Complement-mediated HUS in post-kidney transplant patients: A Case Series

Natasha Venugopal MD, Hyma V. Polimera MD, Jessica Santucci BS, Erik Washburn MD, Elizabeth Federici MD

Penn State Hershey Medical Center, Hershey PA

PennState Health
Milton S. Hershey
Medical Center

Introduction

- Complement-mediated hemolytic uremic syndrome (CM-HUS) is a rare, potentially fatal thrombotic microangiopathy (TMA).
- It is triggered by complement dysregulation and characterized by the triad of thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and acute renal failure.
- The condition can lead to end-stage renal disease (ESRD), necessitating kidney transplant. In rare instances, it can develop in post-transplant patients.
- The regulation of the complement system can lead to resolution.

Methods

- This is a noncontrolled, observational case report focused on two post-kidney transplant patients who developed CM-HUS.

Case Presentations

Case 1: A 44-year-old male with ESRD, secondary to hypertensive nephrosclerosis status post kidney transplant four years ago, presented with pancytopenia and acute on chronic kidney disease (CKD). Peripheral smear revealed increased schistocytes, consistent with MAHA and suggestive of TMA. Further workup with ADAMTS13 activity assay and stool culture ruled out TTP and HUS. Given low serum C3 and C4 levels, CM-HUS was suspected. Eculizumab was initiated, resulting in the stabilization of his creatinine and resolution of his pancytopenia. Given this improvement, the medication was discontinued in favor of surveillance. Subsequent lab checks demonstrated relapse, prompting the re-initiation of eculizumab, which once again proved effective. The patient transitioned to ravulizumab, and to date, continues to on the therapy without relapse.

Case 2: A 58-year-old male with CKD secondary to hypertension, underwent a deceased donor renal transplant in 2017. One week post-transplantation, he developed elevated creatinine, thrombocytopenia, and anemia. Work-up revealed a positive CFHR3-1 mutation, depleted CHF50 and APFA, and normal levels of C3 and C4, suggesting CM-HUS. The patient was started on eculizumab and eventually transitioned to ravulizumab without any evidence of relapse.

