Use of Eculizumab in Transplant-Associated Thrombotic Microangiopathy in a Patient With Polycystic Kidney Disease Immediately Post–Kidney Transplant: A Case Report

Amandeep Godara, Daniel R. Migliozzi, Monika Pilichowska, Nitender Goyal, Cindy Varga, and Craig E. Gordon

Transplant-associated thrombotic microangiopathy (TMA) in the post–organ transplantation setting occurs from a number of potential inciting factors, such as the use of calcineurin inhibitors, ischemic injury, infections, or antibody-mediated rejection leading to unchecked complement activation and end-organ damage. Delayed recognition of this condition can result in allograft loss. In this case description, we describe the first case of de novo TMA in a patient with polycystic kidney disease that occurred immediately after kidney transplantation. The diagnosis was made promptly on the basis of clinical and laboratory characteristics by a multidisciplinary team and confirmed through kidney biopsy, which showed acute TMA. The patient was successfully managed by replacing tacrolimus with belatacept, which targets cytotoxic T lymphocyte antigen 4, and use of eculizumab, a C5 inhibitor. Eculizumab treatment was discontinued after 3 months of complement inhibition on the patient's request, and relapse of TMA has not been encountered after more than 1 year of follow-up.

INTRODUCTION

Transplant-associated thrombotic microangiopathy (TMA) is a rare complication encountered after kidney transplantation. Incidence rates are estimated at 0.8% to 15%, with allograft loss in up to 33% to 50% of cases.[1,2] Key findings associated with this condition include thrombocytopenia, reduced haptoglobin and elevated lactate dehydrogenase (LDH) levels, and either lack of improvement or decline (once stabilized) in glomerular filtration rate, a set of laboratory findings that can arise from several other conditions in the usual post-transplantation course.

Calcineurin inhibitors (CNIs) are frequently implicated in transplant-associated TMA, especially in the early period (3-6 months) after transplantation.[3,4] Mammalian target of rapamycin inhibitors have also been associated with TMA and only belatacept (cytotoxic T lymphocyte antigen 4–immunoglobulin fusion protein that inhibits T-cell function) exists as an alternative to these agents.[5,6] Withdrawal of CNI treatment alone may not be sufficient to fully reverse the adverse effects of the alternative pathway of complement activation associated with this condition.[2,3] To adequately reverse complement activation, eculizumab (C5 inhibitor) has been successfully used in a number of resistant cases of de novo transplant-associated TMA.[7-9] We describe the successful use of eculizumab in a transplant recipient with kidney failure secondary to polycystic kidney disease (PKD) who developed de novo transplant-associated TMA in the immediate post-surgical setting.

CASE REPORT

An unsensitized (panel-reactive antibody, 0%) 63-year-old woman of Korean ethnicity with kidney failure secondary to PKD underwent deceased donor kidney transplantation (HLA antigen match, 3/10). Donation was performed after cardiac death and Kidney Donor Profile Index was 51%. On the day of the transplantation she started her immunosuppressive regimen, which included 3 doses of thymoglobulin, tacrolimus, mycophenolate, and a rapid steroid taper. The patient experienced delayed graft function but also anemia and thrombocytopenia. Hematologic evaluation (Table 1) on postoperative day (POD) 2 revealed an elevated LDH level (1,359 IU/L), undetectable haptoglobin (<8 mg/dL), and the presence of schistocytes (2-5/high-power field) on review of the peripheral smear. These findings were concerning for posttransplantation TMA and tacrolimus treatment was discontinued on POD 3. Tacrolimus 12-hour trough levels decreased from 6.0 (POD 3) to 2.3 ng/mL (POD 4).

