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Case Report

A Lifeline For Patients With Complement-Mediated Hemolytic Uremic Syndrome Following Renal Transplantation: Ongoing Anticomplement Therapy.

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Abstract

The rare but potentially lethal thrombotic microangiopathy (TMA) known as complement-mediated hemolytic uremic syndrome (CM-HUS), formerly known as atypical HUS, is typified by the triad of acute kidney injury, microangiopathic hemolytic anemia(MAHA), and thrombocytopenia. The main cause of it is complement dysregulation. End-stage renal disease (ESRD), which frequently calls for a kidney transplant, can develop from the illness. Rarely, persons who have had a kidney transplant may acquire it.

Methods: Two patients with thrombocytopenia, anemia, and acute renal damage who had ESRD status after kidney transplantation are described here. The work-up in both cases suggested CM-HUS, and eculizumab was used to stabilize the condition.

Discussion: Complement inhibitors like eculizumab can be used for both initial care and relapse prevention because the pathophysiology of CM-HUS involves deregulation of the complement system. After eculizumab treatment, the relapse rate might be anywhere between 20 and 67%. Compared to people with native kidneys, patients with a history of kidney transplantation are more likely to relapse. Relapses can be well managed with complement inhibitor retreatment, and long-term use of complement inhibitor drugs is advised to avoid recurrence.

Conclusions: CM-HUS is uncommon and potentially lethal, particularly in post-transplant patients. Clinicians must identify and treat this problem as soon as possible. Complement inhibitors are frequently used in management. Patients with a history of kidney transplantation are especially at risk for relapse, but long-term use of these drugs can help avoid relapse.

Keywords : *complement-mediated hemolytic uremic syndrome; thrombotic microangiopathy;eculizumab; hematology.*

INTRODUCTION

Although thrombotic microangiopathies (TMAs) are uncommon, they must be treated immediately in order to stop or reverse tissue ischemia damage.Microangiopathic hemolytic anemia (MAHA), thrombi, and test evidence of thrombocytopenia are used to establish the diagnosis, which is frequently nonspecific [1].Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are the two most common forms of TMA [1]. TTP is caused by a lack of the plasma metalloprotease ADAMTS13, which cleaves the von Willebrand factor (VWF). VWF is a plasma glycoprotein that promotes platelet adhesion, aggregation, and clot formation by stabilizing factor VIII in the clotting cascade [2]. VWF cleavage, VWF platelet aggregation, and thrombus formation are all hampered in TTP when ADAMTS13 is absent, frequently as a result of acquired autoantibodies [2].Shiga toxin-producing E. coli is usually the cause of HUS. It damages cells by attaching to glycosphingolipids, which leads to the production of microthrombi because of increased levels of fibrin and thrombin [3]. The trio of acute renal damage, thrombocytopenia, and MAHA is a common manifestation [4]. This clinical triad is shared by complement-mediated HUS (CM-HUS), formerly known as atypical HUS (aHUS), which is caused by complement dysregulation.As a component of the immune system, the complement system uses proteins to initiate inflammatory reactions and eliminate infections [5]. The three routes are alternative, lectin, and classical [4]. The creation of antigen–antibody complexes, which ultimately result in phagocytosis, is a component of the classical route [4]. After detecting a mannose-binding protein on the surface of bacteria, the lectin pathway eventually aligns with the classical pathway to trigger phagocytosis [4]. To operate further down the process and to continue cleaving C3 into C3b,

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the alternative pathway entails the spontaneous hydrolysis of complement component 3 (C3) into complement component 3b (C3b), which then interacts with factor B to generate the C3 convertase (C3bBb) [4].After the C3 convertase and C3b unite to create the C5 convertase (C3bBbC3b), complement component 5 (C5) is broken down into complement components 5a (C5a) and 5b (C5b). The cell-lysing membrane attack complex (C5b–C9) is formed when C5b attaches to complement components 6 (C6), 7 (C7), 8 (C8), and 9 (C9) [4,5]. Regulatory proteins often govern the complement system [5]. The pathophysiology of CM-HUS is frequently linked to the alternative pathway, one of the three complement pathways [5]. In the context of mutations or acquired antibodies, CM-HUS arises when the regulatory proteins are blocked, leading to uncontrolled activation and consequent endothelial and microvascular damage, hemolysis, platelet aggregation, and thrombus formation [5]. The condition may become better or perhaps go away with re-regulation.Eculizumab prevents the cleavage of C5 into C5a and C5b, as shown in Figure 1, which stops the membrane attack complex (MAC) from forming and the terminal complement system from being deployed [5]. Table 1 illustrates how complement inhibition with ravulizumab and eculizumab controls the complement system, aiding in the treatment of CM-HUS. Eculizumab was successfully used to treat two case reports that describe patients who acquired CM-HUS following kidney transplants.

