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Case Report

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A Rare Case: Improved Heart Failure with Anti-Complement Therapy in Complement-Dependent Hemolytic Uremic Syndrome

Hakan Özer, Yasin Öztürk, Kültigin Türkmen, Zeki Halil Tonbul, Nedim Yılmaz Selçuk

Department of Nephrology, Necmettin Erbakan University, Meram School of Medicine, Konya, Türkiye

ABSTRACT

Extrarenal involvement occurs in approximately 20% of patients with complement-mediated hemolytic-uremic syndrome. The involvement is usually of the nervous system, and cardiac involvement occurs in 3%-10% of patients. Cardiac manifestations vary, including myocardial infarction, cardiomyopathy, and acute decompensated heart failure. Among these patients, thrombotic microangiopathy-related cardiac dysfunction is mainly due to the continuous activation of the complement system, which leads to endothelial damage and thrombosis in the coronary microvessels. We wanted to highlight the importance of cardiac evaluation at the time of diagnosis or during follow-up in thrombotic micro-angiopathy patients by presenting a case of heart failure with low ejection fraction in a 24-year-old young patient in whom we detected complement-mediated hemolytic-uremic syndrome, a secondary mutation of complement factor H receptor. It is still an unknown issue because of the rarity of cardiac involvement in complement-mediated hemolytic-uremic syndrome patients. Primary myocardial involvement is increasingly recognized as a possible concomitant feature of hemolytic-uremic syndrome. Failure to perform a detailed cardiac evaluation both at diagnosis and during follow-up in complement-mediated hemolytic-uremic syndrome patients can lead to fatal outcomes. Anti-complement therapy can also lead to good cardiac outcomes in these patients.

Keywords: Acute kidney injury, anti-complement therapy, complement-mediated hemolytic-uremic syndrome, heart failure, thrombotic microangiopathy

Corresponding author: Hakan Özer ✉ hakanozer724@gmail.com

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INTRODUCTION

Thrombotic microangiopathies (TMA) are a group of diseases associated with microangiopathic hemolytic anemia, thrombocytopenia, and kidney dysfunction that can be fatal if not diagnosed and treated early. The most common TMAs are hemolytic-uremic syndrome (HUS) following Shiga toxin-producing *Escherichia coli* infection, thrombotic thrombocytopenic purpura (TTP), and complement-associated HUS (CM-HUS/a-HUS), which is caused by genetic or acquired dysregulation of the complement system.[1,2] Irregularities in the alternative complement pathway cause the CM-HUS disease, the most common cause being a factor H mutation.[3] With the use of eculizumab, a recombinant monoclonal antibody developed against human complement factor C5, a significant reduction in morbidity and mortality rates has been recorded during treatment.[4]

Extrarenal involvement occurs in approximately 20% of patients with CM-HUS. This involvement is usually related to the nervous system, and cardiac involvement occurs in about 3%-10% of patients.[5,6] Cardiac manifestations vary, including myocardial infarction, cardiomyopathy, and acute decompensated heart failure. Thrombotic microangiopathy-related cardiac dysfunction in these patients is mainly due to the continuous

activation of the complement system, which leads to endothelial damage and thrombosis in the coronary microvessels.[5,7]

We wanted to highlight the importance of cardiac examination at the time of diagnosis or during follow-up in TMA patients by presenting a case of heart failure with low ejection fraction (EF) in a 24-year-old young patient in whom we detected CM-HUS, a secondary complement factor-H (CFH) receptor mutation.

CASE PRESENTATION

A 29-year-old female was diagnosed with ulcerative colitis 3 years ago and was treated with methylprednisolone, budesonide, and 5-aminosalicylic acid. One month before her, kidney function tests and blood counts were normal. The patient presented with complaints of diarrhea that had occurred 4-5 times for a long time. In addition to diarrhea, she complained of weakness, fatigue, exertional dyspnea, fatigue, palpitations, and edema of the feet. On physical examination, the heart rate was 110 beats/min, arterial blood pressure was 100/60 mmHg, and pretibial edema was detected. Except for pretibial edema, there are no physical examination findings to suggest hypervolemia. At presentation the biochemical results were as follows: hemoglobin (Hgb): 4.5 g/dL, platelet count: 88 000 × 10^3/μL, creatinine: 6.75 mg/dL, estimated glomerular filtration rate (e-GFR): 7 mL/min, serum albumin 2.7 g/L, and spot urine protein/creatinine ratio was 1.2 g. No pathology was observed in the chest x-ray. When hemolysis parameters were evaluated for the etiology of anemia, lactate dehydrogenase (LDH): 692 U/L, haptoglobin < 0.1 g/L, direct–indirect coombs tests were negative, and the percentage of reticulocytes was 11%. Stool tests and evaluation of viral and autoimmune markers did not reveal any pathological findings (antinuclear antibodies, anti-phospholipid antibodies, anti-double-stranded DNA, anti-histone antibodies, and anti-neutrophil cytoplasmic antibodies were negative). The C3 level was low, and C4 was normal. Tests for leptospirosis and COVID-19 PCR were negative.