Despite these interventions, the patient's serum creatinine and LDH levels remained elevated and hemoglobin level (nadir, 6.4 g/dL) and platelet count (nadir, 26 K/μL) continued to decline (Fig 1A). Kidney biopsy was not performed initially because of the degree of thrombocytopenia. The PLASMIC (platelet count, combined hemolysis variable, absence of active cancer, absence of stem-cell or solid-organ transplant, mean corpuscular volume, international normalized ratio, creatinine) score was 4, which is consistent with a low likelihood of thrombotic thrombocytopenic purpura, which was confirmed by ADAMTS13 (von Willebrand factor protease) activity of

Table 1. Laboratory Test Results During the Pre- and Postoperative Period

	Presurgery	POD 0	POD 2	POD 3	POD 4	POD 5	POD 7	POD 14	POD 28	3 mo Later
WBC, K/µL	6.4	4.4	3.3	3.2	2.1	3.9	6	7.6	8.1	5.2
Hemoglobin, g/dL	12	10	8.1	7.5	6.4	8.5	8.6	6.8	10.1	9.9
Platelets, K/µL	154	107	56	40	32	26	65	145	239	167
Creatinine, mg/dL	5.59	5.88	6.49	7.27	8.54	5.48	7.83	7.72	1.54	1.30
LDH, IU/L			1,359	1,260	1,106	1,173	1,043	396	181	167
Haptoglobin, mg/dL			<8	<8	<8	<8	<8	145	186	122
CH50 (complement total), U/mL						56			<10	<10
Tacrolimus, ng/mL			4.3	6	2.3					
Infectious workup	EBV IgG: positive; EBV IgM negative; CMV IgG positive; CMV IgM negative; HIV: negative					CMV DNA: negative; Parvo IgM: negative; EBV PCR: negative			BK virus DNA: negative	
Autoimmune			Coombs: negative	Anti-PF4: negative						
Start of treatment						Eculizumab	Eculizumab	Eculizumab	Eculizumab	Eculizumab

Abbreviations: Anti-PF4, anti–platelet factor 4 antibody; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; IgG, immunoglobulin G; LDH, lactate dehydrogenase; PCR, polymerase chain reaction; POD, postoperative day; WBC, white blood cells.

55% (reference value ,>67%). Negative anti–platelet factor 4 antibody test results ruled out heparin-induced thrombocytopenia as a cause for thrombocytopenia. Coombs test was performed to investigate an autoimmune cause for the anemia and results were negative. The initial workup included testing for infections such as bacterial, Epstein-Barr virus, cytomegalovirus, and parvovirus. Epstein-Barr virus and cytomegalovirus polymerase chain reaction did not detect any viral reactivation. Serum protein electrophoresis did not detect monoclonal protein. After a comprehensive evaluation by the members of our multidisciplinary TMA team constituting experts from hematology, nephrology, and transplant surgery, a diagnosis of transplant-associated TMA was made in the absence of any other alternative diagnoses.

On POD 5 (36 hours after discontinuation of tacrolimus therapy), eculizumab, 900 mg, was administered for 4 weekly doses followed by 1,200 mg every 2 weeks. On POD 7, hemoglobin level improved to 8.6 g/dL, LDH level decreased to 1,043 IU/L, and platelet count improved to 65 K/µL. After the second dose of eculizumab, urine output increased further and serum creatinine level decreased from 8.5 to 4.06 mg/dL. Total complement activity was sent before and after the first dose to assess complement inhibition.

After the improvement in platelet count, a kidney biopsy was pursued and confirmed a diagnosis of acute TMA with no evidence of rejection. Evaluation of glomeruli showed no evidence of necrosis, but arterioles showed reactive endothelium and expanded subendothelial space (1 arteriole with red blood cells and fibrin beneath the endothelium) with minimal mononuclear infiltrate in the interstitium (Fig 1E-H). C3 and C4d deposition was noted on intimal staining in the arteriole.

Prophylaxis against meningococcal infections was accomplished with penicillin VK (250 mg twice daily) for antibacterial prophylaxis, along with meningococcal group B and meningococcal (groups A, C, Y, and W-135) vaccines. In the absence of a CNI, immunosuppression was maintained with the aid of belatacept, while mycophenolate mofetil therapy was continued and low-dose prednisone was added (5 mg daily). The belatacept dosing protocol was based on the package insert: 10 mg/kg on days 1 and 5 and weeks 2, 4, 8, and 12, followed by 5 mg/kg monthly.[10] By POD 30, serum creatinine and hemoglobin levels improved to 1.78 mg/dL and 9.6 g/dL, respectively, while both platelet count and LDH level normalized (Fig 1A).

