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Case Report

Extreme essential thrombocytosis in a healthy asymptomatic 6-month-old child

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ABSTRACT

In healthy child essential thrombocytosis is always an incidental finding during routine check. Essential thrombocytosis (primary thrombocythemia) is a non-reactive, chronic myeloproliferative disorder in which sustained megakaryocyte proliferation leads to an increase in the number of circulating platelets, on the other hand reactive or secondary thrombocytosis is the more common form, with infectious diseases being the most common cause. Mutations in Janus kinase 2 (JAK2), calreticulin (CALR), or myeloproliferative leukemia (MPL) are found in approximately 90% of patients with essential thrombocytosis. We describe a case of extreme thrombocytosis in a healthy 6-month child. She required admission for workup (maximum number of platelets 1900,000/mm^3). With this case, we reviewed the different causes of thrombocytosis in childhood, differential diagnosis, World Health Organization (WHO) criteria for diagnosis of essential thrombocytosis, and the available treatments in case of extreme thrombocytosis.

Keywords: Thrombocytosis essential and reactive, JAK2, CLAR, MPL

INTRODUCTION

Thrombocytosis is defined as a platelet count of more than two standard deviations higher than the upper limit of normal values, in children and adults is defined as an elevated platelet count ≥450×10^9/l. A normal platelet counts ranges between 150–450×10^9/l.[1] Primary thrombocytosis can be due to bone marrow disease, for example, myeloproliferative neoplasm (essential thrombocythemia, polycythemia vera, and others) as shown in Table 1. Secondary (or reactive) thrombocytosis refers to elevated platelet count in the absence of the primary causes. Essential thrombocythemia (ET), one of the pH-negative chronic myeloproliferative neoplasms (MPNs), develops as an acquired clonal defect of myeloid precursor cells driving uncontrolled myeloid proliferation and comprise different entities, such as BCR-ABL-positive chronic myeloid leukemia, chronic eosinophilic leukemia, mastocytosis, some myelodysplastic syndromes, and the three entities within BCR-ABL-negative chronic MPN, i.e., ET, polycythemia vera (PV), and primary myelofibrosis (PMF).[2] Thrombocytosis is the main hematological feature in ET, which, albeit typical of advanced age, is the most common MPN of childhood. World Health Organization (WHO) defines diagnostic criteria for essential thrombocythemia as mentioned in Table 1. Diagnosis of ET requires 4 major criteria or the first 3 major criteria and the minor criterion to be met.[3] Thrombocytosis should be re-evaluated within at least 1 month.

CASE REPORT

A 6-month-old female, medically free, born to 40-year-old female G10 P7+2 she had history of previous two pregnancies with lethal fetal anomalies (passed away) known case of hypothyroidism. Child had no history of neonatal intensive care unit admission, vaccinated till age brought with history of cough, runny nose since 2 weeks ago treated as case of mild bronchiolitis, there was no

history of fever respiratory distress, abnormal movement, shortness of breath, vomiting or poor feeding. On examination child is non dysmorphic, active and playful, not in distress, general examination is normal, mild splenomegaly and no hepatomegaly. Head to toe examination is normal. Abdomen is soft and lax with non-tender. No edema, no skin rash, incidentally child was found to severe thrombocytosis on complete blood count (CBC). Platelet count was 1900,000/mm^3, other two cell lines were normal. child was admitted as a case of thrombocytosis for investigation. A provisional diagnosis of reactive thrombocytosis versus essential thrombocythemia was made and detailed lab panel was sent. During hospital stay platelet never crossed below 1000,000/mm^3. Labs for partial septic with inflammatory markers, iron profile, fibrinogen, platelet function test, coagulation profile were normal. Vitamin D, B12 and folate level were normal, and abdominal ultrasound was normal except mild splenomegaly. Metabolic work up, her ammonia and lactate levels were normal. Direct coombs test was negative. Parents platelet count was normal. Thrombocytosis gene panel was negative for molecular JAK2 V617F and CALR mutation. The targeted pathogenic variant was identified in the MPL gene in homozygous state. During in patient child was started on IV fluids to ensure good hydration and on multivitamin and low dose aspirin to prevent thrombotic complication.

