Essential Thrombocythemia in a 15-Year-Old Female: Presentation, Workup, and Treatment Considerations in the Pediatric Population

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Abstract

Essential thrombocythemia (ET) is a diagnosis most often seen in adults but can also present in children in rare cases. This article reviews the presentation, diagnosis, and treatment of ET in a 15-year-old female followed by a review of the literature regarding special considerations in the workup, diagnosis, treatment, and follow-up of ET in the pediatric population.

CASE STUDY

A 15-year-old white female with no significant past medical or surgical history presented to her primary care provider following an episode of collapse without loss of consciousness and with associated symptoms of confusion, dizziness, headache, and vomiting with neurologic symptoms, including scotoma and aura.

History

The episode of collapse occurred a few days prior to her presentation, after the patient finished a cross country race. Her mother reported that she looked pale upon finishing the race and then fell to the ground. The only precipitating symptom was a severe pulsatile headache during the race. Following the episode of collapse, she felt unwell and fatigued for the following day. Her past medical history was significant for chronic headaches and migraines beginning at 4 years old and worsening in frequency and severity to daily migraines with aura by 10 years old. Her migraines are often associated with photophobia, phonophobia, and vomiting, which has caused her to miss a significant amount of school.

Her review of systems was negative for current focal neurologic symptoms but was positive for at least two previous episodes of binocular am-

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aurosis fugax. The rest of the review of systems was negative other than the presenting symptoms. Her medications included acetaminophen or ibuprofen as needed for her migraines. She had not been worked up by a neurologist nor had any laboratory studies done to evaluate the etiology of her headaches. There was no pertinent family medical history. She does not smoke or consume alcohol and is a straight-A student.

Physical Examination

The patient was a well-appearing young female in no acute distress. She was 168 cm (5 ft 5 in) tall and weighed 71.1 kg (156.7 lb) with a body mass index of 26.1 kg/m^2. Her vitals were a temperature of 36.2°C (97.2°F), heart rate of 58, respiratory rate of 18, and blood pressure of 114/72 mm Hg from her right arm, sitting. Cardiopulmonary, abdominal, musculoskeletal, and neurologic examinations were unremarkable. Cardiac examination revealed a normal rate and rhythm with no murmurs. Lungs were clear to auscultation bilaterally. Her abdomen was nontender with no hepatosplenomegaly. No focal neurologic deficits were noted.

Diagnostic Testing

Following the collapse, her mother pressed for further workup. A complete blood count (CBC) revealed an elevated platelet count of 850 × 10^9/L, and repeat testing showed a count of 950 × 10^9/L. No abnormalities were noted on the patient's total white blood cell count or hemoglobin level. Differential diagnosis for thrombocytosis includes primary or secondary conditions. Secondary (reactive) thrombocytosis can be caused by iron deficiency anemia, infections, chronic inflammatory states, medications, or neoplasms. Primary thrombocytosis is caused by either essential thrombocythemia (ET) or familial thrombocytosis (FT; Aladily et al., 2017). Since she had persistent thrombocytosis without evidence of a secondary condition and did not have family history of FT, she was placed on low-dose daily aspirin for concern of ET and referred to the local children's hospital for further workup.

A peripheral blood smear showed marked thrombocytosis with large platelets. White blood cell count was 8.3 × 10^9/L, hemoglobin was 14.4 g/dL, hematocrit was 42.6%, and red blood cells were normocytic and normochromic. The rest of the CBC and comprehensive metabolic panel was unremarkable. She was also found to have acquired type 1 von Willebrand disease. Bone marrow biopsy demonstrated a hypercellular marrow with a marked increase in atypical and hyperlobulated large megakaryocytes. Biopsy showed mild fibrosis without an increase in blasts. Molecular analysis was positive for the Janus kinase 2 (*JAK2*) receptor mutation and was confirmed by cytogenetic studies. BCR-ABL1 fusion transcript was not detected. With these findings, she was diagnosed with ET.

Treatment and Management

Initially, the patient was maintained on daily low-dose aspirin because her platelet count was less than one million. However, 3 weeks later, she was still having headaches. Since she was still symptomatic and had a history of amaurosis fugax, which was concerning for thrombotic events, she was placed on cytoreductive therapy after a discussion of the risks vs. benefits of treatment. It was debated between starting her on anagrelide or hydroxyurea, but hydroxyurea was chosen due to tolerability and ease of administration. She was started at a dose of 15 mg/kg, which calculated to be 1,000 mg once daily.

