Case Reports in Oncology

Case Rep Oncol 2020;13:606–610
DOI: 10.1159/000507363
Published online: June 4, 2020

Case Report

Extreme Levels of Platelet Count in Essential Thrombocythemia: Management and Outcome, Report of Two Cases

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Keywords
Essential thrombocythemia · Thrombocytapheresis · Myeloproliferative neoplasm · Cytoreduction

Abstract
Myeloproliferative neoplasms including essential thrombocythemia (ET) is usually caused by somatic mutations in multiple genes, including the JAK2 (most frequently), CALR gene, and MPL. In rare cases, the disease is caused by other mutations such as THPO or TET2 gene; however, around 10–15% with ET might have triple-negative mutations. Here we present 2 cases of ET who were asymptomatic on diagnoses, but found to have extremely high platelet counts as never reported earlier. The management and treatment plan can be a challenging step. The objective is to draw attention to the early introduction of thrombocytapheresis in the management of such patients given its notable outcomes.

Introduction

Myeloproliferative neoplasm (MPN), mainly essential thrombocythemia (ET), is caused by megakaryocyte hyperplasia and thrombocytosis. ET is due to mutations in JAK2 (50–60%), CALR (15–30%), and MPL (1–5%) genes. Some patients may present with extremely high platelet counts with no symptoms, but still holding the high risk of thrombotic/hemorrhagic complications. Treatment methods for those patients with such high platelet counts are mainly cytoreduction. Thrombocytapheresis as a first step has shown significant results in the reduction of platelets count dramatically, with few side effects.

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However, it still needs to be accompanied by another cytoreductive therapy such as hydroxyurea to maintain therapeutic results. There are certain indications and complications associated with thrombocytapheresis [1]. Here we shed light on thrombocytapheresis as a tool for the management of ET.

Case Presentation

Case 1

A 34-year-old male patient, with no past medical history, presented to a private clinic in 2016 with complaints of headache and a couple of episodes of vomiting. CBC showed high levels of platelet counts, so the patient was referred to the hospital. The repeated platelet level was 3,602 × 10^3/μL. The patient had a CT scan of the head, which was unremarkable. Patient peripheral smear showed marked thrombocytosis with mild neutrophilic leukocytosis, and later he had bone marrow done with findings in favor of an MPN, with no evidence of the V617F missense mutation within the JAK2 gene, no evidence of an insertion/deletion mutation within exon 9 of the CALR gene, MPL exon 10 was negative, and FISH analysis using BCR/ABL1 t(9;22)(q34;q11.2) revealed normal hybridization pattern. The patient then had an urgent session of thrombocytapheresis, after which platelets dropped down to 1,700 × 10^3/μL. The patient had non-contributory family history. He was started on cytoreduction therapy with hydroxyurea maintained with regular follow-up till the moment. During this period, the patient had no episode of thrombosis, strokes, bleeding, or any other complaints.

Case 2

A 30-year-old female patient, with no chronic medical illness, was referred from an outpatient clinic in 2016, after visiting for itching and rash. Labs showed elevated platelet levels, so the patient was referred to the hospital for further care. The patient denied any symptoms of headache, blurred vision, or any other complaints, with unremarkable physical examination and negative family history. Initial platelet levels were 2,917 × 10^3/μL. The patient was admitted to the hospital and had a peripheral smear, which showed marked thrombocytosis, followed by bone marrow, showing positive insertion within exon 9 of the CALR gene, no evidence of the V617F missense mutation within the JAK2 gene, with findings consistent with MPN. FISH analysis using BCR/ABL1 t(9;22)(q34;q11.2) revealed normal hybridization pattern. The patient then had 1 session of thrombocytapheresis, after which her platelets dropped down to 1,246 × 10^3/μL. The patient then was maintained on cytoreduction therapy with hydroxyurea, with good response, and is currently on regular follow-up with no complications.

Discussion

ET is a BCR-ABL1-negative MPN, attributed for one-third of cases in the developed world, manifesting with excessive, clonal platelet production. Although approximately half of the patients with ET are asymptomatic at the time of diagnosis, most patients develop thrombotic, vasomotor, or hemorrhagic features at some point during the course of their disease; venous or arterial thromboembolic incidents, including stroke, myocardial infarction, venous thromboembolism, and first-trimester pregnancy loss (either spontaneously or during an otherwise hypercoagulable state). The incident appears to be increased when the white blood cell count is elevated [1–4]. Mostly patients with essential thrombocytosis possess mutations in one of three genes: first, MPL mutations have been associated with around 3–5% of essential thrombocytosis cases. MPL codes for the thrombopoietin receptor protein that promotes the

proliferation of megakaryocytes. The mutations are amino acid substitutions at position 505 in the familial cases or 515 in the sporadic cases. This will cause constitutive activation of the thrombopoietin receptor protein. Second, JAK2 mutations, which possibly turn on the thrombopoietin receptor permanently, causing overproduction of megakaryocytes. JAK2 mutation presents in around 50–60% of patients. Third, somatic mutations in CALR. They are detected in peripheral blood in around 25% of ET cases. CALR mutations are mutually exclusive with JAK2 or MPL mutations. Triple-negative, no JAK2, CALR, or MPL mutation, is present in around 10–15%. There are rare cases that have mutations in the thrombopoietin gene (THPO), which are associated with autosomal dominant hereditary thrombocytosis, and somatic mutations in TET methylcytosine dioxygenase 2 (TET2) [5–8]. The median age at diagnosis is around 60 years, although as many as 20% may be younger than 40 years of age [9]. The cumulative rate of thromboembolism is 1–3% per patient-year. Patients who are in their older age, or have JAK2 mutation, with history of thrombosis and/or cardiovascular risk factors are usually considered high risk for thrombotic complications [1]. Hemorrhagic complications are usually occurring at the mucocutaneous sites (rarely GI) and affecting 1–30% of patients [1], likely due to qualitative and quantitative platelet alterations. The risk is usually stratified by patient/disease-related factors along his comorbidities.