Table 1: WHO defines diagnostic criteria for essential thrombocythemia.

S. no.	Criteria
A	**Major criteria**
1	Platelet count ≥450×10^9/l
2	Bone marrow biopsy showing proliferation, mainly of the megakaryocyte lineage, with increased numbers of enlarged, mature megakaryocytes with hyper lobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers.
3	Not meeting WHO criteria for BCR ABL1 + CML, PV, MF, myelodysplastic syndromes, or other myeloid neoplasms.
4	Presence of JAK2, CALR or MPL mutations.
B	**Minor criterion**
1	Presence of a clonal marker or absence of evidence of reactive thrombocytosis.

Table 2: Causes of thrombocytosis in children.

Primary thrombocytosis	Secondary thrombocytosis
Essential thrombocythemia	Infection
Polycythemia vera	Inflammation
Primary myelofibrosis	Tissue damage
Myelodysplasia with del (5q)	Hyposplenism
Refractory anemia with ring sideroblasts associated with marked thrombocytosis	Post-operative
Chronic myelomonocytic leukemia	Hemorrhage
Atypical chronic myeloid leukemia/childhood	Iron deficiency
Myelodysplastic/myeloproliferative neoplasms, unclassifiable	Hemolysis
Familial thrombocytosis	Drug therapy (e.g., corticosteroids, adrenaline)
	Cytokine administration (e.g., thrombopoietin)
	Rebound following myelosuppressive chemotherapy/splenectomy
	Malignancy

DISCUSSION

ET has an estimated incidence of 1 per 10 million annually.[4] Hereditary/familial thrombocytosis are extremely rare. They share the same clinical aspects of primary thrombocytosis, comprising splenomegaly and the risk of thrombotic complications. Most of them have a Mendelian inheritance, are polyclonal and only affect the platelet lineage, affected genes are usually thyroid peroxidase (TPO) or more frequently, its receptor c-MPL; gain of function mutations in the TPO gene have been described and result in the proliferation of megakaryocytes, the activation of platelets.[4] In reactive/secondary thrombocytosis (ST), children have transitorily increased platelet counts, mostly related to inflammatory conditions (Table 2). Therefore, an isolated finding of thrombocytosis is usually not clinically relevant in children. In contrast, if thrombocytosis is confirmed over at least 3–6 months, it may have a different pathogenesis and clinical impact.