Figure 1. Renal Pathology of Patient One

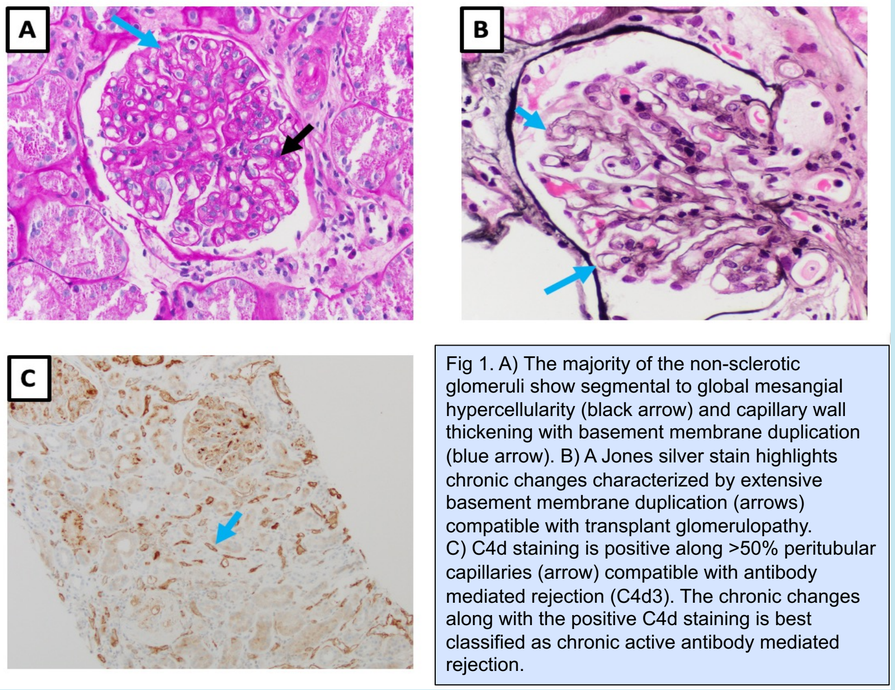

Fig 1. A) The majority of the non-sclerotic glomeruli show segmental to global mesangial hypercellularity (black arrow) and capillary wall thickening with basement membrane duplication (blue arrow). B) A Jones silver stain highlights chronic changes characterized by extensive basement membrane duplication (arrows) compatible with transplant glomerulopathy. C) C4d staining is positive along >50% peritubular capillaries (arrow) compatible with antibody mediated rejection (C4d3). The chronic changes along with the positive C4d staining is best classified as chronic active antibody mediated rejection.

Figure 2. Creatinine Trend of Patient One

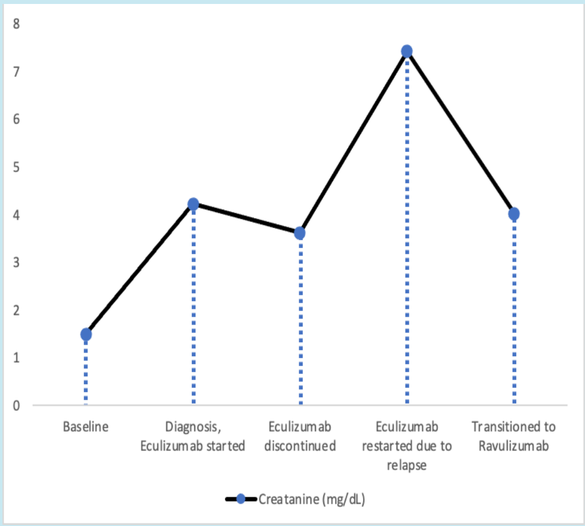

Fig 2. Serum creatinine level at baseline, at initial diagnosis of complement- mediated HUS and start of eculizumab therapy, discontinuation of eculizumab, re-initiation of eculizumab due to relapse, and transition to ravulizumab.

Discussion

- Diagnosis of complement-mediated HUS requires exclusion of other TMAs, such as TTP and HUS, by checking ADAMTS13 activity and Shiga-toxin respectively. To confirm the diagnosis, complement levels can be evaluated.
- The pathogenesis of complement-mediated HUS involves dysregulation of the complement system. Eculizumab inhibits cleavage of C5 into C5a and C5b, hindering the deployment of the terminal complement system, including the formation of MAC. Ravulizumab is a long acting, anticomplement C5 monoclonal antibody. These complement inhibitors can therefore be utilized to regulate the complement system in patients with the condition.
- The relapse rate following eculizumab treatment can range from 20-67%. Existing literature indicates that patients with a history of kidney transplant are more prone to relapse than those with native kidneys.
- Re-treatment with complement inhibitors has proven effective in management of relapses. Therefore, the long-term continuation of complement inhibitor medications is recommended to prevent recurrence.

Figure 3. Mechanism of Action of Eculizumab

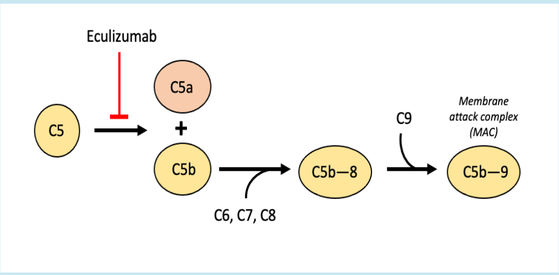

Fig 3. The mechanism of action of eculizumab involves inhibition of the cleavage of C5 into C5a and C5b, which prevents that pathway from continuing into the membrane attack complex.

Conclusions

- Complement-mediated HUS is rare, especially in post-transplant patients, and can be potentially fatal.
- It is crucial for clinicians to recognize and treat this condition promptly.
- Management often involves complement inhibitors. The risk of relapse is particularly high in patients with a history of kidney transplant, but long-term continuation of these medications can prevent relapse.

