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Transplant-associated Thrombotic Microangiopathy Treated with Eculizumab and Romiplostim

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ABSTRACT

Transplant-associated thrombotic microangiopathy (TA-TMA) can occur after solid organ transplantation. It results in thrombocytopenia, haemolytic anaemia and microvascular occlusion. TA-TMA is not fully understood and treatment has not been clearly established. However, there is increasing evidence to suggest an immune-complement mediated component to its development. Eculizumab is a monoclonal antibody that inhibits the cleavage of C5 into pro-inflammatory, prothrombotic terminal complement elements and has been utilized in the treatment of atypical haemolytic uremic syndrome. We report a case of TA-TMA successfully treated with eculizumab and romiplostim. This case adds to the evidence that TA-TMA is triggered by complement dysregulation and suggests possible interventions for refractory cases.

LEARNING POINTS

- Transplant-associated thrombotic microangiopathy (TA-TMA) may occur in solid organ transplant patients.
- Eculizumab may be used for the treatment of TA-TMA.

KEYWORDS

Eculizumab, romiplostim, transplant thrombotic microangiopathy

INTRODUCTION

Thrombotic microangiopathy (TMA) is a potentially fatal condition characterized by thrombocytopenia, haemolytic anaemia and microvascular occlusion. Calcineurin inhibitors (CNI) are frequently used following solid organ transplantation. However, their use has been linked to the development of TMA in transplanted patients [1]. Transplant-associated thrombotic microangiopathy (TA-TMA) is a rare, severe microvascular occlusive condition resulting in platelet aggregation, thrombocytopenia and mechanical injury to erythrocytes with end-organ damage [2]. In contrast to other causes of thrombotic microangiopathy, treatment for TA-TMA has not been clearly established. We report a case of TA-TMA following liver transplantation successfully treated with eculizumab.

CASE DESCRIPTION

A 43-year-old woman with a history of decompensated cirrhosis secondary to alcohol use, underwent orthotopic liver transplant in July 2018. Her immunosuppressive regimen included tacrolimus 0.5 mg twice daily. Her post-operative course was unremarkable.

The patient presented in November 2019 with petechial rash on her arms and legs. Her complete blood count was significant for a platelet count of <2,000. The initial blood smear showed a dramatically reduced platelet count as well as large platelets. Schistocytes were not increased. She received 4 days of IVIG and dexamethasone for presumed immune thrombocytopenic purpura with no sustained improvement in platelet count. She was also started on romiplostim 10 µg/kg subcutaneous weekly.

She initially underwent splenic artery embolization with a transient improvement in the platelet count to 41,000. At this time her blood smear was significant for schistocytes at 4–5/hpf. The ADAMTS13 level was found to be normal.

Despite the normal ADAMTS13 level, the patient underwent plasma exchange (PEX) due to refractory thrombocytopenia and the presence of schistocytes. The platelet count which was 17,000 before the first exchange on 13 November improved to 55,000 on 16 November after the third exchange. PEX was held for 1 day with a transient decline in platelet count and then resumed on 17 November with an improvement in platelet count to >100,000. However, the platelet count again declined even though PEX was continued.

A bone marrow biopsy performed on 27 November 2019 showed increased megakaryocytes and erythroid hyperplasia with no significant abnormalities.

Because of severe thrombocytopenia and a high schistocytes burden with a modest decline in ADMATS13, atypical haemolytic uremic syndrome, transplant-induced TMA and drug-induced TMA were considered in the differential diagnosis.

Tacrolimus was stopped due to possible drug-induced TMA and the patient was started on mycophenolate mofetil (MMF) but her platelet count did not improve. The patient received eculizumab and romiplostim on 3 December 2019. She received four weekly doses of both drugs, and her platelet count improved from <2,000 on discharge date of December 18th 2019 to 14,000 on 3 January 2020.

On a follow-up visit on 14 January 2020, the platelet count was 1.9 million. Eculizumab and romiplostim were held. The patient remained in haematological remission but died several months later from acute liver rejection and overwhelming sepsis.

