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Eltrombopag-Induced Thrombocytosis and Thrombosis in Patients With Antiphospholipid Syndrome and Immune Thrombocytopenic Purpura

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Abstract

Antiphospholipid syndrome (APS) may be either as a primary or in association with an underlying systemic autoimmune etiology (36.2%), particularly systemic lupus erythematosus (SLE). Thrombocytopenia is infrequently observed in APS patients, with an occurrence of 22% to 42% with the frequency of thrombocytopenia, higher in APS and SLE combination than in primary APS. There have been some controversial reports regarding the treatment of APS syndrome with thrombocytopenia with TPO agonists. We like to report a case with APS syndrome with severe thrombocytopenia treated with TPO-RA and developed severe thrombocytosis and thrombosis. Our case represented the first case of TPO-RA in treating APS syndrome developed severe thrombocytosis and our case also concurred that use of TPO-RA agents should be strongly discouraged in APS until larger studies clarify the safety of TPO-RA agents in APS.

Keywords

anti-phospholipid syndrome, hematology oncology, thrombosis

Introduction

Antiphospholipid syndrome (APS) is a condition in which thrombosis might involve any arteries, veins as well as the microvasculature[1] and appears to be related to the anti-β2 glycoprotein antibody.[2-5] Generally, patients with APS have approximately 25% chance to experience thrombocytopenia of mild-moderate degree.[6] Initial treatment include corticosteroids and intravenous immunoglobulin (IVIGs) for severe or fatal thrombocytopenia.[7,8] Approved second-line therapy for primary immune thrombocytopenia (ITP) such as thrombopoietin-receptor agonists (TPO-Ras), Romiplostim and eltrombopag, have substantiated clinical efficacy regarding an improvement of platelet count with a sustainable manner in 70% to 80% of cases.[9,10] When APS is complicated by severe thrombocytopenia, there has been limited data regarding the safety of these TPO-RA. Although limited researches revealed favorable results,[11,12] there has been 3 published cases documenting thrombotic sequelae in patients with secondary thrombocytopenia due to APS treated with TPO-RA.[13,14] But in a series of patients with severe thrombocytopenia and APS syndrome treated with TPO-RA, no thrombosis was found.[15] We report a case where APS treated with TPO-RA developed a severe thrombocytosis and pulmonary embolism (PE).

Case Report

A 76-year-old female with a past medical history of recent pulmonary embolism and hyperparathyroidism post-parathyroidectomy was initially referred to us for severe thrombocytopenia with ecchymosis in January 2019. She was diagnosed with PE in March 2018 and hypercoagulable state work up at that time showed negative for factor V leiden mutation and Prothrombin gene 20210A mutation, Protein C activity, and Protein S Free antigen levels were normal. Anticardiolipin antibodies were positive with IgM-51MPL (0-12.5 MPL), IgG-0.7MPL, anti-β2 glycoprotein were normal (IgA-1.5, IgM-2.7, IgG $<$ 0.6). Lupus anticoagulant was positive for DRVVT at that time, confirmed by silica clotting time ratio of 1.35 (normal range 0.00-1.16) using phospholipid at low and high concentration. Therefore, she was diagnosed as APS syndrome with mild thrombocytopenia

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(platelet counts were 100 x 10^9/L). She was then placed on Eliquis through her primary doctor. Later in June 2020, because of severe thrombocytopenia with platelet counts of 1 x 10^9/L, she was then referred to hematology. She was treated with high-dose steroids for possible ITP associated with APS. After 2 weeks, the platelet count improved to 170 x 10^9/L. Platelet count failed to sustain with initial steroid treatment, and rituximab (anti-CD20 monoclonal antibodies) was started. Platelet count did improve but went down after, with platelet counts of 50 x 10^9/L. Eltrombopag (Promacta) 50 mg/day was then started and platelet count improved. Patient has been following up closely for the treatment biweekly. One month later, the patient was hospitalized for dyspnea and pulmonary embolism was diagnosed by computed tomography (CT)—pulmonary angiogram. Platelet count was 1,600 x 10^9/L, D-dimer was elevated and SARS COV-2 PCR was negative. Eltrombopag was stopped and she was treated with subcutaneous Enoxaparin. During hospitalization, her platelet count went up to 1,411,000. In all, 12 days after stopping Eltrombopag, her platelet count was 747,000 and she was discharged home on warfarin. Her platelet count remains normal up to the date of publication.