The aHUS Genetic Panel (Machaon Diagnostics Inc) revealed a stop-loss variant (c.1708T>C, p.Ter570-ArgextTer37) in exon 10, the last exon of the CFHR5 gene. No previously reported cases of transplant-associated TMA are associated with this variant. Three polymorphisms were also detected in the CFH gene (homozygous change in the promoter 2, homozygous silent variant in exon 13 [c.2016A>G, p.Gln672Gln], and homozygous missense variant in exon 18 [c.2808G>T, p.Glu936Asp]), which
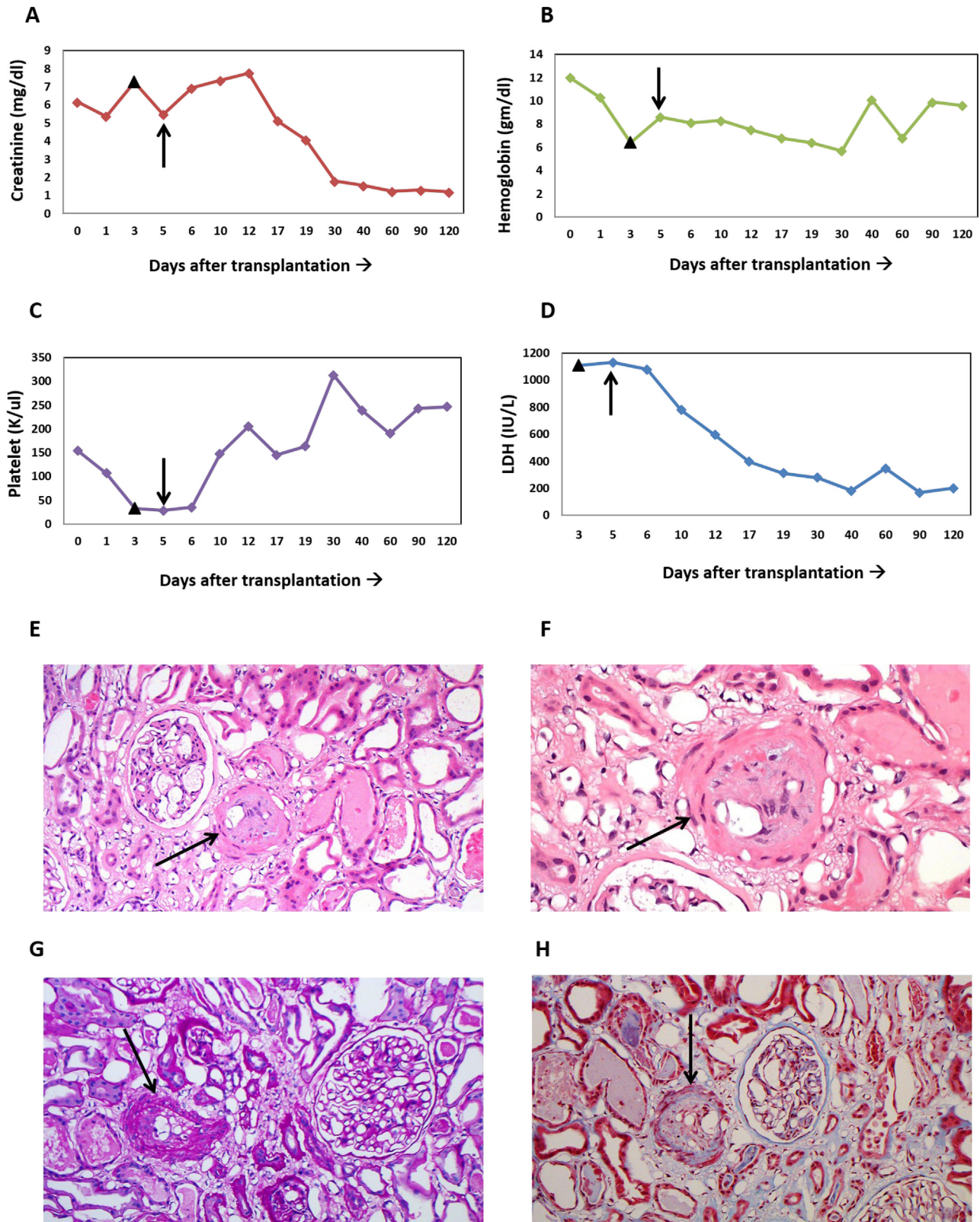
Figure 1. Laboratory results and kidney biopsy findings are consistent with thrombotic microangiopathy involving the transplanted kidney. (A-D) Laboratory parameters show improvement after complement inhibition with eculizumab was initiated on postoperative day 5, with creatinine, hemoglobin, platelet, and lactate dehydrogenase (LDH) levels returning to normal range. Filled triangle marks the day of discontinuation of tacrolimus therapy, arrow marks the start of eculizumab therapy followed by the introduction of belatacept therapy on the following day. (E-F) Light microscopy of the kidney biopsy specimen (hematoxylin and eosin stain) is shown. Occluded arteriole (indicated by arrow) can be seen along with reactive endothelium and expanded subendothelial space. Red blood cell fragmentation can be seen beneath the endothelium. (G) Periodic acid–Schiff and (H) trichrome stain show similar findings.

