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OLGU SUNUMU

THROMBOTIC THROMBOCYTOPENIC PURPURA: A REPORT OF TWO RESISTANCE CASES AND REVIEW OF THE LITERATURE

TROMBOTİK TROMBOSİTOPENİK PURPURA: DİRENÇLİ İKİ OLGUNUN BİLDİRİMİ VE LİTERATÜRÜN GÖZDEN GEÇİRİLMESİ

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ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is a rare hematological disease, but it is a hematological emergency with fatal consequences if not promptly diagnosed and appropriately treated. Plasmapheresis is the most effective therapy of TTP through which more than 80% of patients have been cured. Immunosuppressive therapy is used for patients who have resistance TTP. Rituximab is an important immune modulator therapy in certain autoimmune and malignant disorders. Herein, we report two patients with resistance TTP to conventional therapy who were successfully treated by rituximab. Using rituximab as part of the standard therapy may be more effective to prevent potential mortality and morbidity of TTP than standard approach.

Key words: TTP, rituximab, treatment

ÖZET

Trombotik trombositopenik purpura (TTP) nadir görülen bir hematolojik hastalıktır. Ancak, acilen tanı koyulup tedavi edilmezse, ölümcül sonuçları olan bir hematolojik acildir. TTP'in en etkin tedavisi hastaların %80'inden fazlasında kür elde edilebilen plazmaferezdir. Dirençli TTP'si olan hastalarda immunsupresif tedavi kullanılabilir. Rituksimab otoimmun ve malign hastalıklarda kullanılan önemli bir immunmodulator tedavidir. Biz burada, konvensiyonel tedaviye dirençli olan ve rituksimab ile başarıyla tedavi edilen iki hastayı sunduk.

Anahtar kelimeler: Trombotik trombositopenik purpura, rituksimab, tedavi

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INTRODUCTION

Thrombotic Thrombocytopenic Purpura (TTP) is an acute, rare, and life-threatening disorder. It is characterized by platelet aggregation in hemolysis of red blood cells, consumption of platelets, and occlusion of microvasculature. TTP causes multi-organ dysfunction as a consequence of widespread microvascular ischemia. Yet, the pathophysiology of TTP is not clearly understood(1). However, the current view of its pathophysiology includes endothelial cell damage and the presence of abnormally large molecular weight von Willlebrand factor (vWF) multimers. The vWF plays a role in primary hemostasis, which connects the subendothelial matrix and platelets. In normal circumstance, ADAMTS13 (adisintegrin and metalloprotease with thrombospondin type 1 repeats, member 13) acts to cleave highly hemostatically active ultra-large vWFmultimers into smaller fragments which are less adhesive form of vWF. However, in TTP, ADAMTS13 activity decreases (2-4). An annual incidence of TTP is about 11 cases 1,000,000 persons and is greater in women than men(5).The classic clinical description of TTP is known as ''classic pentad''fever, thrombocytopenia, microangiopathic hemolytic anemia, renal dysfunction, and neurological symptoms. But the majority of the patients with TTP do not have this pentad, which generally mimics more common disorders including malignant hypertension, sepsis, gastroenteritis(6-8). The most common symptoms of TTP are nausea, vomiting, diarrhea, weakness. TTP still causes approximately 20% mortality. The reasons of death are delayed diagnosis and implementation of the appropriate therapy. Plasmapheresis is the most effective therapy of TTP which cures more than 80% of patients (2,3,9,10). Plasmapheresis generally is used with steroid therapy as an adjuvant.

Rituximab, which is a chimeric monoclonal antibody, consumes B cells by binding CD20 expressed on the surface of premature and mature B lymphocytes. This effect continues nearly 6-9 months following the treatment(11-13). Rituximab has been used for treatment in some type of malign and auto-immune diseases such as lymphoma, rheumatoid arthritis, systemic lupus erythematosus(14-17). In recent years, rituximab has been used in patients with refractory TTP, which may be effective for TTP because of its immune-modulator feature.

