American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2023; 24: e938367
DOI: 10.12659/AJCR.938367

Received: 2022.09.12
Accepted: 2022.10.21
Available online: 2022.12.31
Published: 2023.01.21

Complement-Mediated Thrombotic Microangiopathy with 10 Years of Stable Renal Function After a Year-Long Treatment with Eculizumab with Coincidental Polycystic Kidney Disease

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ACDEF Mehul P. Dixit
ABEF Lucy Woolverton
EFG Sabahat Afshan

Department of Pediatrics, Division of Nephrology, University of Mississippi Medical Center, Jackson, MS, USA

Corresponding Author: Mehul P. Dixit, e-mail: mdixit@umc.edu
Financial support: None declared
Conflict of interest: None declared

Patient: Female, 5-year-old
Final Diagnosis: Atypical hemolytic uremic syndrome • polycystic kidney disease
Symptoms: Uremic symptoms
Medication: —
Clinical Procedure: Hemodialysis
Specialty: Nephrology • Pediatrics and Neonatology
Objective: Rare disease

Background: Complement-mediated thrombotic microangiopathy (cTMA), is a genetic disease that results when an unchecked alternative complement pathway is triggered by an external factor, resulting in endothelial cell injury with microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure, though other organ systems may be involved.

Case Report: A 5-year-old girl presented with non-bloody diarrhea, hemolysis, renal failure, and thrombocytopenia. She was negative for Shiga toxin. She was diagnosed with cTMA, and this diagnosis was confirmed later by a mutation in the complement factor H (CFH) gene. The patient was started on eculizumab 8 weeks after onset of symptoms. A month later, she was able to stop hemodialysis. Eculizumab was given for a year, and then, because of clinical remission, was stopped. At the time of stopping hemodialysis, serum creatinine was 2.07 mg/dL; at the end of eculizumab therapy, it was 1.23 mg/dL. Now, 10 years later, it is 1.10 mg/dL. Glomerular filtration rate by Schwartz equation was 52 mL/min/1.73 m^2 after eculizumab and 60 mL/min/1.73 m^2 currently. The cTMA lab parameters normalized after 2 doses of eculizumab and have remained normal for 10 years. Two years ago, on routine ultrasound, renal cysts were noted. Recent genetic testing re-confirmed the CFH mutation and additionally showed a polycystic kidney disease (PKD1) mutation. Notably, there is no family history of either. Currently, the patient has mild proteinuria.

Conclusions: Instead of lifelong eculizumab treatment, we successfully managed the patient's condition with a year of eculizumab and intensive followup on sixty occasions over a decade. This approach can work if there are no relapses. Genetic tests revealed mutations for cTMA and autosomal dominant polycystic kidney disease (ADPKD)/PKD1 in the same patient. These have not been reported before, to the best of our knowledge.

Keywords: Atypical Hemolytic Uremic Syndrome • Eculizumab • Polycystic Kidney Disease 1 Protein • Renal Insufficiency, Chronic

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/938367

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Background

Genetic disease complement-mediated thrombotic microangiopathy (cTMA), is a result of an unchecked alternative complement pathway triggered by an external factor, resulting in endothelial cell injury and organ failure [1]. The 3 main components are microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure, though many other organs may be involved [1]. It often results from a combination of an underlying genetic susceptibility with environmental factors triggering unchecked activation of the alternative complement pathway. Pathogenic variants in at least 5 complement genes, coding for complement factor H (CFH), complement factor I (CFI), membrane cofactor protein (CD46), the complement component C3, and complement factor B (CFB), have been shown to be responsible for the majority of the increased risk of developing the disease [1-3]. Typical hemolytic uremic disease (HUS) is an infectious disease most commonly caused by Shiga toxin-producing *Escherichia coli* (STEC) [2,3]. Because of similarity of presentation, historically, clinicians have labeled cTMA as "atypical" HUS disease, although it is a complement-mediated process with a genetic basis [3]. Individuals with confirmed genetically based cTMA frequently experience relapse, and 60% are at risk for progressing to end-stage renal disease [2-4]. In contrast, classical HUS patients do not have a relapsing disease. There have been successful trials with the complement inhibitor eculizumab, for cTMA. Eculizumab is a humanized, chimeric monoclonal antibody directed against complement component C5 [3,5]. By blocking unchecked complement 3 activation, endothelial injury can be prevented. Eculizumab is very effective in the treatment of cTMA, but based on current scientific data, it is recommended to be taken as a lifelong treatment [5-9].