Management of ET patients can become a challenging step, especially in extreme cases, as we report 2 cases of ET presented with extremely high platelet levels, who were almost asymptomatic, with a diagnosis with ET established according to WHO criteria 2016 [10]. Currently, treatment includes low-dose aspirin, which is indicated for thromboprophylaxis in low-risk patients, as it helps to reduce vasomotor symptoms, such as headache and erythromelalgia. In high-risk patients, cytoreductive therapy with hydroxyurea is indicated. Other therapies include interferon-α (treatment of choice in pregnancy) and anagrelide, which is associated with an increased risk of post-ET myelofibrosis. Patients with extreme hemorrhage and thrombocytosis are usually treated to lower the platelet count with medical therapy and/or thrombocytapheresis [1]. Although platelet count does not always predict thrombohemorrhagic complication [1], an assessment of thrombotic and hemorrhagic risk is done for each individual. Patients with ET have higher risk of thrombosis and can be treated with an antiplatelet agent such as aspirin reducing the risk. On the other hand, some patients with platelet counts >1 million/μL will have bleeding associated with an acquired von Willebrand disease [8–13]; although the mechanism of acquired von Willebrand disease in individuals with ET is not fully understood, available evidence suggests that it is not due to impaired platelet function but rather due to an acquired von Willebrand disease, which is caused by proteolytic reduction of von Willebrand factor (VWF) multimers, given an inverse relationship between VWF levels and platelet counts. The VWF large multimer deficiency emerges when platelet counts are around 1,000 to 1,500 × 10^9/L and rises thereafter. Taking aspirin may unmask a latent bleeding tendency and cause severe hemorrhagic complications. It is, therefore, contraindicated in patients with a history of bleeding and an extremely high platelet count (over 1,500 × 10^9/L leading to the acquisition of von Willebrand deficiency). Low-dose aspirin should not be used in patients with evidence of AVWS; however, if indicated, it can be used if the ristocetin level is >30% [1, 14–16].

The intensity and choice of cytoreduction rely on the severity of thrombocytosis and the impending risk for ischemic/hemorrhagic incidents. Patients with ET who have additional cardiovascular and/or thrombotic risk factors or who have active ongoing complications should be treated [17]. Age >60 years, prior thrombohemorrhagic event, and platelet counts >1,500 × 10^9/L confer a high risk for thrombohemorrhagic events in ET, and if patients meet any of these criteria, they should receive cytoreductive treatment [18]. Another reason for thrombopheresis is usually during pregnancy to decrease the chances of recurrent fetal loss in high-risk patients with ET, as rapid cytoreduction is believed to enhance the prothrombotic

factors associated with the dysfunctional platelets. Restoring normal platelet level corrects the short plasma half-life of large VWF multimers with ET, which might be important in patients with AVWS and >1,000–1,500 × 10^9/L platelets [1, 19].

Thrombocytapheresis may be the only available option to achieve rapid platelet count reduction during the first critical days, thus providing symptomatic relief and preventing new or worsening major vascular complications. Usually, each procedure lowers the platelet count by ~30–60% [1]. However, it is important to mention that thrombocytapheresis is only a bridging therapy and does not treat the etiology of hyperthrombocytosis, so maintaining the patient on cytoreduction therapy is essential to prevent platelet rebound after the procedure [1]. It is considered one of the safe procedures, linked with a small number of side effects [20], most commonly, hemodynamic complications, such as vasovagal syncope and citrate-related complications, including citrate toxicity and hypocalcemia [20, 21]. Women are usually more affected by hypotension than men [22]. Other factors affecting the risk of hypotension include the height of the individual, model of apheresis machine, and mode of plasma collection.

Conclusion

Patients with ET carry mutations in JAK, CALR, and MPL genes and around 10–15% may present with triple-negative mutations. Patients with ET can rarely present asymptomatically with extremely high platelet counts. We report the effect of thrombocytapheresis when used as a first-line treatment, showing its remarkable results with fewer side effects to mention.

Acknowledgment

I wish to show my gratitude to the Internal medicine residency program, to Dr. Ahmed Ali Almohammed and Dr. Dabia Hamad Almohanadi for their scientific support.

Statement of Ethics

Written informed consent was obtained from our patients to allow the publication of information.

Disclosure Statement

The authors have nothing to disclose.

Funding Sources

This article was funded by Qatar National Library.

Author Contributions

Mohammad Abu-Tineh: writing the manuscript. Mohamed A. Yassin: writing and editing. The authors contributed equally.

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