Transplantation Reports 3 (2018) 5–8

Contents lists available at ScienceDirect

Transplantation Reports

journal homepage: www.elsevier.com/locate/tpr

Thrombotic microangiopathy after kidney transplantation successfully treated with eculizumab: A case report

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ARTICLE INFO

Keywords:
Transplantation-associated thrombotic microangiopathy (TA-TMA)
aHUS
Eculizumab

ABSTRACT

Background: Transplantation-associated thrombotic microangiopathy (TA-TMA) is relatively rare and may cause graft failure. Atypical hemolytic uremic syndrome (aHUS) is caused by dysregulation of the alternative complement pathway, resulting in TMA. Eculizumab, a humanized anti-C5 monoclonal antibody, inhibits terminal membrane-attack complex formation and TMA progression in aHUS. Eculizumab can be successfully used to treat aHUS recurrence after transplantation.

Case report: We report the case of a 43-year-old Japanese man who developed TA-TMA and was successfully treated with eculizumab. He was diagnosed with end-stage renal disease with an unknown cause. Thrombocytopenia, hemolytic anemia, elevated lactate dehydrogenase, and graft dysfunction soon developed after kidney transplantation. We diagnosed TA-TMA and administered daily plasma-exchange (PEx) sessions, steroid pulse, intravenous immunoglobulin, an additional rituximab, as well as blood transfusion. The effects of these therapies were limited. Renal allograft biopsy on day 11 revealed TMA and no evidence of rejection. We administered 600 mg eculizumab on days 11 and 18, considering a diagnosis of aHUS. The patient's laboratory test results improved remarkably, and he was discharged on day 36. Genetic testing revealed only a polymorphism on the gene of complement factor H (CHF). Anti-Factor H autoantibody assays were negative.

Conclusion: To our knowledge, there are only 3 cases reports on successful use of eculizumab for the treatment of TMA following kidney transplantation. In the case of TA-TMA, the amount and duration of eculizumab administration remains unclear.

In our patient, eculizumab was safely and effectively used for TA-TMA. Eculizumab might be beneficial for the treatment of PEx-resistant kidney TA-TMA.

1. Introduction

Transplantation-associated thrombotic microangiopathy (TA-TMA) in kidney transplantation is uncommon and may be a cause of graft loss. It is characterized by hemolytic anemia, thrombocytopenia, and organ damage, especially manifesting as kidney dysfunction. TA-TMA is caused by multiple factors, including viral infection, immunosuppressant drugs and antibody-mediated rejection (AMR), resulting in severe endothelial damage.

De novo TA-TMA and the recurrence of complement-mediated atypical hemolytic uremic syndrome (aHUS) are clinically very similar.

aHUS is associated primarily with mutations or autoantibody production, resulting in dysregulation of the alternative complement pathway and TMA; mutations are identified in about 60% of individuals [1]. Secondary aHUS occurs owing to triggers, such as autoimmunity, transplantation, infection, certain cytotoxic drugs, or pregnancy.

Eculizumab, a humanized anti-C5 monoclonal antibody, inhibits terminal membrane-attack complex formation and TMA progression in aHUS [2,3]. Eculizumab can be successfully used in cases of aHUS recurrence after transplantation [4].

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https://doi.org/10.1016/j.tpr.2018.03.002
Received 19 March 2018; Accepted 21 March 2018
Available online 22 March 2018