We present a case of a 5-year-old girl who presented with cTMA and was treated with eculizumab for a year. A decade later, her chronic kidney disease was at stage 3a; the same glomerular filtration rate as the day she came off the eculizumab. We present an alternative approach of intensive monitoring to allow patients to be weaned off eculizumab while maintaining glomerular filtration rate (GFR), as long as there are no relapses. Unfortunately, she developed multiple renal cysts and has been newly diagnosed as positive for PKD1, an autosomal dominant polycystic kidney disease (ADPKD) gene that is unrelated to cTMA. This may lead to progression of the CKD at some point in the future. Genetic tests revealing mutations for cTMA and ADPKD/PKD1 in the same patient have not been reported before, to the best of our knowledge.

Case Report

A previously healthy 5-year-old girl presented with persistent abdominal pain, vomiting, and diarrhea. During the initial workup at an outside hospital, the patient was found to be uremic and thrombocytopenic and was transferred to our hospital. She was negative for *E. Coli* 0157: H7, a strain of *E. coli* that produces Shiga toxin, and for other Shiga toxin-producing *E. coli* (STEC) strains, separately. Uremia continued to worsen with a peak serum creatinine level of 8 mg/dL and blood urea nitrogen (BUN) level of 99 mg/dL. Two days after presentation, the patient became anuric and the decision was made to begin hemodialysis.

At this time a preliminary diagnosis of cTMA was made. Genetic testing was not approved immediately as factor H level was normal, but was later performed and revealed a mutation in the C3 factor H gene. Eculizumab, which was newly approved for this purpose, was offered as the treatment of choice. However, since it is a lifelong therapy, and the family had constraints as they lived 2 hours from the hospital, they were understandably hesitant to start this lifelong treatment, which requires an infusion every 2 weeks and is very expensive. The patient remained hospitalized for 2 weeks on hemodialysis 3 times weekly. She was then transitioned to the outpatient pediatric dialysis unit. During those 2 weeks of hospitalization, plasmapheresis was offered but the family wanted to consider their options for a while longer, and it was not started. Meningococcal conjugate and pneumococcal conjugate vaccines were given in case the family were to agree to eculizumab, in the future.

After 2 months, the insurance approved the treatment and the family agreed to begin eculizumab infusion. It was started at 600 mg intravenous (IV) for the first dose, followed by 300 mg IV at week 2, then 300 mg IV every 2 weeks thereafter. By then, the need for hemodialysis had decreased to twice a week, which is not uncommon for a 5-year-old child. Eculizumab is a humanized monoclonal antibody targeted against complement C5. It inhibits the cleavage of C5 into C5a and C5b and hence inhibits deployment of the terminal complement system [3-5]. In the first week of illness, the nadir of hemoglobin was 58 g/L (normal for 5 years of age: 120-150 g/L). After 4 blood transfusions over 2 months, before the start of eculizumab, it was 86 g/L, and improved to 114 g/L a month into therapy when hemodialysis was stopped (**Figure 1**). It leveled off at 126 g/L a year into the illness and has remained normal since. The lactate dehydrogenase (LDH) peaked at 8,781 U/L, decreased to 1,340 U/L at the start of eculizumab therapy, normalized after 2 doses when she came off hemodialysis at 284 U/L (normal range, 135-345 U/L) and has remained normal a decade later. The thrombocytopenia improved after the start of eculizumab therapy (**Figure 1**). The C3, C4, factor H antibody, and A Disintegrin-Like and Metalloproteinase with Thrombospondin (ADAMTS) 13 levels were normal at the onset.

A month after starting eculizumab infusions, serum creatinine was 2.07 mg/dL, LDH was normal at 284 U/L, platelets

