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Case report

A case report of refractory immune thrombocytopenia: Challenges in choice of therapies in resource limiting center

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ABSTRACT

Introduction and importance: Refractory immune thrombocytopenic purpura (ITP) is a rare but serious condition causing significant morbidity and mortality due to inadequate response to standard treatments, resulting in persistent thrombocytopenia and increased bleeding risk.
Case presentation: An 18-year-old female patient, diagnosed with ITP two years prior following excessive vaginal bleeding and fatigue, was initially treated with oral prednisolone for two months and discharged in improved condition. Eighteen months after treatment cessation, she presented with recurrent excessive vaginal bleeding, intermittent bilateral nasal bleeding, skin rash, blurred vision, fatigue, tinnitus, vertigo, and intermittent headaches (one-month duration). Following a one-month admission during which she proved unresponsive to steroids, she received rituximab 500 mg IV weekly for four weeks, along with supportive care.
Clinical discussion: Refractory ITP in conjunction with COVID-19 is a rare and serious condition associated with significant morbidity and mortality, and a low survival rate. Effective, coordinated medical and surgical management, along with comprehensive rehabilitation from COVID-19, are crucial for improving outcomes in this severe condition.
Conclusion: Refractory ITP is a challenging and rare condition that can result in significant health complications, economic burdens, and a reduced quality of life for those affected.

1. Introduction

Immune Thrombocytopenia (ITP) is a disease characterized by isolated thrombocytopenia $<100 \times 10^9$/L due to immune mediated destruction leads to variety of bleeding complications [1]. Refractory ITP is defined as absence of response in which failure to build platelet count above 30,000/μL and doubling of baseline platelet counts or relapse after splenectomy [2]. While in 2020 refractory ITP is defined when there is no response to ≥2 treatment agents with no single medication to which they respond, and associated with bleeding and low platelet count; so refractory ITP can be diagnosed without the need for splenectomy [3]. Even though lots of treatment advances in management of refractory ITP in developed world still challenges treatment in developing countries. Among challenges to limited choices of treatment, unknown exact sequence of treatment options as well as the role of combination therapy is not well defined.

In this case report we present the case of a 18-old female who first responded for systemic steroid treatment and later after 1 year diagnosed to have severe ITP refractory to initial standard management including steroids and requiring further management including splenectomy, rituximab, and antiD. The case report narrated with Surgical Case Report (SCARE) 2023 guideline [4].