Education included teaching her and her parents that ET cannot be cured and that management includes monitoring for disease progression and preventing further complications. They were educated on the possibility that patients with ET can progress to acute or chronic leukemia as well as myelofibrosis and the need for continued monitoring. They also discussed her seeing a gynecologist to place her on non-estrogen-containing birth control due to the teratogenicity of hydroxyurea.

On follow-up 1 month after starting hydroxyurea, her platelet count decreased to 403 × 10^9/L and her symptoms had completely resolved (Figure 1). She has been stable on the 1,000 mg once daily and 81 mg aspirin once daily, with platelet counts maintaining around 400 × 10^9/L. Current management includes blood counts every 3 months and a yearly bone

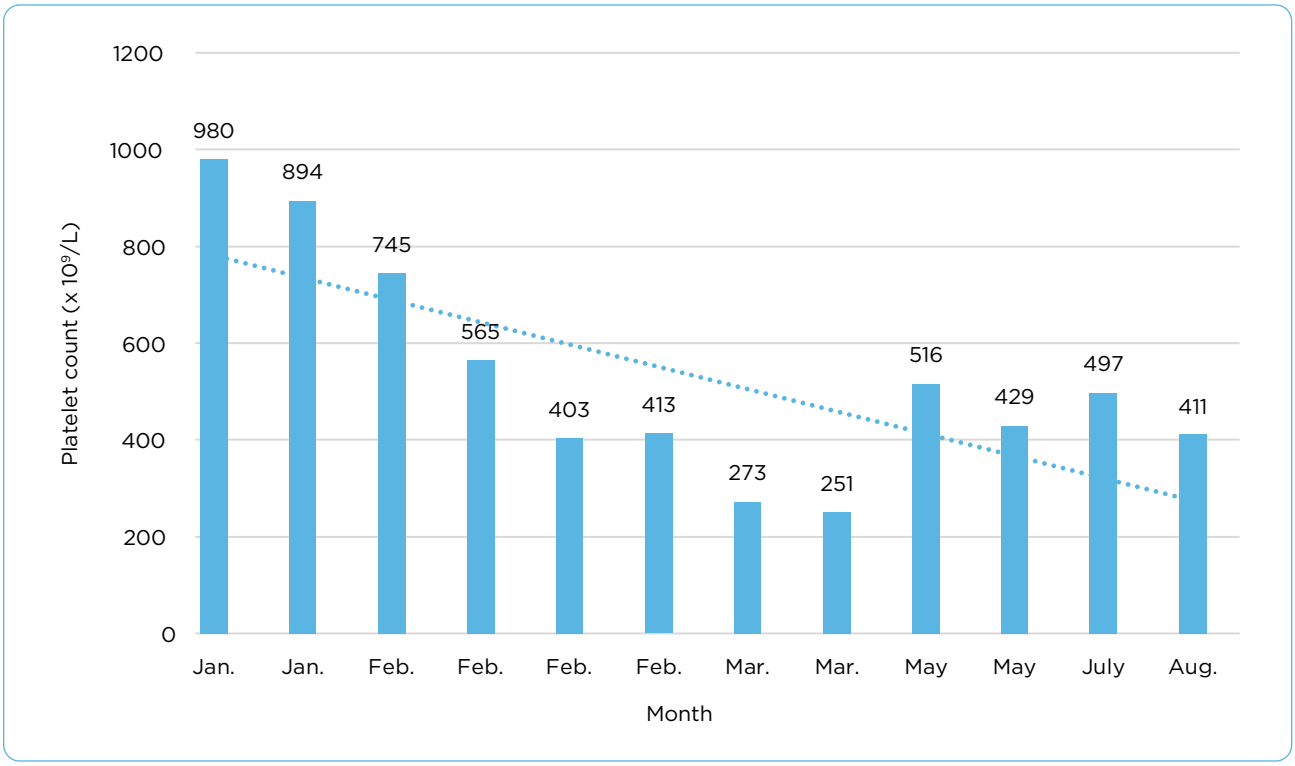

Figure 1. Patient platelet count.

marrow biopsy to monitor for myelofibrosis or preleukemic changes. Currently, she is a healthy 21-year-old who has not had any progression of her ET or any serious complications.

