

CASE REPORT

Thrombotic thrombocytopenic purpura possibly triggered by Graves' disease

Saurabh D. Chitnis^{1,*}, Tuoyo O. Mene-Afejuku¹, Amandeep Aujla¹, Ahmed Shady¹, Gaby S. Gil¹, Eder Hans Cativo¹ and Andrea Popescu-Martinez²

¹Department of Internal Medicine, New York Medical College, Metropolitan Hospital Center, New York, NY, USA, and ²Division of Hematology and Oncology, Department of Internal Medicine, New York Medical College, Metropolitan Hospital Center, New York, NY, USA

*Correspondence address. Department of Internal Medicine, New York Medical College, Metropolitan Hospital Center, 1901 1st Avenue, New York, NY 10029, USA. Tel: +12133619700; E-mail: saurabhdchitnis@hotmail.com

Abstract

Thrombotic thrombocytopenic purpura (TTP) is a part of a spectrum of thrombotic microangiopathy syndromes which are mainly characterized by platelet aggregation causing microangiopathic hemolytic anemia, thrombocytopenia and microvascular occlusion. In literature, very few cases expressing a direct association between pre-existing Grave's disease and TTP have been described. A 37-year-old African-American woman with past medical history of Grave's disease and polysubstance abuse who presented with complaints of dyspnoea at rest and chest pain was diagnosed to have TTP on further evaluation. Patient also showed severely elevated thyroid hormones and suppressed thyroid stimulating hormone levels indicating severe thyrotoxicosis. Initiation of prompt management of TTP and thyrotoxicosis led to a favorable patient outcome. In conclusion, patients presenting with thyrotoxicosis, thrombocytopenia and microangiopathic hemolytic anemia without an alternative cause should be treated and screened for TTP due to the high fatality associated with untreated or untimely detection of this disease.

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a part of a spectrum of thrombotic microangiopathy (TMA) syndromes which are mainly characterized by platelet aggregation resulting in microangiopathic hemolytic anemia, thrombocytopenia and microvascular occlusion which may be associated with organ damage [1, 2]. TTP may be further classified based on etiology as either hereditary or acquired [1, 2]. Several etiologies have been proposed for acquired TTP but there are very few cases stating a direct association between pre-existing Grave's disease and TTP. TTP is a medical emergency and carries a very

high fatality rate of ~90% if undetected or untreated [3]. On the other hand, prompt initiation of therapy is associated with a low mortality rate of 10–20% [3, 4]. In view of the above stated prognosis of TTP, we present this case report to buttress the need for a high index of suspicion of TTP in the light of atypical predisposition such as Graves' disease.

CASE PRESENTATION

A 37-year-old African-American woman with past medical history of Grave's disease, bronchial asthma and polysubstance abuse was brought in by the emergency medical service on

Received: May 21, 2017. Revised: 0, 0. Accepted: July 26, 2017

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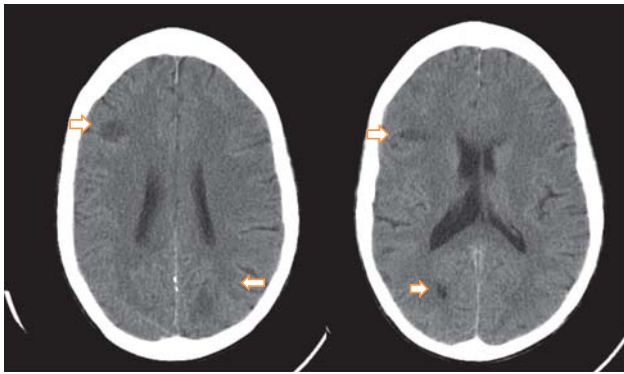


Figure 1: Brain CT revealing multiple bilateral areas of hypodensities (white arrows).