PRESENTATIONS OF CASES

Case 1

A deceased donor kidney transplant was performed six years prior to the presentation of a 44-year-old male patient with a substantial medical history of hypertension, hyperlipidemia, and end-stage renal disease (ESRD)due to hypertensive nephrosclerosis, necessitating peritoneal dialysis and complicated by peritonitis. Anti-rejection medications such as prednisone, tacrolimus, and mycophenolate mofetil were started at the time of transplantation. He experienced chronic allograft nephropathy after the transplant, which was indicated by a baseline blood creatinine level of 1.5–1.9 mg/dL. The patient was referred to hematology for examination because of mild-to-moderate pancytopenia, hematuria, and proteinuria, which were caused by renal allograft rejection. Figure 2 shows that a renal biopsy had positive complement component 4d (C4d) staining, which is consistent with antibody-mediated rejection.Mycophenolate toxicity was initially thought to be the cause of the patient's pancytopenia; therefore, the mycophenolate dosage was decreased, improving pancytopenia and resolving leukopenia. But after a few months, the thrombocytopenia and anemia rapidly deteriorated, reaching a platelet nadir of 51 K/uL and a hemoglobin nadir of 6.3 g/dL. Serum creatinine levels peaked at 4.3 mg/dL, indicating a deterioration in renal function as well. A low tacrolimus level was discovered after more research, which led to an increase in dosage. Intravenous immune globulin (IVIG) was used to treat the patient, and rituximab therapy was to be administered later for antibody-mediated rejection. But after receiving two IVIG doses, the patient experienced a hypertensive crisis and was sent to the emergency room. A 6.4 g/dL hemoglobin level, thrombocytopenia with a platelet count falling to 67 K/uL, an elevated serum creatinine level of 3.24 mg/dL, an elevated lactate dehydrogenase (LDH) of 553 unit/L, and haptoglobin below 10 g/dL were all reported in the laboratory results. The results of a direct antiglobulin test were negative. The results of the peripheral smear analysis were in line with MAHA and included macrocytic, normochromic red blood cells, increased reticulocytosis, increased schistocytes (5–6/high power field), neutrophils with normal morphology, and a decreased platelet count.TMA was suspected because of the renal failure, MAHA, and thrombocytopenia. An ADAMTS13 activity assay was part of the follow-up, and the result was 77 U/dL (normal value ≥ 70 U/dL).Furthermore, the stool culture showed no signs of Salmonella, Shigella, or Campylobacter, and the Shiga toxin PCR was negative. Consequently, TTP and HUS were excluded.Antinuclear antibody (ANA) was negative at <1:80, anti-double-stranded DNA antibody was negative at 10.9 IU/mL (<30 IU/mL), serum C3 was low at 84 mg/dL (90–180 mg/dL), and serum complement component 4 (C4) was normal at 34 mg/dL (10–40 mg/dL). Hypertensive emergency, CMHUS, antibody-mediated rejection, and medication-induced TMA from calcineurin inhibitors (tacrolimus) were among the differential diagnoses for TMA. A TMA genetic susceptibility panel showed a heterozygous variant CFH c.2171C>A (p.Thr724Lys) and homozygous variant CFH c.2171C>A (p.Thr724Lys) of uncertain significance in complement factor H (CFH) and a heterozygous variant CFHR1 c.59-14T>C of uncertain significance in complement factor H receptor 1 (CFHR1), but no known pathogenic variants were found. Complement factors B, H, and I autoantibody results were normal, and factor H autoantibody results were normal. When complement-mediated HUS was suspected, eculizumab induction therapy was started. This involved four weekly doses of 900 mg IV, followed by maintenance therapy at 1200 mg IV every two weeks. If you are not immunized, eculizumab has a black box warning for meningococcal meningitis. Because it was unclear whether the patient had received a meningitis vaccination, we started a three-dose meningococcal vaccination series over three months, along with a prophylactic oral amoxicillin 500 mg twice daily, which was continued for two weeks after the vaccination series was finished. The patient's hematological parameters, such as hemoglobin, platelets, and LDH, returned to normal following two doses of maintenance eculizumab, and his blood creatinine level

