Cardiology in the Young

cambridge.org/cty

Case Report

Cite this article: Pike D, Hulbert M, and Kamsheh A (2025) Eculizumab treatment of tacrolimus-associated autoimmune haemolytic anaemia and thrombotic microangiopathy in a child with orthotopic heart transplant. *Cardiology in the Young* **35**: 1469–1471. doi: 10.1017/S1047951125101339

Received: 10 February 2025
Revised: 7 May 2025
Accepted: 30 June 2025
First published online: 1 August 2025

Keywords:
Orthotopic heart transplant; haemolysis; tacrolimus

Corresponding author:
Daniel Pike; Email: dpike@wustl.edu

Eculizumab treatment of tacrolimus-associated autoimmune haemolytic anaemia and thrombotic microangiopathy in a child with orthotopic heart transplant

Daniel Pike[1], Monica Hulbert[2] and Alicia Kamsheh[3]

[1]Department of Pediatrics, St. Louis Children's Hospital and Washington University School of Medicine, St. Louis, MO, USA; [2]Dana Farber/Boston Children's Cancer and Blood Disorders Center, Department of Pediatrics, Harvard Medical School, Boston, MA, USA and [3]Division of Cardiology, Department of Pediatrics, Washington University School of Medicine, St. Louis, MO, USA

Abstract

Background: Tacrolimus is the standard immunosuppressant used in paediatric orthotopic heart transplantation, but it can be associated with rare and life-threatening haemolysis. *Methods:* Retrospective chart review was used for this case report. *Results/Conclusion:* We present the case of a 6-year-old heart transplant recipient who developed life-threatening haemolysis in the setting of mycoplasma infection while on tacrolimus immunosuppression that was treated successfully with eculizumab.

Introduction

Tacrolimus is the standard immunosuppressant used in paediatric orthotopic heart transplantation. Tacrolimus-associated haemolytic anaemia is a rare and life-threatening side effect seen in patients after haematopoietic stem cell transplant or solid organ transplant, and it can present with different phenotypes with complement activation as a common pathway.[1,2] We present a case of a 6-year-old patient with a history of orthotopic heart transplant on tacrolimus immunosuppression who developed life-threatening and refractory haemolysis. He recovered fully following treatment with eculizumab, a monoclonal antibody directed towards complement C5. This is the first reported case describing the use of eculizumab in a paediatric orthotopic heart transplant recipient to treat severe haemolytic anaemia associated with tacrolimus immunosuppression.

Case description

The patient is a 6-year-old with Noonan syndrome with prenatally diagnosed double outlet right ventricle and hypoplastic aortic arch that was repaired in infancy. At one year of life, he had worsening subaortic stenosis leading to a cardiac arrest requiring veno-arterial extracorporeal membrane oxygenation support, and he ultimately received an orthotopic heart transplant. Following transplant, his immunosuppression was maintained with tacrolimus and azathioprine.

Four years after transplant, he presented to his local institution with emesis and was found to be anaemic, with a haemoglobin of 5.0 g/dL. Laboratory workup demonstrated significant haemolysis, coagulopathy, and an acute kidney injury. An echocardiogram demonstrated new mild to moderate tricuspid regurgitation and elevated right ventricular systolic pressures. He received 5 mL/kg packed red blood cells and was transported to our institution for further management.

Rapid *ex vivo* haemolysis in our patient's samples suggested that cold haemolysis was driving his condition. However, direct antiglobulin test suggested warm and cold haemolysis, as both IgG autoantibodies and C3 were detected. Therefore, methylprednisolone was initiated to treat warm haemolysis in addition to rituximab for cold agglutinin-mediated haemolysis. Tacrolimus trough was 18.7 ng/mL (goal trough 5–8 ng/mL) and subsequently replaced with sirolimus. He also received doxycycline for presumed *M. pneumoniae* infection, as IgG and IgM antibodies reactive to *Mycoplasma pneumoniae* were detected in his serum—IgM *M. pneumoniae* antibodies are classically associated with cold haemolysis.

Soon after arrival, the patient decompensated, requiring vasoactives, intubation, chest tube placement, and continuous renal replacement therapy. The patient's haemolysis persisted, and he also developed microangiopathy with thrombocytopenia and schistocytes. He was initiated on plasma exchange therapy in attempt to remove the antibodies contributing to his haemolysis.

