



ORIGINAL RESEARCH PAPER

General Medicine

REFRACTORY IMMUNE THROMBOCYTOPENIA WITH ANTIPHOSPHOLIPID ANTIBODIES

KEY WORDS: Immune Thrombocytopenia (ITP) , Refractory Thrombocytopenia, rituximab , Thrombopoietin Receptor Agonists (TPO-RAs), Antiphospholipid Antibodies (aPL), Azathioprine Therapy .

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ABSTRACT

This case report details a 28-year-old female with refractory immune thrombocytopenia (ITP) and antiphospholipid antibodies (aPL). Initial management with corticosteroids, IVIG (intravenous immunoglobulin), and thrombopoietin receptor agonists (TPO-RAs) failed to sustain adequate platelet counts. The patient later suffered a subarachnoid haemorrhage and suspected adrenal thrombosis, complicating her condition. This report highlights the challenges of managing refractory ITP with aPL, emphasizing the need for individualized therapeutic strategies and vigilant monitoring to balance thrombosis and bleeding risks. Long-term immunosuppression with azathioprine stabilized her platelet count, providing a viable management approach for similar complex cases.

CASE REPORT :

A 28-year-old female presented to the emergency department with severe menorrhagia and wet purpura over the oral mucosa. She had no history of fever, joint pain, rash, jaundice, dyspnea, easy fatigability, weight loss, or general tiredness. Additionally, there was no history of recurrent abortions, photosensitivity, oral ulcers, or polyarthralgia. General and systemic examinations were unremarkable. Routine blood tests revealed severe thrombocytopenia with a platelet count of 3000/mm³. The patient was admitted to the ICU for further management.

Secondary causes of thrombocytopenia, including drug-induced, infectious, and vitamin B12 deficiency, were excluded. Peripheral smear was showing normocytic normochromic anemia with thrombocytopenia . Initial treatment included intravenous methylprednisolone (125 mg/day for 5 days) and IVIG (50 g/day for 2 days), which did not yield an adequate platelet response.

Patient was shifted to ward and Further diagnostic workup including ANA by IF, LIA, DCT, and bone marrow biopsy showed reactive marrow . However lupus anticoagulant, IgG anticardiolipin, and IgG anti- 2 glycoprotein antibodies were strongly positive but had not satisfied APS criteria and was manged as ITP . The patient initially responded to TPO-RA therapy, but this response was not sustained, leading to recurrent thrombocytopenia. As the patient was not keen on major surgery like splenectomy, a better alternative therapy despite low evidence she was started on rituximab (1) (600 mg weekly for 4 weeks) was administered. Subsequently, the patient was started on a thrombopoietin receptor agonist (TPO-RA) discharged and followed up on outpatient department.

Reccurent ICU admissions despite a close watch on platelet count

One month later, the patient suffered a subdural hemorrhage , when on TPO - RA therapy which was managed conservatively questioning the efficacy of platelet response from same .

Three months after her initial diagnosis, the patient returned with severe abdominal pain, recurrent vomiting, and hypotension and was admitted to ICU . Given her positive antiphospholipid antibody (aPL) profile, including lupus anticoagulant, IgG anticardiolipin, and IgG anti- 2 glycoprotein antibodies, clinically adrenal thrombosis was

suspected. A contrast-enhanced CT scan of the abdomen showed a bulky left adrenal gland with moderate periaudrenal fat stranding, suggesting a possible adrenal haemorrhage secondary to adrenal vein thrombosis. However, normal levels of serum fibrinogen, D-dimer, and cortisol, along with a normal platelet count, indicated that adrenal vein thrombosis or haemorrhage was unlikely at that time. She was treated symptomatically and discharged.

The patient was started on low-dose aspirin due to increased thrombotic risk from positive aPL profile (lupus anticoagulant, IgG anticardiolipin antibodies, and IgG anti- 2 glycoprotein antibodies). Anticoagulation was not initiated. She experienced instances of high platelet counts up to 800,000/mm³, necessitating adjustments in Tpo-ra therapy dosing and frequency.

