10.5152/turkjnephrol.2023.21141125

Case Report

Turkish Journal of Nephrology

Two Different Presentation of C3 Glomerulonephritis Treated with Eculizumab: Two Cases and Brief Overview

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ABSTRACT

C3 glomerulopathy is a newly defined glomerular disease dominated by C3 complement storage and uncertain C1, C4, and immunoglobin accumulations. Hereditary mutations associated with Complement Factor H (CFH) causing hyperactivation of the alternative complement pathway were identified. Most mutations associated with C3 glomerulopathy are associated with the N-terminal end. Whether mutations are pathogenic or not will direct diagnosis and treatment. We present 2 cases, one 61-year-old and one 24-year-old attending our clinic at different times with hematuria, proteinuria, edema, and kidney failure. Both patients had C3 glomerulopathy diagnosed based on the results of kidney biopsy and were treated with eculizumab. Both cases had CFH-associated mutations.

Keywords: Clinical nephrology, C3 glomerulopathy, CFH, eculizumab, mutation, pathology

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Received: November 6, 2021 **Accepted:** May 1, 2022
Publication Date: January 1, 2023

Cite this article as: Öztürk Y, Özer H, Baloğlu İ, Türkmen K. Two different presentation of C3 glomerulonephritis treated with eculizumab: Two cases and brief overview. *Turk J Nephrol.* 2023;32(1):86-89.

INTRODUCTION

C3 glomerulopathy (GP) is a rare disease with an estimated incidence of 1-2 cases per million.[1] It is seen equally in both sexes and the average age of onset is stated to be 21 years in the literature.[2] Nephritic syndrome symptoms such as proteinuria (90%-95%), microscopic (64%-88%) or macroscopic hematuria (16%-38%), kidney failure (14%-59%), and hypertension (21%-46%) may be present.[3,4] The risk of 10-year progression to end stage kidney disease (ESKD) is 25%.[5] The risk of recurrence after transplantation is 60% and it is usually seen after allograft removal.[5] The disease is proposed to be caused by inherited mutations or acquired defects (CFH, Complement Factor B [CFB], and C3 convertase autoantibodies) with antibody development in the genes coding complement system factors (C3, CFB, CFH, Complement factor I [CFI], and Complement Factor H-related Proteins [CFHP-5]). However, it was suggested that the genetic defect alone may not be enough to initiate the disease in many patients.[6] Most risk factors that trigger glomerulonephritis (GN) are infections and others include vaccination, immunosuppressive, cytotoxic and contraconceptive drugs, pregnancy, and delivery.[7] Treatments that were shown to be effective are immunosuppressive agents such as mycophenolate, prednisone, and complement inhibitors such as eculizumab.[8] Here we present 2 cases who had C3 glomerulopathy and were treated with eculizumab.

CASE 1 PRESENTATIONS

Case - 1

A 61-year-old male presented to another health institution with high blood pressure, kidney failure and nephrotic syndrome symptoms. Hemodialysis treatment was started there due to uremic symptoms and he was admitted to our clinic approximately 6 months after the onset of symptoms. At the first evaluation in our center,

