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Atipik Hemolitik Üremik Sendrom Olgusunda Eculizumab Deneyimi

Eculizumab Experince at a Patient With Atypical Hemolitic Uremic Syndrome

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ÖZ

Trombotik mikroanjiyopati, arteriollerin ve kapiller damarların duvarlarındaki mikrovasküler tromboz gelişimine neden olan anormallikleri tanımlayan spesifik bir patolojik lezyondur. Mikroanjiyopatik hemolitik anemi ise, periferik yaymada şistosit oluşumuna neden olan, damar içindeki kırmızı kan hücrelerinin fragmantasyonundan kaynaklanan non-immün bir hemolitik anemi tipidir. Atipik hemolitik üremik sendrom (AHÜS), primer trombotik mikroanjiyopati nedenlerinden biri olup tedavide erken dönemde eculizumab kullanımı geri dönüşümsüz böbrek hasarı riskini azaltmaktadır. Mikroanjiyopatik hemolitik anemi ve trombositopeni ile gelen olgumuzda hem erken tanısal yaklaşımın önemini hem de atipik hemolitik üremik sendrom (AHÜS) olgularında erken eculizumab kullanımının böbrek fonksiyonları üzerine olan olumlu etkisini vurgulamayı amaçladık.

Anahtar Kelimeler: *Tailgut kisti; nöroendokrin tümör; presakral alan*

ABSTRACT

Thrombotic microangiopathy discribes a specific pathologic lesion in which abnormalities in the vessel wall of arterioles and capillaries lead to microvascular thrombosis. Microangiopathic hemolytic anemia is a descriptive term for non-immun hemolytic anemia resulting from intravascular red blood cell fragmentation that produces schistocytes on the peripheral blood smear. Atypical hemolytic uremic syndrome is a type of primer thrombotic microangiopathy and using eculizumab in the early phase of therapy reduces the risk of irreversible renal damage. We mentioned both the importance of early diagnosis at the patients presenting with microangiopathic hemolytic anemia and thrombocytopenia like our patient and the benefit of eculizumab therapy at the early phase of atypical hemolytic uremic syndrome therapy.

Keywords: *Microangiopathy, Eculizumab, Complement*

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INTRODUCTION

Thrombotic microangiopathy (TMA) discribes a specific pathologic lesion in which abnormalities in the vessel wall of arterioles and capillaries lead to microvascular thrombosis (1,2). Microangiopathic hemolytic anemia (MAHA) is a descriptive term for non-immun hemolytic anemia resulting from intravascular red blood cell fragmentation that produces schistocytes on the peripheral blood smear(3). MAHA is often caused by abnormalities in small arterioles and capillary vessels, and sometimes mechanical factors such as prosthetic heart valves. Typical laboratory findings of MAHA are negative direct coombs test, increased lactate dehydrogenase (LDH) levels, increased indirect bilirubin levels and low haptoglobulin levels. TMAs can be primary or secondary. The primary causes of TMA are thrombotic thrombocytopenic purpura (TTP), shiga toxin-mediated hemolytic uremic syndrome (ST-HUS), atypical hemolytic uremic syndrome (aHU) or complex-mediated thrombotic microangiopathy, drug-induced thrombotic microangiopathy and metabolism-mediated thrombotic microangiopathies.

The primary causes of TMA are thrombotic thrombocytopenic purpura (TTP), shiga toxin-mediated hemolytic uremic syndrome (ST-HUS), atypical hemolytic uremic syndrome (aHUS) or complex-mediated thrombotic microangiopathy, drug-induced thrombotic microangiopathy and metabolism- mediated thrombotic microangiopathies.

Secondary causes of TMAs are severe preeclampsia, pregnancy related syndromes such as HELLP syndrome, severe hypertension, systemic infections, malignancies, autoimmune diseases such as systemic lupus erythematosus (SLE) and bone marrow and solid organ transplant complications (4-10). In disseminated intravascular coagulopathy (DIC), which is clinically and laboratoryally similar to TMA, plasma fibrinogen concentration and dimer levels are abnormal, while TMA is normal. TTP results in a low (<10%) result of ADAMTS13 activity. AHUS is due to the presence of hereditary abnormalities in proteins (complement factor B(CFB), complement 3) which accelerate activation of alternative complement pathway and due topresence of hereditary impairment of regulatory proteins (complement factor I(CFI), complement factor H(CFH), complement factor H-related proteins(CFHR) and membrane cofactor proteins(MCP, CD46)) which allow the inhibition of alternative complement pathway activation. Deficiencies in CFH and CFI may be hereditary or may have been gained due to autoantibodies that inhibit the activity of these factors. Unlike the others in primary TMAs, renal function impairments are minimal in TTP. Plasma exchange is life-saving in TTP and plasma exchange should be done within hours in presence of doubt of TTP. In order to minimize the risk of irreversible renal damage in the AHUS, treatment with eculizumab should be started within the first 24-48 hours. Approximately half of the cases of AHUS are preceded by a history of infection such as diarrhea and upper respiratory tract infection. central nervous system involvement mostly was seen in 20% of patients, while hypertension and renal damage, cardiac involvement, pulmonary hemorrhage and respiratory failure, pancreatitis, liver involvement and intestinal bleeding were also observed. Kidney biopsy can be used to distinguish acute tubular necrosis from TMA, but it can not provide a clear distinction between primary TMA causes. Since the use of eculizumab increases the risk of encapsulated bacterial infections (pneumococcus, meningococcus and H. influenza), vaccination should be performed before treatment. Prophylactic antibiotics can be used for at least 2 weeks (sometimes throughout the treatment period) until the vaccine is effective. The most important problems in the treatment of eculizumab, which is quite reliable and has low side effect profile, are that the appropriate treatment duration is not clear andare an expensive treatment methods.