Essential thrombocythemia (ET) is a chronic myeloproliferative neoplasm involving the upregulation of megakaryocyte production. Most patients with ET are diagnosed over the age of 50, and the incidence in pediatric patients is very rare, with an estimated rate of 1 in 10 million (Aladily et al., 2017). It is characterized by persistent thrombocytosis, increased numbers of large megakaryocytes in the bone marrow, increased risk of thrombosis and hemorrhage, and risk for progression to primary myelofibrosis (PMF) or acute myeloid leukemia (AML; Aladily et al., 2017; Giona et al., 2012; Randi et al., 2015).

DIAGNOSIS

The diagnosis of ET follows the World Health Organization (WHO) 2016 criteria (Table 1). Major criteria are a platelet count greater than 450 $\times$ 10^9/L, bone marrow biopsy findings, presence of clonal mutations, and no evidence of reactive thrombocytosis. Typical bone marrow morphology is proliferation of large and mature megakaryocytes with hyperlobulated nuclei. Bone marrow findings must also have no significant increase in left shift of neutrophil granulopoiesis or erythropoiesis (Barbui et al., 2018). However, in children, the bone marrow biopsy can be normal, and so lack of typical findings should not exclude diagnosis of ET (Aladily et al., 2017). In a systematic review by Ianotto and colleagues (2019), one of the studies found that only 76% of young patients with ET had bone marrow biopsies that met the requirements for diagnosis.

Another major criterion for diagnosis of ET is the presence of *JAK2* V617F, calreticulin (*CALR*), or the thrombopoietin receptor (*MPL*) gene mutations (Barbui et al., 2018). In 90% of adults with ET, one of these clonal markers is present (Randi et al., 2015). The *JAK2* V617F mutation is the most common cause of ET in adults and is present at a rate of 50% to 60%, followed by CALR at 25%,

Table 1. WHO Diagnostic Criteria for ET

Diagnosis requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion

Major Criteria

1. Platelet count ≥ 450 × 10^9/L
2. Bone marrow biopsy showing proliferation of megakaryocyte lineage that are large and mature with hyperlobulated nuclei, no significant increase of left shift in neutrophil granulopoiesis or erythropoiesis, and minor increase in reticulin fibers
3. Must not meet diagnostic criteria for BCR-ABL CML, PV, PMF, or other myeloid neoplasms
4. Presence of *JAK2*, *CALR,* or *MPL* gene mutation

Minor Criterion

1. Presence of a different clonal marker or the lack of evidence of reactive thrombocytosis

Note. CML = chronic myelogenous leukemia; PV = polycythemia vera; PMF = primary myelofibrosis.

and MPL at 3% to 5% (Aladily et al., 2017; Giona et al., 2012; Randi et al., 2015). The *JAK2* gene is part of the Janus kinase family of nonreceptor tyrosine kinases and is a signal transducer for hematopoietic cell proliferation. This is a constitutively active mutation that activates the JAK/STAT signaling pathway leading to cellular proliferation. *CALR* and *MPL* are also driver mutations that activate the JAK/STAT pathway (Kucine et al., 2014; Petruk & Mathias, 2020). This causes myeloproliferative neoplasms to develop: ET, polycythemia vera (PV), and PMF (Vannucchi et al., 2017). However, the majority of children do not have one of these clonal markers, which further differentiates pediatric ET from the adult form. This also suggests that the diagnostic criteria are not adequate for ET in a pediatric patient (Aladily et al., 2017; Giona et al., 2012; Ianotto et al., 2019; Randi et al., 2015).

The diagnosis of ET is one of exclusion, and the diagnostic criteria must not be met for BCR-ABL chronic myelogenous leukemia, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms. Minor criterion is the presence of a different clonal marker or the lack of evidence of reactive thrombocytosis. Diagnosis of ET requires all of the major criteria or presence of the first three major criteria and minor criterion (Barbui et al., 2018).

The clinical course in pediatric patients can be significantly different than in adults. Childhood ET is most commonly familial, but it can also occur sporadically, as was the case with the patient described previously (Randi et al., 2015). Most children are asymptomatic, but when symptoms occur, they most commonly include headache and epistaxis (Aladily et al., 2017; Giona et al., 2012). In general, children can have little to no morphologic findings on bone marrow biopsy, lower instance of clonal mutations, lower risk of thrombohemorrhagic events, and a longer disease course than in adults (Aladily et al., 2017).

COMPLICATIONS

The major complications of ET are progression to PMF or AML and thrombohemorrhagic events (Aladily et al., 2017; Giona et al., 2012). Transformation of ET to PMF or AML is one of the most serious complications, resulting in a short median survival and requiring a change in treatment strategy to utilizing ruxolitinib (Jakafi), allogenic transplantation, or intensive chemotherapy. Luckily, in children, transformation seems to occur less frequently than in adults.

