DE GRUYTER OPEN

ENDOCRINE REGULATIONS, Vol. 51, No. 3, 153–156, 2017

doi:10.1515/enr-2017-0016

Using plasma exchange to successfully manage thyrotoxicosis in a patient with possible antithyroid drug-related thrombotic thrombocytopenic purpura

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Objective. Thrombotic thrombocytopenic purpura (TTP) is a rare disease characterized by microangiopathic hemolytic anemia, thrombocytopenic purpura, neurologic abnormalities, fever, and renal insufficiency. The association or co-existence of thyrotoxicosis or antithyroid drugs with TTP has not been previously reported.

Subject and Results. Herein, we present a 54-year-old female patient newly diagnosed with toxic multinodular goiter accompanying with TTP, possibly triggered by either thyrotoxicosis or antithyroid drugs.

Conclusions. The present report is the first in the literature to demonstrate the co-existence of these two diseases and the use of plasma exchange as a modality to treat both conditions.

Key words: toxic multinodular goiter, methimazole, thrombotic thrombocytopenic purpura, thyrotoxicosis, plasma exchange

Thrombotic thrombocytopenic purpura (TTP) is a rare disease characterized by microangiopathic hemolytic anemia, thrombocytopenic purpura, neurologic abnormalities, fever, and renal insufficiency. The association or co-existence of thyrotoxicosis or antithyroid drugs with TTP has not been previously reported. The present report is the first in the literature to demonstrate the co-existence of these two diseases and the use of plasma exchange as a modality to treat both conditions.

Subject and Results

A 54-year-old female patient was presented to an Internal Medicine outpatient clinic with palpitations about a month ago. She had been experiencing palpitations for the last several months. Her other symptoms included episodes of excessive sweating and diarrhea. There was no history of accompanying hair loss, heat intolerance, irritability, muscle weakness, or weight loss. Physical examination revealed the following: body temperature = 36.3 °C, blood pressure = 118/71 mmHg, and heart rate = 117 beats per minute. Thyroid examination revealed multiple painless nodules. Routine blood tests revealed normal hemoglobin level 14.2 g/dl, and leukocyte and thrombocyte count of 9 800/mm^3 and 308 000/mm^3, respectively. Results of liver and kidney function tests were within normal ranges. The electrocardiogram revealed sinus tachycardia. Thyroid function test revealed thyrotoxicosis (Table 1). Moreover, findings of thyroid scintigraphy and ultrasonography indicated

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toxic multinodular goiter, and the test results for thyroid autoantibodies (Anti-TPO, Anti-hTG, and TSH receptor antibody) were negative. Consequently, she was diagnosed with toxic multinodular goiter and administered with propylthiouracil. Two weeks later, she consulted another physician for the second opinion who prescribed methimazole instead of propylthiouracil. No blood tests were conducted at that time.

One week later, she was admitted to our emergency room with disseminated purpura, altered consciousness, palpitations, and fever. She was in a disoriented and confused state. Physical examination revealed a temperature of 37.8 °C, blood pressure of 147/72 mmHg, and heart rate of 142 beats per minute. She could only respond to questions with inappropriate words and could only localize pain (Glasgow Coma Scale: eye: 3; verbal: 3; and motor: 5; 11/15). She had no history of recent immunization or infections. She had no other comorbid diseases other than hyperthyroidism. She was only using methimazole at the time of admission. Blood count revealed mild anemia (hemoglobin: 9.6 g/dl), normal leukocyte and neutrophil counts (7 300/mm^3 and 4 200/mm^3, respectively), and severe thrombocytopenia (13 000/mm^3). Blood chemistry revealed elevated creatinine (4.8 mg/dl) and lactate dehydrogenase (1.547 U/l). Peripheral blood smear revealed normocytic normochromic anemia with 5–6 shistocytes per high power field, normal leukocyte and granulocyte count, and severe thrombocytopenia. Prothrombin and activated partial thromboplastin times were normal. The patient was diagnosed with TTP and hospitalized. Investigations for autoimmune markers such as antinuclear antibodies and anti-ds DNA yielded negative results. ADAMTS13 activity assay showed reduced activity (0.8%) (reference range 40–130%), ADAMTS13 antigen level was 0.04 μg/ml (reference range 0.6–1.6 μg/ml), and the test for ADAMTS13 inhibitor was positive (76.48 U/ml) (positive: higher than 15 U/ml). Hence, the patient was diagnosed with acquired TTP. At the time of admission, her thyroid stimulating hormone (TSH) level was low, whereas free thyroxine (fT4) and free triiodothyronine (fT3) levels were elevated (Table 1). The electrocardiogram showed rapid ventricular response of arterial fibrillation, and therefore, beta blocker was administered. A daily plasma exchange (40 ml/kg) after administering 80 mg of methylprednisolone as premedication was initiated for the management of both TTP and hyperthyroidism.

