# A SUCCESSFUL MULTIMODALITY TREATMENT IN A PATIENT WITH RESISTANT THROMBOTIC THROMBOCYTOPENIC PURPURA

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**Ö.Alpdoğan, M.D.*** / T.Budak Alpdoğan, M.D.*** / H.Direskeneli, M.D.**
M.Bayık, M.D.* / T.Akoğlu, M.D.***

* *Professor, Unit of Hematology-Immunology, Department of Internal Medicine, Faculty of Medicine, Marmara University, Istanbul, Turkey.*
** *Assistant Professor, Unit of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Marmara University, Istanbul, Turkey.*
*** *Resident, Unit of Hematology-Immunology, Department of Internal Medicine, Faculty of Medicine, Marmara University, Istanbul, Turkey*

## ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is still a life threatening disease, despite vast developments in treatment modalities. We report a case of severe TTP who did not respond to high dose intravenous steroids, plasmapheresis, defibrotide and splenectomy. However, after splenectomy with plasma replacement and intravenous immune globin infusion as a maintenance therapy, she improved and had durable complete remission. This observation led us to consider the importance of maintenance treatment in frequently relapsing TTP cases.

**Key Words:** Thrombotic thrombocytopenic purpura, Plasma infusion, Intravenous immune globulin

## INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a life threatening disease that presents itself clinically with thrombocytopenia, microangiopathic hemolytic anemia, fluctuating neurological symptoms, fever and renal insufficiency. The outcome of the disease has improved by 80-90% with current treatment modalities, especially, plasmapheresis and plasma infusions (1,2). However, some patients still remain resistant to initial therapy or they relapse in a few months (3-5).

We report a severe TTP case who was resistant to high-dose intravenous steroids, plasma exchange, defibrotide and splenectomy. She improved and had complete remission with plasma and high-dose intravenous immune globulin (IV Ig) infusions after splenectomy.

## CASE REPORT

A fifty year-old female was admitted with fatigue, petechia, headache, palpitation and numbness in her right side in January, 1994. In her past medical history there were two medical abortions due to intra-uterine fetal loss in 1965 and 1968. Preceeding symptoms as severe ecchymotic lesions, weakness, severe oedema with hypertension and convulsions had been observed in both intrauterine fetal losses. During those periods, she was said to have severe anemia and thrombocytopenia and was treated with whole fresh blood transfusions and corticosteroids (60 mg/d) with tapered doses for up to three months.

She had an attack of mild transient thrombocytopenia following an upper respiratory tract infection in 1989. Thrombocytopenia was considered to be due to concomitant antibiotic usage (TMP-SMX).

In June 1992, she developed severe symmetric polyarthritis affecting small joints of the hands and wrists, elbows and knees. Symyptoms disappeared with 20 mg/day prednisolone within three days. ANA and RF were all negative. Intermittent ecchymosis and purpuras developed later on and thrombocytopenia ($50.000/mm^3$) have been observed. She was given 40-60 mg/day prednisolone and since no improvement was observed, 200 mg/d azathioprine was started in November 1993. After five weeks she was hospitalised with dysartria, right-sided hemiparesia and facial palsy in a rheumatology clinic. She was normotensive, with no major neurological

deficit except dysartria and positive right Babinsky at that time. Laboratory results were as follows: Hgb:7.8 gr/dl, Hct;24%, Reticulocyte count; 3%, WBC; 12.600/mm$^3$, Platelet count; 22.000/mm$^3$, SGOT; 173 IU/L, SGPT; 103 IU/L, Alkaline Phosphatase; 89 IU/L, LDH; 1579 IU/L (N;<350), BUN; 24 mg/dl and Creatinine; 1.0 mg/dl. She was given pulse methylprednisolone 1 gm/day for 2 consecutive days and was transfused whole blood and platelets. Neurological symptoms completely resolved on the next day. Azathioprine was stopped and 500 mg pulse cyclophosphamide for every 15 days was started when the possibility of systemic lupus erythematosus (SLE) was raised.

