Thrombotic thrombocytopenic purpura with Graves' disease during pregnancy

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ABSTRACT

Thrombotic thrombocytopenic purpura may be seen with several autoimmune disorders such as immune thrombocytopenia purpura, immune hemolytic anemia, and systemic lupus erythematosus, but it is rarely associated with Graves' disease. We report a patient with thrombotic thrombocytopenic purpura associated with Graves' disease.

KEYWORDS Graves' disease; plasma exchange; thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) is an uncommon disease with a high mortality. Most TTP cases are associated with autoantibodies to ADAMTS13, which normally degrades large, thrombogenic von Willebrand factor multimers. The loss of functional ADAMTS13 results in intravascular platelet aggregation and microangiopathic hemolytic anemia with associated hemorrhage. Plasma exchange is considered the mainstay of treatment; however, immunosuppressive therapies such as corticosteroids and rituximab are also used.¹ Graves' disease (GD) is another autoimmune disorder characterized by hyperthyroidism and diffuse hyperplasia associated with thyroid-stimulating hormone receptor autoantibodies. Management generally involves antithyroid medications, beta-blockers, radioiodine ablation, and surgery, but plasma exchange may also be effective.² We describe herein a pregnant woman with combined TTP and GD.

CASE DESCRIPTION

A 39-year-old morbidly obese woman (body mass index 42 kg/m²), who had had two previous full-term pregnancies, developed TTP while pregnant (ADAMTS13 activity <3 units with reference range of 68–163 units). Her mother had immune thrombocytopenic purpura (ITP) and her grandmother had systemic lupus erythematosus. Her platelet level on admission was 6000/μL, and her total 12-lead QRS voltage was 79 mm (standard 10 mm tracing). Her TTP initially responded to plasma exchange but quickly relapsed, prompting

a therapeutic abortion at 17 weeks' gestation. Unfortunately, TTP recurred weeks later despite the abortion, and it remained refractory to additional plasma exchanges. Terminally, she developed gastrointestinal hemorrhage and cardiac arrest.

The autopsy disclosed myocardial hemorrhage, most pronounced within the dilated right ventricular wall, the ventricular septum, and the right and left atrial walls (*Figure 1a*). The heart weighed 495 g. Occlusive platelet-rich microthrombi were present in the small arteries and arterioles of the myocardium (*Figure 1b*), the lungs, and the intestines. The thyroid gland was diffusely enlarged (weight 95 g). Histologically, the gland was composed of uniform admixtures of mainly hyperplastic follicles and scattered quiescent colloid-filled follicles with no normal parenchyma (*Figure 1c, 1d*).

DISCUSSION

Patients with an autoimmune disorder are at risk for additional autoimmune diseases, resulting in various combinations including immune-hemolytic anemia,³ systemic lupus erythematosus,⁴ Sjögren syndrome,⁵ systemic sclerosis,⁶ and others. However, we found only six reported cases of concomitant TTP and GD (*Table 1*),^{7–12} although several mechanisms have been proposed in which GD may be causally related to TTP.^{10,12}

The differential diagnosis for thrombocytopenia in pregnancy is broad and includes ITP, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), gestational

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Figure 1. (a) Multifocal myocardial hemorrhage. (b) Occlusive platelet-rich fibrin thrombi within small intramyocardial vessels (trichrome stain). (c) Uniform admixture of hyperplastic follicles and quiescent colloid-filled follicles with no normal parenchyma. (d) Follicular hyperplasia with papillary in-folding and colloid scalloping.

Table 1. Previous cases of concomitant thrombotic thrombocytopenic purpura and Graves' disease (all women)

Variable	Reference number						
	7	8	9	10	11	12 (case 1)	12 (case 2)
Age (years)	49	51	66	51	37	40	25
Pregnant	No*	No*	No*	No*	No*	No*	Relapsed**
TTP duration (days)	7	10	365	120	1	2190	1460
GD duration (days)	7	730	—	120	—	1	730

GD indicates Graves' disease; TTP, thrombotic thrombocytopenic purpura; —, no information available.

*Pregnancy not noted in case report.

**TTP relapsed after uneventful pregnancy.

thrombocytopenia, hemolytic-uremic syndrome, congenital TTP (Upshaw-Schulman syndrome), acquired TTP, and heparin-induced thrombocytopenia.¹³ Furthermore, the

occurrence of ITP and TTP is greatly increased during pregnancy. ITP complicates 1 in every 1000 to 10,000 pregnancies, accounting for 3% of all thrombocytopenic pregnancies, and pregnancy- or postpartum-related TTP accounts for 10% to 25% of all TTP cases. In addition, preexisting ITP is a known risk factor for developing TTP during pregnancy.¹⁴

Our patient had recurrent thrombocytopenia, and her ADAMTS13 level met the diagnostic criteria for TTP. However, the TTP subtype (congenital vs acquired) remains unknown since anti-ADAMTS13 IgG levels and genetic analysis were not performed.¹⁵

The uniform microscopic finding of hyperplastic follicles with scattered quiescent colloid follicles in a diffusely abnormal and enlarged thyroid is highly characteristic of partially treated GD (as opposed to nodular goiter, which exhibits areas of normal parenchyma). However, reliable postmortem serum tests for GD were not possible due to extensive plasma exchange therapy, and no thyroid function tests were available in the medical records. In addition, the plasma exchange

therapy for TTP resulted in inadvertent treatment of the GD, altering the histological appearance of the thyroid gland and probably masking other clinical features of GD.

Although combined TTP and GD is uncommon, patients diagnosed with GD who develop thrombocytopenia should be screened for TTP, due to the high mortality associated with delayed treatment of TTP. Conversely, clinical and laboratory evaluation for GD should be considered in patients with relapsed or refractory TTP, and obviously if they develop thyrotoxicosis.

Extremely low platelet levels, as seen in this patient, are known to cause intramyocardial hemorrhage,¹⁶ and myocardial ischemia due to platelet thrombi was contributory to this death. Also, pregnancy is clearly a trigger for the development of ITP and TTP,^{12,14,15,17} warranting a high index of suspicion in pregnant patients who develop thrombocytopenia.

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