account of worsening dyspnea on exertion over three days that progressed to dyspnea at rest and wheezing. She also complained of retrosternal non-radiating chest pain lasting ~30 min that was associated with palpitations, dizziness and pre-syncope. Patient stated that she had not been adherent with her home medications and admitted to using multiple illicit drugs including 'ecstasy' a week before her admission. Examination revealed a cachectic looking female who was awake and cooperative but forgetful with stable blood pressure and mild tachycardia. She had decreased attention span but with intact remote memory and no obvious focal neurological deficits. She was also noted to be in mild respiratory distress with tachypnea but no desaturation. No lymphadenopathy, organomegaly or skin rash was noted. Initial laboratory tests demonstrated that severe anemia (hemoglobin 5.1 g/dl), thrombocytopenia (14 000/ μ l), elevated reticulocyte count (32%), elevated lactate dehydrogenase (LDH; 2024 units/l; reference range: 100–190 units/l) and decreased haptoglobin (<20 mg/dl; ref range: 34–200 mg/dl). Numerous schistocytes were seen on peripheral blood smear. Her renal function, electrolytes, coagulation profile and fibrinogen levels were within normal range. Cardiac troponins (7.5 ng/ml) were elevated without ischemic changes on electrocardiogram. Hemoglobin electrophoresis was normal. Urine toxicology screen was positive for multiple illicit drugs including opiates, benzodiazepines, heroin and methadone. Brain CT done on admission (Fig. 1) showed several multiple bilateral areas of hypodense lesions suggestive of a possible embolic process. Peripheral smear was negative for blasts. Based on these findings, presumptive diagnosis of TMA was made. Management for possible TTP in the intensive care unit was initiated with daily plasma exchange (PEX) and intravenous methylprednisolone. Drug-induced TMA (DITMA) due to the multiple illicit drugs used was also taken into consideration. On presentation, patient was also noted to have very low thyroid stimulating hormone (TSH; <0.01 μ l U/ml; ref range 0.27–4.20 μ l U/ml) as well as elevated triiodothyronine (T3) and thyroxine (T4) (10.48 pg/ml; reference range: 1.80–4.60 and 3.8 pg/ml; reference range: 0.9–1.8 pg/ml, respectively) indicating severe thyrotoxicosis. Thyroid ultrasound revealed features of nodular Graves' disease. Management with methimazole was started. Patient's mental status improved gradually with the management of the TTP. Brain MRI was refused by the patient.

The initial markedly elevated troponins (7.5 ng/ml) trended down to 1.1ng/ml over a period of 5 days. The constellation of anemia and thyrotoxicosis was thought to be the major etiology for the patient's elevated troponins. Type 2 non-ST elevation myocardial infarction was suggested in the setting of the patient's hyperdynamic state with associated myocardial

oxygen supply and demand discrepancy. After therapy with PEX and steroids was initiated, ADAMTS13 was reported as severely diminished at <5% and the presence of ADAMTS13 inhibitor was also noted. Patient was also negative for human immunodeficiency virus, hepatitis B, hepatitis C and she was not pregnant. Complement levels (C3, C4 and CH50) were normal, stool for Shiga toxin was negative, cold agglutinins, anti-nuclear antibody and double stranded-DNA antibody were also negative thus ruling out other etiologies of TMA. Hence, the diagnosis of acquired TTP was confirmed.

Patient was noted to be responding to PEX but her course was complicated with Ludwig's angina that was associated with a concomitant fall in platelet levels. Patient was started on ampicillin/sulbactam and vancomycin and the swelling resolved after she completed the 10 day antibiotics course. PEX sessions were continued uninterrupted during this event. Patient had a total of 24 sessions of PEX with steroid therapy throughout her hospital course. She was discharged after her platelet count improved to 242 000/ μ l and remained stable after PEX was terminated. Oral prednisone with slow taper and anti-thyroid medications were to be continued on discharge. Thyroid scan was scheduled post-discharge after resolution of TTP. Patient was deemed lost to follow-up after multiple attempts to reach her were unsuccessful.

DISCUSSION

TTP is a rare disease (5–10 cases per million persons per year) and occurs two to three times in females than males [5, 6]. TTP is characterized by the massive formation of platelet rich thrombi in the microcirculation of multiple organs [5].

The presence of the classic pentad of thrombocytopenia, microangiopathic hemolytic anemia, abnormal neurological findings, renal damage and fever, are no longer required for diagnosis of TTP [5, 6]. The current theory is that the presence of microangiopathic hemolytic anemia and thrombocytopenia without an alternative cause are enough to arouse a suspicion of TTP [1]. TTP is also unique when compared to the other TMA syndromes through the lack of association with kidney injury [1]. Also, TMA with severe ADAMTS13 deficiency typically <10% and the presence of an inhibitor represents acquired TTP [1].