We present a 39-year-old female patient who was diagnosed with AHUS and eculizumab treatment was given and have had full clinical response.

CASE REPORT

A 39-year-old woman was admitted to the emergency services with complaints of fatigue, loss of appetite, nausea. The general condition of the patient who was learned to have diarrhea in the last 1 week was medium, conscious open, full orientation and co-operative.

Table 1. **The laboratory values on the patient's admission, at the follow-up in the clinic and on the discharge are presented**

LABORATORY RESULTS	Admission	Discharge time
BUN(mg/dl)	52	9
Creatinine(mg/dl)	6,02	0,50
Na(meq/L)	129	141
K(meq/L)	5,05	4,36
Ca(mg/dl)	8,43	10,09
Hb(g/dl)	10,3	12,5
Hct(%)	30,7	36,3
Erythrocyte ($10^{6/u}$)	3,68	4,15
Leukocyte($10^{3/ul}$)	4	13,6
Platelet($10^{3/ul}$)	24	422
PTT(sec)	13,3	12,9
aPTT(sec)	32,3	30,13
INR	1,178	1,08
AST(U/L)	110	14
ALT(U/L)	177	27
LDH(U/L)	3521	237
Urine examination /Spot urinary protein, creatinine	PH 7,06 Density:1,012 Glucose:Normal; Blood:+1; Protein(-);	13,2/135,6 (123 mg/day)
Bilirubin(total/indirect) (mg/dl)	1,76/1,3	1,01/0,07
GGT(U/L)	52	39
D-Dimer(mg/L)	34,25	0,44
Reticulocytes (%)	1,38	1,28

BUN, Blood Urea Nitrogen; **Na,** Sodium; **K,** Potassium; **Ca,** calcium; **Hb,** Hemoglobin; **Hct,** Hematocrit; **Plt,** Platelet; **PTT,** Protrombin time; **aPTT,** Active Partial Thromboplastin Time; **INR,** International Normalize Ratio; **AST,** Aspartat aminotransferase; **ALT,** Alanin aminotransferase; **LDH,** Lactate Dehydrogenase; **GGT,** Gamma Glutamyl Transferase

The patient's body temperature was 38.40C, pulse rate was 102 beats / min, blood pressure was 160/100 mmHg. Increased urea, creatinine, AST (aspartate aminotransferase), ALT (alanine aminotransferase), LDH, indirect bilirubin levels and pancytopenia were detected in the laboratuar results **(Table 1).** Fragmented erythrocytes and schistocytes were seen in the peripheral blood smear. Because of TTP diagnosis couldn't excluded, plasma exchange was performed followed by hemodialysis after the sampling for ADAMTS 13 activity. Bone marrow biopsy was performed, and no atypical cells were seenin bone marrow smear. Suspicious infiltrative appearance compatible with lobar pneumonia was seen on patient's torax tomography. Combine antibiotherapy (piperacillin tazobactam and ciprofloxacin) was initiated to patient.

Echocardiography showed an ejection fraction of 62%, pulmonary artery systolic pressure (sys PAB) 36 mmHg and minimal noncollapsed pericardial fluid was detected. Renal ultrasonography revealed normal renal size and parenchyma echogenicity and renal artery stenosis was excluded by renal doppler ultrasonography. No abnormal findings other than hepatomegaly was revealed in abdominal tomography. Because the ADAMTS13 level and activity were found to be normal, and a second cause was not found in the patient, the diagnosis of the patient was accepted as AHUS. Under prophylactic antibiotic treatment with pneumococcal, meningococcal, and H. influenza vaccine, eculizumab treatment was performed 900 mg on the 5th day of admission then weekly 900 mg continued and, 5th week 1200 mg and followed by 1200 mg every 15 days. In the ongoing period, the levels of Hemoglobin and platelets normalized. Renal function improved and hemodialysis was not needed. A total of 10 sessions of plasma exchange and 14 sessions of hemodialysis were performed. The patient, whose follow-up and treatment are still continuing in our clinic, is being monitored in full remission clinically and laboratory.

DISCUSSION

It was thought to be a TMA clinic with microangiopathic hemolytic anemia due to the presence of schistocytes, fragmante erythrocytes in peripheral blood smear and increased LDH and indirect bilirubin levels in patient with anemia, thrombocytopenia and acute renal damage. Since the complaints of diarrhea did not continue to develop, the patient was unable to study shiga toxin in the stool. In cases with AHUS, as in our case, approximately 50% of infectious diseases including diarrheal diseases can be found before clinical findings.Acute kidney damage is not a common finding in TTP, but plasma exchange has begun because TTP diagnosis in the patient could not be excluded. TMA induced by the drug has not been considered in our patient because she has no drug use history. Since vitamin B12 levels were also normal, TMA due to vitamin B12 metabolism disorder was not considered. Because left ventricular hypertrophy was not detected in the patient echocardiography, it was not considered in TMA due to severe hypertension. In our blood and urine cultures were negative, TMA due to infection was excluded.A malignancy scan was performed and malignant tumors were excluded. TMA induced by autoimmune causes was excluded in patients with negative autoantibody tests and without clinic findings. After the ADAMTS13 activity outcome was normal and systemic causes were excluded, the diagnosis of AHUS was performed. Elevation in liver function tests that were determined in the patient's admission and normalized in follow-up was assessed as extrarenal involvement of AHUS.

Early treatment of eculizumab was planned to reduce the risk of permanent renal damage. After meningococcal, pneumococcal and H. influenza vaccines were administered, eculizumab therapy was started under prophylactic antibiotic treatmens. Early differential diagnosis is life-saving in patients with microangiopathic hemolytic anemia and thrombocytopenia, while early eculizumab therapy in AHUS cases is a safe and effective treatment option for renal function.

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