Herein, we report the two resistance TTP patients, who were successfully treated with rituximab.

CASE DESCRIPTIONS

During 2012-2013, 2 patients with resistance TTP to conventional therapy had been diagnosed at Bozyaka Training and Research Hospital, Izmir, Turkey. The clinical features of 2 cases of TTP are summarized in the following of the text.

We initially treated our patients with plasma exchange and immunosuppressive therapy with corticosteroids, but this treatment failed. We administered rituximab, which was used standard intravenous infusion of 375 mg/m^2 each week for 4 weeks. After the second dose of rituximab, resolution of clinical symptoms and hematological abnormalities was observed. The completion of treatment was effective for both patients and they were treated without any sequel.

CASE 1

A 36-year-old female patient admitted to the emergency department with deterioration of her consciousness. She did not have any chronic disease in her past medical history, however two weeks ago she had diarrhea problem and which were improved spontaneously. Her physical examination revealed that, body temperature was 38.3 ^{0}C, arterial blood pressure 120/70 mmHg, and her heart rate 130 beats per minute. Furthermore, there was a peteschial and ecchymotic rash all over the body especially on the lower extremities. She was slightly pale and jaundice. Central nervous system examination showed that the patient was unconscious and who responded to painful stimulus. The rest of the examination was normal and revealed no focal deficit.

Initial laboratory tests revealed her white cell count and differential count were normal, her platelet count was 12.000 per millimeter and her hemoglobin level was 8.4 g/dL. The peripheral-blood smear shows occasional fragmented and polychromatophilic red cells. Laboratory analyses revealed that lactate dehydrogenase (LDH): 1334 U per liter (normal < 270 U/L), reticulocytes: 12.4 %, total bilirubin: 3.1 mg/dL, direct bilirubin: 2.1 mg/dL. Her cranial MRI no acute intracranial abnormality. Another laboratory test results; aPTT: 31 seconds, INR:1.4, bleeding time: 8 minutes, clothing time: 5 minutes, direct coombs test: negative, anti-nuclear antibody: negative.

She has been diagnosed as TTP with all these clinical and laboratory findings. The patient was hospitalized and classic treatment (plasma exchange daily and metyl prednisolone 80 mg/day) of TTP was started to the patient. Plasma exchange and steroid treatments were continued for 17 days, but it could not be effective for complete therapy. For that reasons, we administered rituximab therapy, which was used standard intravenous infusion of 375 mg/m^2 each week for 4 weeks. After the second dose of the rituximab, resolution of clinical symptoms and hematological abnormalities was observed. She was treated without any sequel and two years after discharge, TTP remained in remission.

CASE 2

A 44 years old female patient admitted to the hematology polyclinic with peteschial and ecchymotic rash all over the body which started a week ago and became more frequently. Her past medical history; she was suffering from type 2 diabetes mellitus and hyperlipidemia who has been using 1000 mg

metformin therapy twice a day and atorvastatin therapy 20 mg a day.

Upon physical examination, we noticed that peteschial and ecchymotic rash all over the body especially on the lower extremities. She was slightly pale and appeared jaundiced. Except for a slightly elevated temperature of 38 ^{0}C, her vital signs were normal. Examination of her other systems were unremarkable.

Initial laboratory tests revealed that total bilirubin: 3.6 mg/dL, direct bilirubin: 2.2 mg/dL, hemoglobin:8.9 g/dL, platelets: 22.000 per millimeter, reticulocytes: 9.4%, LDH: 1100 U/L, aPTT: 32 seconds, INR:1.8, bleeding time: 8 minutes, clothing time: 5 minutes, direct coombs test: negative, anti-nuclear antibody: negative .

