**Research Article**

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**Area of Expertise:** Internal Diseases

**Title:** Outcomes of patients with complement-mediated thrombotic microangiopathy.

**Short title:** Outcomes of patients with CM-TMA.

**Abstract**

**Purpose:** Complement-mediated thrombotic microangiopathy (CM-TMA)) is a rare, progressive and life-threatening type of thrombotic microangiopathy (TMA) characterized by microangiopathic hemolytic anemia, thrombocytopenia and associated acute kidney disease (AKI) caused by dysregulation of the alternative complement pathway. The aim of this study was to retrospectively analyze the clinical features, follow-up, treatment and mortality of patients with CM-TMA.

**Materials and methods**: This was a retrospective study evaluating 13 patients diagnosed with CM-TMA who were followed retrospectively from 2024. Data were collected through a comprehensive review of electronic medical records of patients diagnosed with CM-TMA and receiving Eculizumab in the Department of Hematology and Nephrology.

**Results:** Thirteen patients with a mean age at diagnosis of 36.0±17.8 years were included. Age at disease onset ranged from 17 to 66 years. Only 3 (23.1%) patients were over 50 years of age. All patients were female. The mean follow-up period was 78.6±34.6 months. After an increase in GFR with eculizumab treatment, 76.9% of patients were weaned from dialysis.

**Conclusion:** CM-TMA was found to be predominant in young women. Eculizumab treatment provided significant improvements in clinical and laboratory values of the patients.

**Keywords**: CM-TMA, aHUS, C5 inhibitorleri, eculizumab, Complement-mediated thrombotic microangiopathy.

**Makale başlığı:** Kompleman aracılı trombotik mikroanjiyopatili hastaların sonuçları

**Öz**

**Amaç:** Kompleman aracılı trombotik mikroanjiyopatili (CM-TMA), alternatif kompleman yolunun düzensizliğinden kaynaklanan mikroanjiyopatik hemolitik anemi, trombositopeni ve eşlik edebilen akut böbrek hastalığı (ABH) ile karakterize nadir, ilerleyici ve yaşamı tehdit eden bir trombotik mikroanjiyopati (TMA) türüdür. Bu çalışmada retrospektif olarak izlenilen CM-TMA hastaların klinik özellikleri, takibi tedavisi ve mortalitesinin incelemesi amaçlanmıştır.

**Gereç ve yöntem:** Bu çalışma, 2024 yılından itibaren geriye dönük olarak izlenilen 13 CM-TMA tanılı hastaları değerlendiren retrospektif bir çalışma olarak yapıldı. Veriler, Hematoloji ve Nefroloji Bölümü'nde CM-TMA tanısı konulan ve Eculizumab alan hastaların elektronik tıbbi kayıtlarının kapsamlı bir incelemesiyle toplanmıştır.

**Bulgular:** Tanı anındaki yaş ortalamaları 36,0±17,8 olan 13 hasta alındı. Hastalık başlangıç yaşı 17 ile 66 arasında değişmekteydi. 50 yaş üzerinde olan sadece 3 (%23,1) hasta vardı. Hastaların tümü kadındı. Hastaların ortalama takip süresi 78,6±34,6 aydı. Eculizumab tedavisi ile GFR de artma sonrası hastaların %76,9 diyalizden çıkarılarak iyileşti.

**Sonuç:** CM-TMA genç kadınlarda baskın olduğu görüldü. Eculizumab tedavisi ile hastaların klinik ve laboratuvar değerlerinde önemli düzelmeler sağladı.

**Anahtar kelimeler:** CM-TMA, aHUS, C5 inhibitörleri, eculizumab, kompleman aracılı trombotik mikroanjiyopati.



## Introduction

Complement-mediated thrombotic microangiopathy (CM-TMA), also called atypical hemolytic uremic syndrome (aHUS), is a rare, difficult-to-diagnose disease with a serious risk of morbidity and mortality. Clinical criteria include thrombocytopenia, microangiopathic hemolytic anemia and threshold renal dysfunction. Often there may be no evidence of other TMA syndromes such as TTP or Shiga toxin hemolytic uremic syndrome. These criteria are not specific for CM-TMA and the diagnosis of CM-TMA can be challenging due to the lack of specific criteria [1].

In the last decade, great progress has been made in understanding the etiology and pathophysiology of CM-TMA. The role of complement regulation has emerged. The traditional classification of diarrhea-positive HUS (D+HUS) and diarrhea-negative HUS (D-HUS) was replaced by a new classification of HUS based on pathogenic mechanisms. This classification is organized considering the etiology of HUS: 1) HUS caused by infection (Shiga toxin-producing Escherichia coli, Streptococcus pneumoniae, Influenza A, human immunodeficiency virus); 2) HUS with coexisting diseases or conditions (bone marrow or solid organ transplantation, systemic malignancies, autoimmune conditions, drugs, malignant hypertension); 3) HUS due to cobalamin C deficiency; and 4) HUS due to alternative complement pathway dysregulation and mutation in the diacylglycerol kinase ε (DGKE) gene [2-5].