During 7 weeks of plasma exchange, the patient did not develop any other symptoms of hyperthyroidism. After the first week of treatment, her platelet count gradually increased. On the 11th day of the treatment, the daily plasma exchange frequency doubled because of only partial improvement in her platelet count. After 7 weeks, the patient was in a remission from TTP, and plasma exchange was gradually stopped. Thyroid function test was still deranged with low TSH levels, and increased fT4 and fT3 levels. During follow-up, thyroid cancer was ruled out by fine-needle aspiration biopsies from non-functioning nodules. Radioactive iodine treatment (20 mCi) was administered and she was discharged without any complaints. At 3-months follow-up, she was in the remission from TTP but her thyroid function tests revealed subclinical hyperthyroidism (Table 1).

Discussion

Acquired TTP has a prevalence of 3 to 6 cases per million, and is more commonly observed in women in their fourth decade. TTP is characterized by microangiopathic hemolytic anemia, thrombocytopenic

Table 1
Thyroid function tests and thrombocyte count of the patient during follow up

Parameter	Diagnosis of toxic multinodular goiter	Diagnosis of TTP, Admission (3 weeks from hyperthyroidism)	TTP Remission (7 weeks from admission)	3 months after remission from TTP
TSH (0.35–5.5 mIU/ml)	0.01	0.01	0.01	0.01
Free T4 (0.72–1.56 ng/dl)	>10	3.28	2.70	1.14
Free T3 (1.8–4.6 pg/mL)	>20	16.3	11.7	4.6
Thrombocyte (150 000–450 000/mm^3)	308 000	8 000	306 000	359 000

Abbreviations: TTP – thrombotic thrombocytopenic purpura; TSH – thyroid stimulating hormone; T4 – thyroxine; T3 – triiodothyronine

purpura, neurologic abnormalities, fever, and renal insufficiency. The commonly involved organ systems include central nervous system (focal deficiencies, seizures, and altered consciousness), heart (angina, myocardial infarction, and cardiac insufficiency), kidneys (hypertension, proteinuria, and acute renal failure), and gastrointestinal tract (abdominal pain and mesenteric ischemia) (Mariotte and Veyradier 2015). Because of acute onset of symptoms, elevated lactate dehydrogenase level, anemia, severe thrombocytopenia, and shistocytes in blood smear along with microangiopathic hemolysis, a preliminary diagnosis of TTP was made. ADAMTS13 assay further confirmed TTP in this patient.

It is unclear what may trigger TTP, but certain factors which are known to play a role including pregnancy, drugs, solid organ and hematologic malignancies, infections (especially HIV), major surgery, and hematopoietic stem cell transplants (Kulaksizoglu et al. 2012; George and Cuker 2016). However, thyrotoxicosis has not been previously associated with the isolated thrombocytopenia or TTP.