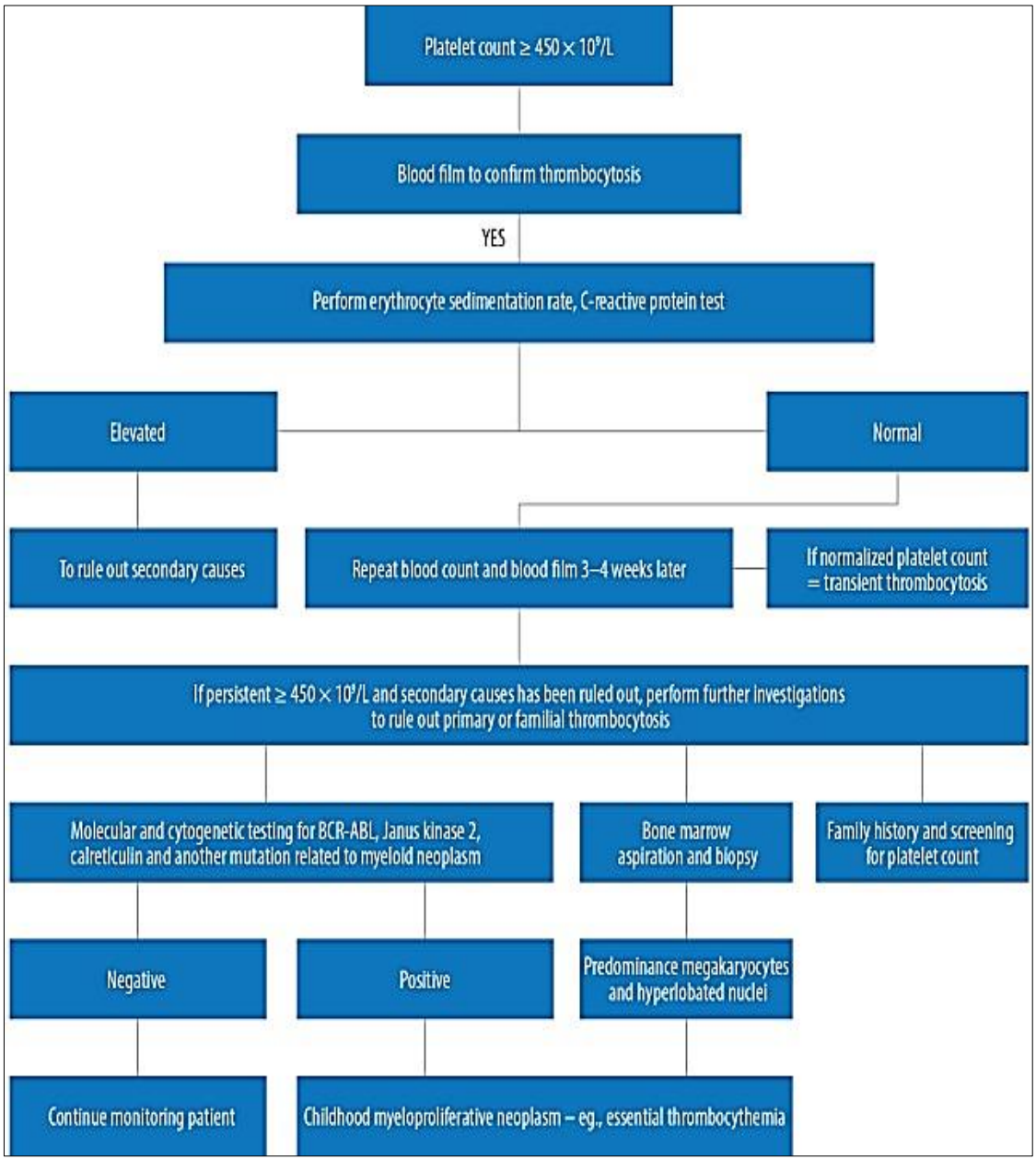

Figure 1: Algorithmic approach for child hood thrombocytosis.

Once thrombocytosis is confirmed, work up is guided to known the cause and differentiate primary from secondary thrombocytosis. Four degrees of thrombocytosis have been described: mild (500,000-700,000/mm^3), moderate (700,000-900,000/mm^3), severe (>900,000/mm^3) and extreme or massive (>1,000,000/mm^3).[5] History taking, proper interpretation of the diagnostic tests and a thorough physical examination (ruling out the presence of visceromegaly or adenopathy), as soon as the patient is admitted, help to guide the diagnosis. ET is characterized by persistently elevated platelet counts greater than 450,000/µl, megakaryocytic hyperplasia, splenomegaly. Suggested approach of laboratory investigation for childhood thrombocytosis is shown in Figure 1, With proper history taking, thorough physical examination, and further investigation, it would be possible to narrow down to the possible differential diagnosis. For ET, WHO defines diagnostic criteria for essential thrombocythemia as mentioned in Table 1 to diagnosis of ET requires 4 major criteria or the first 3 major criteria and the minor criterion to be met.

A clinical course is complicated by thrombotic or hemorrhagic episodes or both. Treatment should be individualized on the basis of risk factors for thrombosis or bleeding. Treatment options range from observation to low-dose aspirin to cytoreductive therapy. In emergencies, plateletpheresis may be useful to achieve a rapid decrease in platelet counts.[6]

A high platelet count can be associated with vasomotor phenomena (headache, visual symptoms, nausea, chest

pain, dysesthesia, aphasia, dysarthria, vertigo, instability, shivering or erythromelalgia), thrombotic phenomena or hemorrhagic complications.[7] As most prevalent causes of thrombocytosis in childhood are secondary , the following tests could be considered: sterile body fluid cultures, acute phase reactants, molecular biology technique for viruses, bacteria and parasites; rule out anemia, of any cause, alterations in red blood cell morphology, peripheral blood film and blood clotting factor assay; consider test to rule out autoimmune diseases; perform imaging tests aimed at ruling out neoplasms, visceromegaly, adenopathy and Kawasaki disease (echocardiogram); assess the need to carry out suction and biopsy of bone marrow; and genetic test for mutations in JAK2, CALR and MPL gene when primary causes is suspected.