The patient with diffuse schistocytes in her peripheral smear was considered to have thrombotic microangiopathy; intermittent hemodialysis and 5 plasmapheresis sessions were performed. The patient's disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 level was 61%, and her thrombocytopenia improved after the plasmapheresis sessions, whereas hemodialysis was still required. On transthoracic echocardiography, left ventricular ejection fraction (LVEF) was 30%, pulmonary artery pressure was 40 mmHg, and right atrial and ventricular sizes were average. There was no evidence of acute ischemic changes in the electrocardiogram; only sinus tachycardia was detected. Because of her acute kidney injury, cardiac catheterization was not performed. Heart failure due to kidney pathologies was not considered in the patient, who had sufficient urine output in the follow-ups and did not have findings supporting the diffuse volume overload and pulmonary edema. Multiplex ligation-dependent probe amplification analysis performed after genetic testing for CM-HUS revealed a deletion of complement factor H receptor-1 (CFHR1) and complement factor H receptor-3. After administration of meningococcal, pneumococcal, and *H. influenza* vaccines, treatment with eculizumab of 900 mg/week (4 weeks) was started under antibiotic prophylaxis. At follow-up, the dose was titrated to 1200 mg for 2 weeks. It was observed that the patient's kidney function tests regressed after the third dose of eculizumab treatment. After 2 months of treatment, the patient was weaned off hemodialysis, and hemolysis parameters did not deteriorate again. As of the second month of treatment, serum creatinine was 1.84 mg/dL, Hgb was 11 g/dL, and platelet count was 456 000 μ/L. Reticulocyte, haptoglobin, and LDH levels were also at normal levels. Control echocardiograms performed during the third and sixth months of treatment showed improvement. At the control echocardiogram at month 6, LVEF was 60%, and pulmonary artery pressure was 25 mmHg. The patient was followed at month 12 of eculizumab treatment, with no need for hemodialysis and no symptoms of heart failure.

DISCUSSION

In a young patient diagnosed with CM-HUS due to the deletion of complement factor H receptor, we found severe heart failure at the time of diagnosis. The patient had no disease other than TMA that could cause heart failure. We thought that heart failure was related to the TMA. Under anti-complement therapy, the patient's heart failure improved during follow-up.

The incidence and clinical impact of cardiac abnormalities in TTP-HUS are unknown. In several case reports and small retrospective studies, cases of TMA-associated myocarditis, myocardial infarction, and heart failure have been reported. The only case series to date that examined the incidence of heart failure in TMA patients was conducted on 220 patients. The estimated incidence of acute heart failure was 9.5% and was shown to be one of the significant determinants of mortality in the early stages of thrombotic microangiopathies.[6] There is no study reporting the incidence of cardiac dysfunction only in CM-HUS patients. Cardiac dysfunction is a condition that is rare in CM-HUS patients but contributes significantly to morbidity and mortality.

MAIN POINT

- Extrarenal involvement occurs in approximately 20% of patients with complement-mediated hemolytic-uremic syndrome (CM-HUS). Cardiac involvement is rare in patients with CM-HUS and can often be missed.
- Primary myocardial involvement is increasingly recognized as a possible concomitant feature of HUS. Failure to perform a detailed cardiac evaluation both at diagnosis and during follow-up in patients with CM-HUS can lead to fatal outcomes.
- Anti-complementary therapy may also lead to good cardiac outcomes in these patients.

These patients' TMA-associated cardiac injury and dysfunction are mainly due to the complement system's continuous activation, leading to endothelial damage and thrombosis in coronary microvessels. Possible mechanisms of cardiac involvement also include high-flow heart failure secondary to anemia, vasculopathy caused by microangiopathic injury, and cardiomyopathy.[5,7-9]

Although anemia and volume overload already contribute to cardiac dysfunction in TMA, the primary pattern of injury is thought to be tissue ischemia secondary to microvascular thrombosis. When the pathological changes due to HUS are examined, it causes the thickening of arterioles and capillaries, causing swelling and detachment of the endothelium in the target organ. It may lead to thrombosis and obstruction of the lamina of the microvessels, causing tissue ischemia.[7] Microvascular thrombosis is the main factor responsible for the occurrence of both renal and extrarenal manifestations.[7] Endothelial damage caused by sustained complement activation may not be limited to arterioles and capillaries, but thrombus formation rarely reaches critical dimensions to cause acute obstruction.[4] Complement components increase the expression of adhesion molecules, exerting pro-inflammatory effects on the endothelium and vessel wall by releasing cytokines, prostanoids, and leukotrienes that increase leukocyte release, activation, and transendothelial migration.[4] All these processes of complement activation contribute to the formation of microvascular thrombosis leading to tissue ischemia.