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

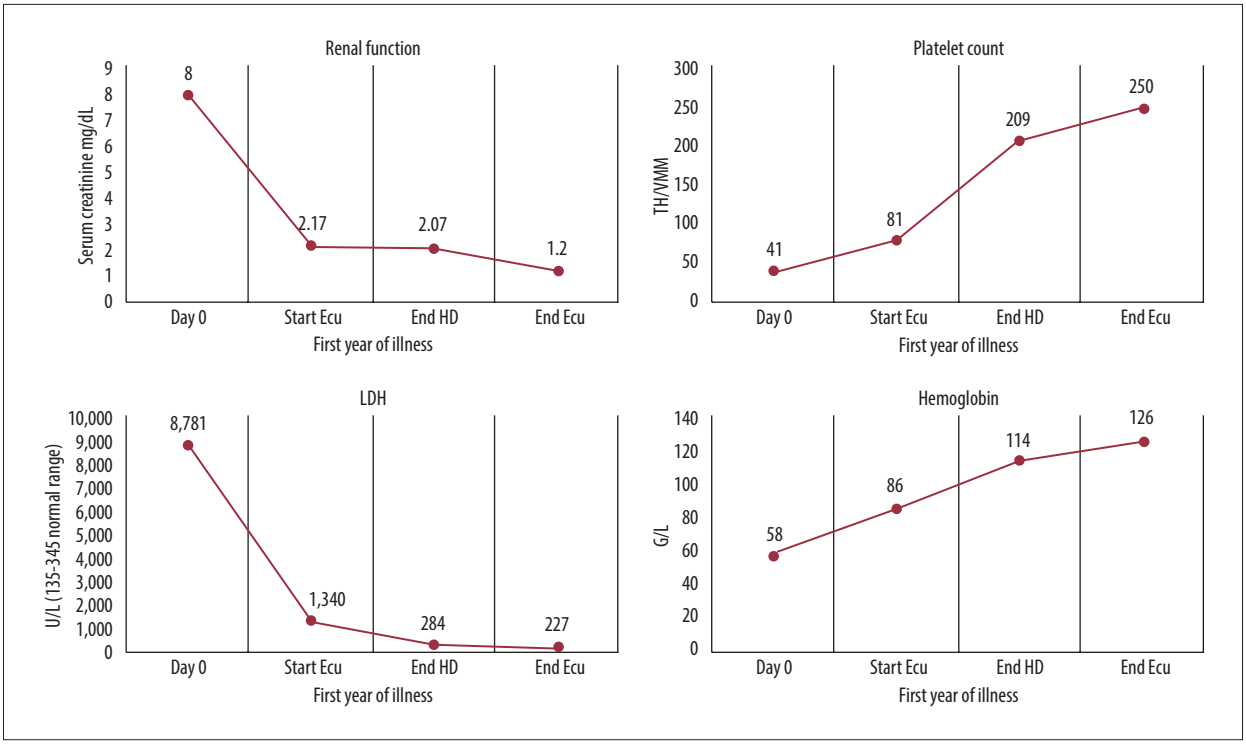

Figure 1. Patient's laboratory values during the first year of illness. The graphs demonstrate recovery from cTMA, as indicated by improved kidney function, increased hemoglobin, and restoration of LDH back to within the normal range. cTMA – complement-mediated thrombotic microangiopathy; LDH – lactate dehydrogenase; Day 0 – nadir values at onset of the disease; Start Ecu – start of Eculizumab therapy; End HD – end of hemodialysis treatment: End Ecu – end of eculizumab treatment.

normalized from 81,000 to 209,000, and hemoglobin was stable at 114 g/L. The patient reported normal urine output and reported that full levels of energy had returned by her sixth birthday. She began full-time school at a local kindergarten and was symptom free. A decision to take her off dialysis was taken. The patient received eculizumab infusions twice monthly for a total of 18 doses and then monthly for 2 more doses, for a total of 20 infusions. On completion of the last infusion, the serum creatinine was 1.23 mg/dL, LDH was 227, hemoglobin was 12.6, and platelet count was 250,000. The GFR by Schwartz formula was 38 mL/min/1.73 m^2. The patient has grown in height from 113 cm to a final adult height of 161 cm.

Eight years after the initial admission, the patient had a routine renal ultrasound that showed multiple complicated cysts in the left kidney measuring up to 2.0 cm with internal septations (**Figure 2**). This finding was confirmed on CT scan. The patient had no known family history of any cystic renal disease including polycystic kidney disease (PKD), but they have not been investigated for this. The patient's twin sister is healthy.

Currently, the patient is 15 years old; it has been 10 years since the original cTMA episode. At the time of last followup, her serum creatinine was 1.10 mg/dL and her GFR by Schwartz formula was 60 mL/min/1.73 m^2. The patient has mild proteinuria that is managed on enalapril 2.5 mg/day (0.05 mg/kg/day). The current urine protein: creatinine ratio is 0.39 (normal <0.2). Blood pressure is normal. The patient has had no relapses of cTMA since the original presentation. She has had over 50 clinic visits and over 60 lab draws in the 10 years since coming off dialysis, but she has had no hospitalizations since then. A Natera Renasight genetic testing panel confirmed a complement factor H mutation, c.2207G>A (p.Arg736Gln), but additionally, showed a PKD1 mutation: c.11801G>C (p.Gly3934Ala). The patient is an identical twin but neither her sister nor any other members of the family have been tested for either genetic variation.