References

1. Arnold, D. M., Patriquin, C. J., & Nazy, I. Thrombotic microangiopathies: A general approach to diagnosis and management. *Canadian Medical Association Journal* **2016**, *189(4)*, E153-E159
2. Tsai, H. M. Pathophysiology of thrombotic thrombocytopenic purpura. *International Journal of Hematology* **2010**, *91*, 1-19.
3. Bhandari, J., & Sedhai, Y. R. Hemolytic uremic syndrome - StatPearls - NCBI bookshelf. National Center for Biotechnology Information. Available online: https://www.ncbi.nlm.nih.gov/books/NBK556038/ (accessed on 10 August 2022)
4. Kavanagh, D., Goodship, T. H., & Richards, A. Atypical Hemolytic Uremic Syndrome. *Seminars in Nephrology* **2013**, *33(6)*, 508-530.
5. Wijnsma, K. L., Ter Heine, R., Moes, D. J., et al. Pharmacology, pharmacokinetics and pharmacodynamics of Eculizumab, and possibilities for an individualized approach to Eculizumab. *Clinical Pharmacokinetics* **2019**, *58(7)*, 859-874.
6. Tsai, H. Physiologic cleavage of von Willebrand factor by a plasma protease is dependent on its conformation and requires calcium ion. *Blood* **1996**, *87(10)*, 4235-4244.
7. Yan, K., Desai, K., Gullapalli, L., et al. Epidemiology of atypical hemolytic uremic syndrome: A Systematic Literature Review. *Clinical Epidemiology* **2020**, *12*, 295-305.
8. Fayek, S. A., Allam, S. R., Martinez, E., et al. Atypical hemolytic uremic syndrome after kidney transplantation: Lessons learned from the good, the bad, and the ugly. A case series with literature review. *Transplantation Proceedings* **2020**, *52(1)*, 146-152.
9. Gonzalez Suarez, M. L., Thongprayoon, C., Mao, M. A., et al. Outcomes of kidney transplant patients with atypical hemolytic uremic syndrome treated with Eculizumab: A systematic review and meta-analysis. *Journal of Clinical Medicine* **2019**, *8(7)*, 919.
10. Noris, M., Caprioli, J., Bresin, E., et al. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. *Clinical Journal of the American Society of Nephrology* **2010**, *5(10)*, 1844-1859.
11. Nester, C. M., Barbour, T., De Cordoba, S. R., et al. Atypical aHUS: State of the art. *Molecular Immunology* **2015**, *67(1)*, 31-42.
12. Afshar-Kharghan, V. Atypical hemolytic uremic syndrome. *Hematology: the American Society of Hematology Education Program* **2016**, *2016(1)*, 217-225.
13. Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online. Waltham, MA: UpToDate, Inc.; Feb 11, 2024. Available online: https://online.lexi.com (accessed on 11 February 2024)
14. Duineveld, C., Bouwmeester, R., Van der Heijden, J. W., et al. Outcome of atypical haemolytic uraemic syndrome relapse after eculizumab withdrawal. *Clinical Kidney Journal* **2020**, *14(8)*, 1939-1945.
15. Konar, M., Lujan, E., & Granoff, D. Effect of complement inhibition by Anti-C5 (Eculizumab) or a small molecule inhibitor of factor D (ACH-4471) on survival of meningococci in blood from vaccinated adults. *Blood* **2016**, *128(22)*, 2429-2429.
16. McNamara, L., Topaz, N., Wang, X., et al. High risk for invasive meningococcal disease among patients receiving Eculizumab (Soliris) despite receipt of meningococcal vaccine. *American Journal of Transplantation* **2017**, *17(9)*, 2481-2484.
17. Crew, P. E., McNamara, L., Waldron, P. E., et al. Antibiotic prophylaxis in vaccinated eculizumab recipients who developed meningococcal disease. *Journal of Infection* **2020**, *80(3)*, 350-371.