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Thrombotic Thrombocytopenic Purpura Associated with Cyclocyporin Use in a Liver Transplant Patient

Karaciğer Nakilli Hastada Siklosporin Kullanımına Bağlı Trombotik Trombositopenik Purpura
Gastroenteroloji

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Özet

Karaciğer transplantasyonu yapılmış hastalarda kullanılan immünsüpresif ilaçlara bağlı olarak pek çok komplikasyon gelişebilmektedir. Bu komplikasyonlardan biri olan trombotik mikroanjiyopati (TMA) oldukça nadir görülen ve tedavi edilmediği takdirde hayatı tehdit eden bir durumdur. Literatürü incelediğimizde karaciğer nakli sonrası kalsinörin inhibitörü kullanımına bağlı gelişen az sayıda trombotik trombositopenik purpura (TTP) olgusuna rastladık. Yine bizim bilgilerimize göre bu olgu ülkemizde karaciğer nakli sonrası siklosporin kullanımına bağlı gelişen ilk TTP olgusudur. Karaciğer nakli olan hastamızda siklosporin kullanmakta iken TTP tablosu gelişmiş olup pulse steroid ve plazma exchange tedavisi ile hastalık kontrol altına alınmıştır.

Anahtar kelimeler: *Siklosporin*, *Trombotik trombositopenik purpura*, *Karaciğer nakli*

Abstract

Many complications may develop due to immunosuppressive drugs given to patients with liver transplantation. Thrombotic microangiopathy (TMA), which is one of those complications, is encountered very rarely and if untreated, it endangers life. When we reviewed the literature, we came across to a few thrombotic thrombocytopenic purpura (TTP) cases, which have developed due to calcineurin inhibitor use after the liver transplantation. And according to our knowledge, this present case was the first TTP case, which occurred due to cyclosporine use after the liver transplantation. While our patient with liver transplantation was receiving cyclosporine, clinical picture of TTP was developed, and the disease was controlled by using pulse steroid and performing plasma exchange treatment.

Keywords: *Cyclosporine*, *Thrombotic thrombocytopenic purpura*, *Liver transplantation*

Introduction

Thrombotic microangiopathy (TMA) term includes thrombotic thrombocytopenic purpura (TTP) syndrome and hemolytic uremic syndrome. This clinical picture is characterized by rapid increases in erythrocyte fragmentation and serum lactate dehydrogenase (LDH) levels. Complications like acute renal failure, neurological disorders and fever are seen frequently during the clinical progression. Bacterial or viral infections, autoimmune diseases, malignancies, pregnancy, drugs (cyclosporine-tacrolimus, ticlopidine, clopidogrel, mitomycin), factor H deficiency, vWF protease activity reduction, female gender and hereditary factors are responsible for predisposing factors and etiology [1-4]. TMA is a rare but significant complication of bone marrow and renal transplantations [5,6]. TTP is rarely reported under orthotopic liver transplantation [7,8]. TMA encountered in transplant receivers, has been related to the uses of calcineurin inhibitors (CNIs) such as cyclosporine (CsA) and tacrolimus. TMA encountered in non-transplantation population is suggested to be related to a deficiency in coagulation mechanism [2,9]. On the other hand, TMA encountered in transplant receivers is proposed to be developed secondarily to endothelial damage caused directly by CNIs, and that hematological signs have been observed as a secondary phenomenon. Diagnosis is performed by clinical, laboratory and histological signs. If TTP is not treated, mortality rate is >90%. Positive response is provided approximately at 80% of cases by plasma exchange, and patient

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survival rate is >90%. Impacts of plasma exchange have been shown in a prospective, randomized clinical trial [3].

Case Report

32-years old male patient has been followed up at our clinic due Child B liver cirrhosis related to alcohol and hepatitis B for 3 years. Cadaveric liver transplantation from a 35 years old subject, who had the brain death after a traffic accident, was performed. Patient received cyclosporine and steroid treatments as the immune suppressive treatment. Lamivudine treatment was employed as the antiviral treatment. Patient, who was discharged on the postoperative 7th day, was scheduled for control visits at the transplantation outpatient clinic.

Patient applied to the outpatient clinic with complaints of fever, fatigue, yellow coloring of body 14 months after the transplantation. In his anamnesis, there was no cough, sputum production, diarrhea, abdominal pain, and dysuria. In the physical examination, fever was 38.3°C, sclera was icteric and conjunctivas were pale. As the laboratory results were creatinine= 2.2 mg/ dL, GGT= 1953 U/L, ALP= 1628 U/L, total bilirubin= 4.7 mg/ dL, direct bilirubin= 4 mg/ dL, Hb= 8.2 g/dL, leukocyte= 3400/mm^3, and thrombocyte= 65000/mm^3, he was internalized in the organ transplantation service. Blood and urine samples were provided for culturing. It was thought that deterioration of the renal function might be due to cyclosporine toxicity. However, cyclosporine level was within normal limits. Bile ducts were evaluated by MRCP, and stenosis was detected at the site of anastomosis. ERCP was performed 1 day after the hospitalization, and a stent was implanted in the choledochus. On the second day of hospitalization, headache and mild agitation started, hemoglobin and thrombocyte count were decreased to 6.7 g/ dL, and 34.000/mm^3, respectively. Because levels of LDH, reticulocyte values were increased, whereas haptoglobin level was decreased, the patient was decided to have TTP, and hematology consultation was requested. In his peripheral blood smear, prominent fragmentation was defined (Figure 1).

