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Complement Factor H and Complement Factor H-Related Protein 5 Mutations Associated with Atypical Hemolytic Uremic Syndrome in a Systemic Lupus Erythematosus Patient: Efficacy of Eculizumab

Atipik Hemolitik Üremik Sendrom ile Başvuran Sistemik Lupus Eritematozus Olgusunda Kompleman Faktör H ve Kompleman Faktör H-İlişkili Protein 5 Mutasyonları: Ekulizumab Etkinliği

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ABSTRACT

Atypical hemolytic uremic syndrome (aHUS) is a disorder characterized by a propensity to thrombotic microangiopathy (TMA) due to defective regulation of the alternative complement pathway. Mutations in genes encoding complement factor H (CFH) and complement factor H-related proteins (CFHR) can be related with aHUS and identified in patients with rheumatologic diseases.

Atypical HUS typically presents as acute kidney injury (AKI) associated with microangiopathic hemolytic anemia (MAHA) and thrombocytopenia. We describe a SLE patient with severe AKI due to aHUS related CFH and CFHR5 mutations. The patient was refractory to immunosuppressives and plasmapheresis but responded well to eculizumab.

KEY WORDS: SLE, aHUS, Eculizumab

ÖZ

Atipik hemolitik üremik sendrom (aHUS) alternatif kompleman yolağının kontrolündeki kusura bağlı trombotik mikroanjiyopati (TMA) yatkınlığı ile karakterize bir bozukluktur. Kompleman bileşenlerinden kompleman faktör H (CFH) ve CFH-ilişkili protein (CFHR) mutasyonları aHUS ile ilişkilidir ve bazı romatolojik hastalıklara da eşlik edebilir.

AHUS tipik olarak akut böbrek hasarı (ABH) ile birlikte mikroanjiyopaik hemolitik anemi ve trombositopeni ile ortaya çıkmaktadır. Ciddi ABH ile başvuran Sistemik Lupus Eritematozus (SLE) olgumuzda aHUS ilişkili CFH ve CFHR5 mutasyonları saptadık. İmmünsüpresif tedavi ve plazmafereze dirençli olan olguda ekulizumab tedavisine yanıt alındı.

ANAHTAR SÖZCÜKLER: SLE, aHUS, Eculizumab

INTRODUCTION

The pathophysiology of aHUS involves endothelial injury caused by uncontrolled activation of the alternative complement pathway mostly due to mutations in genes coding for regulatory and activatory proteins (1-3). Mutations in the CFH/CFHR gene cluster have been reported in other disorders including C3 glomerulopathy, SLE, and age related macular degeneration (4,5). CFH gene mutation is the most common one with a frequency of 12-20% in sporadic, and 32-42% in familial cases (6-9). In SLE patients, certain mutations in the regulatory complement proteins related with aHUS have been reported to increase susceptibility to SLE and early onset of nephritis (10,11).

As dysregulation of the alternative complement pathway has been elucidated as a major pathogenetic factor in aHUS, targeted inhibition of this pathway has paved the way for a disease-specific therapy. Eculizumab, a humanized monoclonal antibody directed against complement component C5, has

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profoundly changed the management (1-3,12). The efficacy of eculizumab was shown in SLE-associated aHUS cases (13-15). In murine models of lupus, selective alternative pathway inhibition improved kidney function and increased survival (13).

Here we defined a unique SLE patient associated with aHUS in whom damaging CFH and CFHR5 mutations were identified. The patient was refractory to standard therapy of immunosuppressives and plasmapheresis, and managed favorably by eculizumab. The importance of DNA analysis of mutations of all complement factors in an aHUS patient in the presence of a secondary known cause is emphasized.

CASE REPORT

A 54-year old 80 kg woman was admitted to emergency department with hypertension, fever, dyspnea, tachypnea and anuria. A week before admission she developed shortness of breath, edema on legs, nonproductive cough without sputum production. She reported easy fatigability, chest discomfort, nausea, and vomiting. On examination she was pale, had a temperature of 37.8 °C, blood pressure of 180/100 mmHg, orthopnea with bilateral crackles at bases of lungs, and pretibial edema. There was no known chronic disease history or drug use in the patient's history. First investigations revealed AKI accompanied by thrombocytopenia, and increased peripheral blood schistocytes consistent with MAHA. Abdominal ultrasound demonstrated bilateral small kidneys (~7 cm) with increased echogenicity. The renal parencyhma was usual. There was no additional disease that could cause renal atrophy. No hypertensive retinopathy findings were detected on ophthalmological examination. The patient underwent hemodialysis and a blood sample for ADAMTS-13 activity was collected. Atypical HUS was highly suggestive with the presence of MAHA and AKI.

