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Complement-Mediated Thrombotic Microangiopathy after Kidney Transplant: Should Treatment with C5 Inhibitor Be Lifelong?

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Abstract
Complement-mediated thrombotic microangiopathy (CM-TMA) is a rare and life-threatening complication that can occur in kidney transplant recipients, with various potential triggers including immunosuppressive medications. The optimal management and duration of treatment with C5 inhibitors (C5i) for CM-TMA in this patient population remain areas of ongoing investigation. We present the case of a 38-year-old female with a history of IgA nephropathy who underwent preemptive living-related kidney transplantation and subsequently developed CM-TMA 7 years post-transplant. Treatment with ravulizumab led to a rapid hematologic response and stabilized platelet counts. Serial measurements of complement functional tests and clinical stability guided the discontinuation of C5i therapy. The case highlights the complexity of managing CM-TMA in kidney transplant recipients, particularly in determining the appropriate duration of C5i therapy. The absence of an established protocol for discontinuation necessitates a personalized approach based on clinical and laboratory stability, absence of complement gene variants, and serial complement functional tests. Further prospective investigations are warranted to define the optimal strategies for monitoring and safely discontinuing C5i therapy in this unique patient population. This case underscores the importance of individualized care in the management of CM-TMA post-kidney transplantation, offering insights into potential criteria for therapy discontinuation.

Introduction

Thrombotic microangiopathies (TMAs) can manifest in kidney transplant recipients either de novo or as a recurrence of the underlying pathology that led to chronic kidney disease. De novo TMA affects 3–14% of kidney transplant cases and may result from several factors, including medications such as calcineurin inhibitors (CNIs) and mammalian target of rapamycin inhibitors (mTORi), infections like cytomegalovirus and BK virus, as well as antibody-mediated rejection. Often, it is a combination of these factors [1, 2].

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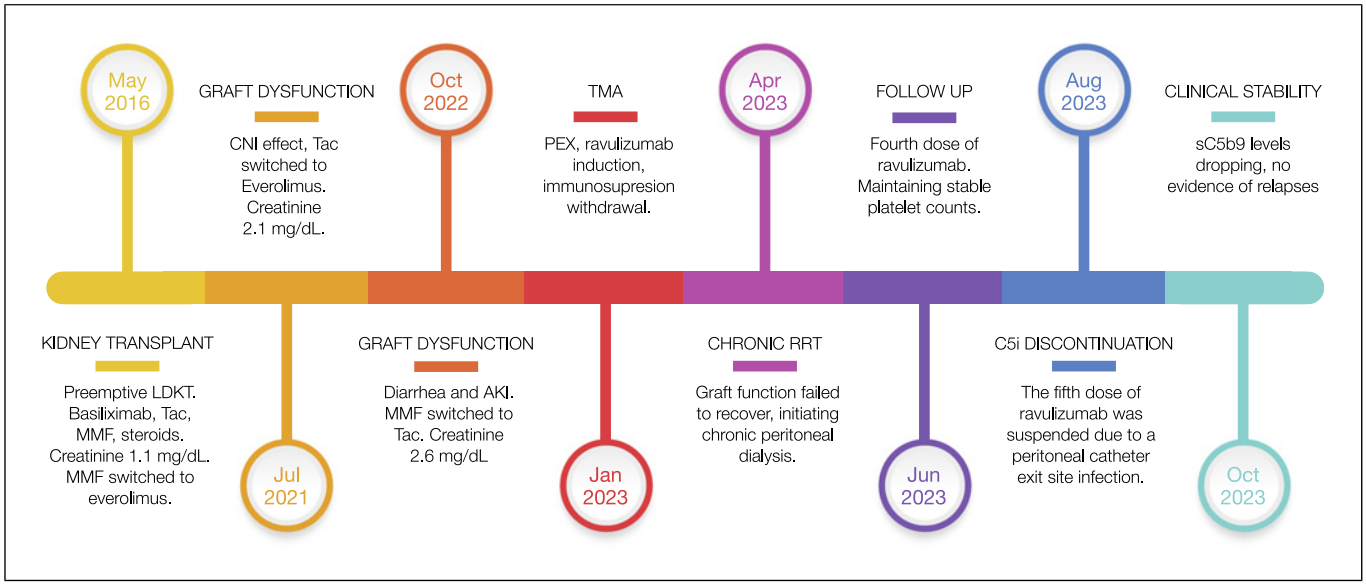

Fig. 1. Timeline of case presentation. LDKT, living donor kidney transplant; Tac, tacrolimus; MMF, mofetil mycophenolate; CNI, calcineurin inhibitor; AKI, acute kidney injury; PEX, plasma exchange; RRT, renal replacement therapy.