Blood urea nitrogen (BUN) and creatinine were 46 mg/dL (normal range: 5-20) and 2.1 mg/dL (normal range: 0.5-1.3), respectively. Urinalysis revealed that proteinuria and hematuria. Schistocytes, anisopoikocytosis and fragmented red cells were seen on the peripheral blood smear.She has been diagnosed as TTP with all these clinical and laboratory findings.

The patient was hospitalized and plasma exchange daily and metyl prednisolone 80 mg/day were started to the patient. Plasma exchange and steroid treatments were continued for 14 days and she began to improve but it could not be effective for complete therapy. We administered rituximab therapy, method was described before. After the second dose of the rituximab, resolution of clinical symptoms and hematological abnormalities was observed similarly previous case. She was treated without any sequel and a year after discharge, TTP remained in remission.

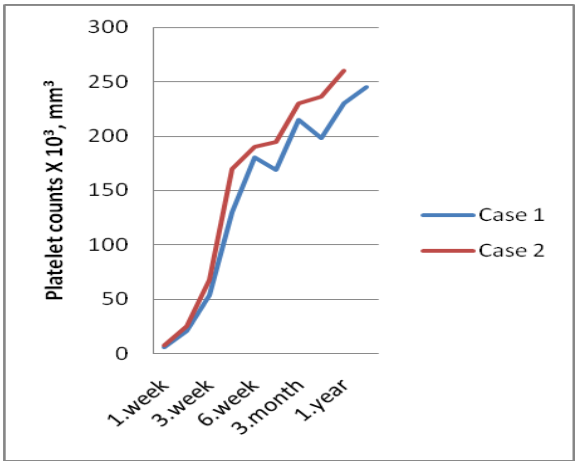

Figure 1. After administration of rituximab therapy platelet counts were shown in the figure for the both cases.

DISCUSSION

As the diagnosis and treatment of TTP is still a challenge, it causes vital results. For that reason early diagnosis and appropriate treatment is crucial to prevent mortality and morbidity in TTP. Plasmapheresis is the most effective therapy of TTP which cures more than 80% of patients [18]. The principle of plasmapheresis is exchanging the plasma of patients with TTP. Plasma exchange is used to remove unwanted substances (antigen antibody complexes) from the blood. This treatment is repeated daily until blood tests show improvement.Also, plasma exchange is not a disease-modifying treatment. In some patients this treatment is not effective. Immune-suppressive therapy or splenectomy are used in patients with resistance TTP [19–21]. Herein we report two TTP patients who have resistance to conventional therapy. We treated them successfully by rituximab therapy four weekly-doses and nearly two years after discharge of the both patients, TTP remained in remission.

Rituximab is an important immune modulator therapy in certain autoimmune disorders. In literature, it has been reported that rituximab therapy is effective and safe for patients with refractory or relapse TTP. The response of rituximab therapy generally starts within one or two weeks after first administration [22–25]. After successful therapy of rituximab, duration of remission have been reported to vary between 6 and 15 months [25–27]. Our patients have been in remission for two years after rituximab therapy. There are two ways of using rituximab therapy for TTP; 1-Plasmapheresis is continued, with rituximab administered immediately following, 2-Rituximab administered weekly without plasmapheresis. In general, the former is used for treatment of TTP, but we used only rituximab therapy without plasmapheresis.

Cyclosporine, which is generally used in immunosuppression, is another option for TTP treatment in addition to plasmapheresis. But, the effect of cyclosporine takes time, nearly 3 weeks. For that reason, using of cyclosporine is limited on treatment of TTP [28–30]. It is more appropriate to use cyclosporine to prevent relapse in TTP patients who have gone into remission by plasmapheresis.

The mortality rate of TTP is approximately 20%, it is often a result of delay in diagnosis and administration of the appropriate therapy. Taken together, early use of rituximab with plasmaphresis may be efficacious in patients who have severe TTP and also it may be added to standard therapy of TTP as an adjuvant. It may be more effective than standard therapy to prevent potential mortality and morbidity.

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