Discussion

We report a case of cTMA in a previously healthy 5-year-old girl who is currently 15. It has been 10 years after her initial presentation, and she has stable chronic kidney disease (CKD 3a). She was treated with eculizumab for a year at the onset of illness. In the pre-eculizumab era, researchers showed that 57-82% of relapses occurred in the first year of followup [9]. In our patient, renal function was slowly recovering before the

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

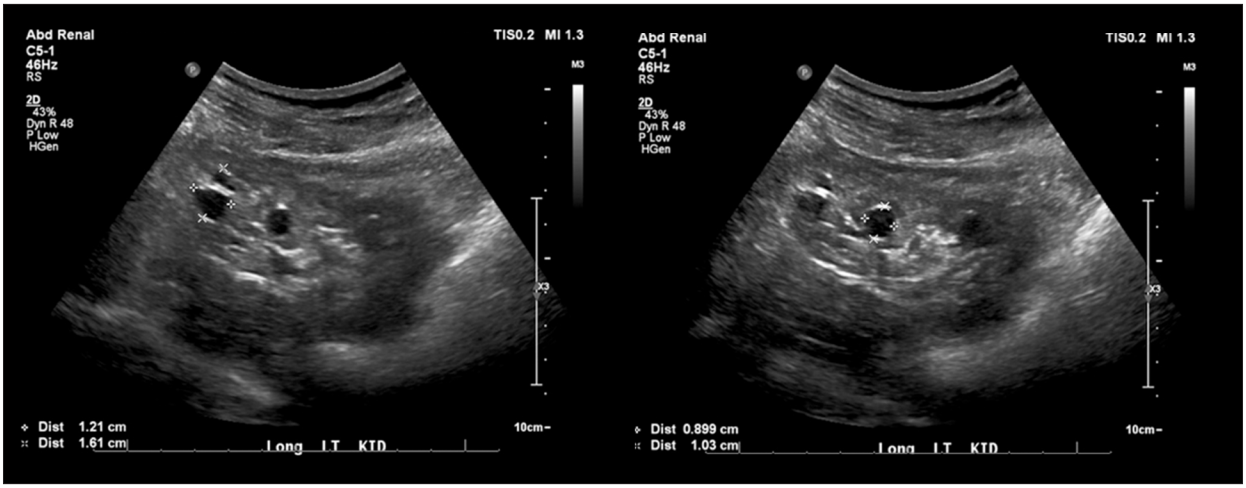

Figure 2. Renal ultrasound of left kidney demonstrating multiple cysts. The renal ultrasound was performed 10 years after the original cTMA diagnosis as part of a surveillance followup. cTMA – complement-mediated thrombotic microangiopathy.

start of eculizumab, but a month into infusion therapy, after 2 doses for induction, she was able to come off hemodialysis. Now, a decade later, she has a stable GFR and mild proteinuria managed by enalapril. It is unknown whether earlier treatment with eculizumab would have helped her renal function to recover fully and whether it helped her to come off hemodialysis. Eculizumab therapy very effectively reverses unchecked complement activation and reduces death from cTMA [6-8]. Initial guidelines suggested that treatment should be lifelong. However, there is little evidence to support that [9]. A decade ago, discontinuation of eculizumab for cTMA that was rooted in a proven genetic mutation was considered unscientific. The approval reports of the Food and Drug Administration in the USA and similar counterparts abroad emphasize the risks of withdrawal of eculizumab [9].

