Successful treatment of severe transplantation-mediated alloimmune thrombocytopenia with efgartigimod

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INTRODUCTION

Transplantation-mediated alloimmune thrombocytopenia (TMAT) is a rare cause of thrombocytopenia in patients following solid organ transplantation. We describe a rare case of TMAT secondary to passenger lymphocytes and production of human platelet antigen-1a antibodies in a patient following orthotopic liver transplantation. His thrombocytopenia was refractory to first-line treatments including corticosteroids, intravenous immunoglobulins, and rituximab. However, he responded to therapy with efgartigimod, an antagonist to the neonatal Fc receptor.

CASE PRESENTATION

- **Transplant History:** A 70-year-old man with cirrhosis secondary to non-alcoholic steatohepatitis and complicated by hepatocellular carcinoma underwent deceased donor orthotopic liver transplantation. On post-operative day 5, he developed acute hepatic artery thrombosis and required emergent retransplantation on post-operative day 7. His second liver transplant was hepatitis C nucleic acid testing positive and cytomegalovirus immunoglobulin G (IgG) positive with negative recipient testing. Seven days after retransplantation, the patient developed severe thrombocytopenia with platelet count <1x10^9/L. His platelet counts prior to and immediately following his first transplantation were consistently between 50-100x10^9/L.
- **Workup** for alternative causes of thrombopenia was negative, including HIT and hemolysis. Hematology was consulted due to concern for immune-mediated thrombocytopenia.
- **Complications:** Two days following his platelet nadir of <1x10^9/L, he developed hemoperitoneum secondary to spontaneous splenic rupture requiring emergent exploratory laparotomy and splenectomy.
- **Treatments:** Figure 1, and eltrombopag 75mg daily for 6 weeks prior to efgartigimod administration.
- **TMAT Diagnosis:** Presence of human platelet antigen- (HPA) 1a antibodies in the recipient serum with reactivity against platelet GPIIb/IIIa. HPA genotyping revealed a mismatch between the donor and recipient with donor genotype HPA 1b/1b and the recipient genotype HPA 1a/1a. Findings were consistent with the diagnosis of transplantation-mediated alloimmune thrombocytopenia (TMAT).
- **Efgartigimod:** The patient underwent four weekly infusions of efgartigimod at 10 mg/kg. After the third infusion, he developed a sustained improvement in platelets to >100x10^9/L without the need for transfusion.
- **Preserved Effect:** He was discharged from the hospital and continued to have sufficient platelet levels during outpatient follow-up.

Table 1: Reference Cases

Reference, year of Liver Transplant TMAT	Sex, age	Platelet nadir (x10^9)	Treatments	Outcome
(1), 2017	Male	<5	IVIG, Rituximab, Thrombopoietin, Antigen-negative platelets	Required HPA-1a antigen-negative platelet transfusions until POD60
(2), 1999	Female, 43	12	Corticosteroids, Antithymocyte globulin	Resolution of thrombocytopenia after treatment for rejection with antithymocyte globulin
(3), 2017	Male, 59	3	Methylprednisolone, IVIG	Resolution of thrombocytopenia POD28
Current case	Male, 70	1	Methylprednisolone, IVIG, Plasmapheresis, Rituximab, Splenectomy, Romiplostim, Eltrombopag, Efgartigimod	Sustained platelet increase > 100x10^9 following Efgartigimod

Table 1. Previously described cases of TMAT following liver transplantation.

Figure 1.

