Complement-Mediated Hemolytic Uremic Syndrome Due to MCP/CD46 Mutation: A Case Report

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Abstract

Thrombotic microangiopathy (TMA) is a severe condition characterized by microangiopathic hemolytic anemia, thrombocytopenia, and end-organ damage, often involving the kidneys. Complement-mediated hemolytic uremic syndrome (cHUS), a rare form of TMA, arises from dysregulated alternative complement pathway activation, frequently due to genetic mutations. We report the case of a 23-year-old male presenting with TMA secondary to a heterozygous mutation in the membrane cofactor protein (MCP/CD46) gene. The patient exhibited severe renal and cardiovascular complications, including acute kidney injury requiring hemodialysis, uremic pericarditis, and persistent anemia. Diagnostic evaluation confirmed complement dysregulation, and management with eculizumab, plasmapheresis, and hemodialysis was initiated. Renal biopsy revealed classic TMA features, and genetic testing identified the MCP mutation, underscoring the importance of genetic predispositions in guiding diagnosis and therapy. This case emphasizes the critical role of genetic testing in TMA evaluation and highlights the potential for improved outcomes through targeted complement inhibition and individualized care strategies.

Keywords

thrombotic microangiopathy, atypical hemolytic uremic syndrome, MCP/CD46 mutation, eculizumab, complement-mediated hemolytic uremic syndrome

Introduction

Thrombotic microangiopathy (TMA) is a pathological condition defined by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and ischemic organ injury.[1] Complement-mediated hemolytic uremic syndrome (cHUS), also known as atypical hemolytic uremic syndrome (aHUS) is a severe type of TMA that primarily affects the kidneys, often leading to end-stage renal disease in the absence of timely intervention.[2] Extra-renal manifestations occur in about 20% of patients with cHUS, with the frequency of complications involving specific organ systems varying widely, from isolated case reports to affecting up to 50% of documented cases.[3] Cardiac complications have also been reported in 3% to 10% of patients with cHUS.[4]

Advances in understanding complement genetics have significantly reshaped the approach to cHUS and other forms of HUS. Among these, cHUS is uniquely associated with genetic susceptibility factors linked to complement regulation.[5] These advances have revolutionized treatment through C5 inhibitors, drastically improving patient outcomes.[6] However, timely diagnosis remains a critical challenge, compounded by ambiguities in defining the disorder and its overlap with other TMA variants.

Here, we present a challenging case of TMA triggered by a heterozygous mutation in the membrane cofactor protein (MCP/CD46) gene, leading to a complex interplay of renal and cardiovascular complications. This case emphasizes the importance of recognizing genetic predispositions in the context of TMA, as it can significantly impact management strategies and prognosis.

Case Presentation

A 23-year-old male with a past medical history of hypertension, hyperlipidemia, Bell's palsy, and nephrolithiasis

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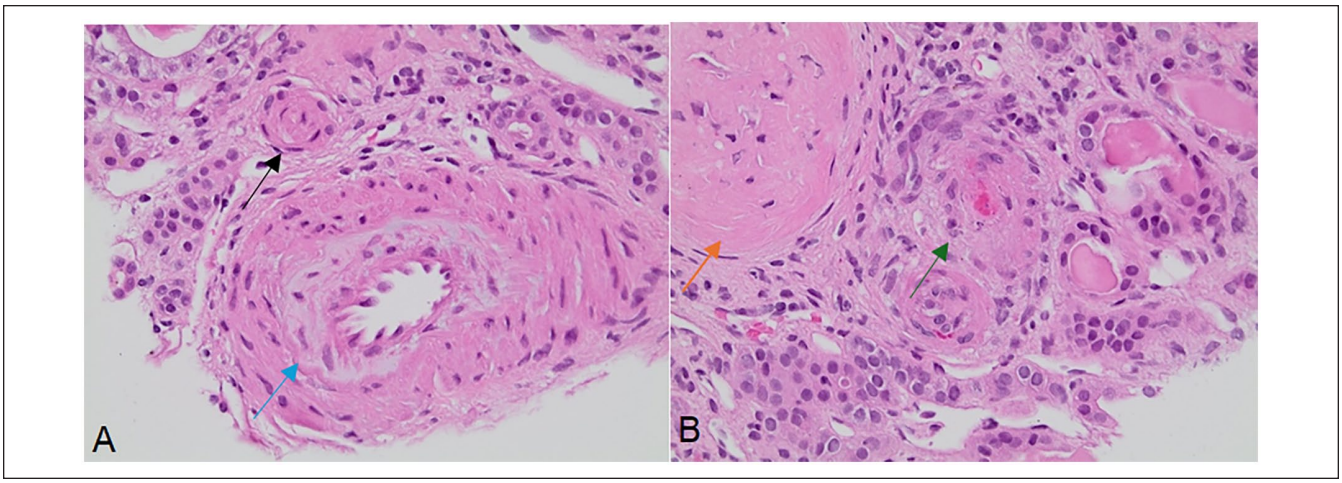