Risk for thrombosis or hemorrhage also occurs at a lower rate in children compared with adults with ET; however, this is still a major complication (Agarwal et al., 2015; Aladily et al., 2017; Ianotto et al., 2019). Risk for vascular events is increased with the presence of clonal mutations or very high platelet counts of over 1,500,000/L. However, the occurrence of symptoms and thrombosis can occur independently of the high platelet count. Median platelet count is between 1,100,000/L to 1,700,000/L, and platelet function is usually abnormal (Aladily et al., 2017; Birgegård et al., 2018). In addition, ET has been associated with acquired von Willebrand syndrome, like with our patient. The

rate of occurrence of these two disorders together is uncertain, but in a study conducted by Mital and colleagues (2015), it was found to be present in 20% of patients. The presence of acquired von Willebrand syndrome places a patient with ET at increased bleeding risk, and screening for this concurrent syndrome should be performed.

TREATMENT

Goals of therapy include decreasing platelet count, decreasing symptom burden, decreasing risk of thrombohemorrhagic events and disease progression, and managing special situations, such as pregnancy (Agarwal et al., 2015). Risk stratification in adults is based on age, history of thrombosis or hemorrhage, and platelet count. High-risk patients are classified as being over the age of 60, having a history of thrombosis or hemorrhage, or having a platelet count of over $1,500 \times 10^9$/L. These patients should be treated with cytoreductive medications. Low-risk patients lack these findings, and first-line therapy is aspirin for antiplatelet treatment (Birgegård et al., 2018; Ianotto et al., 2019).

However, it is unknown how well this risk stratification translates to pediatric patients, and there is much debate over which treatments should be utilized in this population. Kucine and colleagues (2014) proposed risk stratification and treatment guidelines for pediatric ET. They proposed that asymptomatic patients should be observed and blood counts should be monitored every 3 to 6 months. Low-risk patients can have symptoms, including hepatosplenomegaly, headaches, erythromelalgia, cardiac risk factors, or additional thrombophilia or bleeding risk factors. They should be managed with aspirin, and their symptoms should be monitored. High-risk patients include those who failed low-risk therapy, have a history of thrombosis or bleeding, or have platelet counts over $1,000 \times 10^9$/L. High-risk patients should be treated with cytoreductive therapy.

Cytoreductive medications are used to reduce platelet counts and the risk of thrombosis or hemorrhage in high-risk patients. However, there are risks associated with these medications. Since patients have a long duration of disease, reducing the risk of medication complications is a major consideration in treatment and a reason why cytoreductive medications should be last line while more conservative treatment with aspirin is preferred. (Aladily et al., 2017; Birgegård et al., 2018; Giona et al., 2012). When utilized, there is debate over which cytoreductive medication should be used in the first line in pediatric patients. European LeukemiaNet recommendations are to use interferons as first-line cytoreductive therapy (Ianotto et al., 2019). However, previous recommendations from other sources have also suggested ANA and hydroxyurea as first-line therapies in pediatric patients (Agarwal et al., 2015; Birgegård et al., 2018). This demonstrates the need for established guidelines on the treatment and management of pediatric patients with ET.

Hydroxyurea has been shown to decrease platelet counts and the risk of thrombotic events, but it is uncertain how this carries over to pediatric patients. It is also uncertain if hydroxyurea should be preferred over other cytoreductive medications in a pediatric patient (Aladily et al., 2017). There are concerns regarding the safety of hydroxyurea and its leukemic transformation potential (Ianotto et al., 2019; Kucine et al., 2014). Patients with ET are at increased risk for leukemic transformation even without receiving hydroxyurea. However, it is difficult to distinguish if hydroxyurea increases the risk of transformation or if this is part of the natural disease course (Birgegård et al., 2018).

Hydroxyurea works by inhibiting DNA synthesis through its effects on ribonucleotide reductase. Due to this, hydroxyurea has been associated with increased chromosomal abnormalities in cultured cells, and causes an increase in carcinogenic potential. The rate of squamous cell carcinoma is estimated to be around 20%, and other skin changes can include skin and nail atrophy, dryness, violaceous papules, and dermatomyositis. Other side effects of hydroxyurea include rebound thrombocytosis when discontinued, gastrointestinal upset, and transient renal abnormalities (Silver & Hasselbalch, 2016). European LeukemiaNet recommends "caution" when utilizing hydroxyurea for treatment in younger patients (Birgegård et al., 2018). However, the relative safety of hydroxyurea has been shown in cohorts of young patients being treated for sickle cell disease (Ianotto et al., 2019; Kucine et al., 2014).