Complement-mediated thrombotic microangiopathies (CM-TMAs) arise from dysregulation of the alternative pathway of the complement system, secondary to pathogenic variants in complement genes or the presence of autoantibodies against complement factor H (CFH). These cases are frequently triggered by the aforementioned factors [3]. TMA is associated with poorer graft outcomes [1], but the introduction of C5 inhibitors (C5i) has revolutionized the prognosis in recent years [3, 4]. Nevertheless, questions remain regarding the optimal duration of C5i treatment.

We present a case study of a patient who developed CM-TMA 7 years post-transplant following the reintroduction of tacrolimus (Tac) and achieved an excellent response with the C5i ravulizumab. Additionally, we are reviewing the existing literature to explore strategies and tools for determining the most appropriate duration of C5i therapy.

Case Presentation

A 38-year-old female with a diagnosis of IgA nephropathy received a preemptive living-related kidney transplantation in May 2016 shown in Figure 1. Her immunosuppressive regimen included basiliximab, Tac, mycophenolate mofetil, and steroids. She was discharged with creatinine of 1.1 mg/dL. Mycophenolate was early switched to everolimus due to gastrointestinal intolerance.

In December 2019, the patient exhibited a decline in graft function (creatinine 2.1 mg/dL). Biopsy revealed borderline changes for cell-mediated acute rejection, and immunofluorescence only showed traces of C3 and fibrinogen. Pulses of methylprednisolone were administered, and a creatinine of 1.6 mg/dL was achieved.

In July 2021 experienced a gradual decline in kidney function (up to creatinine 2.35 mg/dL). A new biopsy showed 30% of sclerotic glomerulus, moderate to severe arteriolosclerosis, mild tubular atrophy, and interstitial fibrosis. Immunofluorescence showed reactivity to IgG +/−, IgM 1+, C3 +/−, and fibrinogen +/−. No reaction for C4d, IgA, C1q, or light chains was observed. This result led to the suspension of Tac and restarting of mycophenolate, resulting in the stabilization of creatinine levels at 2.1 mg/dL.

In October 2022, she presented with several weeks of diarrhea and acute kidney injury (up to creatinine 2.6 mg/dL). FilmArray gastrointestinal panel and cytomegalovirus viral load were negative, and a colonic biopsy revealed unspecific colitis. As a result of it, mycophenolate was discontinued, and Tac was reintroduced. Diarrhea ceased, but creatinine continued to increase, reaching 3.1 mg/dL in January 2023; therefore, a new biopsy was performed. Light microscopy revealed arteries and arterioles with severe wall thickening, fragmented erythrocytes, and collapsed capillaries consistent with severe TMA shown in Figure 2. More than 50% of the glomerulus of the sample were sclerotic, along with interstitial lymphocyte infiltrate, without signs of tubulitis. There was no evidence of glomerulitis or capillaritis. Immunofluorescence showed reactivity to IgG +/−, IgM 1+, C3 2+, C1q +/−, fibrinogen 2+, and kappa light chains +/−. No reaction for C4d, IgA, or lambda light chains was observed.

The following days after the biopsy, graft function continued deteriorating, requiring renal replacement therapy, and