Figure 1. Histologic sections of the renal core biopsy demonstrate (H&E images; 400× original magnification) (A) a cross-section of an interlobular-size artery with intimal thickening and mucoid intimal edema (blue arrow). The smaller arteriole (black arrow) shows concentric luminal narrowing to the point of occlusion. (B) Smaller arterioles demonstrating concentric luminal narrowing with some red blood cell fragments in the wall (green arrow) and luminal damage and fibrin deposition (orange arrow).

presented to a regional medical center for evaluation of chest pain, dyspnea, and syncope. He denied any preceding infection, fever, diarrhea, or cough. He also denied worsening of symptoms with exertion. The patient had been experiencing these symptoms for 1 month before they acutely worsened, which prompted him to seek treatment. On arrival to the emergency department (ED), his vital signs were blood pressure (BP) 209/132; heart rate (HR) 93; respiratory rate (RR) 18; and pulse oximetry 98% on room air. Laboratory testing revealed: hemoglobin 5.9 g/dL; hematocrit 16.7%; platelets 157 mcL; partial thromboplastin time (PTT) 37.5 seconds; blood urea nitrogen (BUN) 252 mg/dL; creatinine (Cr) 32.5 mg/dL; brain natriuretic peptide (BNP) 2816 ng/L; and troponin 225 ng/L. Arterial blood gas analysis revealed: pH 7.29; CO_2 20.2 mm Hg; O_2 98.1 mm Hg; and HCO_3 9.6 mm Hg. Urinalysis showed protein >500 mg/dL and 6 to 10 red blood cells (RBCs). Signs of fluid overload were noted on physical exam. The patient received clonidine 0.2 mg, Lasix IVP 80 mg, potassium chloride 40 mg, and 1 unit of packed RBCs while in the ED.

Upon admission to the intensive care unit (ICU), the patient's blood pressure was markedly elevated at 219/130 mm Hg, concomitant with acute kidney injury with a creatinine of 31.96 mg/dL and BUN of 247 mg/dL. The patient was initially started on a nicardipine drip; later, in his stay, a regimen of nifedipine 90 mg, carvedilol 12.5 mg BID, and losartan 100 mg was used for blood pressure control. Repeat laboratory investigations revealed MAHA, with a hemoglobin level of 6.9 g/dL, hematocrit of 20.3%, reticulocyte count of 11.5%, and a lactate dehydrogenase (LDH) of 619 U/L. Microcytic hypochromic anemia, anisopoikilocytosis, and schistocytes were observed on peripheral blood smear examination. Imaging studies further showed bilateral pulmonary edema and pericardial effusion, suggestive of fluid overload.

Nephrology was consulted for severe acute kidney injury (AKI) with high anion-gap metabolic acidosis. A renal ultrasound was ordered and found no evidence of renal artery stenosis. Lab workup including C3/C4 levels, ANCA, and ADAMSTS13 activity was also ordered and returned with negative results. The patient's ADAMSTS13 activity was slightly decreased at 52% but did not meet the thrombotic thrombocytopenic purpura (TTP) diagnostic criteria (<10% activity). Prompt interventions, including initiation of hemodialysis and plasmapheresis, were undertaken following nephrology consultation. The patient underwent daily hemodialysis and 4 sessions of plasmapheresis during his hospital stay. Empirical initiation of eculizumab was also commenced to attempt to slow the progression to end-stage renal disease.

