

## Thrombotic thrombocytopenic purpura concomitant with autoimmune thyroiditis

### *Trombotik trombositopenik purpura ile eş zamanlı otoimmün tiroidit*

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Geliş Tarihi / Received:04.04.2011, Kabul Tarihi / Accepted: 09.09.2011

#### ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is characterized by disseminated thrombotic occlusions located in the microcirculation, microangiopathic hemolytic anemia, thrombocytopenia, fever, and renal and neurologic abnormalities. A 14 year old girl admitted to our hospital complaining bruising on her body and prolonged menstrual bleeding. On her physical examination there were very common bruising on four extremities. On the laboratory studies, Hemoglobin was 9 g/dL; Hematocrit, 24%; white blood count 11600/mm<sup>3</sup> and thrombocyte count, 9.000/mm<sup>3</sup>. According to these findings our first diagnose was idiopathic thrombocytopenic purpura so intravenous immunoglobulin was given to patient for two days. Bone marrow aspiration was performed because of persisting thrombocytopenia despite two days IVIG therapy. Increased number of megakaryocytes was seen in bone marrow. Some accompanying symptoms like headache, numbness in per oral region and extremities, difficulty in speaking, and fluctuation in consciousness for short time occurred. The patient was reevaluated; because thrombocytopenia persisted and some neurological symptoms was observed. Due to these findings we thought that TTP was the diagnosed and plasma exchange was started. Increase was seen in platelet count in the second days of treatment. TTP should be considered in children presenting with atypical thrombocytopenia.

**Key words:** Thrombotic thrombocytopenic purpura, autoimmune thyroiditis, thrombocytopenia, adolescent

#### INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is rare disease characterized with fever, thrombocytopenia, microangiopathic hemolytic anemia, renal failure, and fluctuating neurologic impairment.<sup>1</sup>

#### ÖZET

Trombotik trombositopenik purpura (TTP); mikrosirkulasyonda lokalize yaygın trombotik tıkanıklıklar, mikroangiopatik hemolitik anemi, trombositopeni, ateş, renal ve nörolojik anormallikler ile karakterizedir. 14 yaşında kız hasta vücutta morluklar oluşması ve uzamış mens kanaması nedeniyle hastanemize başvurdu. Fizik muayenede 4 ekstremitede çok sayıda morluk vardı. Laboratuvar çalışmalarında hemoglobin 9 g/dl, hematokrit %24, beyaz küre sayısı 11.600/mm<sup>3</sup>, ve trombosit 9.000 mm<sup>3</sup> saptandı. Bu bulgulara göre ilk tanımız immune trombositopenik purpura oldu ve 2 gün intravenöz immunoglobulin (IVIG) verildi. İki günlük IVIG tedavisine rağmen trombositopeni devam edince kemik iliği aspirasyonu yapıldı. Artmış sayıda megakaryositler görüldü. Baş ağrısı, oral bölge ve ekstremitelerde uşuşma, konuşma güçlüğü ve kısa süreli bilinç kaybı gibi nörolojik bulgular oluştu. Trombositopeninin devam etmesi ve bazı nörolojik bulguların gözlenmesi nedeniyle hasta tekrar değerlendirildi. Bu bulgularla TTP tanısı kondu ve plazma değişimi tedavisi başlandı. Tedavinin ikinci gününde trombositlerde yükselme saptandı. Atipik trombositopeni ile başvuran çocuklarda TTP düşünülmelidir.

**Anahtar kelimeler:** Trombotik trombositopenik purpura, otoimmün tiroidit, trombositopeni, adolesan

TTP is first described by Moschowitz in 1924. Most cases of TTP are of the acquired idiopathic type that occurs abruptly in previously healthy individuals. It has an estimated annual incidence of 4-11 cases per million people in the United States, and oc-

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curs about 15-fold more frequently in adults than in children.<sup>2</sup> Thrombocyte and von Willebrand factor rich microthrombus formation in terminal arteriols and capillary vessels leads to ischemic changes in many organs especially in kidneys and brain. Anemia, thrombocytopenia, leukocytosis high levels of LDH, and reticulocytosis are the common laboratory findings in TTP.

