Thrombotic Thrombocytopenic Purpura Associated With Pegylated Interferon Alfa-2a Use in a Patient With Polycythemia Vera

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Abstract
Pegylated interferon alfa-2a (pegIFNa) is being increasingly used for treatment of myeloproliferative neoplasms; however, its side effects, including autoimmune complications, are not unusual. We report on a 47-year-old woman with polycythemia vera (PV) treated with pegIFNa and in complete hematologic remission who developed thrombotic thrombocytopenic purpura (TTP). To our knowledge, thrombotic microangiopathy has been reported as a side effect of interferon (IFN) use in patients with hepatitis and chronic myeloid leukemia, but not in those with PV. Our patient had a low ADAMTS13 level due to an inhibitor, which normalized after withholding pegIFNa and initiating treatment for TTP with therapeutic plasma exchange and corticosteroids. She experienced refractory TTP, necessitating treatment with rituximab and splenectomy. Postsplenectomy, she developed a high platelet count, warranting the need to restart treatment for PV. However, JAK2V617F allelic burden by real-time PCR was 0.7%, indicating that the increased platelet count was likely secondary to splenectomy. Therefore, we elected to monitor her counts and JAK2V617F allelic burden closely. With this case report, we hope to alert treating physicians that TTP should be considered as a complication of pegIFNa therapy in PV and that prompt discontinuation of the drug with necessary treatment should be instituted to prevent fatal complications.

Background
Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disease caused by germline predisposition or acquired autoantibodies. It is characterized by thrombotic microangiopathy (TMA), thrombocytopenia, neurologic symptoms, renal dysfunction, and fever. Only a minority of patients present with all of these symptoms, which overlap with other clinical conditions, posing a diagnostic challenge. Acquired TTP occurs due to development of inhibitory antibodies against von Willebrand factor (VWF)—cleaving protease ADAMTS13 (a disintegrin and metalloprotease with thrombospondin motif-13), which specifically cleaves multimeric VWF at the Tyr1605-Met1606 peptide bond of the A2 domain. Various clinical conditions, such as pregnancy, infections, malignancies, autoimmunity, stem cell transplantation, and certain drugs, can cause TMA. Drug-induced TMA can be classified into either immune-mediated or non–immune-mediated cytotoxicity, and is commonly seen with the use of antibiotics, chemotherpay, immunosuppressants, narcotics, and cardiac medications.

We report a case of TTP due to the development of antibodies to ADAMTS13 in association with pegylated interferon alfa-2a (pegIFNa) use in a patient with polycythemia vera (PV) that resolved after discontinuation of pegIFNa, and treatment with therapeutic plasma exchange (TPE), corticosteroids, rituximab, and splenectomy.
Case Report

A 47-year-old Ashkenazi Jewish woman was diagnosed with PV 5 years prior to presentation. She had a stroke at age 39 years when her WBC count was 13 x 10^9/L, hematocrit was 42%, and platelet count was 678 x 10^9/L. Her protein C, protein S, antithrombin III, factor V Leiden, and antinuclear antibody levels and erythrocyte sedimentation rate were normal at that time. She was on oral contraceptives, which were thought to have contributed to the stroke, and her high blood counts were considered to be reactive. She developed significant fatigue and depression after the stroke, limiting her ability to work. She was referred to our department 3 years after the stroke for a persistently elevated CBC count. Her WBC count was 13.02 x 10^9/L, RBC count was 5.30 M/mcL, hemoglobin level was 16.7 g/dL, hematocrit was 49%, mean corpuscular volume was 92.4 fl, and platelet count was 866 x 10^9/L. Her erythropoietin level was 4 mU/mL. She had a positive JAK2V617F mutation, erythropoietin-independent erythroid colonies, and a narrow morphology consistent with PV.6,8

She was treated with hydroxyurea at 1 g/d for a brief period and then started on pegIFNa as part of a randomized clinical trial. She experienced a hematologic remission within a few months of treatment, and her JAK2V617F allelic burden in clonal granulocytes markedly improved from 21% and remained detectable at <1% for a long time. Her hematopoiesis converted from clonality to polyclonality, determined by X chromosome transcriptional quantitative analysis.10 After 48 months of therapy with pegIFNa, she presented to the emergency department with an intense headache and generalized weakness. A head CT did not show any acute intracranial process. Her WBC count was 6.8 x 10^9/L, hemoglobin level was 5.7 g/dL, and platelet count was 18 x 10^9/L (previously normal at a clinic visit 6 weeks earlier). Her lactate dehydrogenase (LDH) level was 1,002 U/L (normal, 100–253 U/L), she had elevated reticulocytes at 11.3%, an indirect bilirubin level of 2.1 mg/dL, a creatinine level of 0.9 mg/dL, negative direct antiglobulin test results, a haptoglobin level <10 mg/dL, a D-dimer value of 2.1 mcg/mL, a fibrinogen level of 399 mg/dL, a prothrombin time of 13.1 seconds, a partial thromboplastin time of 34 seconds, and her urine had 2 RBCs per high power field with an increased urobinogen level of 4 mg/dL. Numerous schistocytes were present on peripheral smear, raising concern for TMA. Her pegIFNa was discontinued and prednisone at 1 mg/kg was started. TPE was initiated with 1 volume of exchange, using fresh frozen plasma as replacement fluid. Her ADAMTS13 activity was <5% with an inhibitor level of 1.5 inhibitor units, confirming the diagnosis of TTP.