The computed tomography (CT)-guided renal biopsy was necessitated by negative results from vasculitis workup and complement assay. Samples were sent to the Ohio State University revealing active TMA with severe fibro-intimal thickening and mucoid intimal edema in large vessels. Onion skin-like intimal thickening was observed in some of the smaller vessels, nearing luminal obstruction (Figure 1). Despite these findings, the biopsy was inconclusive regarding the underlying etiology, prompting genetic analysis. While awaiting the results of genetic testing, the patient continued to experience anemia with hemoglobin levels ranging from 6.7 to 10.1 g/dL. He required multiple transfusions throughout his hospitalization.

Approximately 5 weeks after the patient initially presented to the hospital, genetic testing results returned and showed a heterozygous variant in the MCP/CD46 gene, confirming a hereditary predisposition to TMA.

Despite therapeutic efforts, the patient's clinical course was complicated by worsening pericardial effusion due to uremic pericarditis, necessitating pericardiocentesis for

symptom relief. The patient's hospital stay was prolonged due to difficulty meeting the transportation requirements that daily outpatient hemodialysis would pose. He was discharged once his renal function allowed for 3-times-weekly hemodialysis. Ultimately, the patient also required arteriovenous fistula creation for ongoing renal support.

Discussion

Thrombotic microangiopathy is a syndrome characterized by the triad of MAHA, thrombocytopenia, and organ dysfunction, particularly affecting the kidneys.[1,7] Known risk factors include drugs, hematologic disorders, infections, genetic predispositions, and pregnancy-related conditions.[8-10] Genetic susceptibility plays a critical role, with both inherited and acquired deficiencies in complement pathway regulators, such as ADAMTS13, factor H, factor I, MCP/CD46, and thrombomodulin, contributing to dysregulated complement activation. This disruption leads to endothelial injury and the subsequent development of TMA.[11-14] Furthermore, renal biopsy findings are critical for confirming TMA and differentiating it from other mimicking disorders.[15] Histopathological evidence of concentric luminal obliteration in small vessels substantiated the diagnosis and highlighted both acute and chronic TMA features.

Complement-cHUS is a rare form of TMA primarily caused by dysregulation of the alternative complement pathway. Unlike typical hemolytic uremic syndrome (HUS), which is triggered by Shiga toxin-producing pathogens such as *Escherichia coli* O157:H7 or *Shigella dysenteriae*, cHUS arises from alternative mechanisms, including genetic mutations or sporadic factors. It now accounts for about 10% of HUS cases.[16] The annual incidence of cHUS is approximately 2 per million in adults and 3.3 per million in children under 18 years old.[17] Genetic or acquired defects leading to uncontrolled activation of the alternative complement pathway are identified in approximately 60% of cases.[18] Clinically, patients may present with milder or fluctuating anemia and thrombocytopenia, and a subset may lack overt renal involvement at diagnosis.[19] The condition is associated with significant morbidity and mortality, with 65% of patients developing end-stage renal disease or dying within the first year of diagnosis.[18]

The patient's clinical presentation and laboratory findings prompted consideration of several differential diagnoses, including TTP, HUS, disseminated intravascular coagulation (DIC), malignant hypertension, and Evans syndrome.[20] Specific diagnostic criteria helped exclude these conditions. The TTP was ruled out due to the absence of ADAMTS13 deficiency and vasculitis, despite the presence of schistocytes indicative of MAHA.[20] The HUS was excluded based on the lack of recent gastrointestinal infections or exposure to Shiga toxin-producing bacteria.[17] The DIC was deemed unlikely due to the absence of systemic consumptive coagulopathy and the predominance of renal and cardiovascular manifestations.[21] Similarly, malignant hypertension was ruled out as the patient had no history of severe, uncontrolled hypertension preceding the presentation.[9]