A month later, on January 1994, she was hospitalised in our clinics after three cycles of pulse cyclophosphamide. Physical examination on admission revealed normal vital signs, cushingoid appearance and widespread petechial lesions. Neurological examination revealed loss of muscle strength in upper and lower extremities, 3/5 and 4/5 respectively. She had mild anemia (Hb- 11.4 g/dl), leukocytosis (WBC-22.000/mm$^3$) and prominent thrombocytopenia (Platelets-29.000/mm$^3$) Because of high reticulocyte count (4.2%) and fragmented erytrocytes, normoblasts, anlsocytosis and polychromasla on her peripheral blood smear, she was considered to have microangiopathic haemolytic anemia. Miidly elevated BUN (42 mg/dl), SGOT (52 IU/L), SGPT (70 IU/L) were also observed with markedly elevated LDH activity (2336 IU/L). ANA, antiglobulin tests, RF, anti-Sm, anti-Ro, anti-La, anti-RNP and anticardiolipin antibodies were all negative. She had a normocellular bone marrow with erythroid hyperplasia and normal megakaryocytes in her bone marrow aspiration.

TTP was diagnosed and pulse methylprednisolone therapy at a dosage of 2 g/d (30 mg/kg/d) was administered for 3 consecutive days and was continued with dose tapering as 1500mg/dx4 days and 1000 mg/dx4 days. Concomitantly, 1200 mg/d defibrotide was given intravenously. But no improvement was observed with that initial therapy and she began to have transient ischemic attacks. Plasmapheresis (2 lt/day) was performed for 5 days. All symptoms improved in the first 48 hours and normal hemoglobin and thrombocyte counts were obtained. But her symptoms recurred and remission was provided by a new course of plasmapheresis in six days and thereafter, urgent splenectomy was done as a salvage therapy. In six days after splenectomy her disease relapsed and a third course of plasmapheresis was performed. At the end of the plasmapheresis, she had 11.2 g/dl Hb, 34% Hct, and 710.000/mm$^3$ platelet count. After ten days thrombocytopenia, reticulocytosis and high LDH activity reappeared and another course of plasmapheresis, for five days, was performed. Her symptoms and microangiopathic hemolytic anemia resolved and on the last day of the plasmapheresis, intravenous immune globulin therapy (500 mg/kg/d) was started as a maintenance therapy, and was continued for subsequent five days. Afterwards the therapy was continued on weekly basis for two months with the same dosage. Plasma infusion therapy (10 ml/kg/day) was given concomitantly with Iv Ig therapy in the first five days and continued three times in a week during the first month and tapered to