CM-TMA is relatively rare, with an estimated incidence of 0.23 to 1.9 per million population per year. Data are limited due to inconsistencies in definitions between studies and lack of general epidemiologic studies [6].

Anti-C5 monoclonal antibodies developed against complement subsequently became standard treatments. The introduction of Eculizumab ravulizumab and Iptacopa, which effectively block complement activation, drastically changed the treatment and outcomes of patients with CM-TMA due to alternative complement pathway dysregulation.

The aim of this study was to retrospectively analyze the clinical characteristics, follow-up, treatment and mortality of patients with CM-TMA followed up in the nephrology department.

## Materials and methods

This was a retrospective study evaluating 13 patients with CM-TMA diagnosed and followed up between 2010 and 2024. Data were collected through a comprehensive review of the electronic medical records of patients diagnosed with CM-TMA and receiving Eculizumab in the Department of Hematology and Nephrology. We were able to identify 13 patients who met the inclusion criteria. All included patients met the CM-TMA criteria, including age older than 18 years, thrombocytopenia, signs of hemolysis and sudden deterioration in renal function.

The study was conducted in accordance with the Declaration of Helsinki and approval was obtained from Pamukkale University Non-Interventional Clinical Research Ethics Committee (approval number: E-60116787-020-569349 (dated 20.08.2024 and numbered 15).

Exclusion criteria were ADAMTS13 deficiency (less than 10% activity, Shiga toxin-associated CM-TMA, Direct Coombs test positive, Patients on chronic hemodialysis or peritoneal dialysis. Demographic data, including age, gender, clinical information, admission characteristics, laboratory results, and treatment administered were collected.

In this study, ABH was defined as an increase in serum creatinine of ≥0.3 mg/dL or ≥1.5 times baseline in the last 48 hours (known or assumed to have occurred in the last 7 days) or an increase in urine volume of <0.5 mL/kg per hour for 6 hours according to the Kidney Disease: Improving Global Outcomes guidelines defined as a urine volume <0.5 mL/kg per hour for 6 hours. Chronic kidney disease (CKD) was defined as the presence of kidney damage (typically urinary albumin excretion ≥30 mg/day or equivalent) or reduced renal function (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 $m^2$) and persisting for 3 or more months. End-stage renal disease (ESRD) was defined as an eGFR <15 mL/min/1.73 $m^2$ with signs and symptoms of uremia such as nausea, vomiting and pericarditis with the need for dialysis.

**Statistical analysis**

Data were analyzed with SPSS 25.0 (IBM SPSS Statistics 25 software (Armonk, NY: IBM Corp.)). Continuous variables were expressed as mean ± standard deviation and categorical variables as number and percentage.

**Results**

Thirteen patients with a mean age at diagnosis of 36.0±17.8 years were included. The age at disease onset ranged between 17 and 66 years. Only 3 (23.1%) patients were over 50 years of age. All patients were female.

İn total of 2 (15.4%) of the patients were transferred while being monitored in the neurology ward for altered consciousness. Four patients (30.8%) presented with diarrhea, two (15.4%) developed symptoms after pregnancy, and the remaining patients presented with gastrointestinal symptoms (38.4%).

At the time of diagnosis, all patients had anemia 13 (100%) and kidney disease (100%), and all but one patient had thrombocytopenia 12 (92.3%) (Table 1). C3 deficiency with hypocomplementemia was detected in 9 patients (69.2%) (Table 2).

The mean follow-up period was 78.6±34.6 months. Supportive therapies such as erythrocyte suspension, platelet suspension, plasmapheresis and hemodialysis were provided. Eculizumab treatment was started within 1 month. 8 (61.5%) of the patients are still continuing Eculizumab treatment. The 3 patients who did not continue Eculizumab treatment were patients who developed CM-TMA while being followed up with a diagnosis of kidney transplantation. All 3 renal transplant patients were receiving

classical triple immunosuppression with mycophenolate mofetil and tacrolimus and methylprednisolone. 3 patients continued with dialysis. One of the patients died in the follow-up. Since the social security institution did not cover the treatment of 2 patients, treatment could not be continued (Table 3).

**Discussion**

All patients in the study had anemia, thrombocytopenia and ABH at the time of diagnosis. The median age at presentation was 35 years and all patients were female. The number of females was similar to the studies by Sperati et al. [7] and Amisha et al. [8] 82.4% and 75%, respectively.

Neurologic involvement is the most important mortality and morbidity of non-renal involvement which can be seen in 20-50% of CM-TMA patients [9]. Neurologic symptoms ranging from irritability to coma may occur due to cerebral microangiopathy, cerebral edema or delay in treatment. Brocklebank et al. [10] found the rate of patients presenting with neurologic symptoms to be 22%. In this study, the proportion of patients presenting with neurologic symptoms was 15.4%.

