Annals of Case Reports
Khagi Y. Ann Case Rep: 7: 1096
www.doi.org/10.29011/2574-7754.101096
www.gavinpublishers.com

Case Report

Concurrent Diagnosis of Thrombotic Thrombocytopenic Purpura (TTP) and Immune Thrombocytopenic Purpura (ITP) in an Otherwise Healthy Female Patient: A Case Report

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Citation: Khagi Y. (2022) Concurrent Diagnosis of Thrombotic Thrombocytopenic Purpura (TTP) and Immune Thrombocytopenic Purpura (ITP) in an Otherwise Healthy Female Patient: A Case Report. Ann Case Report. 7: 1096. DOI: 10.29011/2574-7754.101096

Received Date: 14 December 2022; **Accepted Date**: 17 December 2022; **Published Date**: 20 December 2022

Abstract: Thrombotic Thrombocytopenic Purpura (TTP) and Immune Thrombocytopenic Purpura (ITP) are rare and independent autoimmune hematologic conditions. Although both are characterized by thrombocytopenia, the mechanism of platelet consumption seen in TTP is distinct from the mechanism of platelet destruction seen in ITP. Moreover, the approach to treatment for these two conditions is considerably different. **Case Report:** This is a case of an otherwise healthy female patient with severe thrombocytopenia who met clinical and laboratory criteria for a diagnosis of TTP. Nonetheless, at the time of initial evaluation, she did not require standard treatment for TTP and instead responded to glucocorticoids alone. Although her ADAMTS13 activity level remained severely depressed, consistent with a diagnosis of TTP, her platelet count eventuallyresponded to thrombopoietin agonist monotherapy. This treatment approach would be insufficient to address the pathophysiologic mechanisms governing TTP; therefore, the patient was determined to have an overlying ITP driving the disease phenotype. **Conclusion:** Previous case reports describe concurrent TTP and ITP in patients with underlying malignant or autoimmune conditions. TTP and ITP can occur concurrently in healthy individuals. Additionally, response to treatment can assist in discerning thedominant autoimmune mechanism driving the disease phenotype.

MeSH Keywords: Thrombotic Thrombocytopenic Purpura; Immune Thrombocytopenic Purpura; Thrombopoietin Agonist

Background

Thrombotic Thrombocytopenic Purpura (TTP)

TTP is an autoimmune-mediated coagulopathy in which antibodies are produced against ADAMTS13. ADAMTS13 is the enzyme responsible for cleaving ultra-large Von Willebrand Factor (uvWF) normally released from the endothelium at sites of vascular injury. When ADAMTS13 does not function properly, uvWF accumulates in the microcirculation, free to bind circulating platelets, resulting in microthrombi formation and organ ischemia. This also results in a consumptive thrombocytopenia, which is often severe. TTP is a progressive disease that has broad clinical manifestations, including but not limited to constitutional symptoms (fever, malaise, and severe fatigue), acute renal failure, myocardial infarction, cardiac arrythmias, stroke, seizure, mesenteric ischemia, severe bleeding, and complications related to hemolytic anemia. It is widely understood that TTP "implies a disorder that is fatal without effective treatment." TTP has been associated with pregnancy, certain medications, underlying autoimmune disorders, certain infections, and malignancies. Most often, however, it is idiopathic [1]. Because of the rapidly progressive nature of TTP, treatment with plasma exchange is often initiated based on clinical features, while awaiting the ADAMTS13 activity level, a deficiency in which supports the diagnosis. Treatment of TTP involves plasma exchange for all patients at the time of a presumptive diagnosis, initiation of steroid therapy and various other maneuvers in the event the patient is refractory or develops relapse. The latter involves use of Rituximab, Caplacizumab, and/or other immunosuppressive agents such as cyclosporine or

azathioprine. A thorough discussion of treatment options for TTP is out of the scope of this case report.

Idiopathic Thrombocytopenic Purpura (ITP)

ITP is also an autoimmune-mediated disorder in which antibodies are produced against platelet antigens. The antibody-antigen complex is then destroyed in the splenic circulation, resulting in thrombocytopenia. The degree of thrombocytopenia can range from mild to severe and the disease course can also range from chronic and stable to acute and progressive. Primary ITP is widely regarded as a diagnosis of exclusion. Underlying infections, isolated thrombocytopenia induced by medications, rheumatologic diseases, and lymphoproliferative neoplasms should be ruled out before a diagnosis of ITP is made. The clinical course of the ITP patient is variable; however, isolated thrombocytopenia may be the only finding. The most common sign or symptom of ITP is fatigue, followed by bruising, and in severe cases, bleeding. Acute ITP can have a gradual onset over weeks or a more rapid onset over days. Chronic ITP can also develop (ITP lasting for 12 months or more) [2]. In contrast to TTP, ITP is rarely fatal, with one study citing a 20-year hazard ratio for mortality of 1.5 compared to the general population3. Treatment of acute primary ITP involves use of high dose corticosteroids. Up front IVIG can also be used, and in those with persistent or refractory disease, second line thrombopoietin receptor agonists (TPO-RAs) can be used. For those with chronic ITP, continuation on a TPO-RA is often employed and in certain circumstances Rituximab and splenectomy can be utilized [3]. The use of plasma exchange is not indicated in the setting of ITP.