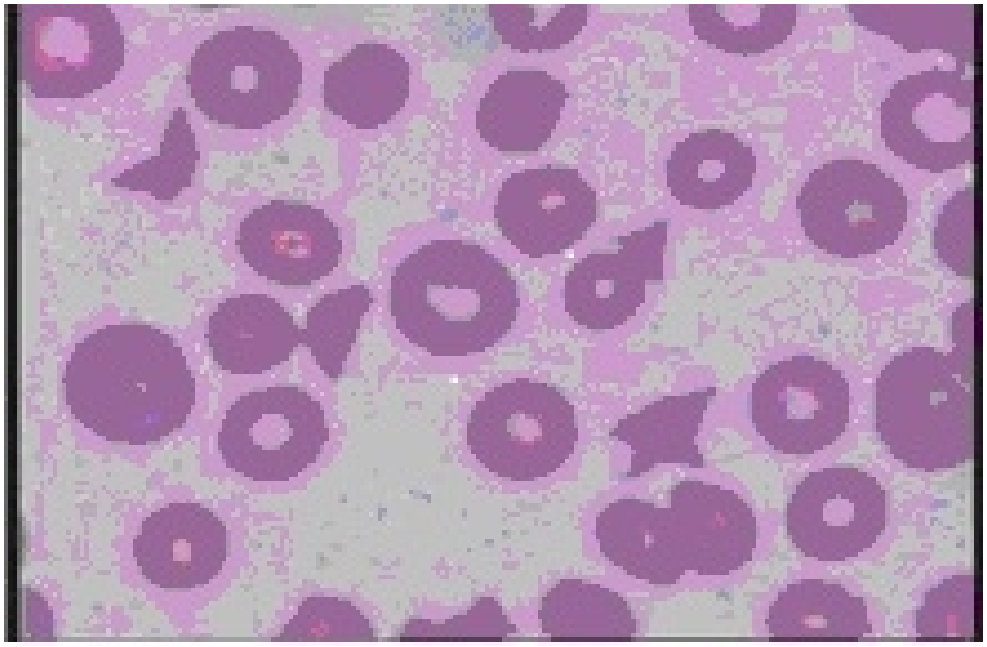

Figure 1
Fragmented erythrocytes and schistocytes in the peripheral blood smear.

Therefore, plasma exchange (a total of 10 sessions with 50 mg/kg plasma) and pulse steroid treatments were started due to TTP on the same day. In the bone marrow aspiration examination directed to etiology, megakaryocyte increase was defined. No hematological infiltration was observed. In concomitant tests for

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possible infections, repeated blood and urine cultures were sterile; EBV, CMV, HSV, Parvovirus, hepatitis markers, HIV antibody, and immunological markers were negative. It was confirmed that patient was not receiving additional drugs other than the drugs he was taking. Therefore, cyclosporine was discontinued because it was believed that TTP developed due to the drug, and it was switched to tacrolimus. However, because there was no improvement in fragmentation values in the laboratory and peripheral blood smear tests under tacrolimus treatment, it was switched to sirolimus treatment. All of laboratory parameters of the patient were improved over days under this treatment. Creatinine values were decreased to basal levels. Fragmentation disappeared in the peripheral blood smear. The patient's general state was recovered, and he was discharged with follow up recommendation at the transplantation outpatient clinic.

Case Discussion

Thrombotic thrombocytopenic purpura is diagnosed by five clinical signs, which appear as fever, neurological disorders, microangiopathic hemolytic anemia, thrombocytopenia and renal disorder [10]. Coagulation profile is generally within normal limits, and this helps in differential diagnosis from disseminated intravascular koagülasyon (DIC). Mild PT elongation was detected in our case, and it was thought that this condition was related to extrahepatic cholestasis. After stent implantation in the choledochus, PT value returned normal level. Underlying pathology in TTP is abnormal thrombocyte aggregation in the microcirculation, which ensues secondary to abnormal thrombocyte-endothelial interaction [11]. TTP itself is a heterogenous disorder [11].TTP may develop due to various reasons in liver transplant patients. If it is not diagnosed and treated at an early phase, it can progress to a mortal disease. TTP can also develop after hematopoietic stem cell, bone marrow, kidney, liver, lung, and cardiac transplantations [12]. It can recur or, as it has been observed in our patient, develop de novo after transplantation.

In the majority of cases, disorders like hemoglobinemia, hemoglobinuria, LDH increase, hiperbilirubinemia, haptoglobin decrease, schistocytes and fragmented erythrocytes in peripheral blood smear, kidney function disorders and thrombocytopenia are detected, and headache, agitation and convulsions may occur as neurological signs [3]. In our case, majority of previously mentioned signs were present. Moreover, bone marrow aspiration and biopsy enabled us both to rule out the causes which might lead to cytopenia, and also to support TTP diagnosis by revealing increased megakaryocytes.

De novo TTP, which is developed after transplantation, may develop due to infections (CMV, HCV, HIV, HHV Type 6, *H. Pylori*, Histoplasmosis) and due to drugs, frequently CNIs. In our case, the infections, which might lead to TTP, were negative. Our patient was receiving cyclosporine, which had TTP development potential and was an immunosuppressive agent. Relationship between TTP and cyclosporine has been well defined between bone marrow and solid organ transplantation conditions [7,13]. In our case, discontinuation of cyclosporine and switching to tacrolimus did not improve clinical and laboratory results. After the treatment agent was switched to sirolimus, clinical and laboratory signs were improved, which indicated that the clinical picture of TTP was most probably developed due to cyclosporine use.

There are different approaches in de novo TTP treatment. These include decreasing dose or discontinuation of CNIs, switching to sirolimus treatment, and the plasma exchange. As the result, the main core of treatment is formed by recovery of underlying pathology, removal of predisposing factors, treatment with pulse steroid and plasma exchange. Blood and blood product should be performed only if a fatal complication is developed during the palliative treatment [14,15].

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Information Presantation

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