occur commonly in healthy individuals but are statistically enriched in patients with atypical hemolytic uremic syndrome (aHUS). There was no family history of TMA or consanguinity. Overall, this analysis was equivocal because no strong genetic risk for aHUS was identified.

Three months post–kidney transplantation, this patient continues on an immunosuppressive regimen of belatacept, mycophenolate mofetil, and prednisone with no ongoing evidence of TMA.

The patient discontinued eculizumab after 3 months of treatment and was followed up with clinical and laboratory assessment at monthly intervals. Laboratory monitoring has confirmed no TMA recurrence at 1 year posttransplantation.

DISCUSSION

The development of hemolytic anemia and thrombocytopenia in the immediate post–kidney transplantation period should raise concern for a microangiopathic process. The diagnosis of posttransplantation TMA poses a diagnostic dilemma, especially in the immediate posttransplantation period in which a multitude of reasons, such as ischemia-reperfusion injury, use of CNIs, or antibody-mediated rejection, alone or together can cause delayed graft function.[11,12] Early and accurate diagnosis of transplant-associated TMA facilitated by a TMA team followed by treatment with eculizumab, which is a recombinant C5 binding humanized antibody, can result in a quick TMA reversal, as seen in this case.[7,8]

Transplant-associated TMA results from endothelial damage due to unregulated complement activation and requires sufficient clinical-pathologic correlation.[13] In a survey of kidney transplantation centers across Japan, 1.5% of patients exhibited evidence of TMA within 1 week of kidney transplantation.[14] A kidney biopsy can be confirmatory in this setting but carries a high risk in a thrombocytopenic patient. In this case, TMA occurred in the immediate posttransplantation course and failed to respond to discontinuation of tacrolimus therapy, suggesting an alternative mechanism, and was only subsequently confirmed by kidney biopsy. An underlying predisposing genetic mutation can be identified in >30% of patients with transplant-associated TMA, including after solid-organ transplantation, and use of conventional therapies such as plasmapheresis can be ineffective in the absence of any quantitative defects in ADAMTS13 or inhibitors of complement pathway or antibody-mediated rejection.[15,16] For this patient, loss of kidney function from PKD was the reason for kidney transplantation and possibly the presence of a *CFHR5* mutation in the setting of surgery triggered the complement activation. In such cases, early use of eculizumab can reverse the complement activation and prevent further organ damage, leading to rapid recovery of hematologic and kidney function.[17]

There is no prevailing consensus on the duration of eculizumab therapy in cases of TMA following solid-organ transplantation.[18] The presence of a predisposing genetic mutation can help assess the recurrence risk and duration of therapy.[19] Often, genetic analysis reveals variants of unknown significance , as evident in this case in which a rare stop-loss variant (c.1708T>C) in exon 10 of the *CFHR5* gene was identified, which has also been reported in a case of immunoglobulin A glomerulopathy and 3 healthy controls, with no cases of TMA identified in relation to this mutation.[20] Additionally, there were also 3 variants in the *CFH* gene. The possibility cannot be excluded that these variants in combination with an inciting event can increase the probability of developing transplant-associated TMA, but this pathogenicity cannot be confirmed at this time given the lack of additional information. As the understanding of variants of unknown significance further evolves, caution is required in its interpretation because it does not necessarily implicate or preclude involvement in the pathogenesis.[21,22] As genetic testing makes inroads into everyday clinical practice, the association of rare genetic variants can be laid bare.