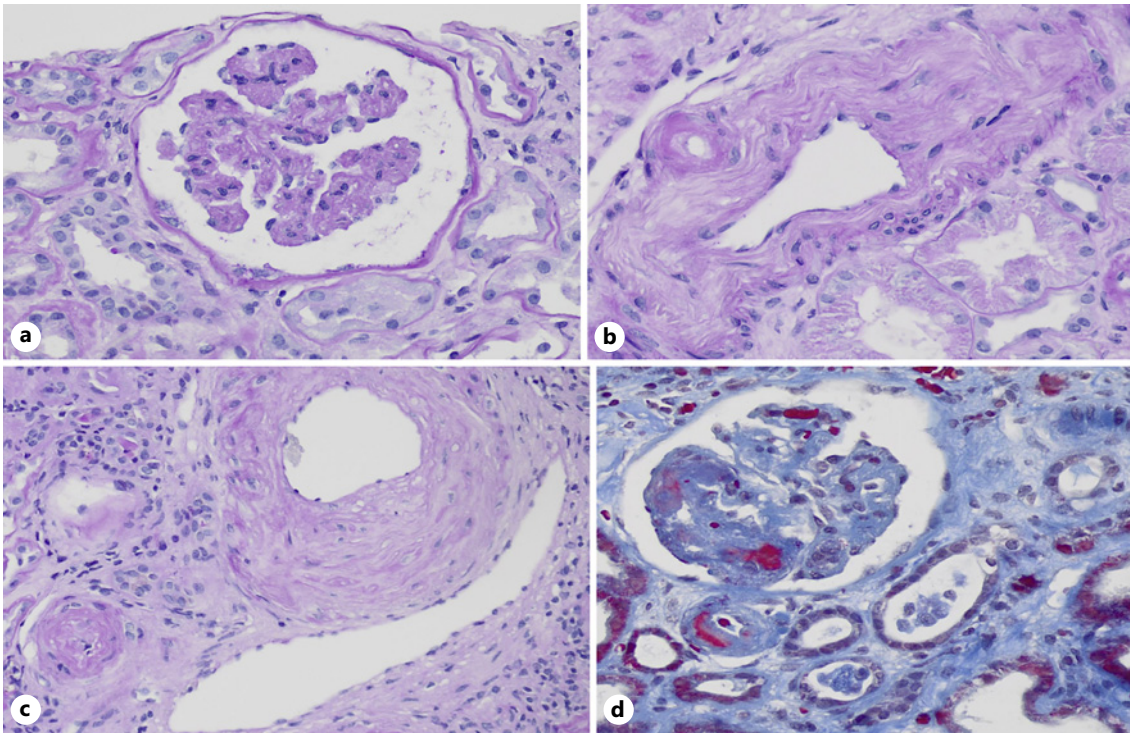

Fig. 2. Kidney graft biopsy, light microscopy. **a** Global collapse of the capillary walls ("bloodless glomerulus" appearance). PAS ×400. **b** Arteries and arterioles with thickened vessel walls. PAS ×400. **c** Blood vessel walls with multilamination ("onion skin" appearance) and interstitial inflammatory infiltrate. PAS ×200. **d** Intraglomerular hilar thrombus and arteriole with fragmented red blood cells. Masson trichrome stain ×400.

developing thrombocytopenia (from a baseline of 308 to 120 × 10^9/L on the first day), lactate dehydrogenase (LDH) elevation (up to 518 U/L [normal value <220 U/L]), and schistocytes. Immunosuppressants were withdrawn, remaining only on steroids. Tac and everolimus trough levels were 2.13 and 8.28 ng/mL, respectively. Study for secondary causes of TMA resulted negative, including donor-specific HLA antibodies, CMV, BK virus, HIV, parvovirus B19, ADAMTS13, pregnancy, antiphospholipid syndrome, complement C3 and C4, rheumatologic and malignancy screening. Antibodies against CFH were not available. Daily plasma exchange with fresh frozen plasma was initiated immediately after the result of the biopsy. However, platelet count continued to decline (to 19 × 10^9/L) after five sessions, so a first dose of ravulizumab was administered, resulting in a rapid and fast response, achieving 260 × 10^9/L platelets within the next 4 days. The genetic analysis did not show any mutations on ADAMTS13, C3, CD46, CD55, CD59, CFB, CFH, complement factor I (CFI), DGKE, INF2, MMACHC, PLG, and THBD genes.

Eleven days after the ravulizumab induction dose, platelet count fell from 248 to 99 × 10^9/L and LDH levels rose again, so it was decided to anticipate the first maintenance dose achieving a good hematologic response. Graft function failed to recover, initiating chronic peritoneal dialysis. Two more ravulizumab doses were administered, maintaining permanently stable platelet counts; however, the fifth dose of ravulizumab was postponed due to a peritoneal catheter exit site infection, with no evidence of disease relapse.

Given persistent clinical and hematological stability, ravulizumab was indefinitely postponed, with serial clinical evaluation and measuring of hemolysis markers and complement activity. Platelet count and LDH remain in normal values. sC5b-9 levels showed a progressive decline (1,923 ng/mL → 1,579 ng/mL → 732 ng/mL), and levels of activity of the complement system (AH50 and CH50) remain persistently low. At the time of the case report, the last dose of ravulizumab was administered 9 months earlier.

Discussion

CM-TMA is a rare, life-threatening disorder caused by uncontrolled alternative complement activation that results in endothelial injury and platelet activation, presenting as microangiopathic hemolytic anemia, thrombocytopenia, ischemia, and systemic end-organ involvement [5]. There are multiple causes of TMA in kidney transplant, with one of the most studied factors being the use of CNIs. These drugs are associated with vasoconstriction, endothelial toxicity, and prothrombotic actions.