Discussion

Based on the updated classification criteria from Sydney in 2006, the Antiphospholipid Syndrome (APS) is a systemic autoimmune disorder characterized by periodic thrombosis involving any arteries, veins, and the microvasculature and/or obstetrical morbidity along with persistent anti-phospholipid antibodies (APLA), including lupus anticoagulant (LA), anti-β2-glycoprotein I (anti-β2GPI), and/or anti-cardiolipin (aCL) antibodies. In order to meet the classification standards, there should be at least medium-high levels of aPL persisting more than 12 weeks, to eliminate transient phenomenon. One sizable multinational cohort study reported the incidence of thrombocytopenia in patients with lupus with APS syndrome and with primary APS being 28% and 16%, respectively.[16] In our patient, she had chronic thrombocytopenia since 2017 and her positive ANA was transient and anticardiolipin antibody was positive at the time of the first PE episode in March 2018. Positive cardiolipin antibodies and lupus anticoagulant (silica clotting time ratio) were noted at the initial office visit. Persistent positive anticardiolipin antibodies after 12 weeks confirmed the diagnosis of APS because ANA positives were only detected once and were at low titer and there were no other stigmata criteria (Anti-dsDNA Antibody <0.5) for lupus that makes diagnosis of systemic lupus unlikely. Severe thrombocytopenia ($<50 \times 109$ /l) was prevalent in 17.6% of APS patients.[17] Severe and life-threatening thrombocytopenic patients mostly require therapeutic intervention[7,8] and TPO-RA is the last option for treatment of refractory severe ITP.[18-20] Therefore, our patient improved her thrombocytopenia with TPO-RA, but instead, she developed severe thrombocytosis and pulmonary embolism.

One long-term, open-label EXTEND study in 2013 revealed 4 out of 299 (1%) enrolled refractory chronic ITP patients treated with Eltrombopag developed high platelet counts for more than 6 months, but the exact number of platelets was not mentioned clearly in the studies.[21] Other reports[22] and Pooled Romiplostim trials[23] reported the increase in platelet counts were up to 450 x 10^9/L and thrombocytosis was not mentioned. Therefore, from all the studies of using TPO-RA in treating ITP, no reports of severe thrombocytosis of platelet counts over 1000 x 10^9/L were reported. Our patient developed severe thrombocytosis with platelet counts up to 1411 x 10^9/L that were not reported previously.

In patients with severe and symptomatic thrombocytopenia unresponsive to conventional therapy with glucocorticoids, splenectomy, and/or rituximab, a TPO-RA will yield a significant platelet count increase[18-20] and may also develop thrombosis. In Bussel et al[20] (2009), 7 out of 142 (5%) ITP patients treated with romiplostin developed thrombosis. In the extended studies by Mansoors et al,[21] 302 patients were registered and the average duration of eltrombopag treatment was 2.37 years with 6% developing thrombosis. But in the Italian studies by Ruggeri et al,[24] a total of 986 patients were analyzed, demonstrating that the 5-year cumulative incidence of venous and arterial thrombosis in ITP is obviously under the default baseline. These thrombotic events are especially observed in splenectomized and elderly patients with ITP.

In patients with APS with thrombocytopenia, 3 patients with definite APS and 1 with only aPL positivity who were treated with Eltrombopag developed thrombotic events.[25] APS has a strong association with direct binding of β2 glycoprotein to endothelial cells platelet activation[26-28] and reenactment of circulating platelets aggravates thrombosis in a given prothrombotic state. One case series[1] involves 5 steroid-resistant ITP patients(4 with SLE and one with concurrent APS) being managed with TPO-RA. Out of 4 cases, the satisfactory recovery of platelet counts with minimal bleeding events were noted in 3 patients. Surprisingly, none of them encountered thrombosis or deterioration of their existing autoimmune disease. Hence, this finding indicates TPO-RA are in favor regarding safety, efficacy and effectiveness in patients with ITP in the setting of SLE or APS. It has yet to be explored whether there is a correlation with APS, thrombocytosis, and thromboembolic events in patients who were treated with TPO-RA, a clinical trial will be necessary to assess the thrombosis effects in using TPO-RA in APS syndrome. Our case suggested that using TPO-RA in APS syndrome needs to be cautiously considered.

Conclusion

We reported a case of APS syndrome and severe thrombocytopenia treated with TPO-RA after refractory steroids, Rituximab, IVIG. Our patient developed severe thrombocytosis and thrombosis. In APS syndrome with thrombocytopenia,

the use of TPO-RA should be discouraged until further studies show beneficial outcomes.

Declaration of Conflicting Interests

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Ethics Approval

Ethics approval to report this case was obtained from Brookdale Hospital IRB Review Board . Our institution does not require ethical approval for reporting individual case reports.

Informed Consent

Informed consent for patient information to be published in this article was obtained .

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