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Case Report

Concurrent Immune Thrombocytopenic Purpura (ITP) and Thrombotic Thrombocytopenic Purpura (TTP) with Underlying Antiphospholipid Syndrome

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Abstract

Background: Immune Thrombocytopenic Purpura (ITP) and Thrombotic Thrombocytopenic Purpura (TTP) are both conditions that lead to thrombocytopenia. It is crucial to recognize TTP because it significantly impacts the treatment options and the prognosis. In clinical practice, both corticosteroids and rituximab can be utilized to treat ITP and TTP. However, plasma exchange therapy is the first-line treatment specifically for TTP, while corticosteroids are strongly recommended as the first-line treatment for ITP. Antiphospholipid syndrome is an autoimmune disorder resulting in a hypercoagulable state and is rarely reported with TTP.

Case Report: A 33-year-old woman with a history of chronic primary ITP presented in the second-trimester of pregnancy with HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome requiring an emergency cesarean delivery. Following the delivery, she required continued prednisone for treatment. Four years later, she presented with acute neurological deficits and a platelet count of 5,000 per microliter. A critically low activity of ADAMTS13 and the presence of autoantibodies targeting ADAMTS13 led to a definitive diagnosis of TTP. Despite her neurological deficits resolving within 45 minutes, a magnetic resonance imaging of her brain showed small subacute punctate ischemic strokes. Her labs were positive for antiphospholipid syndrome. She was treated with dexamethasone, intravenous immunoglobulin, plasmapheresis, rituximab, prednisone, low molecular weight heparin and caplacizumab-yhdp. She was discharged on warfarin for life.

Conclusion: Conducting systematic testing for ADAMTS13 activity and anti-ADAMTS13 antibodies in patients who exhibit neurological symptoms alongside thrombocytopenia while also screening for antiphospholipid antibodies may significantly enhance the diagnosis and management of this rare but serious combination of thrombotic conditions.

Keywords: Immune Thrombocytopenic Purpura D016553; Thrombotic Thrombocytopenic Purpura D011697; Antiphospholipid Syndrome D016736; HELLP Syndrome D017359

Introduction

Immune Thrombocytopenic Purpura (ITP) and Thrombotic Thrombocytopenic Purpura (TTP) are two distinct conditions that lead to thrombocytopenia. ITP is characterized by mucocutaneous bleeding and a platelet count of less than 100,000 platelets per cubic millimeter after excluding other known causes of thrombocytopenia. Primary ITP constitutes 80% of cases, while the remaining 20% are secondary to various other diseases, such as infections, autoimmune disorders, malignancies or primary immune deficiencies [1]. A large proportion of patients suffering from ITP demonstrate elevated levels of platelet-associated immunoglobulin G (IgG) and 57% have been shown to have increased levels of IgM on their platelets which can activate the complement system and initiate progressive platelet removal [1,2]. The prevalence of ITP in the adult population is

approximately 10 -12 per 100,000 persons per year, with approximately 80% having the chronic form [3].

TTP is a thrombotic microangiopathy that results from a severe deficiency of ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13), the von Willebrand Factor (vWF)-cleaving metalloproteinase. TTP is immune-mediated in 95% of the cases and leads to the formation of platelet-rich thrombi within the blood vessels [4-6]. These thrombi can lead to downstream ischemia and organ damage if not treated. TTP is a rare and life-threatening condition characterized by an average annual prevalence of approximately 10 cases per million individuals. The associated mortality rate of TTP ranges from 10% to 20% [5]. Recognizing TTP is essential for timely treatment and a favorable prognosis. In clinical practice, while corticosteroids and rituximab can be used to treat both immune ITP and TTP, Plasma Exchange Therapy (PEX) is considered the first-line treatment for TTP. In contrast, corticosteroids are strongly recommended as the first-line treatment for ITP [7]. Thus, distinguishing between ITP and TTP is crucial in clinical practice. While these conditions rarely occur together, prior case reports have indicated that ITP and TTP can coexist in individuals with Acquired Immune Deficiency Syndrome (AIDS), during pregnancy and in patients with Sjögren's syndrome [8].