stabilized at approximately 4.0 mg/dL (Figure 3). Additionally, antihypertensive drugs were used to successfully regulate his blood pressure.Eculizumab was stopped after two months following an interdisciplinary consultation with nephrology, and the patient was closely watched for relapse. Following a relapse of CM-HUS, the patient was admitted to the hospital for acute renal damage. When eculizumab was started again, the thrombotic microangiopathy indicators disappeared. The patient was then switched to taking ravulizumab every eight weeks. The patient has not shown signs of another CM-HUS recurrence after starting anticomplement treatment. It was decided to carry on with treatment indefinitely.

Case 2

A dead donor kidney transplant was performed on a 58-year-old man who had a history of hypertensive nephrosclerosis-related chronic kidney disease. Tacrolimus, sirolimus, and prednisone were started as anti-rejection medications. He was admitted to the hospital one week after the transplant due to aberrant laboratory results, including as anemia, thrombocytopenia, and an increased blood creatinine level. Acute antibody-mediated rejection was discovered by allograft biopsy. IVIG and therapeutic plasma exchange were started. While the patient was in the hospital, eculizumab 900 mg IV weekly for four doses was initiated due to concerns over CM-HUS in the context of immune-mediated thrombocytopenia and hemolytic anemia. This was followed by maintenance therapy at 1200 mg IV every two weeks. High-dosage steroids were continued along with a single dose of rituximab.For immunosuppression, belatacept, mycophenolic acid, and prednisone were substituted for tacrolimus and sirolimus. To make sure the patient had received the most recent dose of the meningococcal vaccination, his immunization history was examined. The eculizumab treatment was well received by the patient. A homozygous complement factor H related 3 (CFHR3-1) deletion, a decrease in the total complement test (CH50) and Alternative Pathway Functional Assay (APFA), and normal levels of C3 and C4 were found by genetic mutation testing, indicating CM-HUS brought on by tacrolimus and renal transplantation. Before the patient came to our hematology clinic, eculizumab was taken for around six years. He was then switched to ravulizumab, a long-acting anticomplement medication, with infusions every eight weeks and an indefinite treatment plan.The patient has been responding well to medication with no side effects, and follow-up lab tests revealed no signs of MAHA.

DISCUSSION

MAHA, thrombocytopenia, and end organ failure are characteristics of TMA. TTP and HUS are examples of TMA syndromes. CM-HUS and typical/Shiga-like toxin-producing E. coli (STEC) HUS are two other subtypes of HUS [6]. The incidence of CM-HUS ranges from 0.23 to 1.9 per million, making it an uncommon condition [7]. Children are more likely to experience it, and when it does occur in adulthood, women are more likely to be affected. Even less common and associated with a worse prognosis is the first occurrence of CM-HUS in the post-renal transplant phase [8].The complement system is dysregulated in the pathophysiology of CM-HUS, leading to unchecked activation [4]. As a component of the body's immune system, the complement system sets off inflammatory reactions [5]. The MAC is formed by the cleavage and combining of complement component proteins in the alternative pathway, which is the mechanism most frequently associated with CM-HUS [4,5]. In order to prevent overactivation, regulatory proteins regulate the pathway's activity [5]. These regulatory proteins' activity is blocked in CM-HUS by pathogenic mutations of the proteins or developed antibodies against the proteins, which leads to unrestrained pathway action [5]. Endothelial damage results from the overactivity, which causes complement proteins to be deposited on endothelial cells [5].Hemolysis, platelet aggregation, and thrombus development are further problems [5]. Endothelium enlargement and thrombus development in the kidney can cause fibrinoid necrosis, glomerular capillary blockage, thickening of the capillary wall, and renal insufficiency [4]. Due to thrombotic microangiopathy in the renal allograft, CM-HUS might cause allograft loss in post-transplant patients [9].TTP and HUS must be ruled out in order to diagnose CM-HUS [1]. Therefore, by measuring ADAMTS13 activity and testing for Shiga toxin, respectively, TTP and HUS can be ruled out [1]. The ADAMTS13 activity assay revealed normal enzyme activity in our patients, and the Shigella, Campylobacter, and Salmonella stool culture tests, as well as the Shigella toxin polymerase chain reaction (PCR), came back negative. Complement levels can be assessed to bolster the CM-HUS diagnosis. In order to diagnose complement-mediated HUS, a genetic susceptibility panel is very helpful [1].The alternative complement pathway has been found to be activated by loss-of-function mutations in the complement regulators CFH, cluster of differentiation 46 (CD46), and Factor I, as well as by gain-of-function mutations in the genes encoding complement proteins C3, complement factor B (CFB), and autoantibodies against CFH [10]. Cofactors for the conversion of C3b to its inactive form are CFHR3 proteins [10]. Therefore, the loss of CFHR3-1 in Case 2 is suggestive of CM-HUS and would result in complement dysregulation. Mutations in diacylglycerol kinase epsilon (ε) and thrombomodulin are among the additional molecules that are indirectly connected to the complement system [10]. By encouraging the activation of protein kinase C (PKC), these mutations contribute to a prothrombotic condition [10].Of these, 24–28% of CM-HUS cases have mutations in the CFH gene [11]. Particularly in

