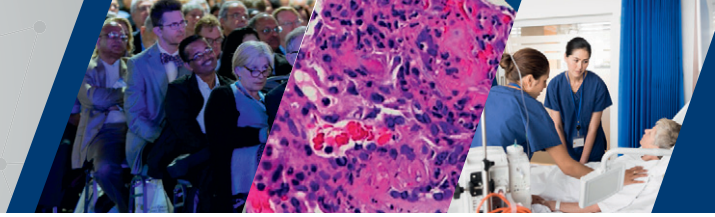

# How I Treat Complement-Mediated TMA

C. John Sperati

*CJASN* 17: 452–454, 2022. doi: https://doi.org/10.2215/CJN.13581021

Division of Nephrology, Johns Hopkins University School of Medicine, Baltimore, Maryland

**Correspondence:**
Dr. C. John Sperati, Division of Nephrology, Johns Hopkins University School of Medicine, 1830 East Monument Street, Room 416, Baltimore, MD 21287. Email: jsperati@jhmi.edu

## Introduction

Thrombotic microangiopathies (TMAs) are a heterogenous group of multisystem disorders characterized by microvascular endothelial injury with intravascular thrombi, microangiopathic hemolytic anemia, and thrombocytopenia. TMAs are syndromes with broad etiologic basis and variable phenotypic penetrance. Although diverse mechanisms for endothelial injury exist, significant focus has centered on complement-mediated pathways of injury. Primarily, complement-mediated TMA has been labeled atypical hemolytic uremic syndrome (aHUS), distinguishing it from Shiga toxin–mediated HUS. As there are no features "typical" of infection-related HUS, the nomenclature has significant shortcomings. In this article, TMA fundamentally due to dysregulated complement activation will be labeled c-TMA. Rapid diagnosis of c-TMA is required for timely initiation of organ and lifesaving therapy.

## Patient Presentation

A 37-year-old woman with ulcerative colitis on 6-mercaptopurine presented to the hospital with 2 weeks of intermittent vomiting and BP of 152/100 mm Hg. Laboratory tests revealed hemoglobin of 7.4 g/dl, platelets at 45,000/mm$^3$, lactate dehydrogenase of 2501 U/ml, and 1+ schistocytes. AKI was present with creatinine of 3.48 mg/dl (baseline 0.8), and urinalysis revealed 2+ proteinuria with 3–5 RBC/hpf. C3/C4 concentrations, coagulation studies, and infectious evaluation were normal.

## Question

Does this patient have c-TMA?

## Discussion

Diagnosis of TMA can be difficult when schistocytes are few and laboratory abnormalities are potentially attributable to other etiologies. Distinguishing etiologies of TMA solely on the basis of clinical presentation is challenging, and delayed treatment of TMA is associated with worse outcomes. Multisystem involvement is common in c-TMA, with gastrointestinal involvement in 30%, central nervous system involvement in 10%–50%, and cardiovascular involvement (*e.g.*, myocardial ischemia and malignant hypertension) in up to 40%. Similar features are present in immune thrombotic thrombocytopenic purpura (TTP), Shiga toxin HUS, catastrophic antiphospholipid antibody syndrome (APS), and others. Although some etiologies have distinct mechanisms, such as absent ADAMTS13 activity in TTP, many etiologies have complex and shared mechanisms. Initial evaluation should consider categories of TMA and TMA-mimics, including TTP, c-TMA, infection (*e.g.*, Shiga toxin, *Staphylococcus*, Pneumococcus, EBV, and CMV), disseminated intravascular coagulation, connective tissue disease, pregnancy, malignant hypertension, monoclonal gammopathy, medications (*e.g.*, gemcitabine, VEGF inhibitors, and calcineurin inhibitors), malignancy, metabolic (*e.g.*, cobalamin deficiency), and transplant associated (1–3).