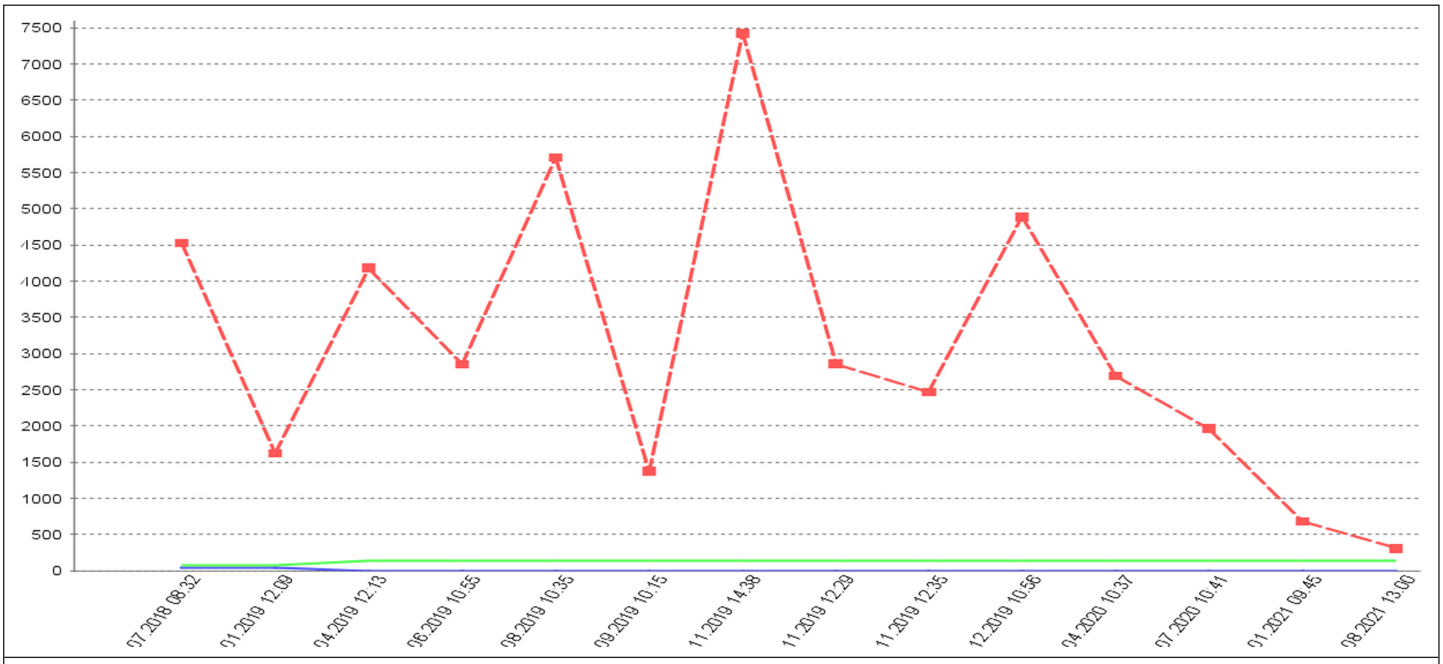

Figure 1. Case 1 Decrease of proteinuria levels after eculizumab treatment.

the dialysis treatment was stopped as the patient did not need dialysis treatment. Kidney biopsy was performed and immunofluorescence findings were negative for immunoglobulins C1q, fibrinogen, kappa, and lambda light-chain staining, but there were strongly positive depositions of C3. In addition, there was a significant increase in cellularity, especially in leukocytes and mesangial cells in all glomeruli. These findings favored the diagnosis of C3 glomerulopathy. In the evaluation of possible mutations of CFH, a heterozygous intronic splice site variant c.3134-5TC> (rs513699) was found and mutations of CFI found a heterozygous intronic c.482+44G>T (rs759704600) variant, which was classified as a variant of uncertain significance (VUS). Corticosteroid and mycophenolate mofetil were initiated and the angiotensin-converting enzyme inhibitor treatment that the patient had been using was continued. However, there was no clinical and laboratory improvement after a month. At this point, eculizumab treatment (900 mg/week for 4 weeks) was started after vaccination against *Neisseria meningitides*. His proteinuria and serum creatinine levels decreased with time to 1 g/day and 1.4 mg/dL, respectively (Figure 1). The patient continues to take 1200 mg of eculizumab every 2 weeks as maintenance treatment without symptoms.

MAIN POINTS

- C3 glomerulopathy (C3G) is characterized by uncontrolled activation of the alternative complement pathway. It is a rare disease with a poor prognosis and often progresses to the development of end-stage kidney disease.
- Hereditary mutations associated with CFH causing hyperactivation of the alternative complement pathway were identified.
- Identification of pathologic variants assists in confirming diagnosis and management of treatment, but due to the lack of genetic information for C3GN, a significant number of variants are reported as variants of unknown significance.
- With no data found in any genetic databases or guidelines about rs759704600 and rs749999830 variants, this article was to contribute to genetic databases by presenting the clinical phenotypes of these variants.