the kidneys, the CFH variation causes enhanced terminal complement deposition and microthrombus formation via impairing binding to C3b to host cells [12]. Patients with CM-HUS typically have normal CH50, which measures total complement activity [12]. Furthermore, whereas 35% of individuals with CM-HUS have normal levels of both C3 and C4, the condition is frequently linked to low C3 and normal C4 [12]. The consumption of proteins in the pathway in the context of dysregulation frequently results in decreased alternative complement pathway activity in patients with CM-HUS, as measured by the Alternative Pathway Functional Assay (APFA) [12].By blocking C5's cleavage into C5a and C5b, eculizumab stops the terminal complement system from deploying, which includes MAC formation [5]. A long-acting anticomplement C5 monoclonal antibody is called ravilumab [13]. Anticomplement therapy can therefore be used in CM-HUS patients to treat the complement dysregulation that underlies the patient's clinical condition in a post-renal transplant scenario, as shown in these two documented patient cases. The relapse incidence of CM-HUS after eculizumab treatment can vary from 20 to 67%, according to the scant evidence that is currently available [11]. Patients with native kidneys have a lower chance of relapsing, and if they do, they might benefit from eculizumab retreatment [14].Relapse, which can happen days to years following a kidney transplant, is more common in people with a history of the procedure [14]. Instead of only initiating eculizumab in the event of a confirmed relapse, research has been done to ascertain its effectiveness as a prophylactic before or right after a kidney transplant. According to a 2019 systematic study, individuals receiving prophylactic eculizumab experienced a 5.5% recurrence rate and a 5.3% allograft loss rate [9]. The predicted risk of allograft loss for post-transplant patients receiving eculizumab for a recurrence was 24.4% [9].Patients with CM-HUS may benefit from eculizumab and ravulizumab's actions on the complement system, although there may also be negative side effects [15]. The drug subsequently reduces bactericidal activity by blocking the terminal complement pathway [14]. Eculizumab's black box warning states that there is a 1000-fold increased risk of meningococcal infections [15].

In order to shield patients against potentially deadly infections brought on by CM-HUS treatment, it is imperative that they acquire the proper vaccinations. Over the course of three months, our patient was given a dosage of the meningococcal B vaccine once a month.Amoxicillin was also recommended as a prophylactic measure to shield unprotected people from meningococcal infections during the interval between vaccinations. The danger of contracting meningococcal disease persists even after vaccination, which is why some healthcare professionals advise continuing antibiotic prophylaxis for the duration of anticomplement therapy, which may last a lifetime [16]. One study found that patients who continued preventive antibiotic therapy had a longer latency to onset of disease, but they were also more susceptible to penicillin [17]. These results emphasize how crucial it is to customize preventative measures for each patient, weighing the advantages of long-term antibiotic prophylaxis against the emergence of antibiotic resistance and the advantages of complement inhibition against infection risks.

CONCLUSIONS

In summary, complement-mediated HUS is uncommon and may be lethal, especially in patients who have had a kidney transplant. Following a renal transplant, CM-HUS may occur due to a variety of factors, such as immunological dysregulation, antirejection medications, and hereditary predisposition. Clinicians must identify and treat this problem as soon as possible. Anticomplement treatment is frequently used in management. Patients with a history of kidney transplantation are especially at risk for relapse; nevertheless, as these two cases show, long-term use of these drugs can avoid relapse.