The most important diagnoses, however, to initially exclude are TTP, defined by ADAMTS13 activity <10%, and active infection. A seven-component clinical prediction tool, the PLASMIC score (platelets <30,000 cells/mm$^3$, hemolysis variable, absence of malignancy, absence of organ transplant, MCV<90 fl, INR<1.5, and creatinine <2 mg/dl), estimates the likelihood of deficient ADAMTS13 to guide initial therapy (4). This is particularly valuable when measurement of ADAMTS13 activity in <24 hours is not possible, as a score of five or higher can support initial therapy with plasma exchange. Although a low score (less than or equal to four) is not diagnostic of c-TMA, the probability of c-TMA is greater when TTP is unlikely. Importantly, most patients with c-TMA present before the age of 60.

Activation of complement occurs along classic, lectin, and alternative pathways, with germline or acquired dysregulation of the alternative pathway underlying the majority of c-TMA. Unfortunately, there are no validated clinical assays for diagnosis of c-TMA analogous to ADAMTS13 activity. C3 is normal in approximately 50% of c-TMA, and complement activation products (*e.g.*, Bb and soluble C5b-9) are increased in multiple diseases, including c-TMA, TTP, sepsis, and others. Measurement of IgG autoantibody against complement factor H should be performed at presentation. Approximately 60% of patients will have variants in genes integral to complement

  

regulation (5). Challenges in variant interpretation and lengthy turnaround time render sequencing data less important acutely but vitally important in longer-term management (6). The minimum core panel should include *CFH*, *CD46*, *CFI*, *C3*, *CFB*, *CFHR5*, *THBD*, *DGKE*, *MMACHC*, and assessment of deletion/rearrangement through the *CFH-CFHR5* gene region. Reduced cell surface CD46 expression as measured by flow cytometry can suggest the presence of a germline variant in this gene. Evaluating for reduced plasma concentrations of factors H, B, and I can be useful in select patients (*e.g.*, nonsense variants) but is typically normal. The most promising tests for rapid diagnosis of c-TMA are endothelial *ex vivo* assays of complement activation, currently available only in research settings (7,8).

Kidney biopsy is valuable and performed in virtually all patients, although it is deferred until platelet count is $\geq$50,000/mm$^3$. Predominately glomerular involvement is typical of c-TMA and APS, whereas preglomerular arteriolar disease is characteristic of malignant hypertension and scleroderma. Biopsy helps establish a definitive diagnosis of TMA, evaluates for diseases such as SLE, and excludes other etiologies of AKI such as acute tubular injury.

Given the difficulty in quickly confirming germline or acquired dysregulation of complement, initial management is predicated on excluding TTP. The presence of severe AKI (creatinine >2) is more common in c-TMA as compared with TTP. This patient's PLASMIC score was four, supporting a non-TTP etiology of TMA. Neither ulcerative colitis nor 6-mercaptopurine are particularly associated with TMA. Given this, eculizumab, a monoclonal antibody to C5 that prevents formation of the C5 convertase, was administered. Although PLASMIC score–guided management has not been validated prospectively, with TMA and AKI without other clear cause, an empirical trial of anti-C5 therapy may be appropriate.

ADAMTS13 activity returned at 71% (70%–150%), formally excluding TTP. Thrombocytopenia improved to 93,000/mm$^3$ within 24 hours of administration. We measure CH50 24 hours after eculizumab administration and again prior to the second dose, with a value <10 U/ml (42–62) indicating terminal complement blockade. If available, eculizumab level >50–100 $\mu$g/ml is the goal. Complete terminal blockade may not be achieved in states of increased complement synthesis and/or increased volume of distribution, and supplemental dosing is indicated. We do not routinely administer simultaneous plasma exchange and eculizumab, but if this is performed, a supplemental dose of eculizumab is required after exchange. Failure of the platelet count to normalize within 7 days should prompt investigation of eculizumab resistance due to C5 polymorphism, inadequate dosing of anti-C5 therapy, concomitant processes such as antiplatelet antibodies or bone marrow suppression, or an alternate non–c-TMA diagnosis. Although improvement in microangiopathy is expected, increased LDH and schistocytes may persist for many weeks despite clinical improvement. Kidney biopsy was performed and revealed fibrin thrombi in glomeruli, segmental necrotizing lesions with mesangiolysis, unremarkable immunofluorescence, and no deposits on electron microscopy. The absence of C3 staining in c-TMA is common.