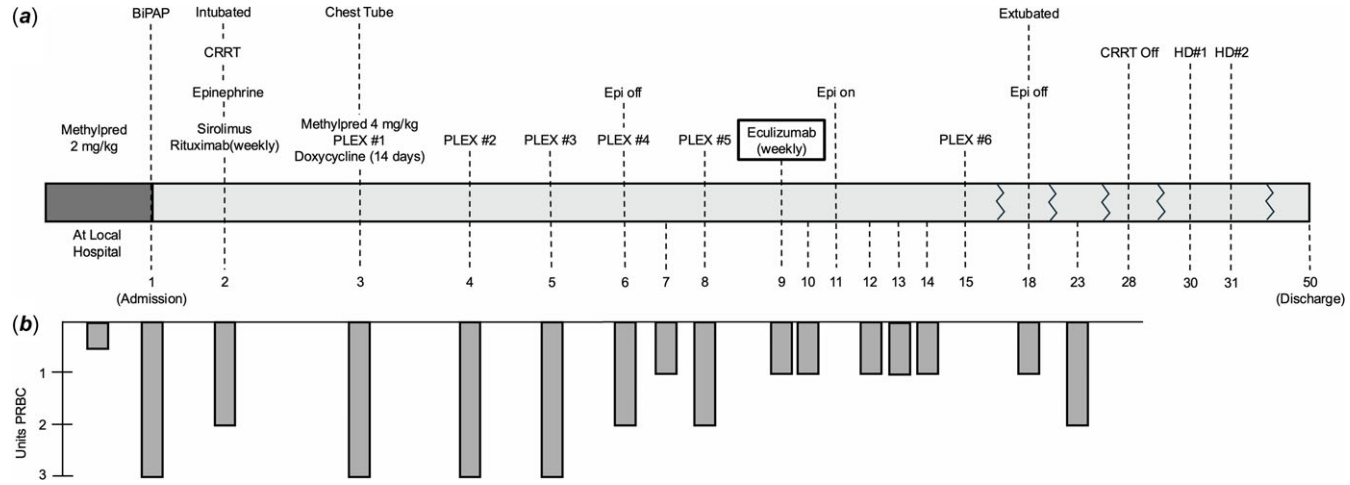

Figure 1. (***a***) A timeline of the patient's hospitalisation by hospital day. Shown in dark grey is the time spent at the patient's local hospital prior to being transferred to our institution. Pertinent clinical events and initiation of treatments are labelled. Days are not shown to scale. PLEX (plasma exchange therapy). Epi (epinephrine). CRRT (continuous renal replacement therapy). HD (haemodialysis). (***b***) Number of transfusions of RBCs (red blood cells) administered per day of hospitalisation. Units are approximately 250 mL – 300 mL in volume. A 5 mL/kg transfusion of RBC was given at the local hospital prior to transfer.

A summary of the patient's course can be seen in Figure 1A. Because of the patient's continued critical illness and ongoing need for transfusions despite systemic steroids, rituximab, and plasma exchange, the decision was made to treat with eculizumab with four weekly doses. Following the initial dose of eculizumab, the patient's haemoglobin stabilised; and after the second dose of eculizumab, his clinical status, transfusion requirement (Figure 1B), and haemolysis improved.

After three weeks of continuous renal replacement, he was transitioned to intermittent haemodialysis before his kidney function recovered sufficiently. He developed hypertension attributed to his kidney injury necessitating amlodipine and metoprolol. He was initiated on an erythropoietin-stimulating agent and a steroid wean while continuing sirolimus and azathioprine. Due to his treatment with rituximab and eculizumab, he was started on antimicrobial prophylaxis of sulfamethoxazole-trimethoprim and amoxicillin. He ultimately required 27 units of blood, but his haemoglobin has remained stable as of eight months following discharge. Direct antiglobulin test has remained negative. Pertinent laboratory values are listed in Supplementary Table S1.

Discussion

Tacrolimus contributes to the initial immunosuppressant regimen of almost ninety per cent of paediatric heart transplant patients.[3] Haemolytic anaemia is a rare complication of chronic tacrolimus immunosuppression in transplant patients; it can present as either a thrombotic microangiopathy or autoantibody-mediated autoimmune haemolysis, both involving complement activation.[4,5] While the exact pathophysiological mechanism of tacrolimus-induced microangiopathy is unknown, it is hypothesised that calcineurin inhibitors, including cyclosporine, can, in a dose-dependent manner, directly damage endothelial cells and form immune complexes, leading to haemolysis.[6,7] Patients who develop tacrolimus-associated haemolysis are typically transitioned to alternative immunosuppressive agents, such as sirolimus, as was the case with our patient.[6] Eculizumab is a monoclonal antibody targeted to complement component C5 and can treat complement-induced haemolytic anaemias and microangiopathies. Our patient represents the first documented case of eculizumab treating tacrolimus-associated autoimmune haemolytic anaemia in a paediatric patient after orthotopic heart transplant.