Some clinicians decide to use other cytoreductive agents, like anagrelide (ANA) or interferon alpha instead of hydroxyurea. Anagrelide seems to be associated with a lower risk of leukemogenic transformation than long-term hydroxyurea therapy. This is why ANA has been suggested as first-line therapy in younger patients with ET, but its use remains controversial. The age for this suggestion is also debated as either younger than 40 or 60 years old (Birgegård et al., 2018). However, ANA has varying results in regards to thrombohemorrhagic events compared with other cytoreductive medications. In a study by Birgegård and colleagues (2017), ANA was found to have a lower rate of major thrombosis but a higher rate of major hemorrhagic events. Anagrelide may also lead to an increased rate of cardiovascular effects, such as palpitations and tachycardia. These medications are not benign and require ongoing monitoring. They should be utilized under the guidance of a pediatric hematologist when determined necessary.

Another concern for younger female patients with ET is childbearing. This patient is at increased risk for maternal hemorrhage, thrombosis, placental dysfunction, fetal growth restriction, and loss of pregnancy. In addition, there are no guidelines on managing a pregnant patient with ET. Proposed management strategies have included aspirin, heparin, interferon alpha, or a combination of these medications (Alimam et al., 2016; Maze et al., 2019). Hydroxyurea is not an option during pregnancy because of its teratogenic effects (Schlisser & Hales, 2013). Interferon alpha is accepted in pregnancy for cytoreductive therapy and has not been associated with increased fetal loss. Treatment with aspirin with or without interferon increases live birth rate without significant fetal or maternal adverse effects (Alimam et al., 2016). However, cytoreductive treatment may not be necessary during pregnancy due to a spontaneous decrease in platelet count that is common in pregnant women with ET (Giona et al., 2012). Systematic review of the topic has shown the percentage of live births in patients with ET to be 71.3% compared with approximately 80% in the general population (Maze et al., 2019). These patients should be managed as high-risk pregnancies, but there is a high percentage of successful pregnancies in this population (Alimam et al., 2016; Birgegård et al., 2017). This is an area of ongoing research, and more research needs to be done to risk stratify these patients and develop established management guidelines.

ONGOING MANAGEMENT

Ongoing management of these patients can include monitoring symptoms through the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF). These symptoms can significantly affect quality of life, work productivity, and relationships, and are associated with increased rates of depression and anxiety. The MPN-SAF has been validated for all MPNs and includes 27 items to assess the prevalence and severity of symptoms. The symptoms assessed include fatigue, early satiety, abdominal discomfort, inactivity, difficulty concentrating, night sweats, pruritis, bone pain, fever, and unintentional weight loss. This can be used to assess treatment response and aid in identifying disease progression earlier (Petruk & Mathias, 2020). Signs and symptoms that could indicate disease progression include splenomegaly, weight loss, night sweats, progressive leukocytosis, and thrombocytosis (Agarwal et al., 2015).

Other management components include monitoring medication side effects, regular CBCs to monitor platelet counts, and bone marrow biopsies to assess for progression. Evaluation should also include questions about family history and CBCs of direct family members to evaluate for familial thrombocytosis. Treatment decisions should be made with a pediatric hematologist, and referral to cardiology is indicated due to increased rate of cardiovascular events and risk factors. Referral to neurology can also be considered for persistent headaches or other neurologic symptoms, and for monitoring risk of thrombosis (Agarwal et al., 2015; Giona et al., 2012).

CONCLUSION

Essential thrombocythemia is rare in pediatric patients but should be considered in a child with persistent thrombocytosis. The major complications of ET are thrombosis or hemorrhage and transformation to myelofibrosis or acute leukemia. Children have a lower risk of these complications and a longer disease course and should

be managed more conservatively. Due to the risks and monitoring required with cytoreductive medications, this treatment should be reserved for last-line therapy and should be started under the guidance of a pediatric hematologist. Given the rarity of ET in a pediatric patient, there is uncertainty as to how the established clinical guidelines for adults can be applied to pediatric patients, and more research is needed to develop a consensus on the best approach to managing these patients.

Disclosure

The authors have no conflicts of interest to disclose.

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