Antiphospholipid Syndrome (APS) is an autoimmune disorder caused by a group of immunoglobulins targeted at phospholipids and phospholipid-binding proteins resulting in a hypercoagulable state. APS typically presents as unexplained thrombosis or an adverse pregnancy outcome secondary to a uteroplacental vascular disturbance. A diagnosis requires the presence of both laboratory and clinical features [9]. The presence of APS and TTP together is extremely rare [9]. We present a case of a single female patient suffering from three separate immune-mediated diseases that required treatment over a 9-year period.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

Case Presentation

A 33-year-old Caucasian female was found to have a low platelet count on a routine health check in 2014, with a baseline of 70-100 × 10^9/L (100 - 400 × 10^9/L). She did not require treatment until 2019 when she presented at 24 weeks gestation with a platelet count of 48,000 per microliter. She denied alcohol, tobacco, drug abuse, recent vaccination or travel. She stated she had never received a transfusion. To this point, her pregnancy had been uneventful, with no new dermatologic signs, joint manifestations, weight loss, fever, chills, sweating, nausea or vomiting or changed bowel habits. She was diagnosed with recurrent primary ITP and started on oral prednisone 20 mg daily. At that time, she did not meet the prerequisites for a diagnosis of HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count). She returned 3 days later and was admitted with elevated blood pressure, headache, elevated liver function tests (Table 1) and 1+ urine protein. She was diagnosed with HELLP syndrome and because a successful vaginal delivery was considered unlikely, a cesarean delivery was performed. Immediately following the Cesarean delivery, her liver enzymes improved, but her platelet count was noted to be < 11 × 10^9/L. A peripheral blood smear showed no evidence of schistocytes, which can occur with TTP-driven microangiopathic hemolytic anemia, but did show spherocytosis, which was consistent with immunologically mediated hemolytic anemia, especially since both direct and indirect Coombs tests were positive. At the time of the Cesarean, her hemoglobin was 10.5 g/dL (in women, a normal level range between 12.3 gm/dL and 15.3 gm/dL) (Table 1). An abdominal ultrasound was performed on post-op day 3 to rule out free fluid in the peritoneal cavity and it was unremarkable. The hepatitis panel was negative, as well as HIV Ag/Abs (antigen and antibody). The Antinuclear Antibody (ANA) was negative. Her international normalized ratio (INR) was 0.9 (0.8 - 1.2), Prothrombin Time (PT) was 9.8 seconds (11 - 13.5 seconds) and D dimer was elevated at 22,000 ng/mL (< 500 ng/mL of Fibrinogen-Equivalent Units (FEU). She had an unremarkable urinalysis and toxicology screening. The hematology department was consulted because of the chronic ITP and her bone marrow biopsy was normal except for low platelets. She was started on prednisone 60 mg PO, which resulted in improved LDH to 315 U/L, improved liver enzymes and a gradual increase of her platelet counts from the level of 11 × 10^9/L to 34 × 10^9/L. The patient was discharged on a tapered prednisone course for ITP treatment over 4 weeks and her platelet count notably improved to 120,000. She was followed by the hematology department as an outpatient.

Four years later, in 2023, the patient presented to the emergency department with a severe frontal headache associated with right-sided weakness and expressive aphasia that resolved within 45 minutes without residual deficit. She reported no head trauma or seizure activity. At that visit, her physical examination revealed a temperature of 37.3°C, BP (Blood Pressure) of 123/89,