Despite 12 months of treatment, complete response was not achieved. Immunosuppression with azathioprine (50 mg/week) was initiated, leading to stabilization of platelet count over the last 10 months with normal platelet counts and no bleeding manifestations or hospital admissions . The patient currently continues on aspirin 75 mg daily , azathioprine 50mg once a week and is on regular follow-up without any bleeding symptoms necessitating need to reevaluate conventional immunosuppression therapies for ITP .

DISCUSSION

Immune thrombocytopenia (ITP), previously referred to as idiopathic thrombocytopenic purpura, is a condition frequently encountered in clinical practice. It is diagnosed through exclusion, following a comprehensive clinical and laboratory evaluation. Secondary immune thrombocytopenia can be associated with various autoimmune diseases, such as Systemic Lupus Erythematosus (SLE), Antiphospholipid Syndrome (APS), and Autoimmune Lymphoproliferative Syndrome (ALPS), as well as infections like Helicobacter pylori and hepatitis B and C. It is important to consider other causes of thrombocytopenia that mimic ITP, necessitating thorough diagnostic workups, particularly when the condition is refractory to first and second-line treatments. Despite there are few studies showing better platelet response when IVIG is given along with intravenous methylprednisolone , in our case despite adequate immunosuppression the platelet response was inadequate .

Refractory ITP was traditionally defined as thrombocytopenia

unresponsive to first-line treatments like corticosteroids and intravenous immunoglobulin (IVIG), as well as second-line treatments like splenectomy. However, with the advent of new therapeutic agents like rituximab and thrombopoietin receptor agonists (TPO-RAs), which have demonstrated significant clinical efficacy, the definition of refractory ITP warrants reconsideration(2). There are currently no specific guidelines to redefine this term, reflecting the evolving landscape of ITP management.

The relationship between antiphospholipid antibodies (aPL) and ITP has been a subject of interest, with elevated aPL frequently observed in ITP patients, yet not necessarily correlating with the severity of thrombocytopenia. Immunosuppressive therapy and disease activity do not significantly alter aPL levels, suggesting that these antibodies might not play a central role in ITP pathology. Although routine aPL testing in ITP patients is not commonly recommended by experts(3), certain case reports and studies have linked lupus anticoagulant (LA) positivity with an increased risk of thrombotic events(4). Some evidence indicates that ITP patients treated with TPO-RAs might have a higher risk of thrombotic events, potentially due to the increased production of immature platelets. However, data is limited, and a meta-analysis on contrary found no elevated risk of thrombosis in ITP patients on TPO-RAs (5). Clinicians must carefully assess each patient's risk profile when determining treatment strategies.

Regarding antithrombotic therapy, the use of low-dose aspirin (LDA) for primary prophylaxis in asymptomatic aPL carriers has been supported by a meta-analysis of seven observational studies involving 460 individuals. This analysis found that the risk of a first thrombotic event was halved in those who used LDA compared to those who did not(6). However, in the context of concurrent ITP, the bleeding risk increases, especially with platelet counts below 50,000/ L. If platelet counts fall below 30,000/ L, aspirin is generally avoided due to the heightened bleeding risk. Factors such as a high-risk aPL profile and prior thrombotic events may justify the use of LDA or anticoagulation therapy.

A study involving 53 adults with chronic ITP, who had undergone at least one form of therapy including splenectomy, evaluated the role of conventional immunosuppression with azathioprine at a dose of 150 mg/week(7). The study concluded that azathioprine leads to a relatively high incidence of durable responses with minimal side effects in chronic ITP patients for whom splenectomy has failed or is contraindicated. Due to potential delays in response, a four-month course of azathioprine is recommended before considering it ineffective. The optimal duration of azathioprine treatment in responders remains to be determined.

CONCLUSION

This case highlights the complex management of refractory ITP in a patient with aPL positivity. The balance between thrombocytopenia and thrombosis risk, particularly with TPO-RA therapy, requires careful and individualized management. Long-term immunosuppression with azathioprine has stabilized the patient's condition, emphasizing the need for tailored therapeutic strategies in such challenging cases.

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