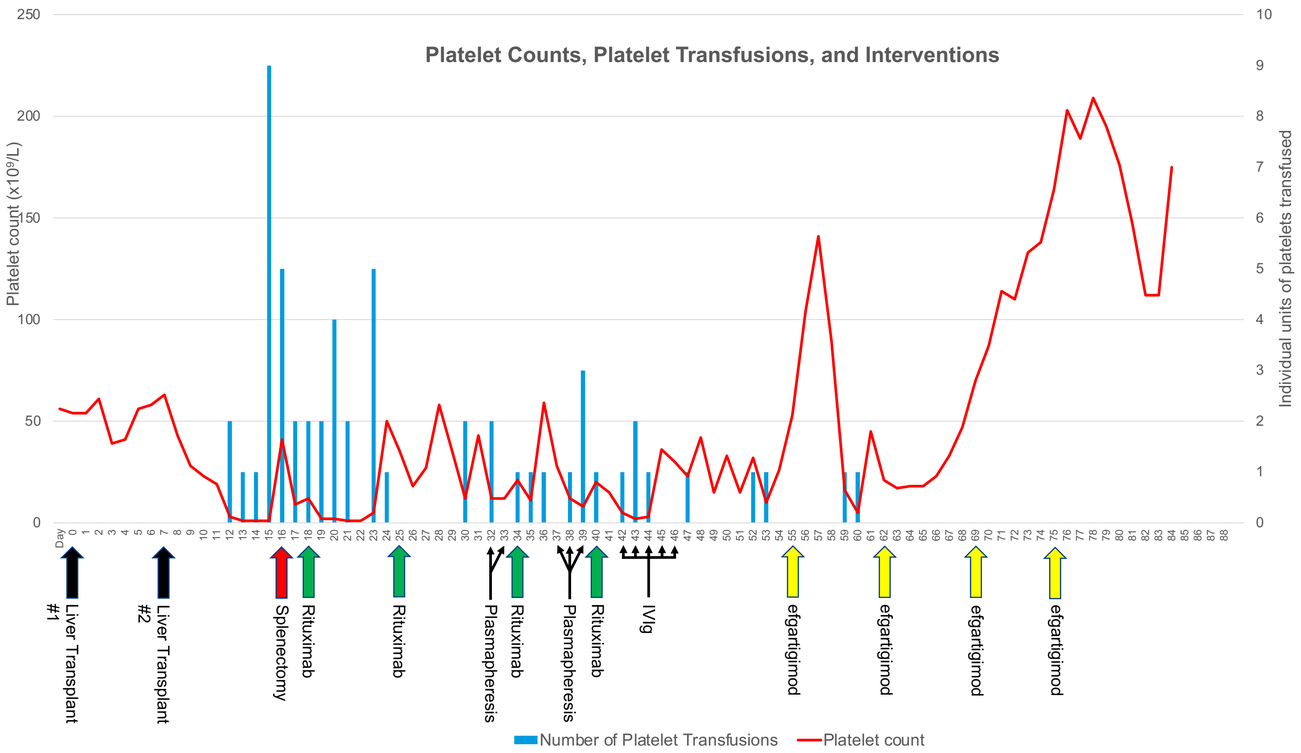

Table 1. Previously described cases of TMAT following liver transplantation.

TABLE 1 REFERENCE CASES

1. Sonnerborg IV, Hoglund P, Nordstrom J, et al. Severe Transplantation-Mediated Alloimmune Thrombocytopenia in 2 Recipients of Organs From the Same Donor. Transplantation. 2017;101(5):e190-e2.
2. West KA, Anderson DR, McAlister VC, et al. Alloimmune thrombocytopenia after organ transplantation. N Engl J Med. 1999;341(20):1504-7.
3. Lindholm PF, Kwaan HC, Ramsey G, et al. Severe thrombocytopenia in a patient following liver transplantation caused by HPA-1a antibodies produced by the liver donor. Am J Hematol. 2018;93(1):150-3.

DISCUSSION

- Transient thrombocytopenia after liver transplant is expected in 60% of cases.
- TMAT Mechanism:
  1. The recipient receives an organ from a donor with known autoimmune thrombocytopenia. The antibodies of the donor react to the same antigen in the recipient causing thrombocytopenia.
  2. Donor passenger lymphocytes produce an antibody against a host antigen (passenger lymphocyte syndrome) that produce antibody against recipient antigen as seen in **this case**.
- This is the 4th case of TMAT following liver transplant reported. (Table 1)
- Efgartigimod is an antagonist to the neonatal Fc receptor that leads to targeted degradation of immunoglobulin G. Although currently FDA approved for treatment of myasthenia gravis, clinical trials are in progress investigating use for immune thrombocytopenia.

CONCLUSIONS

- Transplantation-mediated alloimmune thrombocytopenia is a rare complication following solid-organ transplantation, but should be considered in recipients with persistent and unexplained thrombocytopenia.
- In treatment refractory cases, the novel FcRn antagonist efgartigimod may lead to improvement in thrombocytopenia.