Case - 2

A 24-year-old woman with a kidney transplant was diagnosed with Atypical Hemolytic Uremic Syndrome (aHUS) after termination due to intrauterine fetal death at the seventh month of pregnancy about 1 year ago, followed by acute kidney injury and proteinuria and eculizumab was started. The same patient was admitted to our clinic 2 years later with complaints of swelling and weight gain. It was learned that the patient's eculizumab treatment was terminated at another center in the first year. Deterioration in kidney functions and an increase in proteinuria were detected. Eculizumab treatment was started again in the patient whose kidney biopsy result was compatible with C3 GP and who had no findings compatible with previous aHUS. Genetic evaluation showed mutations in CFH, but mutation analysis was negative for CFI genes. Heterozygous missense and intronic mutations c.2461C> T (rs367687415) and c.59-48C> T (rs74999983) were found and classified as VUS. Eculizumab treatment was discontinued after 3 months because there was no improvement in kidney function. The case was followed up with the diagnosis of chronic kidney disease and hemodialysis treatment was started for the patient who became pregnant again 1 year later (Figure 2).

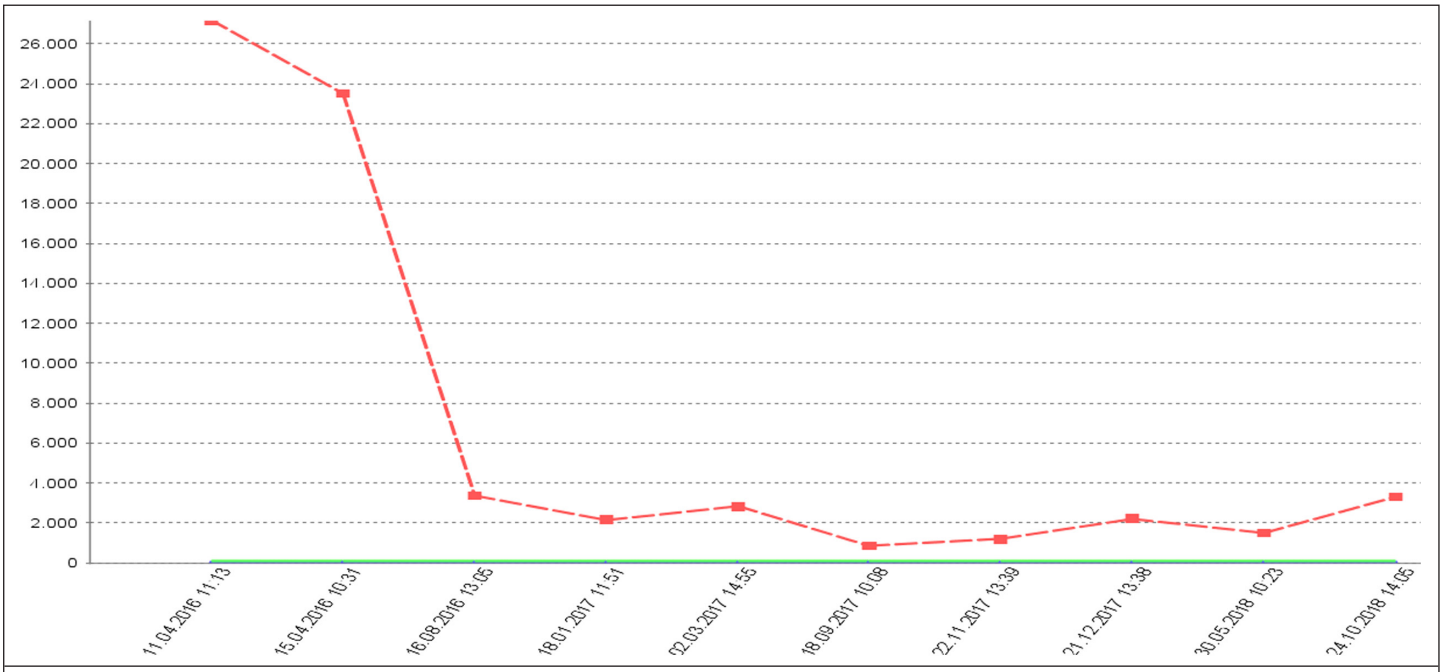

Figure 2. Case 2 Decrease of proteinuria levels after eculizumab treatment.