Drugs may also trigger or be associated with TTP via immune or direct toxic mechanisms. Immune-mediated mechanisms may delay symptoms by as late as 3 weeks. Some chemotherapeutic agents such as gemcitabine, oxaliplatin, vincristine, cyclosporine, and other medication including trimethoprim-sulfamethoxazole, ticlopidine, clopidogrel, quinine, adalimumab, sirolimus, and drugs of abuse have been previously reported to be associated with TTP (Mariotte and Veyradier 2015; George and Cuker 2016). Methimazole administration and thyroid storm has been previously reported to be associated with disseminated intravascular coagulation and multi-organ failure (Kulaksizoglu et al. 2012). However, methimazole toxicity is usually characterized by agranulocytosis and leukopenia, which were not observed in our patient. In addition, neither methimazole nor propylthiouracil have been previously associated with TTP. In the present case, the Naranjo adverse drug reaction probability score for TTP being caused by antithyroid medications was "possible drug reaction" (Naranjo score: 4) (Naranjo et al. 1981). Therefore, in the present case, we suspected that TTP was either triggered by methimazole or the patient's hyperthyroidism.

Initial treatment options for severe thyrotoxicosis are supportive care, beta-blockers, antithyroid medications, and glucocorticoids (Papi et al. 2014). However, some clinical conditions may contraindicate antithyroid medication, surgery, or radioactive iodine for the definitive treatment of thyrotoxicosis. In the present case, we concluded that antithyroid medication was contraindicated owing to the suspicion of antithyroid medication triggered TTP. Radioactive iodine was contraindicated because its clearance during plasma exchange has not been well studied and it may be hazardous to health personnel. Lastly, surgery was contraindicated because of the patient's clinical condition. To prevent further clinical deterioration, the decision to perform rescue therapy was made.

In such extreme cases, when conventional treatment options fail, plasma exchange may be used as a life-saving and stabilizing option. In the "2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis", both plasmapheresis/plasma exchange and emergency surgery have been recognized as a treatment modality for thyroid storm in patients who respond poorly to traditional treatment (Ross et al. 2016). In addition, the "Society for Apheresis (ASFA) guidelines" also recommends the use of plasma exchange in severe thyrotoxicosis on case by case basis and should be considered after other conventional treatment methods have failed. The guideline notes the optimum role is not yet established (Schwartz et al. 2013).

Main goal of the plasma exchange in patients with severe thyrotoxicosis is to reduce circulating thyroid hormones to stabilize the patient's clinical condition. Plasma exchange removes both the free and bound thyroid hormones from circulation, as well as provides new binding sites for the freely circulating hormones. However, the plasma exchange has been previously reported to reduce the thyroid hormones only temporarily (Papi et al. 2014). There is also a limited and unclear literature regarding the requisite numbers of plasma exchange cycles and durations. In the present case, we experienced successful clinical stabilization plus a mild decrease in free thyroid hormones after plasma exchange and corticosteroid treatment, which may help to improve the overall clinical presentation.

Limitations in this case report are that we could not follow up the thyroxine binding globulin during plasma exchange, day-to-day measurements of thyroid hormones were not conducted, and a before-and-after measurement of thyroid hormones during plasma exchange was not done. The thyroid hormone measurements were also always taken before plasma exchange.

Herein, we presented a case of newly diagnosed toxic multinodular goiter accompanying with TTP, possibly triggered by either thyrotoxicosis or antithyroid drugs. We decided to manage the patient with

plasma exchange since surgery, radioactive iodine, and antithyroid medications were contraindicated. Plasma exchange acted as a curative modality for TTP and stabilizing option for thyrotoxicosis. It was not possible to differentiate between drug-induced or idiopathic TTP; however, the possibility of immune mediated drug-induced TTP is higher. Considering this case, clinicians should recognize antithyroid medications as a potential trigger for TTP and the successful use of plasma exchange as a rescue therapy if other main treatment modalities are unavailable or contraindicated.

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