Complement-cHUS was identified as the primary diagnosis, supported by the detection of a mutation in the MCP/CD46 gene, a hallmark of this TMA subtype.[18] However, to understand the pathophysiology of TMA in the context of the MCP/CD46 mutation, it is essential to examine complement dysregulation and endothelial injury. Mutations in CD46 or CFH, as well as anti-CFH autoantibodies, lead to excessive activation of the alternative complement pathway, resulting in endothelial damage and heightened susceptibility to TMA.[22] A prominent example of this is the development of TMA in lupus nephritis (LN), where the activation of the lectin pathway (LP) and alternative pathway (AP) appears to be a key factor. Patients with LN-associated TMA often exhibit more severe clinical and pathological features, along with poorer renal survival outcomes.[23]

Management with eculizumab, a complement inhibitor, was initiated due to its role in blocking the cleavage of complement component C5, thus preventing the formation of the membrane attack complex and subsequent endothelial damage. Menne et al[24] demonstrated the effectiveness and safety of eculizumab in managing cHUS, particularly in achieving and sustaining stable kidney function over 6 years, with a notably low incidence of TMA. Evidence suggests that discontinuing eculizumab may be a safe option in patients with isolated MCP mutations or specific genetic profiles after TMA resolution and stabilization of renal function. This can potentially enhance the care and quality of life for a significant number of cHUS patients while also lowering treatment expenses.[25]

Outcomes in kidney transplantation for TMA are influenced by the underlying genetic abnormalities,[26,27] with MCP/CD46 mutations generally associated with a lower recurrence risk compared with other complement regulatory protein mutations.[22] Given that MCP is a transmembrane protein abundantly expressed in the kidney,[28] transplanting a healthy kidney can potentially resolve the defect in these patients.[22] In contrast, as complement factor H and factor I are primarily produced by the liver, kidney transplantation would not address the underlying genetic defects, increasing the risk of disease recurrence in the transplanted kidney.[22]

The clinical course of the 23-year-old male patient with TMA involved a multifaceted treatment plan, including eculizumab, plasmapheresis, and hemodialysis. The patient showed marked improvements in renal function, evidenced by a decline in creatinine levels. Long-term management challenges include recurrence risk, the need for ongoing renal and cardiovascular monitoring, and potential complications such as graft-versus-host disease (GVHD) in the context of hematopoietic stem cell transplantation.[29]

Conclusion

In summary, this case report highlights a challenging presentation of TMA associated with an MCP/CD46 mutation, revealing the significance of genetic testing in shaping management approaches. Additional studies are needed to further clarify the contribution of genetic factors to TMA development and to optimize targeted treatment strategies.