REFERENCES

1. Arnold, D.M.; Patriquin, C.J.; Nazy, I. Thrombotic microangiopathies: A general approach to diagnosis and management. Can. Med. Assoc. J. 2016, 189, E153–E159. [CrossRef] [PubMed].

2. Tsai, H.M. Pathophysiology of thrombotic thrombocytopenic purpura. Int. J. Hematol. 2010, 91, 1–19. [CrossRef] [PubMed].

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. Semin. Nephrol. 2013, 33, 508–530. [CrossRef] [PubMed].

5. Wijnsma, K.L.; Ter Heine, R.; Moes, D.J.; Langemeijer, S.; Schols, S.E.; Volokhina, E.B.; van den Heuvel, L.P.; Wetzels, J.F.; van de Kar, N.C.; Brüggemann, R.J. Pharmacology, pharmacokinetics and pharmacodynamics of Eculizumab, and possibilities for an individualized approach to Eculizumab. Clin. Pharmacokinet. 2019, 58, 859–874. [CrossRef] [PubMed].

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, 4235–4244. [CrossRef] [PubMed].

7. Yan, K.; Desai, K.; Gullapalli, L.; Druyts, E.; Balijepalli, C. Epidemiology of atypical hemolytic uremic syndrome: A Systematic Literature Review. Clin. Epidemiol. 2020, 12, 295–305. [CrossRef] [PubMed].

8. Fayek, S.A.; Allam, S.R.; Martinez, E.; Pan, G.; Dao, A.; Rofaiel, G. Atypical hemolytic uremic syndrome after kidney transplantation: Lessons learned from the good, the bad, and the ugly. A case series with literature review. Transplant. Proc. 2020, 52, 146–152. [CrossRef] [PubMed].

9. Gonzalez Suarez, M.L.; Thongprayoon, C.; Mao, M.A.; 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, 8, 919. [CrossRef] [PubMed].

10. Noris, M.; Caprioli, J.; Bresin, E.; Mossali, C.; Pianetti, G.; Gamba, S.; Daina, E.; Fenili, C.; Castelletti, F.; Sorosina, A. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clin. J. Am. Soc. Nephrol. 2010, 5, 1844–1859. [CrossRef] [PubMed].

11. Nester, C.M.; Barbour, T.; De Cordoba, S.R.; Dragon-Durey, M.A.; Fremeaux-Bacchi, V.; Goodship, T.H.; Kavanagh, D.; Noris, M.; Pickering, M.; Sanchez-Corral, P. Atypical aHUS: State of the art. Mol. Immunol. 2015, 67, 31–42. [CrossRef] [PubMed].

12. Afshar-Kharghan, V. Atypical hemolytic uremic syndrome. Hematol. Am. Soc. Hematol. Educ. Program 2016, 2016, 217–225. [CrossRef] [PubMed].

13. Lexicomp Online. Pediatric and Neonatal Lexi-Drugs Online; UpToDate, Inc.: Waltham, MA, USA, 2024. Available online: https://online.lexi.com (accessed on 11 February 2024).

14. Duineveld, C.; Bouwmeester, R.; Van der Heijden, J.W.; Berger, S.P.; van de Kar, N.C.; Wetzels, J.F.; Dutch aHUS Working Group. Outcome of atypical haemolytic uraemic syndrome relapse after eculizumab withdrawal. Clin. Kidney J. 2020, 14, 1939–1945. [CrossRef] [PubMed].

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, 2429. [CrossRef].

16. McNamara, L.A.; Topaz, N.; Wang, X.; Hariri, S.; Fox, L.; MacNeil, J.R. High risk for invasive meningococcal disease among patients receiving Eculizumab (Soliris) despite receipt of meningococcal vaccine. Am. J. Transplant. 2017, 17, 2481–2484. [CrossRef].

17. Crew, P.E.; McNamara, L.; Waldron, P.E.; McCulley, L.; Jones, S.C.; Bersoff-Matcha, S.J. Antibiotic prophylaxis in vaccinated eculizumab recipients who developed meningococcal disease. J. Infect. 2020, 80, 350–371. [CrossRef] [PubMed].