The definition of TMA syndromes has currently evolved with respect of the possible etiology and classified as follows; acquired TTP, hereditary TTP, Shiga toxin-mediated hemolytic uremic syndrome (ST-HUS), complement-mediated HUS, DITMA and other rare inherited TMA syndromes [1].

Graves' disease is an autoimmune condition characterized by a unique antibody production that results in increased thyroxine production and subsequent thyrotoxicosis [6]. Graves' disease is the commonest cause of hyperthyroidism in developed countries [6]. The association between Graves' disease and TTP is very rare and has been reported only in a few case reports [7–10]. We postulate based on these reports [7–10] and our case presentation, that there may be a direct correlation between poorly treated hyperthyroidism and TTP. Zheng et al. [7] Chhabra and Tenorio [8] as well as Bellante et al. [9] reported that severely diminished ADAMTS13 activity and the presence of a specific ADAMTS13 inhibitor which is in consonance with findings in our patient. Bellante et al. [9] noted in particular that their patient had no TTP relapse at 6 months of follow-up following thyroidectomy. There may be an association between TTP and Graves' disease as reports have implied that pre-existing autoimmune disease may predispose to the occurrence of another autoimmune disease [10].

Though brain CT findings and altered sensorium were notable in our patient, she did not show any significant neurological

deficit in contrast to that reported Bellante *et al.* [7]. The mild and transient neurological finding in our patient was, however, in consonance with what has been reported by other researchers [7, 8]. This may indicate that in the majority of cases, TTP may be not be associated with severe neurological features.

DITMA was initially considered to have been contributory to the development of TTP in our case presentation because of the patient's documented evidence of polysubstance abuse. However, there is no reported case of drug-dependent inhibition of ADAMTS13 [11, 12]. The presence of ADAMTS13 inhibitor and low ADAMTS13 activity in our case presentation makes DITMA very unlikely.

CONCLUSION

Patients presenting with thyrotoxicosis, thrombocytopenia and microangiopathic hemolytic anemia without an alternative cause should be treated and screened for TTP due to the high fatality associated with untreated or untimely detection of this disease. Prompt therapy is associated with a favorable outcome.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

- George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med* 2014;**371**:654–66.
- George JN, Cuker A. Acquired TTP: Clinical Manifestations and Diagnosis. www.uptodate.com/contents/acquired-ttp-clinical-manifestations-and-diagnosis.
- Scully M, Hunt BJ, Benjamin S, Liesner R, Rose P, Peyvandi F, *et al.* Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *Br J Haematol* 2012;**158**:323–35.
- Appel GB. Thrombotic microangiopathies: similar presentations, different therapies. *Cleve Clin J Med* 2017;**84**:114–6, 126–130.
- Franchini M, Mannucci PM. Advantages and limits of ADAMTS13 testing in thrombotic thrombocytopenic purpura. *Blood Transfus* 2008;**6**:127–35.
- Girgis CM, Champion BL, Wall JR. Current concepts in Graves' disease. *Ther Adv Endocrinol Metab* 2011;**2**:135–44.
- Zheng WL, Zhang GS, Deng MY. Thrombotic thrombocytopenic purpura complicating Grave's disease: dramatic response to plasma exchange and infusion. *Transfus Med* 2011;**21**:354–5.
- Chhabra S, Tenorio G. Thrombotic thrombocytopenic purpura precipitated by Thyrotoxicosis. *J Clin Apher* 2012;**27**:265–6.
- Bellante F, Redondo SF, Springael C, Dethy S. Stroke in thrombotic thrombocytopenic purpura induced by thyrotoxicosis: a case report. *J Stroke Cerebrovasc Dis* 2014;**23**:1744–6.
- Chaar BT, Kudva GC, Olsen TJ, Silverberg AB, Grossman BJ. Thrombotic thrombocytopenic purpura and Graves disease. *Am J Med Sci* 2007;**334**:133–5.
- Al-Nouri ZL, Reese JA, Terrell DR, Vesely SK, George JN. Drug induced thrombotic microangiopathy: systematic review of published reports. *Blood* 2015;**125**:616–8.
- Reese JA, Bougie DW, Curtis BR, Terrell DR, Vesely SK, Aster RH, *et al.* Drug induced thrombotic microangiopathy: experience of Oklahoma registry and Bloodcenter of Wisconsin. *Am J Hematol* 2015;**90**:406–10.