Low C3 level indicates dysregulation in the complement cascade of CM-TMA cases but is not necessary for the diagnosis of aHUS. Different rates have been reported in the literature regarding the presence of low C3 levels in atypical hemolytic uremic syndrome. In a study of 19 patients by Conkar et al. [11] low C3 level was found to be 10.5%, while in a study of 15 patients by Baskin et al. [12] low C3 level was found to be 50%. Štolbová et al. [13] reported low C3 levels in 71% of 21 pediatric aHUS patients. Kara and Kılıç et al. [14] found 64.3%. Similar to this study, we found low C3 levels in 69.2% of 9 patients.

Before eculizumab treatment, CM-TMA was treated with plasma exchanges or infusions. However, plasma exchanges did not affect the underlying problem and only maintained hematologic parameters. CM-TMA was therefore associated with high morbidity and mortality. In 2011, eculizumab was approved by the FDA and EMA for the treatment of CM-TMA, which significantly improved patient lives by inhibiting the underlying mechanism of CM-TMA. Open-label studies in adult patients showed that after 26 weeks, eGFR improved significantly and 79% of patients were taken off dialysis [12]. In this study, all patients were dialyzed. After a fall in GFR with eculizumab treatment, 76.9% of patients were weaned from dialysis.

İn conclusion, the clinical diagnosis of CM-TMA can be challenging, especially when associated with non-renal manifestations. CM-TMA appeared to predominate in young women. The decision to discontinue eculizumab treatment or change treatment to

ravulizumab or Iptacopa is likely to reduce health care costs and change patient compliance, safety. Larger multicenter studies or trials are needed to further confirm the findings of this study.

**Limitation:** The small sample size of the study was an important limitation.

**Authors contributions:** D.A.: Conceptualization, methodology, data curation, investigation, resources, Project administration, writing, review, and editing. The final manuscript has been read and approved by author.

**Conflict of interest:** No conflict of interest was declared by the authors.

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**Table 1.** Mean values of patients with complement-mediated thrombotic microangiopathy at the time of diagnosis, at discharge after treatment and at the last follow-up visit

| | **At the time of Diagnosis mean at presentetation** | | **While being discharged mean at presentetation** | | **The last follow-up visit mean at presentetation** | |
|---|---|---|---|---|---|---|
| | | **n (%)** | | **n (%)** | | **n (%)** |
| **WBC <4 K/uL** | 15.4±8.2 | | | | | |
| **Hb <12 g/dL kadın** | 7.3±1.6 | 13 (100) | 10.6±1.3 | 11 (84.6) | 13.1±1.7 | 3 (23.1) |
| **PLT <150 K/uL** | 80.3±57.7 | 12 (92.3) | 280.2±112 | 1 (7.7) | 250.5±58 | 0 (0) |
| **Urea >48.5 mg/dL** | 110.2±46.0 | 12 (92.3) | 50.3±32.3 | 6 (46.2) | 45.46±42.8 | 3 (23.1) |
| **Creatinine >0.95 mg/dL** | 3.6±1.5 | 13 (100) | 2.0±1.7 | 8 (61.5) | 2.2±2.2 | 6 (46.2) |
| **LDH >214 U/L** | 1263.7±853 | 3 (100) | 255.1±118.1 | 9 (69.2) | 180.3±38.0 | 2 (15.4) |

Anemia: Hb <12 g/dL in women, 13 g/dL in men
Hb: Hemoglobin, Plt: A platelet count, LDH: Lactate dehydrogenase

**Table 2.** Test values of patients with complement-mediated thrombotic microangiopathy at diagnosis

| **Laboratory parameters** | **Patient n (%)** |
|---|---|
| Elevated ALT (>41 IU/L) | 6 (46.2) |
| Elevated AST (>40 IU/L | 7 (53.8) |
| Elevated T. Bil (>1.2 mg/dL) | 6 (46.2) |
| Elevated I. Bil (>0.9 mg/dL) | 5 (38.5) |
| Elevated CRP (<0.5 mg/dL) | 10 (76.9) |
| Low C3 (90-180 mg/dL) | 9 (69.2) |
| Low C4 (10-40 mg/dL) | 2 (15.4) |

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase
TBil: Total bilirubin, IBil: Indirect bilirubin, CRP: C-reactive protein

**Table 3.** Treated patients

| | **n (%)** |
|---|---|
| **Receiving Eculizumab** | 13 (100) |
| **Eculizumab ongoing** | 8 (61.5) |
| **Receiving dialysis treatment** | 13 (100) |
| **Removed from dialysis** | 10 (76.9) |



Akin D. Outcomes of patients with complement-mediated thrombotic microangiopathy. Pam Med J 2025;18:…-…

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Davut Akın, Assoc. Prof. Department of Nephrology, Pamukkale University School of Medicine, Department of Nephrology, Denizli, Türkiye, e-mail: dakin@pau.edu.tr (https://orcid.org/0000-0002-9567-7940) (Corresponding Author)