HR (Heart Rate) of 92 bpm, regular and RR (Respiratory Rate) of 17/min. There were no hemorrhagic lesions on her skin or mucosal membranes, hepatomegaly, splenomegaly or lymph node enlargement. Her neurological examination did not show significant motor or sensory impairment. She had normal cranial nerve function and full muscle strength bilaterally. Her mental status was intact and there were no coordination issues. Before her labs and imaging returned, her differential diagnosis included transient ischemic attack, migraine aura, petit mal seizures, syncope or even hypoglycemia or anxiety. A computed Tomography (CT) was unremarkable. Her lab results revealed severe thrombocytopenia with normal electrolytes (Table 1). Her thrombogenic labs returned simultaneously, suggesting both elements of APS and TTP combined. She had positive lupus anticoagulant and anti-glycoprotein Abs, suggesting a diagnosis of APS. Her ADAMTS13 was <5% (50% - 160%) and positive ADAMTS13 Bethesda Titer at 1.4 (< 0.5 Bethesda unit), which indicated the presence of inhibitors, consistent with a diagnosis of TTP. Her direct Coombs was positive with C3 positive, suggesting the presence of an autoimmune hemolytic anemia. At this point, her working diagnosis included possible ischemic stroke with history and lab evidence of concurrent TTP, ITP and APS. She was admitted for a complete workup and treatment. Other lab results included normal iron, ferritin, B12 and folate. The level of Glucose-6-Phosphate (G6PD) was 13.2 units per gram of hemoglobin (8.6 - 18.6 units per gram of hemoglobin). Thyroid function was normal and the reticulocyte count was 2.5% (0.5% to 2.5%). She had an elevated PTT which is a hallmark of APS but not ITP or TTP, with a normal PT. The beta glycoprotein IgG, IgA and anti-cardiolipin Abs were persistently positive, confirming her APS. Her ANA, anti-U1-RNP, rheumatoid factors and anti-PF4 were negative, suggesting the absence of an active connective tissue disease. The investigations for biologic pathogens were negative. Her rheumatoid factor, anti-Cyclic Citrullinated Peptide (anti-CCP), Anti-Neutrophil Cytoplasmic Antibodies (ANCAs) and serum Angiotensin-Converting Enzyme (ACE) were negative. A Magnetic Resonance Imaging (MRI) of her brain showed small subacute cortical and subcortical ischemic punctate lesions (Fig. 1). A carotid Doppler showed left Internal Carotid Artery (ICA) stenosis of 50 to 69%, CT angiogram of the head and neck was unremarkable. A Transthoracic Echocardiogram (TTE) with bubble study was negative for Patent Foramen Ovale (PFO) detection and bilateral lower extremity and upper extremity doppler studies were negative for thromboembolic disease. An Electroencephalogram (EEG) was performed and did not show epileptiform foci. A lumbar puncture was performed and the Cerebrospinal Fluid (CSF) studies were unremarkable. The hematology department was consulted and plasma exchange was discussed. Ultimately, dexamethasone 40 mg x 4 days and Intravenous Immunoglobulin (IVIG) 1 g/kg x 2 days was given to treat all three active autoimmune-driven hematologic conditions. Because of suboptimal improvement in her platelet count from 5,000 to 13,000 daily, plasmapheresis was started along with Fresh Frozen Plasma (FFP) and fluid replacement for one week. This was followed by twice weekly for another week, daily caplacizumab-yhdp for 10 days and weekly rituximab for 2 weeks, along with a tapered course of prednisone started from 40 mg to 5 mg. These changes resulted in a marked improvement in her platelet count to a level of 200 -250 × 10^9/L within 2 weeks. A decision was made to start the patient on anticoagulant therapy with Low Molecular Weight Heparin (LMWH) with bridging to warfarin. The patient was discharged home following stabilization of her platelet count and complete resolution of her neurological complaint. She is on life-long warfarin and has regular follow up with her hematologist as an outpatient.