Vaccination against encapsulated bacteria (pneumococcal 13 and 23 valent, *Hemophilus influenzae*, and *Neisseria meningitidis* serotype ACWY and B) is required, and antibiotic prophylaxis with a $\beta$-lactam or fluoroquinolone should be started when anti-C5 therapy is initiated. Antibiotics are continued for at least 2 weeks after vaccination, and it is unclear if longer administration results in further reduction in the incidence of *Neisseria* infection. The risk of *Neisseria* infection (0.31 per 100 patient-years) is approximately 2000 times higher than in the general population. Patients and providers must remain vigilant for opportunistic bacterial infection.

## Question

How long should anti-C5 therapy be administered?

## Discussion

Relevant testing—including that for Shiga toxin HUS and other pathogens, connective tissue disease, APS, monoclonal gammopathy, and factor H autoantibody—was negative in this patient. Hematologic remission is often achieved quickly, and we continue anti-C5 therapy until kidney disease has stabilized and, ideally, remitted. In some patients, pharmacokinetics may permit alternative, less expensive dosing strategies provided that continuous, complete terminal complement blockade is maintained (9). Most improvement in GFR is seen within 5 months of diagnosis, and 60%–80% who require dialysis may recover. A 20%–30% relapse rate is reported in cohorts of patients with c-TMA who discontinue anti-C5 therapy (10). The absence of variants on genetic testing is associated with very low rates of relapse in observational studies, whereas pathogenic factor H, factor B, and C3 variants are associated with $\geq$80% risk.

After hematologic and kidney remissions are achieved and in the absence of a recognized high-risk genetic or ongoing acquired disease triggers, we discontinue anti-C5 therapy. If genetic testing results are unavailable, this additional element of uncertainty regarding relapse risk should be discussed with the patient. Laboratory monitoring is performed weekly for 2 weeks, biweekly for 6 weeks, monthly for 3 months, and then every 3 months. Patients are encouraged to perform home urine dipstick monitoring for hematuria and proteinuria, and anti-C5 therapy is promptly reinitiated if relapse is confirmed. In patients who stop therapy, our median duration of treatment is 2 months, with an 11% relapse rate with appropriate monitoring. Although many patients can successfully stop anti-C5 therapy, the potential long-term morbidity of subclinical complement activation is not well defined (11).

Genetic testing for this patient revealed *del(CFH-SCR20-CFHR1-int5)*, a pathogenic gene rearrangement between *CFH* and *CFHR1*. This fusion of factor H and factor H–related protein-1 produces a factor H protein lacking C3 convertase regulation. Why pathogenic variants have variable penetrance in c-TMA remains unknown, but this variant imparts an extremely high risk for relapse off therapy. Biologic relatives can be offered variant screening, although we do not utilize preemptive anti-C5 therapy in unaffected

carriers given the variable penetrance. The patient remains in remission on anti-C5 therapy with a normal GFR, and her relapse risk has been deemed too high to withdraw therapy.

Significant advances have occurred in therapy and the understanding of the mechanisms of c-TMA. Oral inhibitors of complement are in clinical trials, potentially offering another therapeutic revolution. Additional progress is needed in reducing cost of therapy and increasing access to rapid, validated assays specific to c-TMA.

**Disclosures**

C.J. Sperati reports consultancy fees from Q32 Bio; research funding from Achillion Pharmaceuticals, Alnylam Pharmaceuticals, the National Institutes of Health, and Novartis Pharmaceuticals; honoraria from Alexion Pharmaceuticals for serving on the data safety monitoring board for clinical trials NCT02949128, NCT03131219, and NCT04999020; serving on the editorial board of *Advances in Chronic Kidney Disease* and as section editor of *Current Hypertension Reports*; and serving in an advisory or leadership role for the American Board of Internal Medicine Nephrology Longitudinal Assessment Committee and the National Kidney Foundation Education Committee.

**Funding**

None.