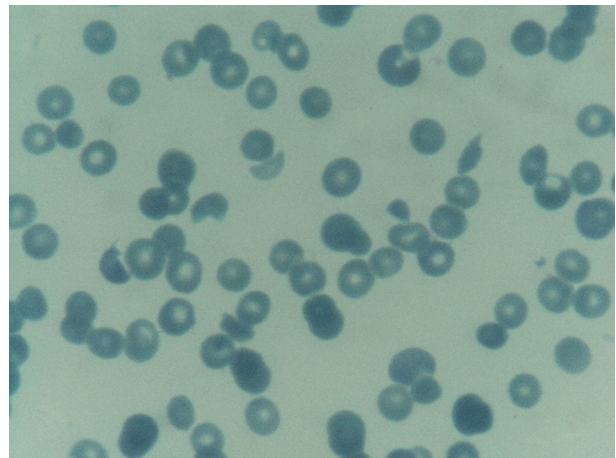
Thrombotic thrombocytopenic purpura can develop secondary to bacterial or viral infections, autoimmune disorders, malignancy, stem cell transplantation, or drugs.<sup>3</sup> In this report, we present a patient with TTP concomitant with autoimmune thyroiditis.

## CASE

A 14 year old girl admitted to our hospital complaining bruising on her body and prolonged menstrual bleeding. She had been in menstrual period over 14 days and had accompanying complaints like tremor, sleep disturbances for a week. Her previous medical history was normal including menstrual periods. On her physical examination, her body temperature was 37.5 °C; pulse, 82/min; respiratory rate, 20/min; and blood pressure, 100/60 mmHg. There were very common bruising on four extremities and paleness were noted. The rest of the examination was unremarkable. On her laboratory studies, her hemoglobin was 9 g/dL; hematocrit 24%; white blood count 11600/mm<sup>3</sup> with 72% neutrophils, 24% lymphocytes, and 4% monocyte; mean corpuscular volume, 82 fL; and thrombocyte count, 9.000/mm<sup>3</sup>. Her aspartate aminotransferase was 46 U/L (0-37); alanine aminotransferase, 44 U/L (0-41); lactic dehydrogenase 636 U/l (200-400), total bilirubin: 1,9 mg/dl, direct bilirubin:0,6 mg/dl, serum creatinin: 0.6mg/dl, blood urea nitrogen 36, reticulocyte 3,2%, and vitamin B12 140 pg/ml (180-987). Direct Coombs was negative. Other biochemical parameters and renal function tests were within normal range.

According to these findings our first diagnose was idiopathic thrombocytopenic purpura (ITP) so intravenous immunoglobulin (IVIg) was given to patient in a dose of 1g/kg/day for two days. Bone marrow aspiration was performed because of persisting thrombocytopenia despite two days IVIg therapy. Increased number of megakaryocytes were seen in bone marrow. Pulse steroid therapy was started (30mg/kg/day for 3 days and 20 mg/kg/

day for 4 days) but no increase was documented in platelet count. Some accompanying symptoms like headache, numbness in per oral region and extremities, difficulty in speaking, and fluctuation in consciousness for short time occurred. No pathological finding was seen on cranial computerized tomography. Although thyroid hormone values were normal, thyroid peroxidase antibodies (anti-TPO), and anti-thyroglobulin antibody (anti-TG) were found to be 50.12 IU/mL (N: 0.00-5.61 IU/mL) and 77.6 IU/mL (N: 0-4.11 IU/mL), respectively. Thyroid ultrasonographic examination revealed hypoechogenic areas and heterogeneity due to these hypoechogenic areas. No medication just follow up was recommended for autoimmune thyroiditis by pediatric endocrinology department. Serological tests for brucella, salmonella, lupus anticoagulants, antinuclear antibody, anticardiolipin antibodies, immunoglobulin G (IgG), and immunoglobulin M (IgM), cytomegalovirus, rubella, toxoplasma, hepatitis A, B, C, human immune deficiency virus, Epstein-Barr virus, and parvovirus were negative.



**Picture 1.** Fragmented erythrocyte was seen on peripheral smear

The patient was reevaluated; because thrombocytopenia persisted and elevation of LDH and bilirubin levels was continued. Ten percent of fragmented erythrocyte was seen on peripheral smear (Picture 1). Due to these findings we thought that TTP was the diagnosis and plasma exchange (PE) was started. Increase was seen in platelet count in the second and third days of treatment (60000/mm<sup>3</sup> and 262000 /mm<sup>3</sup> respectively). Frequency of PE was decreased to twice a week after first week but because of recurrence of thrombocytopenia

switched back to daily PE for 20 days. In follow up platelet count came to normal range, general condition of patient became better so the patient was discharged. On the 6 months follow up period no recurrence was observed and her thyroid hormone values were normal.