In the unique case described below, we identify an otherwise healthy female patient who met clinical criteria for both TTP and ITP. Laboratory data support an ongoing TTP process; however, the patient did not require plasma exchange and instead responded to interventions normally implemented for ITP. Treatment of the patient with a TPO-RA agonist has improved, and maintained, her platelet count within a reasonable range.

Case Report

A 36-year-old Hispanic female patient with no significant past medical history presented to the hospital emergency department in March 2022 with heavy menstrual bleeding and severe fatigue. She was noted to be anemic and thrombocytopenic, with hemoglobin 6.6 g/dL and platelet count 5,000/mL. Prior laboratory testing 6 months prior revealed a normal complete blood count and differential. The patient reported a history of significant febrile reaction with cervical and axillary lymphadenopathy after vaccination for COVID-19 infection in January 2021. She had a similar reaction with her second vaccine in February 2021. Thereafter, she reported a pregnancy miscarriage requiring dilation and curettage in March 2021. From that time to her hospital presentation 1 year later, she endorsed heavy and irregular vaginal bleeding, as well as the development of unprovoked bruising on her face and trunk. She denied a history of menorrhagia prior to this time. Upon review by ER staff, she denied a personal history of cancer, autoimmune disease, recent or recurrent infections, hypertension, or diabetes mellitus. She denied use of tobacco or illicit drugs. She endorsed social alcohol intake in the past, but no current alcohol use. Her surgical history included remote tubal ligation and tonsillectomy and she was not taking any prescription medications on a consistent basis. She endorsed that at the age of 6 her daughter developed mucosal bleeding and petechiae on her lower extremities. She was found to have a platelet count of 0. She was given one dose of IVIG and one unit of platelets with complete resolution of symptoms and normalization of her platelet count. She did not have any recurrence. We could not obtain additional records regarding this event. The patient endorsed a family history of cervical cancer in her mother and hepatitis C infection in her father. Family history was negative for autoimmune diseases.

Upon initial hospital encounter, the patient denied fevers, weight loss, paresthesias, chest pain, shortness of breath, headaches, vision changes, focal weakness, changes in speech, dizziness, double vision, temperature intolerance, cough, rhinorrhea, abdominal pain, nausea, vomiting, diarrhea, arthralgias or myalgias. Her exam was grossly unremarkable, without evidence of bleeding, bruising or petechiae. She was started on high dose oral dexamethasone 40 mg daily for four days. She was also given a unit of packed red blood cells. She was then transferred to another hospital due to her insurance. There, her steroids were continued, and she was given an additional unit of packed red blood cells and 2 units of platelets. A peripheral blood smear was performed at the time and demonstrated moderate schistocytes. An ADAMTS13 activity level was sent, and the patient was transferred to a third hospital for empiric management of TTP.

After completion of four days of dexamethasone, the patient's platelet count improved from 5,000/mL to 18,000/mL. After arriving at the third hospital, Hematology was consulted and given the improvement in the platelet count with steroids alone, a diagnosis of ITP was made. The patient was discharged in stable condition with outpatient hematology follow up.

2 days after hospital discharge, the patient's ADAMTS13 activity level resulted with a value of <0.03% and a positive inhibitor. She was seen by hematology in follow up and diagnosed with TTP based on her markedly suppressed ADAMTS13 activity level. Despite this, however, a complete blood count demonstrated a platelet count of 74,000/mL.

She continued off steroids and her platelet count was 60,000/mL upon recheck 2 weeks later. Her ADAMTS13 activity level at that time remained depressed at <0.03%. She continued to be monitored with another repeat platelet count 2 weeks thereafter, which resulted as 18,000/mL. Due to the drop in platelets, she was

restarted on steroids. She was started on Prednisone 20 mg twice daily and 9 days later, her platelet count improved to 75,000/mL.