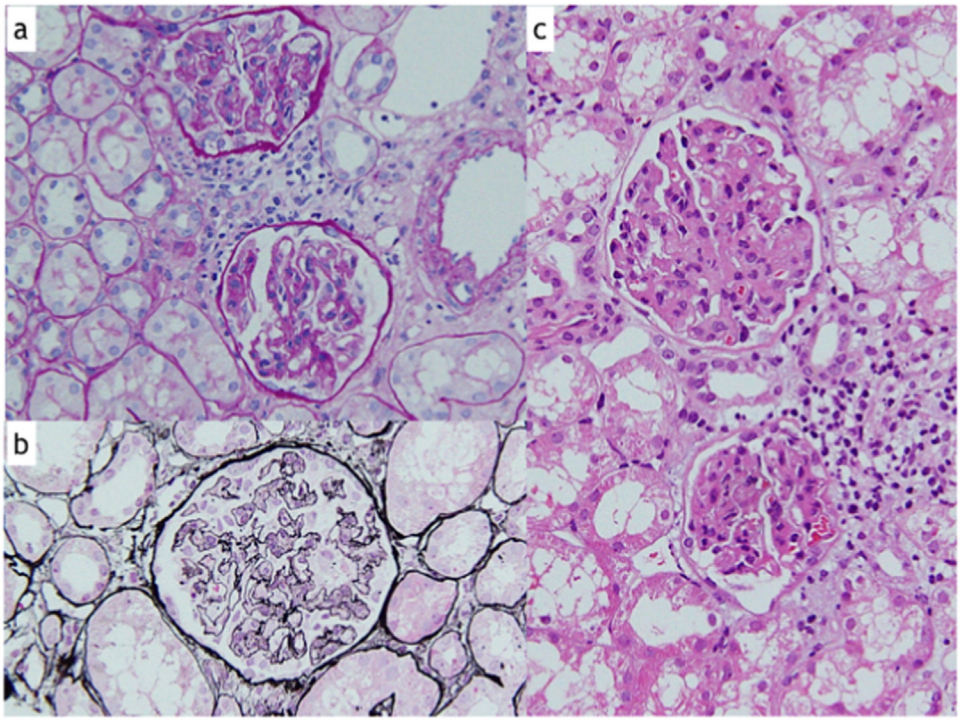

Fig. 1. Light microscopy findings for renal allograft biopsy specimen on day11. It shows a double contour of the glomerular basement membrane, swelling of the endothelial cells, meaning glomerular thrombotic microangiopathy and acute tubular injury, and there was no evidence of rejection. Banff2013;i0,t0, v0,g0,ptc0,ci0,ct0,cv0cg*2,ptcbm0,ah0,aah0, c4d2. IF;C4d on PTC:positive,HLA-DR: negative,SV-40:negative. (a) Periodic acid-Schiff stain; (b) Periodic acid- methenamine-silver stain; (c) Hematoxylin Eosin stain.

However, to our knowledge, there are only 3 reported cases of kidney TA-TMA successfully treated with eculizumab.

We report the case successful treatment of TA-TMA with eculizumab in the early postoperative period, for which limited treatment options are available.

2. Case report

A 43-year-old Japanese man (blood type O) developed end-stage renal disease of unknown origin. He was treated at 34 years of age for malignant hypertension and drug-induced liver dysfunction. His kidney function gradually weakened, and he developed end-stage renal disease. His mother also had renal disease of unknown origin.

He underwent 3 of 6 A-B-DR mismatched ABO-incompatible living kidney transplantations (ABO-ILKT) from his sister (blood type A) after desensitization with one double filtration plasmapheresis (DFPP) session. He was also administered a single 200 mg dose of rituximab.

Preoperative immunological evaluation showed negative complement-dependent cytotoxicity (CDC) through flow cytometric crossmatch test (FCXM), with no donor-specific anti-HLA antibodies (DSA). Anti-A IgG titer was 2. Platelet count 1 day before surgery was $16.7 \times 10^4/\mu L$. Tacrolimus, mycophenolate mofetil (MMF), methylprednisolone, and basiliximab comprised the immunosuppressive induction regimen.

The surgery was free from complications, and intraoperative urine output was observed in 2 min (total ischemic time: 2 h 44 min 35 s).

Postoperative Doppler ultrasonography showed scant low blood flow in the superior pole of the graft kidney.

On postoperative day (POD) 2, laboratory data revealed a platelet count of $6.5 \times 10^4/\mu L$ (nadir $2.9 \times 10^4/\mu L$); on POD3, hemolytic anemia (Hb 9.2 mg/dl), elevated lactate dehydrogenase (LDH 684 U/L), and graft dysfunction (serum creatinine sCr 4.41 mg/dl) were observed.

We diagnosed TA-TMA and administered daily plasma exchange (PEx) sessions, steroid pulse (mPSL 500 mg for 2 days), intravenous immunoglobulin (IVIG; 15 g/day for 3 days), an additional 300 mg dose of rituximab, and blood transfusion (total of 8 units).

We considered a differential diagnosis of TMA.Thrombotic thrombocytopenic purpura (TTP) was not found. In addition, ADAMST13 activity was normal, and ADAMTS13 inhibitor was negative. Shiga toxin-producing *Escherichia coli* (STEC) infection, and cytomegalovirus antigenemia tests were negative. Prothrombin time(PT) and activated partial thromboplastin time (APTT) were normal. De novo DSA was negative and the anti-A IgG titer was 2. After additional rituximab infusion, CD19 was 0.1%. Perioperative blood trough tacrolimus levels were under control. Autoantibody was negative. C3 was slightly low at 64 mg/dl.

We performed a renal allograft biopsy on day 11. Biopsy revealed a double contour of the glomerular basement membrane and swelling of the endothelial cells, compatible with TMA. There was no evidence of rejection (Fig. 1).

We considered the possibility of aHUS and administered 600 mg of eculizumab on day 11, and 18. In addition, 400 mg of moxifloxacin was administered daily to prevent bacterial infection. Laboratory data remarkably improved and a platelet count of $21.6 \times 10^4/\mu L$ (7 day after eculizumab injection), sCr 1.77 mg/dL (65 day after eculizumab injection) were exhibited (Fig. 2).

Hemolytic tests and genetic studies were performed at the division of Nephrology and Endocrinology, The University of Tokyo (Tokyo, Japan). There was no increased lysis in hemolytic tests, and genetic test on CFH (complement factor H), C3, CFI (complement factor I), CFB (complement factor B), MCP (membrane cofactor protein) and THBD (Thrombomodulin), revealed only the polymorphism on the gene of CHF. Anti-CFH autoantibodies were negative.

He was discharged on day 36. Renal allograft biopsy on day 74 showed no evidence of TMA or rejection. The meningococcal conjugate vaccine was administered 3 months after eculizumab injection.

He was free from TMA recurrence 17 months after the operation.

3. Discussion

De novo TA-TMA incidence in renal allografts is 0.8–14% [5,6]. It usually occurs in the first week post-transplantation when patients are treated with high doses of immunosuppressive drugs [7], and is caused by multiple factors, including viral infection, immunosuppressant drugs, and antibody-mediated rejection (AMR).

Complement-mediated aHUS results from chronic, uncontrolled