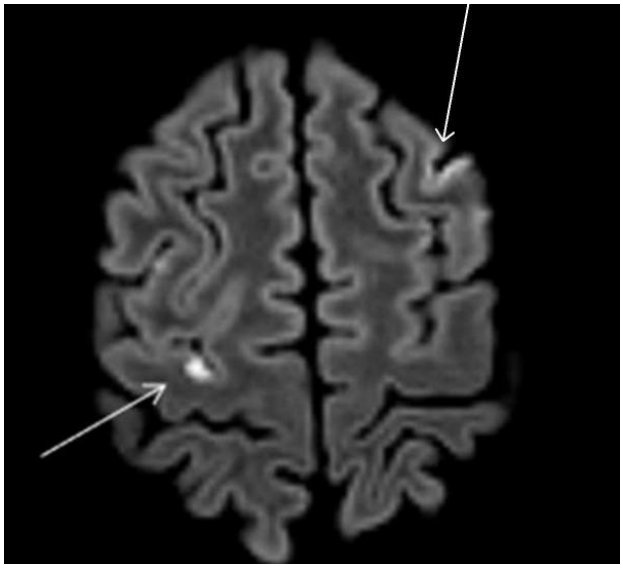

Figure 1: Magnetic Resonance Imaging (MRI) of a cross-section of the brain. The two white arrows show the small subacute cortical and subcortical ischemic punctate lesions.

Time	Normal lab values	2014	2019 - second trimester outpatient visit	Immediately before the operating room	In operating room at Cesarean	Periop erative	Post-op 1st blood draw 4 hours	Post-op 3rd blood draw 24 hours	Post-op 4th blood draw 36 hours		Post-op 8th draw 48 hrs	Post-op 4 weeks	2023		Two weeks after treatment started
Hemoglobin (g/dL)	Women -12.3 - 15.3 gm/dL	13.3		12.5	10.5		9.5	8.3	8.2				7.2		
White blood cell (cells/μL)	4,500 - 11,000 cells/μL	10,000		11,000	23,000		25,700	22,800	19,100				13,100		
Platelet (x10^9/L)	100,000 - 400,000/L	70,000	48,000	15,000	11,000		10,000	13,000	16,000			1,20,000	5,000		2,50,000
Fibrinogen (milligrams per	200 - 400 mg/dL	500		583	392		614	644	499				523		
Creatinine (milligrams per deciliter (mg/dL)	(Cr) (0.6–1.1 mg/dL)	0.92		0.54	0.74		0.65	0.89	0.78				0.64		
BUN/Cr ratio	10:1 - 20:1	15		26.1	21.8		23.3	22.5	23.3				29.3		
Lactic dehydrogenase (U/L)	(LDH) 105–233 units per liter (U/L	136		902	510		315	345	617		315		617		
Alanine transaminase (U/L)	(ALT) (7–55 units per liter)	39		250	176		155	104	102		30		41		
Aspartate transaminase (U/L)	(AST) (8 – 48 U/L)	41		234	104		84	46	61		53		36		
Alkaline phosphatase (IU/L)	(ALP) (44 - 147 international units	91		96	77		97	100	98		96		79		
Total serum bilirubin (mg/dL)	0.1 - 1.2 mg/dL	0.5		0.3	0.2		0.2	0.5	0.6		0.3		1.4		
Haptoglobin (mg/dL)	(41 - 165 milligrams per deciliter						<5.8	57.7					<30		
D-Dimer (ng/mL of	(< 500 ng/mL of fibrinogen-						22000		6020				3394		
Partial thromboplastin time (seconds)	25 - 35 seconds			47.4	49		55.2	66.5	55.1				53.6		
Glucose mg/dL (milligrams per deciliter)	70 - 140 mg/dL	124		130	154		151	146	142				119		
Blood pressure		95/66		130/90	165/90		145/98	134/87	126/87			124/80	119/85		
Systolic blood pressure		95		130	165		145	134	126			124	119		
Oxygen saturation	95 - 100%	98		95	97		96	98	97			96	94		
	Platelet count in red text														
	BUN/Cr = Blood urea														
	Yellow highlight = 2014														
	No highlight = 2019 pregnancy														
	Beige highlight = 2023 neurologic														

Prednisone 20 mg/day started

Two unit packed red blood cell transfusion

Hematology reconsult 60 mg prednisone/day tapered dose
Low platelets on bone marrow biopsy

Dexamethasone 40 mg x 4 days and intravenous immunoglobuli (IVIG) 1 g/kg x 2 days. Poor response so plasmapheresis, fresh frozen plasma, caplacizumab-yhdp, rituximab, and a tapered course of prednisone used.

Table 1: Lab values and treatment summary from 2014-2023.