After 2 weeks on prednisone, the patient's platelet count had normalized to 192,000/mL and her ADAMTS13 activity level was 15%. An extensive work up was performed to evaluate her thrombocytopenia and depressed ADAMTS13 activity. Complement levels were normal, antinuclear antibody testing was normal, hepatitis B and C serologies were negative, HIV serology was negative, blood and fungal cultures were negative, haptoglobin and LDH were normal, G6PD activity level was normal, and a urine pregnancy test was negative. The patient received CT of the chest, abdomen, and pelvis with contrast, which showed two subcentimeter pulmonary nodules, which were nonspecific, and a small subcapsular lesion at the anterior left lobe of the liver, felt to be a hemangioma.

After 2 weeks on Prednisone 20 mg twice daily, the decision was made to taper her steroids and monitor her platelet count. She was tapered off steroids over 5 weeks. Her platelet count remained normal throughout this time, however her ADAMTS13 activity level remained <5%. 2 weeks after stopping steroid therapy, the patient's platelet count began to gradually decrease again; from 111,000/mL to 66,000/mL over a 4-week monitoring period. Her ADAMTS13 activity level remained <5%.

The decision was then made to initiate second line therapy for ITP. She was started on Eltrombopag 50 mg once daily. Her platelet count began to increase after 7 days and was maintained at ~90,000/mL. She has remained without relapse until the time of this writing.

Discussion

It has been established that both TTP and ITP are rare and distinct autoimmune hematologic disorders. TTP is primarily a disorder of platelet consumption and microthrombi formation resulting in organ ischemia; and ITP is a disorder of platelet destruction governed by platelet autoantibodies. Additionally, TTP is considered a disease with a high mortality rate, unless acted upon quickly with the initiation of plasma exchange and immunosuppression. The introduction of plasma exchange increased the survival rate in patients with TTP from 10% to nearly 80% [4]. ITP, on the other hand, has a variable presentation ranging from acute to chronic, mild to severe. 85% of patients with ITP can obtain adequate platelet counts (above 30,000/mL), and these patients have a long- term mortality risk equal to that of the general population [5].

To the author's knowledge, there are only four case reports of ITP coexisting with TTP. In one case, a patient was reported to have concurrent ITP and TTP in the setting of a metastatic neuroendocrine tumor. The patient was urgently treated with fresh frozen plasma and plasmapheresis, with inadequate response. The patient then received multiagent chemotherapy and steroids, with adequate response [6]. In a second case, a patient with known ITP was found to have sequential development of TTP after delivery. Postpartum TTP is a known phenomenon, and this patient was treated with plasma exchange, Rituximab and Mycophenolate Mofetil successfully [7]. The third case report describes a patient with a 2-year history of ITP who subsequently developed TTP. She was treated with plasmapheresis, steroids, and Rituximab successfully [8]. Finally, a fourth case report describes a patient with Primary Sjogren's Syndrome who also had a 2-year history of ITP and then subsequently developed TTP. He was treated with urgent plasma exchange, steroids, and various other immunosuppressants [9].

In all four cases described above, patients required the urgent initiation of plasma exchange to address their TTP. Additionally, in all four cases, patients had a pre-existing diagnosis or known provoking event: malignancy, prior autoimmune disease, or pregnancy. The author describes a case report of a woman with no prior history of autoimmune disease, malignancy, and without concurrent pregnancy. Moreover, the case report outlines a clinical course more consistent with ITP than TTP. The patient in this case report never received plasma exchange and achieved a stable platelet count with steroids, and then Eltrombopag, a TPO agonist. The patient's ADAMTS13 activity level, however, remained severely decreased. This is the first case report of concurrent TTP and ITP responding to interventions for ITP alone.

It is unclear at this time whether the patient has a TTP phenotype that is chronic and non-progressive, or whether she will eventually develop clinical signs and symptoms of an acute episode of TTP. At present, it appears her thrombocytopenia is driven mostly by her concurrent ITP process. She remains grossly asymptomatic at the time of this writing.

Conclusion

Although TTP and ITP are distinct and heterogeneous entities, they are both autoimmune hematologic disorders. At present, we are not aware of a pathophysiologic or biochemical association between the two disorders. There have been a handful of case reports thus far that have identified coexisting ITP with TTP in humans. These reports have described patients with pre-existing conditions such as malignancy, autoimmune disease, or pregnancy. This is the first case report that describes a previously healthy patient with no past medical history who developed concurrent TTP and ITP. Moreover, the patient described in this case responded to treatments that would alone be suboptimal in addressing TTP. This indicates that there may be a governing phenotype in patients with concurrent ITP and TTP. This case appears to challenge our preconceived notions about both autoimmune hematologic conditions, and the management of these conditions if they were to occur together.

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