

# Thrombotic Thrombocytopenic Purpura Associated With Graves' Disease

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## ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is characterized by microangiopathic hemolytic anemia and thrombocytopenia, usually accompanied by fever, renal failure and neurological deficits. TTP usually occurs in previously healthy people, but in a significant number of cases, the syndrome is associated with autoimmune disorders. We report a case of a 53 year old male patient suffering from TTP associated with Graves' disease (GD). After the diagnosis of TTP and Graves' disease plasmapheresis and antithyroid therapy were initiated. After the 15th seans of plasmapheresis, complaints were dissolved and hematologic parameters were recovered. This case draws the reader's attention to a rare condition that TTP associated with GD. Although immune thrombocytopenic purpura (ITP) and pernicious anemia must be initially considered in the event that thrombocytopenia accompanies to GD, TTP is likely in the presence of microangiopathy. The presence of microangiopathic haemolytic anemia and thrombocytopenia is sufficient for the diagnosis of TTP, thus prompt diagnosis and appropriate therapy is crucial for TTP.

**Key Words:** Thrombotic thrombocytopenic purpura, Graves' disease, Thrombocytopenia

## ÖZET

### Graves Hastalığına Bağlı Trombotik Trombositopenik Purpura

Trombotik trombositopenik purpura (TTP), mikroanjiopatik hemolitik anemi, trombositopeni, ateş, böbrek yetmezliği ve nörolojik bulgularla karakterizetir. Öncelikle sağlıklı erişkinlerde ortaya çıkmasına karşın çeşitli otoimmün hastalıklara eşlik ettiği bildirilmiştir. Burada Graves hastalığına eşlik eden TTP tanısı koyduğumuz 53 yaşında erkek hasta bildirildi. Olguya Graves hastalığına eşlik eden TTP tanısını konduktan sonra 15 seans plazmaferez uygulandı. Plazmaferezi takiben hastanın şikayetleri ve hematolojik parametreleri tamamen düzeldi. Graves hastalığına eşlik eden trombositopeni varlığında pernisiyöz anemi ve immün trombositopenik purpura öncelikle akla gelmelidir. Buna karşın trombositopeniye mikroanjiopatik hemolitik anemi eşlik ediyorsa TTP'de ayırıcı tanıda düşünülmelidir. Trombositopeniye eşlik eden mikroanjiopatik hemolitik anemi TTP tanısı için yeterli olduğundan acilen plazmafereze başlanması gerekmektedir.

**Anahtar Kelimeler:** Trombotik trombositopenik purpura, Graves hastalığı, Trombositopeni

## INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is characterized by microangiopathic hemolytic anemia and thrombocytopenia, usually accompanied by fever, renal failure, and neurological deficits (1). The presence of microangiopathic haemolytic anemia and thrombocytopenia is sufficient for the diagnosis of TTP (2), as not the other features are always present at the diagnosis. Ridolfi and Bell reported that 74% of patients had the triad consisting of anemia, thrombocytopenia, and neurologic disorders and only 40% of the patients had the full pentad of features (3). Without treatment, TTP has a mortality rate in excess of 80% due to multi-organ failure. Infections, malignancies, medications and autoimmune diseases are known to precipitate TTP (4). In most patient with familial or acquired types of TTP, plasma ADAMTS 13 activity is less than 5 percent of normal. The activity is normally after recovery. IgG antibodies that inhibit enzyme activity in plasma are found in 48 to 80 percent of this patients (5). Graves' disease (GD) is an autoimmune thyroid disease that occur as a result of an immune response directed against the thyroid gland. GD is characterized clinically by hyperthyroidism, diffuse goitre, ophthalmopathy and pretibial myxedema (6).

We report a case of 53 years old male patient suffering from TTP associated with GD that no other case report detected according to our screening.

## CASE REPORT

53 years old male patient was suffering from weight loss, nervousness, insomnia and palpitation for 2 months. 3 days before the hospitalisation fatigue, vertigo, nausea-vomiting and dispne initiated. He had a history of pulmonary tuberculosis 4 years ago. No regular drug habitude was present at the initial evaluation. On examination, the patient was agitated and confused. Mild jaundice, conjunctival pallor and bilateral petechias in lower extremities were present. Fine tremor, moisty skin, exophthalmos and fine hair were other signs which suggests the presence of Graves' disease. In laboratory examination; WBC: 13.000/mm<sup>3</sup>, Neu: 6.360/mm<sup>3</sup>, RBC: 2.310.000/mm<sup>3</sup>, Hgb: 7.31 g/dl, Hct: 20.4%, Plt: 18.000/mm<sup>3</sup>. Microangiopathic changes and normoblasts were detected in blood smear.