Laboratory evaluations revealed elevated creatinine and blood urea levels at 9.3 mg/dL and 216 mg/dL respectively on admission (Table I). Total bilirubin and lactate dehydrogenase levels were elevated. Urinalysis by dipstick revealed proteinuria (2+), hemoglobinuria (1+), red blood cells 15/hpf, and white blood cells 26/hpf. Complete blood count showed decreased hemoglobin (Hb) and low platelet count, and highly elevated leucocyte count with neutrophil predominance. The protein-creatinine ratio was 1.6 g/g. Microscopic examination of urinary sediment revealed dysmorphic erythrocytes.

Table I: Laboratory investigations before and after eculizumab treatment.

Laboratory values	Pre-treatment	After eculizumab treatment
Urea (mg/dl) (17-43)	216	78
Creatinine (mg/dl) (0.6-1.1)	9.3	1.8
Total bilirubin (mg/dl) (0.3-1.2)	1,36	
LDH (U/L) (0-257)	2500	260
White blood cells (x$10^3/\mu$L)	19.9	8.4
Hemoglobin (gr/dl) (12.2-16.2)	10.5	11.1
Platelet counts (uL/ml) (150-500)	55000	289000
Direct Coombs	negative	-
Prothrombin time (sec) INR	12.7 (11.5-14.5) 0.98 (0.8-1.2)	-
Activated Partial Thromboplastin Time (aPTT) (sec)	27.3 (22.6-38.2)	-
C3 (mg/dl) (79-152) C4 (mg/dl (16-38)	57 8.6	
Haptoglobulin (mg/dl) (30-300)	5	
ADAMTS13 activity	61%	-
ANA titer Anti-dsDNA Anticardiolipin antibodies (IgG/IgM) Antiphospholipid antibodies (IgG/IgM)	1/2560 negative negative negative	
Parathyroid hormone (pg/ml) (10-65)	10.7	
Phosphorus (mg/dl) (2.5-4.5)	4.6	

Further investigations noted hypocomplementemia with decreased levels of C3 and C4, and positive antinuclear antibody (ANA; in homogenous pattern) whereas antibodies to other extractable nuclear antigens were all negative. Coagulation tests were normal and direct antiglobulin test (Coomb's test) was negative. D-dimer was not elevated. Haptoglobulin was suppressed. ADAMTS-13 activity was found to be 61%. Chest radiography demonstrated left-sided pleural effusion. Echocardiographic evaluation was unremarkable except for trace pericardial effusion. ANA positivity, presence of serositis, hypocomplementemia and proteinuria with glomerular hematuria fulfilled the criteria for SLE according to the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria (16). Fulfilling the criteria for the diagnosis of SLE with aHUS, the patient was commenced on pulse methylprednisolone treatment (500 mg/day intravenously for 3 consecutive days) and plasmapheresis.

Pending the result of cultures, cyclophosphamide therapy was withheld. Urinary culture demonstrated significant bacteriuria of *E. coli* (10^5 col/ml). Five days after treatment with the antibiotics the microorganism was susceptible to, the repeat urinary culture was negative.

Plasmapheresis was halted after seven treatments as only platelet counts were responsive. Following vaccinations against meningococci and pneumococci and institution of antibiotic prophylaxis against meningococcal infection, eculizumab 900 mg weekly for 4 weeks was initiated on day-18 of admission. After the second dose, the patient's urinary output promptly commenced reaching 60 cc/h and the creatinine level decreased to 2.46 mg/dl without dialysis. Steroid plus azathiopurine was continued for lupus and after bolus doses of eculizumab the patient was discharged with a creatinine level of 1.8 mg/dl. The steroids were discontinued in three weeks and the patient was put on hydroxychloroquine and azathiopurine therapy. Because of the development of myelosuppression, azathiopurine was withheld on follow-up as well.