Discussion

This patient presented in 2023 with a spontaneous transient neurologic deficit, ITP, low ADAMTS13, positive anti-glycoprotein Abs and lupus anticoagulant, along with elements of immune hemolytic anemia. Therefore, the case was diagnosed as a simultaneous active ITP and TTP with underlying primary antiphospholipid syndrome. She had a history of chronic primary ITP and clinical features of both APS and TTP in her pregnancy 4 years earlier. A search of the english language literature reveals no previous reports of ITP, TTP and APS present concurrently in a single patient. In addition, there have been less than a dozen cases of TTP associated with primary APS reported and the majority of these cases have involved one or multiple strokes [10-12].

Our current case is notable for three reasons. First, there is an extremely complex interaction of three serious immune-mediated disorders resulting in the potential for significant morbidity and mortality. APS and TTP are known to be risk factors in venous or arterial occlusive thrombogenic pathology. Our patient had both a pregnancy disorder and a neurologic disorder secondary to the thrombogenic properties of the two conditions.

Second, the morbidity was expressed intermittently over a 9-year period. Chronic ITP occurs in 80% of ITP cases [13] and 20-40% of TTP is recurrent [14]. APS can chronically damage vascular endothelium and contribute to progressive organ impairment. In addition, over time, even when the patient's features no longer qualify for active APS, the patient still remains at increased risk for thrombotic events, including stroke. Another finding in this case was the positive Coombs associated with a decreased haptoglobin and elevated LDH seen in 2019 and 2023, which may have indicated autoimmune hemolytic anemia. This is not surprising because of the known association between immune-mediated hemolytic anemia and both ITP and APS [13]. Al-Mondhiry, reported a case of lupus, TTP and IgG red cell autoantibodies in a patient with lupus cerebritis which required multiagent therapy for symptom control [12].

The third notable element of this case is the complicated events surrounding her second-trimester pregnancy delivery. In normal pregnancy, the vascular interface between the uterine spiral arteriole supply side and the fetal chorionic villi collection side is characterized by massive volume shifts of maternal Cardiac Output (CO) to the uterus on the way to the placental bed. In a normal pregnancy, up to 17% of the CO shifts to the uterus representing around 500 mL/min. The occlusive vascular characteristic from both TTP and APS can be a risk factor for normal vascular supply and result in a compromised pregnancy

requiring early intervention. Whether TTP was present during her 2019 pregnancy is not clear, but both TTP and APS are known to be associated with HELLP syndrome and are relapsing [14,15].

Her low platelet count in her 2019 pregnancy probably originated as a combination of HELLP syndrome and ITP. The patient responded within 4 weeks to outpatient oral corticosteroids and ending the pregnancy. In retrospect, even though her ANA was negative, her PTT was prolonged, her platelets were low and her fetus was compromised, all findings of APS. Unfortunately, her ADAMTS13 was not obtained during the 2019 admission and although unlikely, TTP could also have played a role in her low platelets during the second-trimester pregnancy admission. Also, anticardiolipins were not obtained.

In 2023, she received a diagnosis of a transient ischemic neurologic event likely caused by the occlusive damage from the TTP and APS. The association between APS and TTP has been documented only in case reports and reviews. A case from 2009 reported a similar incident of concurrent TTP and APS in a 49-year-old woman who developed recurrent arterial brain thrombosis [16]. Also, SARS-CoV-2 was reported as a triggering factor of TTP and APS in a report from 2021 [11]. Finally, in 2017 a possible association between APS and TTP was suggested when 9 cases of simultaneous TTP and APS were reported [10]. Further investigations in our patient in 2023 revealed an ADAMTS13 activity deficiency and positive ADAMTS13 antibody, which confirmed the diagnosis of TTP.