In addition to tacrolimus use, our patient had IgM antibodies to *M pneumoniae*, which is classically associated with cold haemolysis. However, this is typically self-limiting and only rarely requires intervention.[8] Given the severity of the presentation, we hypothesise that tacrolimus played a multifactorial role in our patient's haemolysis. Tacrolimus likely contributed to a dysregulated humoral response, leading to a severe case of infection-associated autoimmune haemolysis, as has been described in other cases.[9] Furthermore, since the patient did not improve following humoral response-directed treatment, his tacrolimus trough was supra-therapeutic, and there was evidence of a microangiopathic process exacerbating his multisystem organ failure, we hypothesise that direct endothelial toxicity from tacrolimus was also driving our patient's haemolysis. While there are reported patient-specific factors predisposing to haemolysis, there are no reports associating Noonan syndrome with haemolysis.[10]

Eculizumab prevents the cleavage product formation of C5b, a necessary component of the membrane attack complex, and it has been used with success in paediatric stem cell and adult solid organ transplant recipients to acutely treat tacrolimus-associated haemolysis, as well as haemolysis from alternative aetiologies that sometimes require chronic treatment.[2,7,11] Reported use of eculizumab in paediatric orthotopic heart transplant recipients to date has been limited to treatment of antibody-mediated rejection or prevention in high-risk recipients.[12] Our use of eculizumab in this patient population to treat refractory complement-mediated haemolysis is unique. Our case highlights several important aspects of the care of paediatric patients after heart transplantation. The first is to have a high index of suspicion for haemolysis in a patient presenting with anaemia, as it can rapidly develop into multi-system organ failure. The second is the ability of eculizumab to acutely stabilise a patient with refractory haemolysis.

https://doi.org/10.1017/S1047951125101339 Published online by Cambridge University Press

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1047951125101339

Acknowledgements. Thank you to Dr Dave Wilson for assistance in editing this manuscript.

Financial support. This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Competing interests. The authors of this manuscript have no conflicts of interest to disclose.

References

1. Wong W, et al. Cold agglutinin syndrome in pediatric liver transplant recipients. Pediatr Transplant 2007; 11 : 931–936.
2. Jodele S, et al. Complement blockade for TA-TMA: lessons learned from a large pediatric cohort treated with eculizumab. Blood 2020; 135 : 1049–1057.
3. Colvin MM, et al. OPTN/SRTR 2022 annual data report: heart. Am J Transplant 2024; 24 : S305–s393.
4. Jodele S. Complement in pathophysiology and treatment of transplant-associated thrombotic microangiopathies. Semin Hematol 2018; 55: 159–166.
5. Berentsen S. Role of complement in autoimmune hemolytic anemia. Transfus Med Hemother 2015; 42 : 303–310.
6. Munjal RS, et al. Beyond immunosuppression: the intricate relationship between tacrolimus and microangiopathy. Cureus 2023; 15 : e49351.
7. Dhakal P, et al. Eculizumab in transplant-associated thrombotic microangiopathy. Clin Appl Thromb Hemost 2017; 23 : 175–180.
8. Berentsen S. New insights in the pathogenesis and therapy of cold agglutinin-mediated autoimmune hemolytic anemia. Front Immunol 2020; 11: 590.
9. Kanellopoulou T. Autoimmune hemolytic anemia in solid organ transplantation—the role of immunosuppression. Clin Transplant 2017; 31 : e13031.
10. Valoti E, et al. Mycoplasma pneumoniae infection associated with anti-factor H autoantibodies in atypical hemolytic uremic syndrome. Nephron 2022; 146 : 593–598.
11. Gill R, Meghrajani V. Tacrolimus-induced thrombotic microangiopathy after orthotopic heart transplant: a case report. Cureus 2022; 14 : e25874.
12. Law YM, et al. Use of the terminal complement inhibitor eculizumab in paediatric heart transplant recipients. Cardiol Young 2020; 30 : 107–113.