2. Case presentation

An 18-year-old female patient from Bahir Dar, Ethiopia, was

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diagnosed with immune thrombocytopenic purpura (ITP) two years prior after presenting with excessive vaginal bleeding and fatigue. She initially responded to two months of oral prednisolone and was discharged improved. Eighteen months later, she presented with recurrent excessive vaginal bleeding, intermittent bilateral epistaxis, skin rash, blurred vision, fatigue, tinnitus, vertigo, and a one-month history of intermittent headaches. Investigations revealed: complete blood count (CBC) showing WBC 12.2 $\times$ 10^3/μL, RBC 2.39 $\times$ 10^6/μL, Hgb 6.1 g/dL, MCV 85.9 fL, and platelets 15 $\times$ 10^3/μL; blood type A+; negative serology for hepatitis B and C, Coombs test, and stool *H. pylori* antigen; normal urea, liver enzymes, and bilirubin levels; and a normal abdominopelvic ultrasound. Regarding autoimmune diseases, testing for antinuclear antibodies (ANA) – both qualitatively and quantitatively – was negative, as was testing for rheumatoid factor. However, testing for anti-double-stranded DNA (anti-dsDNA) antibodies was not performed at that time. Bone marrow aspiration revealed a cellular marrow with scattered megakaryocytes and myeloid and erythroid precursor cells, demonstrating trilineage hematopoiesis with a myeloid: erythroid ratio of 2:1 and 4 % blasts. Peripheral blood smear showed normocytic normochromic red blood cells, thrombocytopenia, and a normal white blood cell count. She was diagnosed with chronic ITP and initiated on oral prednisolone 50 mg daily, but poor adherence led to a rapid relapse within one week, characterized by massive vaginal and nasal bleeding, recurrent hematemesis, a new skin rash, altered mental status, and severe headache (no seizures). On presentation, she was hypotensive (80/40 mmHg), tachycardic (115 bpm), with pale conjunctivae, ecchymoses, and lethargy. Repeat CBC revealed normal WBC, Hgb 4 g/dL, and platelets 10 $\times$ 10^3/μL; random blood glucose was 208 mg/dL. She was stabilized with eight units of whole blood, eleven units of platelets, and dexamethasone 10 mg IV QID for four days (first cycle). Despite this, bleeding only modestly improved. A second cycle of dexamethasone yielded minimal improvement. After one month of hospitalization, she was diagnosed with steroid-refractory ITP and commenced on rituximab 500 mg IV weekly for four weeks with supportive care. Following completion of steroid and rituximab therapy, persistent bleeding and profound thrombocytopenia (Hgb 6.7 g/dL, platelets 0 $\times$ 10^3/μL) led to a surgical consultation and splenectomy after platelet transfusion and pneumococcal vaccination, two months after hospital admission. The midline vertical incision with medial mobilization of the spleen was employed to access spleen. The open splenectomy began with the superior dissection of splenophrenic ligament, followed by the inferior dissection of the splenocolic and splenorenal ligaments. Next, the short gastric vessels within the gastrosplenic ligament were ligated and the ligament dissected. The splenic artery and vein were then individually identified at the hilum, clamped, and ligated to ensure complete vascular control. Following this, the spleen was carefully removed. Meticulous hemostasis was achieved to control any bleeding, no intraoperative accident, and the abdomen was closed in layers.

Post-splenectomy, the patient required continued supportive platelet and whole blood transfusions due to persistent thrombocytopenia (platelet count failing to exceed 4000/μL). Ten days post-operatively, she developed hospital-acquired pneumonia, which was successfully managed. Splenic biopsy revealed only congestion, with no evidence of primary or secondary splenic disorders. On the 90th day of admission (30th post-operative day), she had COVID-19, requiring transfer to a COVID-19 center. Treatment consisted of intravenous dexamethasone (6 mg daily) and supportive care for refractory ITP, post-splenectomy state, and severe COVID-19. Despite these interventions, bleeding persisted and platelet counts remained low (WBC 23 $\times$ 10^3/μL, Hgb 3.6 g/dL, platelets 4 $\times$ 10^3/μL at the COVID-19 center). After one week in the COVID-19 center, her bleeding, cough, shortness of breath, fever, and fatigue improved. Following a negative COVID-19 test (ten days after transfer), she was returned to the medical ward (40th postoperative day). Subsequently, her hemoglobin increased to 9 g/dL, and her platelet count progressively rose to 26,000/μL, with resolution of bleeding. She was discharged on oral prednisolone 40 mg daily (converted from intravenous dexamethasone). One-week post-discharge, her platelet count was 37,000/μL. Prednisolone was subsequently tapered over four weeks and eventually discontinued. One month later, her complete blood count normalized (platelets 365,000/μL), and she remains asymptomatic with normal hematologic parameters.

3. Discussion

Approximately 10 % of immune thrombocytopenic purpura (ITP) patients develop treatment refractoriness within the first year [5]. Our patient initially responded to steroid therapy for two months but subsequently became refractory. Therefore, in the absence of a response to initial treatment, alternative diagnoses for isolated thrombocytopenia must be considered. These include myelodysplastic syndromes (MDS), drug-induced thrombocytopenia, inherited thrombocytopenias, bone marrow failure syndromes, and other secondary causes. In this case, the patient presented with normal bone marrow cellularity, no history of medication use, and negative test results for secondary causes such as *Helicobacter pylori* infection, connective tissue disease, retroviral infection, hepatitis B and C, and a negative family history [6,7]. Investigating secondary causes of ITP is crucial because management focuses on addressing the underlying etiology and removing or discontinuing offending agents [8,9].