DISCUSSION

TMA following liver transplantation is a serious complication, with a poor outcome and high mortality. It results from endothelial injury causing platelet micro-thrombi, platelet consumption and haemolytic anaemia. It could be precipitated by a variety of factors including bacterial and viral infections as well as CNI, which are routinely used after transplantation [1].

Because the pathophysiology of TA-TMA is poorly understood, current treatment options are suboptimal with a high mortality rate. Various treatment strategies have been used including drug withdrawal or exchange in drug-induced TMA as well as PEX, which showed some response although not always complete [3].

Complement system activation has been hypothesized to be an important factor in the development of TA-TMA. Eculizumab is a monoclonal antibody that inhibits the cleavage of C5 into pro-inflammatory, prothrombotic terminal complement elements. It has demonstrated effectiveness in the management of atypical haemolytic uremic syndrome and has been used in the treatment of TA-TMA [4].

TA-TMA has been reported in solid organ transplantation as well as autologous and allogeneic stem cell transplantation [5,6]. A review of the use of eculizumab in TA-TMA found the majority of TA-TMA cases were seen after solid organ transplantation, especially renal transplantation, with only two reported cases of eculizumab use following liver transplantation [7]. In the same review, patients who developed TA-TMA were treated initially with CNI discontinuation or dose reduction with or without PEX. Eculizumab was used after the failure of those therapies. In this study, the median time between transplantation and initiation of eculizumab was 63 days with a median of 5.5 doses. The authors reported the initial response occurred after a median of two doses and that 92% (n=24) of patients recovered. These patients were doing well after a median follow-up of 52 weeks.

In our case, the patient was initially treated with CNI discontinuation with a transient response in platelet count. Given her initial modest decline in ADAMTS13, she also received multiple sessions of PEX with no durable response. During that time, she was started on romiplostim without any significant improvement in her platelet counts. It was only after she received eculizumab that she had a complete and durable response. Clinical response was sustained even after discontinuation of eculizumab.

CONCLUSION

This case report suggests eculizumab and romiplostim are effective in treating TA-TMA not responsive to conventional treatment modalities such as withdrawal of CNI and plasmapheresis. Larger studies are needed to confirm the effectiveness of this treatment for TA-TMA.

REFERENCES

1. Nwaba A, MacQuillan G, Adams LA, Garas G, Delriviere L, Augustson B, et al. Tacrolimus-induced thrombotic microangiopathy in orthotopic liver transplant patients: case series of four patients. *Intern Med J* 2013;**43**(3):328–333.
2. Chapin J, Shore T, Forsberg P, Desman G, Van Besien K, Laurence J. Hematopoietic transplant-associated thrombotic microangiopathy: case report and review of diagnosis and treatments. *Clin Adv Hematol Oncol* 2014;**12**(9):565–573.
3. Tamura S, Sugawara Y, Matsui Y, Kishi Y, Akamatsu N, Kaneko J, et al. Thrombotic microangiopathy in living-donor liver transplantation. *Transplantation* 2005;**80**(2):169–175.
4. Wijnsma KL, Ter Heine R, Moes D, Langemeijer S, Schols SEM, Volokhina EB, et al. Pharmacology, pharmacokinetics and pharmacodynamics of eculizumab, and possibilities for an individualized approach to eculizumab. *Clin Pharmacokinet* 2019;**58**(7):859–874.
5. Okano M, Sakata N, Ueda S, Takemura T. Recovery from life-threatening transplantation-associated thrombotic microangiopathy using eculizumab in a patient with very severe aplastic anemia. *Bone Marrow Transplant* 2014;**49**(8):1116–1118.
6. Peffault de Latour R, Xhaard A, Fremeaux-Bacchi V, Coppo P, Fischer AM, Helley D, et al. Successful use of eculizumab in a patient with post-transplant thrombotic microangiopathy. *Br J Haematol* 2013;**161**(2):279–280.
7. Dhakal P, Giri S, Pathak R, Bhatt VR. Eculizumab in transplant-associated thrombotic microangiopathy. *Clin Appl Thromb Hemost* 2017;**23**(2):175–180.