The duration of complement inhibition with eculizumab for transplant-associated TMA is unclear. It has been proposed that patients with pathogenic complement regulatory mutations should continue eculizumab treatment indefinitely to prevent TMA relapse, although it might be safe to discontinue it after 6 to 12 months of treatment in patients with no genetic predisposition.[23-26] In this case, the genetic association with complement gene variants cannot be confirmed as pathogenic and eculizumab treatment was discontinued after 3 months as per the patient's preference and was followed by close monitoring of kidney function and hemolysis parameters on a monthly basis. When complications of TMA have completely resolved, consideration can be made for discontinuation of therapy on a case-by-case basis, especially in the absence of any ongoing or predisposing triggers.[9] If TMA recurs, reinitiating eculizumab therapy has been successful in suppressing complement activation.[27]

In summary, this case highlights the importance of prompt diagnosis of kidney transplant–associated TMA by a multidisciplinary TMA team and early initiation of eculizumab therapy to allow recovery of renal graft and hematologic parameters.[28] Genetic testing should also be incorporated in the workup of TMA to identify any predisposition and guide the duration of therapy.

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Amandeep Godara, MD, Daniel R. Migliozzi, PharmD, Monika Pilichowska, MD, PhD, Nitender Goyal, MD, Cindy Varga, MD, and Craig E. Gordon MD, MS.

Authors' Affiliations: Department of Hematology-Oncology (AG, CV), Kidney Transplant Team, Division of Nephrology (DRM, NG), and Divisions of Pathology (MP) and Nephrology (CEG), Tufts Medical Center, Boston, MA.

Address for Correspondence: Amandeep Godara, MD, Hematology-Oncology fellow, Tufts Medical Center, 800

REFERENCES

1. Schwimmer J, Nadasdy TA, Spitalnik PF, Kaplan KL, Zand MS. De novo thrombotic microangiopathy in renal transplant recipients: a comparison of hemolytic uremic syndrome with localized renal thrombotic microangiopathy. *Am J Kidney Dis*. 2003;41(2):471-479.

2. Reynolds JC, Agodoa LY, Yuan CM, Abbott KC. Thrombotic microangiopathy after renal transplantation in the United States. *Am J Kidney Dis*. 2003;42(5):1058-1068.

3. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. *Clin J Am Soc Nephrol*. 2009;4(2):481-508.

4. Trimarchi HM, Truong LD, Brennan S, Gonzalez JM, Suki WN. FK506-associated thrombotic microangiopathy: report of two cases and review of the literature. *Transplantation*. 1999;67(4): 539-544.

5. Nava F, Cappelli G, Mori G, et al. Everolimus, cyclosporine, and thrombotic microangiopathy: clinical role and preventive tools in renal transplantation. *Transplant Proc*. 2014;46(7):2263-2268.

6. Vincenti F. Belatacept and long-term outcomes in kidney transplantation. *N Engl J Med*. 2016;374(26):2600-2601.

7. Dedhia P, Govil A, Mogilishetty G, Alloway RR, Woodle ES, Abu Jawdeh BG. Eculizumab and belatacept for de novo atypical hemolytic uremic syndrome associated with CFHR3-CFHR1 deletion in a kidney transplant recipient: a case report. *Transplant Proc*. 2017;49(1):188-192.

8. Yamamoto T, Watarai Y, Futamura K, et al. 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. *Transplant Proc*. 2017;49(1):159-162.