**References**

1. Bayer G, von Tokarski F, Thoreau B, Bauvois A, Barbet C, Cloarec S, Mérieau E, Lachot S, Garot D, Bernard L, Gyan E, Perrotin F, Pouplard C, Maillot F, Gatault P, Sautenet B, Rusch E, Buchler M, Vigneau C, Fakhouri F, Halimi JM: Etiology and outcomes of thrombotic microangiopathies. *Clin J Am Soc Nephrol* 14: 557–566, 2019
2. Kavanagh D, Goodship TH, Richards A: Atypical hemolytic uremic syndrome. *Semin Nephrol* 33: 508–530, 2013
3. Thoreau B, von Tokarski F, Bauvois A, Bayer G, Barbet C, Cloarec S, Mérieau E, Lachot S, Garot D, Bernard L, Gyan E, Perrotin F, Pouplard C, Maillot F, Gatault P, Sautenet B, Rusch E, Frémeaux-Bacchi V, Vigneau C, Fakhouri F, Halimi JM: Infection in patients with suspected thrombotic microangiopathy based on clinical presentation. *Clin J Am Soc Nephrol* 16: 1355–1364, 2021
4. Paydary K, Banwell E, Tong J, Chen Y, Cuker A: Diagnostic accuracy of the PLASMIC score in patients with suspected thrombotic thrombocytopenic purpura: A systematic review and meta-analysis. *Transfusion* 60: 2047–2057, 2020
5. Goodship TH, Cook HT, Fakhouri F, Fervenza FC, Frémeaux-Bacchi V, Kavanagh D, Nester CM, Noris M, Pickering MC, Rodríguez de Córdoba S, Roumenina LT, Sethi S, Smith RJ; Conference Participants: Atypical hemolytic uremic syndrome and C3 glomerulopathy: Conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Available at: https://kdigo.org/wp-content/uploads/2017/02/KDIGO-Complement-conference-rpt-FINAL.pdf. Accessed December 16, 2021
6. Fakhouri F, Frémeaux-Bacchi V: Thrombotic microangiopathy in aHUS and beyond: Clinical clues from complement genetics. *Nat Rev Nephrol* 17: 543–553, 2021
7. Palomo M, Blasco M, Molina P, Lozano M, Praga M, Torramade-Moix S, Martinez-Sanchez J, Cid J, Escolar G, Carreras E, Paules C, Crispi F, Quintana LF, Poch E, Rodas L, Goma E, Morelle J, Espinosa M, Morales E, Avila A, Cabello V, Ariceta G, Chocron S, Manrique J, Barros X, Martin N, Huerta A, Fraga-Rodriguez GM, Cao M, Martin M, Romera AM, Moreso F, Manonelles A, Gratacos E, Pereira A, Campistol JM, Diaz-Ricart M: Complement activation and thrombotic microangiopathies. *Clin J Am Soc Nephrol* 14: 1719–1732, 2019
8. Yuan X, Yu J, Gerber G, Chaturvedi S, Cole M, Chen H, Metjian A, Sperati CJ, Braunstein EM, Brodsky RA: Ex vivo assays to detect complement activation in complementopathies. *Clin Immunol* 221: 108616, 2020
9. Passot C, Sberro-Soussan R, Bertrand D, Caillard S, Schvartz B, Domenger C, Contin-Bordes C, Paintaud G, Halimi JM, Ternant D, Gatault P: Feasibility and safety of tailored dosing schedule for eculizumab based on therapeutic drug monitoring: Lessons from a prospective multicentric study. *Br J Clin Pharmacol* 87: 2236–2246, 2021
10. Chaturvedi S, Dhaliwal N, Hussain S, Dane K, Upreti H, Braunstein EM, Yuan X, Sperati CJ, Moliterno AR, Brodsky RA: Outcomes of a clinician-directed protocol for discontinuation of complement inhibition therapy in atypical hemolytic uremic syndrome. *Blood Adv* 5: 1504–1512, 2021
11. Menne J, Delmas Y, Fakhouri F, Licht C, Lommelé Å, Minetti EE, Provôt F, Rondeau E, Sheerin NS, Wang J, Weekers LE, Greenbaum LA: Outcomes in patients with atypical hemolytic uremic syndrome treated with eculizumab in a long-term observational study. *BMC Nephrol* 20: 125, 2019

Published online ahead of print. Publication date available at www.cjasn.org.