Urea: 101 mg/dl, creatinine: 0.89 mg/dl, total bilirubine: 7.04 mg/dl, indirect bilirubine: 5.74 mg/dl, LDH: 3093 U/L, direct and indirect Coomb's test were negative. Thyroid hormones: TSH: 0.097 uIU/ml, TT3: 3.31 ng/ml, TT4: 24.86 ug/dl, fT3: 1.52 ng/dl, fT4: 7.77 ng/dl. Bilateral diffuse goitre, increased vascularity and hyperdynamic circulation were evident in thyroid doppler ultrasonography. Anti-TPO, antithyroglobuline and anti-TSH receptor antibodies were positive. The diagnosis of TTP and hyperthyroidism due to Graves' disease was established. Plasmapheresis and antithyroid therapy were initiated. In the second seans of plasmapheresis, unconsciousness regressed. After the 15th seans of plasmapheresis, complaints were dissolved and hematologic parameters were recovered.

## DISCUSSION

TTP is a rare, life-threatening syndrome characterized by the classic pentad of clinical features that includes microangiopathic hemolytic anemia, thrombocytopenia, neurologic abnormalities, fever and renal dysfunction (1,4,7). Usually occurs in young females at a rate of 3.7-11.29 in 1.000.000 and has a peak incidence in the fourth decade (1,8-9). Infections, malignancies, medications, and autoimmune diseases are known to precipitate TTP (4). Patient with TTP have a deficiency in spesific protease, named ADAMTS-13, which normally degrades large von Willebrand factor (vWF) multimers into smaller forms in the peripheral circulation. The accumulation of unusually large vWF multimers in TTP promotes abnormal platelet aggregation, resulting in microvascular thrombi and occlusions that may affect numerous organs (1,4,5). There is a increasing evidence that immunological mechanisms play a role in the pathogenesis of TTP. Inhibitory IgG-subtype autoantibodies against to vWF-cleaving protease have been seen in TTP patients as well as antibodies to platelets and endothelial cells (5,10,11). Immunosuppressive therapeutic approaches have been tried in refractory TTP patients, including high-dose immunoglobulin, cyclosporine, splenectomy, chemotherapy and rituximab (1). TTP usually occurs in previously healthy people, but in a significant number of cases, the syndrome is associat-

ed with autoimmune disorders, including systemic lupus erythematosus (12), scleroderma (13), mixed connective tissue disease (14), polymyositis (15), antiphospholipid syndrome (16).

Graves' disease is an autoimmune thyroid diseases that occur as a result of an immune response directed against the thyroid glands. There are increased frequencies of many non-thyroid autoantibodies in thyroid patients, including autoantibody against p53, actin, tubulin, myosin, parietal cell, intrinsic factor, adrenal cortex, mitochondrial, anticardiolipin antibodies, antinuclear antibodies (6,17). The association of thrombocytopenia with autoimmune thyroid disease has been recognized in adult patients (18-19). The reduction in platelet count may be noticed concurrently at the time of diagnosis of the thyroid disorder, precede the thyroid disease or occur during relaps of the thyrotoxicosis. The pathogenesis of thrombocytopenia in patients with Graves' disease is unclear (20). In 1940, Woodruff reported a 14% prevalence of thrombocytopenia in thyrotoxic patients. Six years later, Bechgaard studied hemostatic function in 50 patients with thyrotoxicosis. Ten percent of patients were thrombocytopenic, 16% had prolonged bleeding times and 33% had excessive bleeding during thyroidectomy. Of further interest were the observations of Branehog and colleagues who noted 12% of incidence of thyroid disease in 110 patients with idiopathic thrombocytopenic purpura. Similar observation noted by Marshal and coworkers who reported a frequency of 14% (21).

## CONCLUSION

In our screening, no other report that mentions the association of GD and TTP was detected. Both of the disorders have an autoimmune basis and usually accompany to other autoimmune disease, thus it was suggested that this association wasn't accidental. Although immune thrombocytopenic purpura (ITP) and pernicious anemia must be initially considered in the event that thrombocytopenia accompanies to Graves' disease, TTP is likely in the presence of microangiopathy. The presence of microangiopathic haemolytic anemia and thrombocytopenia is sufficient for the diagnosis of TTP (2), thus prompt diagnosis and appropriate therapy is crucial for TTP.

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