9. Ikeda T, Okumi M, Unagami K, et al. Two cases of kidney transplantation-associated thrombotic microangiopathy successfully treated with eculizumab. *Nephrology (Carlton)*. 2016;21(suppl 1):35-40.

10. FDA Belatacept prescribing information. 2011. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125288s070lbl.pdf. Accessed August 19, 2020.

11. Satoskar AA, Pelletier R, Adams P, et al. De novo thrombotic microangiopathy in renal allograft biopsies-role of antibody-mediated rejection. *Am J Transplant*. 2010;10(8):1804-1811.

12. Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant. *Am J Transplant*. 2011;11(11):2279-2296.

13. Zuber J, Le Quintrec M, Morris H, Fremeaux-Bacchi V, Loirat C, Legendre C. Targeted strategies in the prevention and management of atypical HUS recurrence after kidney transplantation. *Transplant Rev (Orlando)*. 2013;27(4):117-125.

14. Satoh S, Saito K, Harada H, Okumi M, Saito M. Survey Committee for TA-TMA of the Japan Society for Transplantation Survey of thrombotic microangiopathy within 1 week after kidney transplantation between 2010 and 2015 in Japan. *Clin Exp Nephrol*. 2019;23(4):571-572.

15. Ali MN, Syed A, Bhandari S. Case series: hemolytic uremic syndrome—another cause of transplant dysfunction. *Transplant Proc*. 2013;45(9):3284-3288.

16. Le Quintrec M, Lionet A, Kamar N, et al. Complement mutation-associated de novo thrombotic microangiopathy following kidney transplantation. *Am J Transplant*. 2008;8(8):1694-1701.

17. Legendre CM, Campistol JM, Feldkamp T, et al. Outcomes of patients with atypical haemolytic uraemic syndrome with native and transplanted kidneys treated with eculizumab: a pooled post hoc analysis. *Transpl Int*. 2017;30(12):1275-1283.

18. Abbas F, El Kossi M, Kim JJ, Sharma A, Halawa A. Thrombotic microangiopathy after renal transplantation: current insights in de novo and recurrent disease. *World J Transplant*. 2018;8(5): 122-141.

19. Le Quintrec M, Zuber J, Moulin B, et al. Complement genes strongly predict recurrence and graft outcome in adult renal transplant recipients with atypical hemolytic and uremic syndrome. *Am J Transplant*. 2013;13(3):663-675.

20. Zhai YL, Meng SJ, Zhu L, et al. Rare variants in the complement factor H-related protein 5 gene contribute to genetic susceptibility to IgA nephropathy. *J Am Soc Nephrol*. 2016;27(9): 2894-2905.

21. Hoffman-Andrews L. The known unknown: the challenges of genetic variants of uncertain significance in clinical practice. *J Law Biosci*. 2017;4(3):648-657.

22. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-424.

23. Gonzalez Suarez ML, Thongprayoon C, Mao MA, Leeaphorn N, Bathini T, Cheungpasitporn W. Outcomes of kidney transplant patients with atypical hemolytic uremic syndrome treated with eculizumab: a systematic review and meta-analysis. *J Clin Med*. 2019, 919;8(7).

24. Fakhouri F, Fila M, Provot F, et al. Pathogenic variants in complement genes and risk of atypical hemolytic uremic syndrome relapse after eculizumab discontinuation. *Clin J Am Soc Nephrol*. 2017;12(1):50-59.

25. Goodship TH, Cook HT, Fakhouri F, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney Int*. 2017;91(3):539-551.

26. Zuber J, Fakhouri F, Roumenina LT, Loirat C, Fremeaux-Bacchi V. French Study Group for aHUS/C3G Collaborators Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies. *Nat Rev Nephrol*. 2012;8(11):643-657.

27. Macia M, de Alvaro Moreno F, Dutt T, et al. Current evidence on the discontinuation of eculizumab in patients with atypical haemolytic uraemic syndrome. *Clin Kidney J*. 2017;10(3):310-319.

28. Gordon CE, Chitalia VC, Sloan JM, et al. Thrombotic microangiopathy: a multidisciplinary team approach. *Am J Kidney Dis*. 2017;70(5):715-721.