It usually sets in the first weeks post-transplant and reverses with the suspension of the drug [6]. The underlying reasons behind the development of TMA in only a relatively small subset of renal transplant recipients, despite the majority being exposed to the same risk factor, remain elusive. It is hypothesized that these patients have an underlying susceptibility toward endothelial injury and/or pro-coagulant state that favors the development of this complication [7], which could be a pathogenic variant of a complement gene or an autoantibody to CFH [8]. This theory has been investigated in renal specimens from patients with TMA of various etiologies, revealing the presence of C4d in 88.1% of the samples. Notably, C4d was primarily found in glomeruli and arterioles, in contrast to the predominant pattern of antibody-mediated rejection, which mainly affects peritubular capillaries [9].

The use of mTORi is also associated with the development of TMA, and studies suggest that the risk could be even higher than CNIs [10]. In fact, the risk has been reported to be higher when a combination of mTORi and CNI is used, compared with either medication alone, which was the case of our patient [11].

In this instance, all immunosuppressants were suspended, other causes of TMA were discarded, and there was no effect of plasma exchange; therefore, a CM-TMA was suspected. The administration of ravulizumab achieved a great and quick response on platelets and hemolysis markers. Kidney graft function was not expected to greatly improve because of chronicity found in biopsy. C5i therapy was continued for three more scheduled doses.

More than a decade ago, the first C5i, eculizumab, demonstrated its efficacy in improving outcomes for patients with CM-TMA, irrespective of the presence of genetic abnormalities in complement genes, even in kidney graft recipients [12]. A study involving this patient group revealed that 25% of those who developed de novo TMA had genetic complement abnormalities in CFH or CFI genes, while no mutations were identified in those who did not develop TMA [8]. CFH and CFI genes encode factor H and factor I proteins, respectively, which are crucial plasma regulators of the complement alternative pathway. Defects in these genes can predispose to uncontrolled complement activity in the presence of triggering factors [13].

Complement functional tests, such as sC5b-9 or classical complement pathway activity, have been investigated to monitor C5i therapy. Serial measurements of these tests could facilitate the gradual extension of dosing intervals while still maintaining disease remission [14, 15]. In our patient's case, we serially measured sC5b-9, CH50, and AH50 levels after suspending C5i due to a peritoneal catheter exit site infection. These measurements showed a progressive decline with no evidence of hemolysis. It is important to note that infectious events can sometimes trigger CM-TMA relapses, but this did not occur in our patient.

Regarding the adverse effects and costs associated with C5i therapy, several studies have investigated the optimal duration for treating CM-TMA in native kidneys. Fakhouri et al. [16] conducted the first prospective study on eculizumab discontinuation in patients who had achieved remission. Only 23% of patients experienced a relapse, with 84% of them recovering their baseline renal function after reintroducing the C5i. Complement gene variants were found in 92% of those who relapsed, with CFH and MCP gene variants being the most common. Patients with sC5b-9 levels ≥300 ng/mL at the time of withdrawal had an odds ratio of 20.96 for relapse [16]. Chaturdevib et al. [17] reported positive outcome with a clinician-directed protocol for discontinuing C5i therapy, highlighting that no relapse occurred in patients without complement variant genes. The CUREiHUS study evaluated the withdrawal of C5i after a median of 13.6 weeks of treatment. It showed a 22% relapse rate, predominantly in the first year of discontinuation. All relapsing patients were found to have a likely pathogenic complement variant, and in all cases, a suspected viral infection was the trigger. Notably, none of the patients developed subsequent chronic kidney complications [18].

Conclusion

Currently, there is no established protocol for discontinuing C5i therapy in kidney transplant recipients with CM-TMA. However, by extrapolating information from the management of the disease in native kidneys, we may consider a safe discontinuation approach for this population based on clinical and laboratory stability, the absence of complement gene variants, and serial measurements of complement functional tests. Prospective investigations are necessary to determine the most effective strategies for monitoring and safely discontinuing C5i therapy in this patient population.

Statement of Ethics

This case report was reviewed and approved by the Scientific Ethic Committee of the Servicio de Salud Metropolitano Oriente of Chile on 24 October 2023. No decision reference number was

informed. Written informed consent was obtained from participants (or their parents/legal guardians/next-of-kin) for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All the authors reviewed the literature. Pilar Musalem and Cristian Pedreros-Rosales drafted and prepared the manuscript. Cristian Pedreros-Rosales and J. Daniel Carpio: figure preparation. All authors reviewed, read, and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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