## DISCUSSION

TTP can be diagnosed with pentad of thrombocytopenia, neurological impairment (convulsion, coma, fluctuation in consciousness), microangiopathic hemolytic anemia, fever, and renal failure.<sup>1</sup> But currently, there is no necessity to see all criteria together. Thrombocytopenia and microangiopathic hemolytic anemia that can not be explained otherwise are enough to presumptive diagnose of TTP.<sup>4</sup>

Clinical presentation of TTP is rather non-specific and highly variable as it is related to the location of microvascular thrombi. Patients usually come to hospital with symptoms of arthralgia, fatigue, neurologic impairment, and accompanying renal failure. A significant number of patients have mild symptoms for several weeks before diagnosis.<sup>2</sup> TTP may be associated with autoimmune diseases. In a previous study Horton et al<sup>3</sup> reported seven patients with TTP and three of the seven patients had associated autoimmune diseases (thyroiditis, diabetes mellitus, and glomerulonephritis). Our patient also had associated autoimmune thyroiditis (AT) and this is the second case report with AT associated with TTP in the literature.

TTP is a rare occurrence in children who present with thrombocytopenia and can be confused with other thrombocytopenic disorders such as immune thrombocytopenic purpura, Evans syndrome, and hemolytic-uremic syndrome.<sup>4</sup> The distinction between TTP and other causes of acquired thrombocytopenia is crucial since many patients may have initially diagnosed with illnesses other than TTP. In one study, Horton et al<sup>3</sup> reported a series of seven children with suspected acquired TTP. Five of the seven children were initially diagnosed with illnesses other than TTP, including idiopathic thrombocytopenic purpura<sup>2</sup>, hemolytic-uremic syndrome<sup>1</sup>, and Evans syndrome.<sup>2</sup>

Our patient presented with prolonged menstrual bleeding and bruising on her body. First, the patient was diagnosed with ITP. Therefore, the patient was

given IVIG treatment. Red blood cell morphology could not be evaluated exactly due to bad staining in the first blood smear of the patient. High reticulocyte count was attributed to prolonged menstrual bleeding. Due to exacerbation of neurological symptoms, and continuation of thrombocytopenia, the patient was re-evaluated and fragmented erythrocyte was seen on peripheral smear.

TTP is characterized by deficiency of the von Willebrand factor (vWF) cleaving protease ADAMTS13.<sup>5</sup> Accumulation of ultralarge vWF multimers leads to excessive platelet aggregation and microvascular thrombosis with associated end organ damage. Severe ADAMTS13 deficiency (activity less than 5%) appears to be specific for acquired idiopathic TTP.<sup>2</sup> Most patients with acquired idiopathic TTP have antibody-mediated inhibition of ADAMTS13 which is usually due to IgG. Unfortunately, we could not measure plasma ADAMTS13 activity due to technical insufficiency.

In children, the distinction between HUS and TTP may be of more importance as general supportive measures, with dialysis is required. Standard therapy is dialysis in HUS and plasma exchange in TTP. Clinical differentiation of HUS and TTP can be problematic and differentiation is often based on the presence of CNS involvement in TTP and the more severe renal involvement in HUS. In HUS, an antecedent history of diarrheal illness is more often present.

PE therapy is the only efficacious treatment method in TTP.<sup>6</sup> It removes circulating ULVWF multimers with attached platelets as well as pathogenic autoantibodies. Fresh frozen plasma infusion is a choice of initial treatment when PE is unavailable. It is not precisely documented how long or how often PE has to be done for TTP patients. But continuation of PE is recommended until platelets count comes back to normal range. Also continuation of PE at least for 2 days after stabilization of platelet count levels is recommended.

In conclusion, our case is the second pediatric case of TTP associated with AT. TTP should be considered in children presenting with atypical diagnoses of idiopathic thrombocytopenic purpura.

**REFERENCES**

1. McDonald V, Liesner R, Grainger J, et al. Acquired, non-congenital thrombotic thrombocytopenic purpura in children and adolescents: clinical management and the use of ADAMTS 13 assays. *Blood Coagul Fibrinolysis*. 2010; 21(3):245-50.
2. Terrell DR, Williams LA, Vesely SK, et al. The incidence of thrombotic thrombocytopenic purpura-hemolytic syndrome: All patients, idiopathic patients, and patients with severe ADAMTS13 deficiency. *J Thromb Haemost* 2005;3(7):1432-6.
3. Horton TM, Stone JD, Yee D, et al. Case series of thrombotic thrombocytopenic purpura in children and adolescents. *J Pediatr Hematol Oncol* 2003(4);25:336-339.
4. Bouw MC, Dors N, van Ommen H, Ramakers-van Woerden NL. Thrombotic thrombocytopenic purpura in childhood. *Pediatr Blood Cancer* 2009;53(4):537-42.
5. Akbayram S, Dogan M, Peker E et al. Thrombotic thrombocytopenic purpura in a case of brucellosis *Clin Appl Thromb Hemost* 2011;17(3):245-7.
6. Clark WF, Rock GA, Buskard N, et al. Therapeutic plasma exchange: An update from the Canadian Apheresis Group. *Ann Intern Med* 1999;131(6):453-462.