ADAMTS13 is an enzyme found in plasma that is necessary for normal clotting. Decreased ADAMTS13 is characteristic of TTP and low levels promote the formation of platelet-rich microthrombi. Plasma exchange is the primary treatment for TTP, whereas glucocorticoids have been routinely added as an assisted therapy alongside plasma exchange. Plasma-based therapy was not used in her pregnancy in 2019, even though she had soft markers of TTP with spherocytosis, elevated LDH and HELLP. She recovered with the delivery of the infant and glucocorticoids. While the effectiveness of glucocorticoid monotherapy in TTP varies, glucocorticoid therapy is essential for treating ITP and patients with ITP typically respond well to it [17]. The latest therapy for Thrombotic Thrombocytopenic Purpura (TTP) is caplacizumab-yhdp, a humanized, single-variable-domain immunoglobulin that specifically targets the A1 domain of von Willebrand factor (vWF). By inhibiting the interaction between vWF and the platelet glycoprotein Ib-IX-V receptor, caplacizumab-yhdp enhances treatment outcomes. When combined with standard therapy for acquired TTP, caplacizumab-yhdp has been shown to shorten the time it takes for platelet levels to normalize and to reduce the recurrence rate of the condition.

Each of her three autoimmune disorders can result in thrombocytopenia but ITP appears to be the greatest driver of low platelets in each of her encounters [1,18]. The differential diagnosis of her thrombocytopenia included blood dyscrasias, infection, medication reactions or hemolytic uremic syndrome. All of the testing was negative and the low platelets were a recurrent finding. Thus, ITP was the likely diagnosis. On two separate occasions over the 9-year observation period, her platelet counts were < 20,000 and, at times, were documented in the extremely low range of 5,000. Her first two responses to oral glucocorticoid treatment were good, but her attempt in 2023 required second-level therapy. The current guidelines for first-line treatment of uncomplicated ITP are a short course of corticosteroids [19]. Second-line therapy for ITP becomes more complicated and can include either splenectomy or a thrombopoietin-receptor agonist or rituximab instead of splenectomy [20].
Our patient never had evidence of Connective Tissue Disease (CTD), but up to 15% of patients with CTD will have antiphospholipid antibodies. As was offered in our patient, the treatment of APS in patients who have had a thrombosis is long-term anticoagulation therapy. This recommendation requires close monitoring in patients with ITP.

One important item is the patient's future reproductive options. She has three serious and potentially life-threatening recurrent hematologic diseases. Another pregnancy could result in another preterm infant or even HELLP syndrome again, which is associated with severe acute hypertension. She should be counseled accordingly. This case highlights the importance of considering all possible causes of thrombocytopenia in a patient suffering from neurologic manifestation, especially when specific treatments should be given in a timely manner.

Conclusion

Of the few reported cases of concurrent active TTP and APS, there is a high incidence of ischemic neurologic events. Conducting systematic tests for ADAMTS13 activity and anti-ADAMTS13 antibodies in patients who exhibit neurological symptoms and thrombocytopenia, especially in the context of antiphospholipid antibodies, may assist in diagnosing the rare combination of

thrombotic thrombocytopenic purpura and antiphospholipid syndrome. Identifying cases of immune-drive thrombotic neurologic events early may improve outcome. The combination of APS, TTP and ITP has not been reported to this point. All three conditions are immune-driven, associated with low platelets and are relapsing. The natural inclination to stop searching when a solution is found is dangerous, as this case illustrates. Especially since there are different implications and different treatments for the different conditions. Her ITP was recognized and treated quickly even though she was not symptomatic. Her APS and TTP were more subtle and the diagnosis was not clear initially in 2019. This patient should have frequent health checks and counseling about CTD. In addition, she should be offered permanent medically indicated sterilization. Further research into the mechanisms of TTP and APS is needed because of the serious neurological consequences. Also, standardized diagnostic and treatment protocols for complex cases should be developed, reflecting which of the conditions is most active and likely to produce the most morbidity. Based on this case, her ITP treatment was successful using the standard protocols, including glucocorticoids and IVIG. The multiagent therapy and plasma-based treatment were also successful for her TTP and APS. Follow-up is critical.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Consent to Participate

Informed consent was also obtained from each subject who participated in the study.

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Data Availability

Data is available for the journal. Informed consents were not necessary for this paper.

Author's Contribution

All authors contributed equally for this paper.

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