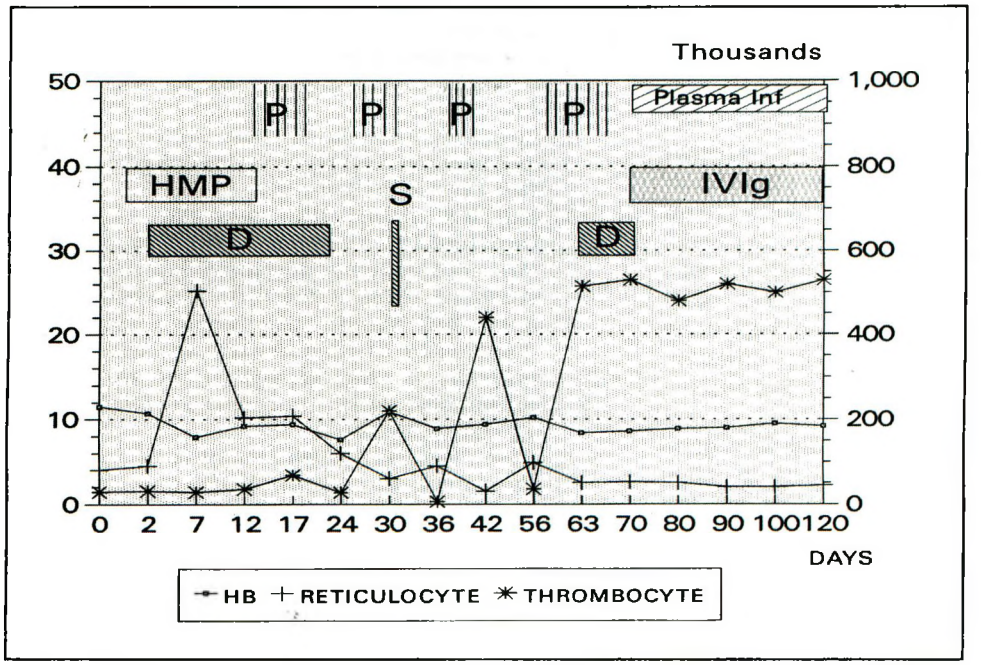


***Fig. 1:*** *Treatment courses and laboratory values. HMP; High dosage methylprednisolone, IVIg; Intravenous immune globulin, P; Plasmapheresis, S; Splenectomy, D; Defibrotide, HB; Hemoglobin, gr/dl*

two times in a week for the second month. After two months. maintenance therapy was stopped. Up to now, she has been followed, in complete remission, for 20 months (Fig. 1).

## DISCUSSION

The factors that trigger TTP include toxic agents, infections and drugs. Most of the patients do not have an apparent cause, however, some authors have reported in a rare group of patients a suggestive correlation with SLE (6). Though TTP and SLE have some similar features, such as thrombocytopenia, neurologic signs and renal disease, the extensive microangiopathic hemolysis in SLE has correlation with severe vasculitic episodes of SLE with extremely active disease. In the revlew of Stricker, 18 TTP cases correlated with SLE have been reported (6). Interestingly, most of the patients (15 of the cases had preceding SLE diagnosis, where eight cases had serologically inactive lupus at the time of TTP attack and all the active cases had positive serology. However, all patients who had serologically inactive SLE, had confirmed SLE diagnosis before the appearance of TTP. Our patient neither had positive serology at any period, nor had confirmed SLE diagnosis before the TTP attacks. Therefore, in our case correlation of the TTP attacks to SLE was considered to be suggestive.

Eventhough we were successful to stop the TTP attacks in our patient, we could hardly predict which modality of treatment had provided this result. As she remained unresponsive to initial treatment with high-dose methylprednisolone and had temporary improvement with plasmapheresis, somewhat experimental treatment modalities had been used.

Endothelial cell dysfunction has been proposed as a cause in the pathogenesis of TTP. Defibrotide is a new drug that modifies impaired endothelial cell function and increases tissue plasminogen activator (t-PA) and prostacycline ($PGI_2$) production while decreasing plasminogen activator inhibitor (PAI) levels. Also defibrotide has inhibitory effect on platelet functions and in animal models its antithrombotic effects have been demonstrated (7). We have prevlously reported a TTP case who had been successfully treated with defibrotide (8). However, defibrotide could not provide remission in this case.

Though splenectomy has been reported as a good treatment choice for patients resistant to initial treatment and has been shown to augment the response of the plasma exchange (9,10) in our patient following salvage splenectomy only a temporary remission with plasmapheresis was achieved.

In other two large series of TTP cases, plasma infusion or plasma exchange has been suggested to provide survival for 71% to 91% of patients (3,4). Considering the high relapse rate with conventional therapies, we planned to give maintenance therapy to our patient both with plasma infusions and IV Ig. Though intravenous immune globulin administration has not been accepted as a standard treatment for TTP, some authors have reported beneficial therapeutic effect of IV Ig (11,12). Prednisolone and immunsupressive drugs such as prednisolone and azathioprine provide remission in some relapsing patients. These observations suggest that autoantibodies against endothelial cells, or against the processing activity for unusually large von Willebrand factors may be involved in pathogenesis of the TTP (13). In correlation with that suggestion, we aimed to neutralise autoantibodies with Iv Ig and replace the abnormal plasma factors with plasma infusions through this maintenane therapy combination. Our patient appeared to have no autoreactive antibodies but her previous history of two thrombocytopenia attacks and symptoms of sero-negative arthritis were suggestive for autoreactivity. A few trials have assessed the value of Iv Ig usage in TTP for remission induction, however, no one has reported the role of IV Ig in preventing relapses. Relase rate has been defined as high as 37% in TTP and in those relapsing patients 17% mortality rate has been observed (5). Our maintenance therapy schedule appears to be effective for long-term remission of TTP in our case and has announced us a need for further investigation of the effect of IV Ig treatment, in preventing early relapses.

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