, she was diagnosed with C4d-negative subclinical AMR. However, her pathologic findings at follow-up biopsy 3 years after transplantation were recovered. We conclude that eculizumab alone, without plasma therapy, is sufficient to treat recurrence of aHUS and AMR due to DSA after renal transplantation and to maintain long-term graft function.

ATYPICAL hemolytic uremic syndrome (aHUS) is a microvascular thrombotic disorder classically characterized by the triad of hemolytic anemia, thrombocytopenia, and acute kidney injury. Genetic anomalies of alternate complement pathway proteins are observed in 60% of aHUS patients and these are responsible for inappropriate complement activation on platelets and endothelial cells [1]. The most frequently reported mutations occur in the gene encoding complement factor H (CFH). The risk of aHUS recurrence after renal transplantation is high for patients with CFH mutations [1-3]. Although plasmapheresis is used to control the progression of the complement cascade [4], that therapy is not effective for all patients. Eculizumab is a humanized mouse monoclonal antibody that recognizes the human complement protein C5 and blocks the cleavage of C5 to C5a and C5b, preventing the induction of the terminal

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complement cascade, including the formation of the membrane attack complex (C5b-9) [5]. Recently, eculizumab has been widely and successfully used for the treatment of antibody-mediated rejection (AMR) after renal transplantation [6]. We report a patient who underwent effective eculizumab therapy against aHUS recurrence secondary to suspicious CFH-related mutations and progression of AMR after renal transplantation with preformed donor-specific antibodies (DSA).

CASE REPORT

A 35-year-old woman with end-stage renal disease due to suspicious severe IgA nephropathy at age 33 years underwent ABO-compatible and DSA-positive living-donor kidney transplantation. She was moderately sensitized with an antihuman globulin–enhanced complement-dependent cytotoxicity crossmatch negative, flow cytometry crossmatch T-cell negative and B-cell positive, and panel reactive antibodies (47% class I and 51% class II) due to her previous pregnancy and blood transfusion. Preformed DSA (mean fluorescence intensity [MFI] of anti-HLA B51, 2,462) was identified with the use of LABScreen single-antigen beads (One Lambda, Canoga Park, California). Therefore, a desensitization protocol consisting of mycophenolate mofetil (MMF) and prednisolone (PRD) administration 2 weeks before transplantation along with plasmapheresis 2 times and 1 dose of rituximab (200 mg) was initiated. Her immunosuppression protocol consisted of the anti-CD25 monoclonal antibody (basiliximab) as induction therapy on days 0 and 4 and tacrolimus (TAC), MMF, and PRD. On postoperative day (POD) 2, her urine output was decreased owing to a subcapsular hematoma and suspected AMR. Therefore, the hematoma was removed and an open-graft biopsy was performed. Pathologic findings were consistent with AMR (i0, t0, g1, ptc1, and ptcbm1 [Banff 2013]). Therefore, she received intravenous immunoglobulins (IVIG; 0.2 g/kg) in addition to rituximab (100 mg) and methylprednisolone (MP) pulses (500 mg/d for 3 days). During and after this treatment regimen, a severe microangiopathic process with anemia (Hb, 6.7 g/dL), thrombocytopenia (platelet count, 7.1 $\times$ 10^4/μL), low haptoglobin (<10.0 mg/dL), and hemolysis (lactate dehydrogenase [LDH] levels, 390 IU/L; schistocyte positive) accompanied by complement activation (C3, 57 mg/dL; C4, 19 mg/dL) suggested a diagnosis of thrombotic microangiopathy (TMA). On POD 15, she underwent kidney rebiopsy which revealed TMA involving the glomeruli and small vessels. Refractory AMR and calcineurin inhibitor (CNI)–induced TMA were considered as an initial differential diagnosis of this de novo biopsy-proven post-transplantation TMA. Therefore, additional MP pulses and IVIG were administered. Moreover, CNI was switched from TAC to cyclosporine (CsA) in addition to several transfusions of red cell concentrates and fresh-frozen plasma. Moreover, hemolytic tests and genetic studies were performed at the Department of Blood Transfusion Medicine, Nara Medical University (Nara, Japan). Hemolysis testing performed on POD 23 was positive for the patient, her father, and her daughters; hemolysis was inhibited by the addition of CFH (Fig 1). However, genetic testing by direct sequencing analysis revealed no mutations of CFH, C3, complement factor I (CFI), complement factor B (CFB), membrane-cofactor protein (MCP), or thrombomodulin. Western blot analysis was negative for antifactor-H antibodies and CFH-related proteins 1,3 (CFHR1/3). Although no mutation was identified in this case, not all genes were studied. Additional laboratory work-up revealed a normal ADAMTS13 level (46.3%). Based on these results, on POD 23 she was diagnosed with CFH-associated aHUS. Daily plasma therapy was performed for 2 days. However, she developed severe anaphylaxis in response to plasma therapy, so

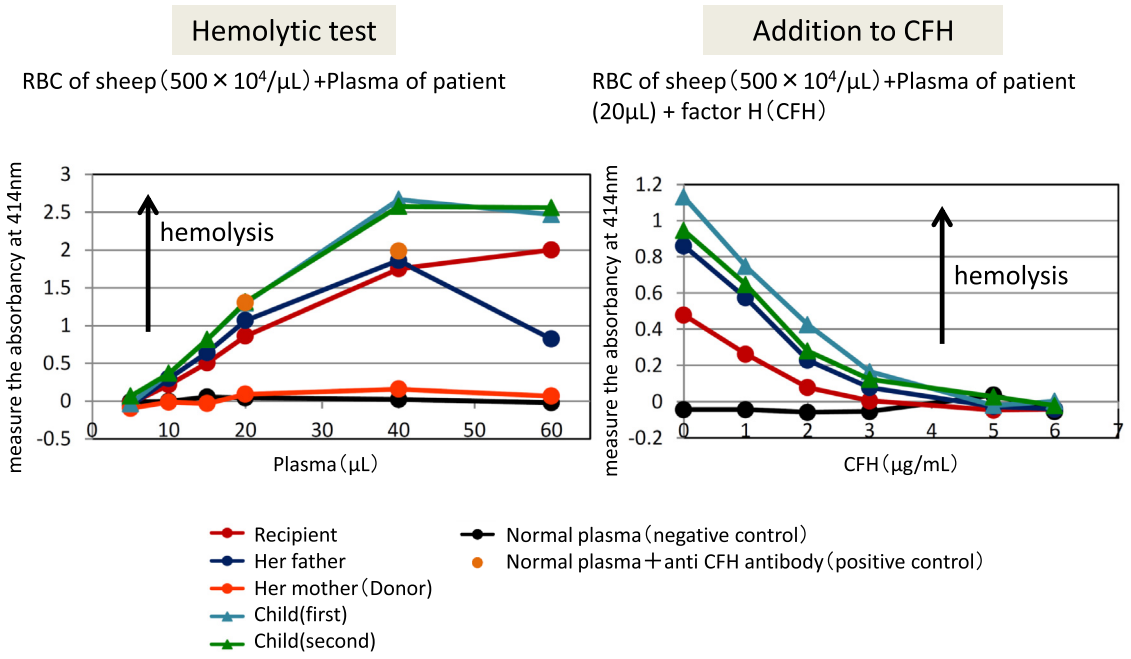

Fig 1. Hemolytic test.