The efficacy of eculizumab in children was confirmed in a prospective trial [9]. Complete cTMA response was achieved after a median of 8.6 (1-22) weeks [9]. The eculizumab treatment was continued for at least 2 years [9]. No advice was given on how to proceed when a patient was stable and in remission. Lack of proven cTMA disease activity does not denote complete renal recovery [6-9]. In addition, the recurrence or progressive rate of cTMA varies for each mutation, so lifelong continuation may be unnecessary for some. Pathogenic variants in at least 5 complement genes coding for CFH, complement factor I (CFI), MCP (CD46), C3, and complement factor B (CFB) have mainly been shown to increase the risk of developing the disease. The risk of recurrence seemed to be higher in patients with pathogenic mutations in CFH (31-55%), MCP (18-52%), and C3 (50%) [3,9], which often present as a fulminant disease for the first time in adulthood [9]. Theoretically, that could mean there might be a prolonged period between initial presentation and relapse or late initial presentation with a milder disease early in childhood that is missed. Although organ transplantation, pregnancies, and chemotherapy agents, amongst others, have frequently been described as triggers, no specific trigger pattern exists [3-6, 9]. This can create anxiety in patients and the clinicians taking care of them. There is no consensus on the optimal dose and duration of treatment, particularly in view of the high costs and potential life-threatening adverse effects of eculizumab. A limited number of case reports and small number of patient studies suggest a restrictive duration of treatment is an alternative approach [9].

ADPKD is transmitted in an autosomal dominant, fully penetrant fashion, so virtually all individuals who inherit a mutated *PKD* allele in their germline will develop detectable renal cysts on sonogram by age 30 or possibly later. The majority of ADPKD patients carry a germline mutation in the *PKD1* gene on chromosome 16p13, and 15 to 20% of patients harbor a *PKD2* mutation on 4q21 [10]. CFH is located in the "regulators of complement activation" cluster on chromosome 1. This gene cluster includes decay-accelerating factor, complement receptor types 1 and 2, membrane cofactor protein, C4-binding protein, clotting factor XIIIb, CFH, and the CFH-related protein genes [3-5]. Therefore, the presence of these 2 mutations in our patient is most likely coincidental, although both diseases have multiple associated, described mutations; for example, PKD1 has >1000 pathogenic mutations described [10]. Scientifically, it will be important to keep a watch if more cases like ours are reported in the future.

Conclusions

We present an alternative method that some have utilized [7,8], of intensive clinical monitoring after completing eculizumab treatment for cTMA for a year and achieving a clinical remission. This intensive followup care strategy was possible because of

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

a reliable family that understood the risks of this illness. Our patient had over 50 visits to a medical provider over a 10-year period and a blood test each time. In a young child, this number of visits is a significant emotional burden and the commitment entailed should not be minimized. Unfortunately, she was found to have a second genetic mutation, PKD1, that was unrelated to CFH, that can affect her renal function in the future. PKD1will in the future increase the risk of deterioration of her renal function, but the resilience of the family portends a slower progression of CKD.

References:

1. Jokiranta TS. HUS and atypical HUS. Blood. 2017;129(21):2847-56
2. Laurence J. Atypical hemolytic uremic syndrome (aHUS): Making the diagnosis. Clin Adv Hematol Oncol. 2012;10(10 Suppl. 17):1-12
3. Noris M, Bresin E, Mele C, et al. Genetic atypical hemolytic-uremic syndrome. 2007 Nov 16 [Updated 2021 Sep 23]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1367/
4. Loirat C, Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis. 2011;6:60
5. Vieira-Martins P, El Sissy C, Bordereau P, Gruber A, Rosain J, Fremeaux-Bacchi V. Defining the genetics of thrombotic microangiopathies. Transfus Apher Sci. 2016;54(2): 212-9.
6. Zhang Y, Ghiringhelli Borsa N, Shao D, et al. Factor H autoantibodies and complement-mediated diseases. Front Immunol. 2020;11:607211
7. Turudic D, Milosevic D, Bilic K, Prohászka Z, Bilic E. A limited course of eculizumab in a child with the atypical hemolytic uremic syndrome and pre-B acute lymphoblastic leukemia on maintenance therapy: Case report and literature review. J Clin Med. 2022;11(10):2779
8. Wijnsma KL, Duineveld C, Wetzels JFM, van de Kar NCAJ. Eculizumab in atypical hemolytic uremic syndrome: Strategies toward restrictive use. Pediatr Nephrol. 2019;34(11):2261-77
9. Greenbaum LA, Fila M, Ardissino G, et al. Eculizumab is a safe and effective treatment in pediatric patients with atypical hemolytic uremic syndrome. Kidney Int. 2016;89(3):701-11
10. Bergmann C, von Bothmer J, Ortiz Brüchle N, et al. Mutations in multiple PKD genes may explain early and severe polycystic kidney disease. J Am Soc Nephrol. 2011;22(11):2047-56

Acknowledgements

We thank Jeanie Craft, Department of Pediatrics, University of Mississippi Medical Center for manuscript preparation.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]