DISCUSSION

C3 glomerulonephritis and dense deposit disease are associated with mutations of the CFH, CFI, and CFHR genes.[9,10] According to the American College of Medical Genetics and Genomics (ACMG) 2015 guidelines, of the variants identified in our male case, the CFH heterozygous intronic splice site variant c.3134-5TC> (rs513699) is a VUS that is probably benign, while the CFI heterozygous intronic c.482+44G>T (rs759704600) variant was assessed as VUS. In our female patient, the c.2461C> T (rs367687415) variant was VUS but probably pathogenic, while c.59-48C> T (rs749999830) variant was VUS and was analyzed as probably benign. However, there was no reference to rs759704600 and rs749999830 variants in ClinVar and GenomAD and no functional evidence. These mutations associated with CFH on the alternative complement pathway brought the complement inhibitor eculizumab to the agenda for treatment.[11]

For our male case, the rs513699 variant was qualified as VUS by ClinVar, while it was associated with basal laminar drusen, age-related macular degeneration, membranoproliferative GN with CFH deficiency, and aHUS with proven evidence from a study by Phillips et al.[12] Additionally, it was stated to be benign in 4 studies according to ClinVar. The rs759704600 CFI variant in the same patient had no data reported in ClinVar. For our female case, the rs367687415 variant was classified as VUS, while it was associated with basal laminar drusen, age-related macular degeneration 4, and CFH deficiency aHUS 1 citing a study by Martín Merinero et al.[13] The other variant in the same case of rs749999830 had no data reported in ClinVar. Our first case provided full clinical response to eculizumab. However, our second case began eculizumab treatment again after a break, but sufficient response could not be obtained. There is no data about whether these different responses to treatment are associated with the variants.

For patients without rapidly progressive glomerulonephritis (RPGN) clinic, conservative approaches are recommended if proteinuria is below 1500 mg/day.[14] For those with proteinuria more than 1500 mg/day or with kidney dsyfunction without RPGN clinic, immunosuppressive treatment is recommended along with conservative treatment.[15] Initial treatment for up to 6 months is recommended with mycophenolate mofetil and oral glucocorticoids. This approach is largely consistent with recommendations from the 2017 KDIGO Controversies Conference.[15] If there is no response in proteinuria at the end of 6-month treatment, or if there is change in of kidney functions, steroid and mycophenolate mofetil may be discontinued and eculizumab may be started. The optimal duration of eculizumab treatment is uncertain and some patients relapse when treatment is stopped or treatment frequency is reduced. In our first case, 1-month steroid and mycophenolate mofetil treatment did not provide a clinical response, so eculizumab treatment was started. In the second case, eculizumab treatment did not provide benefit within 3 months of the second course of eculizumab treatment, so it was stopped.[14]

The 2 cases presented had different genetic variants and different clinical responses to treatment. Though some variants may be poor prognosis indicators for some of the patients, the effect of the previously unidentified variants in our cases is unknown. It was reported that adequate therapeutic levels of eculizumab

may not be reached in patients with high proteinuria (30). The massive proteinuria (27 g/day) detected in our second case may be one of the causes of poor response. Treatment monitoring with CH50 activity is recommended for those patients with excessive proteinuria.[16]

In conclusion, we presented clinical data from cases with CFH variants not previously included in the literature and treated with eculizumab. Accurate classification of CFH variants as pathogenic or benign is critical, but a significant number of variants are reported as VUS; functional studies are lacking.

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – K.T, Y.Ö.; Design – H.Ö., Y.Ö.; Supervision – K.T., H.Ö.; Data Collection and/or Processing – K.T., İ.B.; Analysis and/or Interpretation – K.T; Literature Search – İ.B., Y.Ö.; Writing – Y.Ö., K.T.; Critical Reviews – K.T., Y.Ö., H.Ö., İ.B.

Declaration of Interests: The authors declare that they have no conflict ofinterest.

Funding: The authors declared that this study has received no financial support.

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