Mutation analysis for aHUS panel involving sequencing and analysis of the exonic regions of 12 genes revealed CFH, CD46 (MCP: membrane cofactor protein), CFI, CFB, C3, C5, DGKE, CFHR1, CFHR3, CFHR5, THBD, ADAMTS13 identified damaging heterozygote CFH (p.Glu936Asp) and CFHR5 (p.Arg356His) mutations.

On follow-up, the patient's creatinine level increased to 2.3 mg/dl with resurgence of peripheral schistocytes. As we can not precisely differentiate between SLE flare-up and an aHUS attack we were reluctant to give another course of anticomplement therapy for that attack. Steroid therapy was reinstituted and decrease of creatinine to hospital discharge levels was achieved. The patient is currently clinically and biocemically well under low-dose alternate day steroid plus hydroxychloroquine therapy.

DISCUSSION

This case describes the efficacy of eculizumab in an adult patient with aHUS-related complement mutations in the presence of SLE. Molecular defects in complement regulation has been described in patients with aHUS and may be triggered by activation of the complement system through inflammation and immune complexes as observed in the setting of some autoimmune diseases such as Sjögren's syndrome, rheumatoid arthritis and SLE (3).

Histological data from lupus patients has shown that occurrence rate of disorders of TMAs is 8-10% and 1-4% of cases develop thrombotic thrombocytopenic purpura (TTP) (17,18). In a cohort of 114 patients with SLE, fifteen patients (13%) had laboratory features of MAHA with negative Coombs' test result (19). As previously reported by Hunt et al. (20), those cases with MAHA and proteinuria identified as SLE and TTP before the advent of ADAMTS13 assay could have been aHUS due to lupus nephritis instead. Accordingly, our case with AKI, MAHA, thrombocytopenia, and ADAMTS-13 activity of more than 10%, prompted us to diagnose aHUS in SLE. Both lack of neurological manifestations and detectable ADAMTS-13 activity argued against the diagnosis of TTP. Unfortunately, small kidney sizes with decreased cortical thickness and the presence of thrombocytopenia precluded renal biopsy.

Both deficiencies of early components of the complement cascade and defects in adequate inhibition of the complement system predispose to development and/or exacerbation of SLE (10,21). Moreover, variants of genes encoding complement inhibitors CD46 and CFH have been related with early onset nephritis in SLE patients, and some genetic mutations in CFH and CFHR3 and CFHR1 has been shown to be associated with increased SLE susceptibility (10,11). Some mutations have been related with certain clinical manifestations in different ethnic groups such as tag SNP rs16840639 of CFHR1 being demonstrated in African American SLE patients with the absence of anti-dsDNA and the presence of serositis (11,22).

In our case, the identified mutations in both CFH and CFHR5 have been associated primarily with aHUS. Elucidation of whether these mutations have also increased the risk of SLE requires further studies in a larger dataset.

According to a large body of evidence accumulated in support of the major role of dysregulation of the alternative complement pathway, therapeutic strategies based on complement blockade has been reported recently to treat these disorders (1,2,13,15). Eculizumab is currently approved for treatment of aHUS and paroxysmal nocturnal hemoglobinuria (1,15). The efficacy of eculizumab as targeted therapy in SLE has been recently documented (2,13,15). Raufi et al. (2) demonstrated a patient with aHUS secondary to lupus nephritis who responded to eculizumab after being refractory to standard therapy.

Coppo et al. (23) showed the similar effect of eculizumab in their case report of aHUS in a child with diffuse proliferative lupus nephritis. Similarly, our patient demonstrated a significant improvement of both renal functions and hemolytic picture after institution of eculizumab therapy. Treatment of SLE-associated aHUS is most often guided by the treatment of SLE itself. However, in the presence of known aHUS gene mutations in a SLE patient as in our case, standard therapy may fail to achieve recovery and anti-complement therapy should be considered.

Knowing the genetic mutations in an aHUS patient is of prognostic value for the future kidney transplantation outcome and kidney donation. Patients with a mutation in the CFH or FI gene have a worse outcome after kidney transplantation and should therefore be discouraged from undergoing a renal transplantation although the recent advance of integrating eculizumab to transplant protocols promises better renal outcomes for transplant patients with aHUS (6,8).

In conclusion, despite the presence of a secondary known cause of aHUS, patients refractory to primary treatment interventions should be considered for eculizumab treatment and for complete evaluation of DNA analysis for mutations of complement components. Although the genetic background of the patient does not affect the acute therapy response, it does help to plan long-term care of the patient.

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