She responded well to TPE initially, with her platelet count increasing to 100 x 10^9/L by the seventh day of hospitalization, then gradually declining with a simultaneous increase of LDH. She was started on rituximab at 375 mg/m^2 on day 9 of hospitalization and underwent laparoscopic splenectomy on day 11, after which her platelet count normalized in 4 days (Figure 1). Repeat ADAMTS13 activity level was 6% and her inhibitor level was 0.5 inhibitor units on day 14. She completed 4 doses of weekly rituximab and received a steroid taper for 1 month. Her VWF multimer analysis showed ultralarge multimers in all samples during the acute TTP episode and interestingly preceded her TTP clinical presentation (Figure 2). They subsequently normalized on repeat testing 4 months later.

In a follow-up visit 2 months after onset of TTP, her WBC count and hemoglobin level were normal, but her platelet count was 852 x 10^9/L and remained elevated on subsequent testing. Repeat JAK2V617F allelic burden on real-time PCR was 0.7%, indicating that the increased platelet count was likely secondary to splenectomy, and we elected to monitor her JAK2V617F allelic burden along with her CBC count to further guide management. Her repeat ADAMTS13 level was >100% and her inhibitor level was undetectable at <0.4 inhibitor units. Similar to previous reports,11 she may have prolonged clinical remission from the pegIFNa she received, and may not need therapy for PV. Her WBC count and hemoglobin level have remained normal, and her platelet count has been mostly around 500 x 10^9/L on follow-up visits. If her JAK2V617F allelic burden or blood counts increase in the future, we plan to treat her with hydroxyurea or ruxolitinib.

Discussion

PegIFNa is an antiviral agent that also has antitumoral activity and is better tolerated than the conventional interferon (IFNa). It is commonly used in the treatment of viral hepatitis and several malignancies, including myeloproliferative disorders,
hairy cell leukemia, and metastatic melanoma. TMA, mostly in hemolytic uremic syndrome and in some cases of TTP, has been reported as a side effect of IFNa use in patients with viral hepatitis and chronic myelogenous leukemia (CML), but to our knowledge has not been reported in PV. Development or exacerbation of autoimmune disorders is a known side effect from IFNa use and chronic hepatitis C, making it difficult to identify the exact cause of these complications. Because TMA has been reported with the use of hydroxyurea, IFNa, and dasatinib in CML, it is difficult to assess whether it was secondary to the medication or to the disease process itself. The interval between the initiation of IFNa and the development of TMA varies among different reports, questioning whether TMA is a true side effect of IFNa therapy. Most of the reported cases had abnormal renal function, some requiring dialysis. However, our patient had normal renal function throughout her hospitalization.

The exact mechanism for IFNa-associated TTP is unknown, as autoantibodies were found in some, but not all, reported cases with low ADAMTS13. IFNa is known to exert complex immunomodulatory effects on endothelial cells, alter the expression of cell surface markers, and increase leukocyte adherence to the vascular endothelium. They may also initiate the development of autoantibodies against ADAMTS13 or endothelial cells, causing endothelial cell damage to release ultralarge VWF multimers that are highly
active in aggregating platelets and promoting intraluminal microthrombosis.\textsuperscript{12,20} Our patient had large VWF multimers not only during the acute episode but also before the onset of TTP, attesting to their essential role in TTP genesis.\textsuperscript{21} She had good initial response to TPE, but then developed refractory disease with a decline in platelet count and an increase in LDH. Increasing the frequency of plasmapheresis or the exchange volume to 1.5 times the plasma volume and using cryoprecipitate-poor plasma, splenectomy, treatment with rituximab, immunosuppressive agents, and, more recently, bortezomib have all been described for the treatment of refractory TTP, although there are limited data on the effectiveness of these treatment modalities. Clinical remission occurred in 87% to 100% of patients treated with rituximab, and platelet recovery is seen within a median of 11 to 14 days after the first dose.\textsuperscript{22} Although splenectomy increases the risk of bleeding, venous thromboembolism, and infections in general and in patients with myeloproliferative disorders,\textsuperscript{23} mortality and morbidity seem to be lower in patients undergoing laparoscopic splenectomy versus open surgery for relapsed/refractory TTP.\textsuperscript{24}

All of the treatment options and risks and benefits were considered in our patient, and, due to rapidly declining platelet count, splenectomy was performed in addition to rituximab, because it was shown in previous reports to induce rapid response and lower relapse rates.\textsuperscript{22,24}

Conclusions

We suggest considering TTP in the differential diagnosis when there is a precipitous decrease of platelets or evidence of TMA in patients with PV being treated with IFNa. Clinicians should be watchful of this complication and immediately discontinue IFNa in these cases, and promptly initiate necessary treatment to prevent fatal complications. Our patient had elevated blood counts after splenectomy, and her low JAK2\textsuperscript{V617F} allelic burden helped to differentiate post-splenectomy elevation in counts from PV. We are periodically monitoring her JAK2\textsuperscript{V617F} allelic burden along with CBC to help guide management.

References