Following an ITP diagnosis, initial management typically involves first-line therapy with either prednisone or a high-dose dexamethasone regimen. Given our patient's history of excessive bleeding, severely low platelet count, and prior steroid treatment, we initiated high-dose dexamethasone (10 mg IV every 6 h) [10]. While intravenous immunoglobulins (IVIg) were unavailable in our setting, they represent an alternative first-line treatment option, either alone or in combination with steroids, for the rapid, albeit transient, control of life-threatening hemorrhage and platelet recovery [11]. Following the failure of first-line therapy, despite excluding other causes of isolated thrombocytopenia and bone marrow failure, our patient—who presented with both thrombocytopenia and bleeding—required second-line treatment. Options include splenectomy, rituximab, and thrombopoietin receptor agonists (TPO-RAs; eltrombopag, romiplostim), although the optimal treatment sequence remains undefined. Given the patient's residence in a low-socioeconomic setting, where splenectomy carries an increased risk of infection and TPO-RAs were unavailable, we administered weekly intravenous rituximab with concurrent platelet transfusions. Unfortunately, this treatment failed, prompting consideration of splenectomy following routine pre-splenectomy vaccinations [6,7]. While rituximab achieves responses lasting at least one year in 40–60 % of ITP patients [12], with some studies reporting a 21 % response rate maintained for at least five years in adults [13], our patient did not respond. Splenectomy offers a higher response rate with reduced morbidity in ITP [14]. Although not utilized in this patient, TPO-RAs demonstrate higher efficacy, with 70–80 % response rates and sustained responses in 50–60 % of patients [15,16]. Other second-line treatments, such as cyclophosphamide, ciclosporin A, and mycophenolate mofetil, either alone or in combination, were not employed in this instance [17]. Time to response for different second line treatment is different in which for splenectomy the initial response time 1–56 days while peak response time is 7–56 days while rituximab is 7–56 days for initial response and 14–180 days for peak response time [18]. Our patient's admission coincided with the COVID-19 pandemic. The impact of SARS-CoV-2 on refractory immune thrombocytopenic purpura (ITP) is variable. Given the lack of alternative treatment options, the patient received rituximab, which carries an increased risk of COVID-19 infection due to prolonged immunosuppression. Consequently, the patient developed a COVID-19 infection requiring treatment. During the COVID-19 era, thrombopoietin receptor agonists (TPO-RAs) are generally preferred for managing ITP; however, our patient did not receive TPO-RA therapy due to financial constraints [19].

These patients require strict follow-up, including a protocol-based steroid taper and strong emphasis on infection prevention. This includes consistent mask use, avoiding contact with individuals exhibiting cough symptoms, and the consistent use of bed nets. Early presentation to a health center for any complaint is crucial, as asplenic patients have an increased risk and severity of infections.

4. Conclusion

Refractory Immune Thrombocytopenia is a challenging and rare condition that can result in significant health complications, economic burdens, and a reduced quality of life for those affected.

Abbreviations

HCT	hematocrit
Hgb	hemoglobin
ITP	immune thrombocytopenia
IV	intravenous
K	killo cells (1000)
MCV	mean corpuscular volume
PLT	platelet
QID	quarter in die (four times a day)
RBC	red blood cell
WBC	white blood cell

Author contribution

AA: Conceptualization, design of the study, acquisition of data, drafting the article, revising it critically for important intellectual content, approval of the version to be submitted.

AF: Analysis, interpretation of data, drafting the article, revising it critically for important intellectual content, approval of the version to be submitted.

DN: Conceptualization, analysis, drafting the article, revising it critically for important intellectual content, approval of the version to be submitted.

MA: Acquisition of data, analysis, revising it critically for important intellectual content, approval of the version to be submitted.

WA: Acquisition of data, analysis, revising it critically for important intellectual content, approval of the version to be submitted.

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Patient's consent

Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical approval

Ethical approval for this study was provided by the Department of Internal Medicine Ethical review committee (Inte 19/2024), Debre Tabor University, Ethiopia, on June 12, 2024.

Guarantor

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Conflict of interest statement

All authors declare that they have no conflict of interest.

Appendix A. Supplementary data

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