Our patient did not have coronary angiography because of acute kidney injury, and an endomyocardial biopsy was not performed because the patient did not consent to it. Therefore, we were unable to detect TMA-related lesions. The etiology of heart failure associated with CM-HUS was first described in the case report by Campbell et al[10] as acute thrombotic microangiopathy involving small intramyocardial arterioles. There is only 1 case in the literature that previously showed cardiac biopsy and TMA in a typical HUS patient, and there are similar pathological features.[11] The detection of coronary microthrombi and TMA is not uncommon in patients with CM-HUS when there is clinically significant primary cardiac involvement.[12]

There are 5 cases in the literature in which CM-HUS-related cardiac dysfunction was noted and reported to improve after initiation of eculizumab treatment (Table 1). Only one of the cases was diagnosed with heart failure at the time of diagnosis, as in our case, and in the other cases, heart failure developed during follow-up. After treatment with eculizumab, cardiac functions improved at different rates in all cases.

The risk of cardiovascular disease is not the same in all CM-HUS patients; it varies depending on the molecular defect. Patients with a genetic or acquired defect in CFH are even more prone to developing such cardiac complications compared to CM-HUS patients without the acquired defect.[17,18] Patients with CFH mutations, anti-CFH autoantibodies, complement factor B, or C3 mutations are particularly at risk of developing cardiovascular complications.[7,17] In these patients, echocardiographic screening, troponin monitoring, and imaging to detect cardiovascular changes should be performed on both admissions and follow-up visits. During hemodialysis, treatment with eculizumab may prevent severe vascular injury in patients with complement-associated CM-HUS with angiographic evidence of vascular changes. It is not clear that cardiac complications or vascular lesions occur in only <10% of CM-HUS patients. One reason for this may be that some mutations that cause CFH, C3, CFB, or high anti-CFH antibody levels cause a high degree of complement activation in endothelial cells. The fact that a CFH receptor mutation was detected in our patient also supports similar data in the literature.

Initiation of treatment with eculizumab in our patient resulted in improvement in cardiac, hematologic, and kidney functions. Although there is increasing evidence that eculizumab can be discontinued in some cases, the persistence of terminal complement activation in our patient suggests that continuation of therapy is necessary.

Table 1. Cases of CM-HUS with Heart Failure Treated with Eculizumab.

Publication	Case	Heart Failure	Diagnosis Time	Cardiac Improvement	Genetic mutation
Vilalta et al[13]	4-year-old girl	Ejection fraction 32%	8 weeks after diagnosis of CM-HUS	After 2.5 years ejection fraction normalized (64%-70%)	Factor H (CFH) (heterozygous mutation)
Hu et al[14]	19-month-old child	Ejection fraction 30%	At the time of diagnosis of CM-HUS	After 15 days, ejection fraction improved to 40%-45%	Factor H (CFH) c.2867 C>T (mutation)
Vaughn et al[15]	49-year-old woman	Ejection fraction 20%	1 month after eculizumab	After 7 weeks, ejection fraction improved to 40%-45%	Genetic variants of C3 and factor I (CFI) C3 gene and CFI gene:
Emirova et al[16]	18-month-old child	Ejection fraction, 42%	1 month after diagnosis of CM-HUS	After 43 months, ejection fraction normalized (71%)	Heterozygous mutation in CFH exon 23
Campbell et al[10]	63-year-old man	Ejection fraction 20%-25%	6 weeks after eculizumab	After 3 months, ejection fraction (60%-65%)	Complement regulator protein, CFHR3-1

CFH, complement factor H; CFHR3, complement factor H receptor-3; CM-HUS, complement-mediated hemolytic-uremic syndrome.

The most important limitation of our study is that cardiac TMA lesions could not be demonstrated histopathologically because the patient did not accept tissue biopsy.

CONCLUSION

Because cardiac involvement is rare in CM-HUS patients, there are still many unknowns. Primary myocardial involvement is increasingly recognized as a possible concomitant feature of HUS. Failure to perform a detailed cardiac evaluation in CM-HUS patients, both at diagnosis and during follow-up, can lead to a fatal outcome. Anti-complement therapy can also lead to good cardiac outcomes in these patients.

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

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