Authors' Note

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

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References

1. George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med*. 2014;371(7):654-666.
2. Fakhouri F, Zuber J, Frémeaux-Bacchi V, et al. Haemolytic uraemic syndrome. *Lancet*. 2017;390(10095):681-696. doi:10.1016/S0140-6736(17)30062-4
3. Formeck C, Swiatecka-Urban A. Extra-renal manifestations of atypical hemolytic uremic syndrome. *Pediatr Nephrol*. 2019;34(8):1337-1348.
4. Noris M, Remuzzi G. Cardiovascular complications in atypical haemolytic uraemic syndrome. *Nat Rev Nephrol*. 2014;10(3):174-180.
5. Fakhouri F, Frémeaux-Bacchi V. Thrombotic microangiopathy in aHUS and beyond: clinical clues from complement genetics. *Nat Rev Nephrol*. 2021;17(8):543-553.
6. Fakhouri F, Hourmant M, Campistol JM, et al. Terminal complement inhibitor eculizumab in adult patients with atypical hemolytic uremic syndrome: a single-arm, open-label trial. *Am J Kidney Dis*. 2016;68(1):84-93.
7. Brocklebank V, Wood KM, Kavanagh D. Thrombotic microangiopathy and the kidney. *Clin J Am Soc Nephrol*. 2018;13(2):300-317.
8. Mazzierli T, Allegretta F, Maffini E, et al. Drug-induced thrombotic microangiopathy: an updated review of causative drugs, pathophysiology, and management. *Front Pharmacol*. 2023;13:1088031.
9. Juarez A, Galindo L, Gondal M. Hypertension-induced thrombotic microangiopathy leading to end-stage renal disease. *Cureus*. 2023;15(1):e33890.
10. Adamski J. Thrombotic microangiopathy and indications for therapeutic plasma exchange. *Hematology Am Soc Hematol Educ Program*. 2014;2014(1):444-449.
11. Fremeaux-Bacchi V, Fakhouri F, Garnier A, et al. Genetics and outcome of atypical hemolytic uremic syndrome: a nationwide French series comparing children and adults. *Clin J Am Soc Nephrol*. 2013;8(4):554-562.
12. Palma LMP, Sridharan M, Sethi S. Complement in secondary thrombotic microangiopathy. *Kidney Int Rep*. 2021;6(1):11-23.
13. Bu F, Borsa NG, Jones MB, et al. High-throughput genetic testing for thrombotic microangiopathies and C3 glomerulopathies. *J Am Soc Nephrol*. 2016;27(4):1245-1253.
14. Benz K, Amann K. Thrombotic microangiopathy: new insights. *Curr Opin Nephrol Hypertens*. 2010;19(3):242-247.
15. Kim YJ. A new pathological perspective on thrombotic microangiopathy. *Kidney Res Clin Pract*. 2022;41(5):524-532.
16. Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. *N Engl J Med*. 2009;361(17):1676-1687.
17. Mele C, Remuzzi G, Noris M. Hemolytic uremic syndrome. *Semin Immunopathol*. 2014;36(4):399-420.
18. 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. *Clin J Am Soc Nephrol*. 2010;5(10):1844-1859.
19. Menne J, Nitschke M, Stingele R, et al. Validation of treatment strategies for enterohaemorrhagic Escherichia coli O104:H4 induced haemolytic uraemic syndrome: case-control study. *BMJ*. 2012;345:e4565.
20. Scully M, Hunt BJ, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *Br J Haematol*. 2012;158(3):323-335.
21. Wada H, Matsumoto T, Suzuki K, et al. Differences and similarities between disseminated intravascular coagulation and thrombotic microangiopathy. *Thromb J*. 2018;16:14.
22. Caprioli J, Noris M, Brioschi S, et al. Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. *Blood*. 2006;108(4):1267-1279.
23. Zhang B, Xing G. Thrombotic microangiopathy mediates poor prognosis among lupus nephritis via complement lectin and alternative pathway activation. *Front Immunol*. 2022;13:1081942.
24. Menne J, Delmas Y, Fakhouri F, et al. Outcomes in patients with atypical hemolytic uremic syndrome treated with

eculizumab in a long-term observational study. *BMC Nephrol*. 2019;20(1):125.
25. Fakhouri F, Fila M, Hummel A, et al. Eculizumab discontinuation in children and adults with atypical hemolytic-uremic syndrome: a prospective multicenter study. *Blood*. 2021;137(18): 2438-2449.
26. Bresin E, Rurali E, Caprioli J, et al. Combined complement gene mutations in atypical hemolytic uremic syndrome influence clinical phenotype. *J Am Soc Nephrol*. 2013;24(3): 475-486.
27. Duineveld C, Verhave JC, Berger SP, van de Kar NCAJ, Wetzels JFM. Living donor kidney transplantation in atypical hemolytic uremic syndrome: a case series. *Am J Kidney Dis*. 2017;70(6):770-777.
28. Liu Y, Xu K, Xiang Y, et al. Role of MCP-1 as an inflammatory biomarker in nephropathy. *Front Immunol*. 2024;14:1303076.
29. Mii A, Shimizu A, Yamaguchi H, et al. Renal complications after hematopoietic stem cell transplantation: role of graft-versus-host disease in renal thrombotic microangiopathy. *J Nippon Med Sch*. 2020;87(1):7-12.