Primary thrombocytosis is rare in children. ET is over 60-times more common in adults than children.[5] Managing thrombocythemia in children are aimed to prevent vascular complications. Risk identification as seen in adult patients like age more than 60 years or previous thromboembolic event does not fit completely in pediatric patients as majority of pediatric patient are asymptomatic and do well clinically. A pediatric series by Putti Mc et al showed that very high platelet counts are better tolerated by children and adolescents, with a low frequency of even minor hemorrhages. Microvascular symptoms are common in pediatric ET. Aspirin can be used to control headache or erythromelalgia and doses can be tapered to the minimum according to efficacy.[4] In fact, 1 mg/kg is usually effective for the control of symptoms. Caution is to be used in case of infection by varicella-zoster and influenza virus (for the possibility of hepatotoxicity and Reye syndrome). Aspirin seems to be the most suitable drug. It suppresses thromboxane A2 production, decreasing platelet activation but without reducing the risk of thrombosis. Nor is it clear that a prophylactic anticoagulant (LMWH) is indicated, even with extreme thrombocytosis counts in asymptomatic children, the use of anticoagulants is suggested in both adults and children with deep vein thrombosis which are counted as high-risk individuals. A systematic review of antithrombotic treatments adopted in patients with MPN and a history of Venous thromboembolism (VTE) showed that direct oral anticoagulants and vitamin K antagonist have a comparable, relatively low risk of recurrent thrombosis and bleeding events.[4,5]

Hydroxyurea (HU) and interferon-alpha (IFN-a) or pegylated IFN alpha (Peg-IFNa) are considered first-line therapies for ET at any age. Initially, cyto-reductive drugs such as HU, anagrelide and IFN-a were quite commonly used in thrombocythemic children even in the absence of high-risk factors, high-risk children who have already experienced a thrombotic event (usually the first event leading to diagnosis) need cyto-reduction, together with the addition of antithrombotic drugs.[7] JAK2-inhibitors ruxolitinib is the first developed JAK2 inhibitor, mainly used for MF and approved for HU-resistant polycythemia vera. In asymptomatic children, a wait-and-watch approach is considered the best managing option. This requires careful, strict hematological and clinical observation, and prolonged follow up of 3 to 30 years.

In our case it was genetic mutation MPL gene in homozygous state detected by using an advanced DNA sequencing method, for mutations of the thrombopoietin receptor (MPL), platelet production is stimulated by the interaction of the cytokine thrombopoietin (THPO) with its receptor c-MPL on megakaryocytes and their progenitors with subsequent activation of several downstream pathways, including the JAK/signal transducer and activator of transcription pathway, the phosphatidylinositol 3-kinase pathway, and the mitogen-activated protein kinase pathway.[8-10] The homeostasis of platelet numbers in the blood is maintained by a negative feedback loop, which requires the clearance of THPO from the plasma by c-MPL–carrying megakaryocytes and platelets. The interaction between thrombopoietin (THPO) and its receptor c-MPL regulates downstream cytokine signalling and platelet homeostasis. Hereditary mutations of c-MPL can either result in loss-of-function and thrombocytopenia or in gain-of-function and thrombocythemia (HT).[11-13] Our hematological team has kept child regular follow up initially was on aspirin low dose but as no symptoms have appeared she is off medication; she gaining her mile stones and is immunized as per her age.

CONCLUSION

The diagnosis of ET is rare but not impossible in children. Possible causes like secondary reactive condition and genetic mutations should be kept in mind thus work up is extensive and aim is to rule out all primary and secondary causes of thrombocytosis. The diagnostic WHO criteria for ET can be used in children as in adults, pediatric diagnostic guidelines should consider the possibility of familial hereditary cases. Children with confirmed ET rarely have thrombotic and hemorrhagic events and can be considered as low-risk patients The treatment will essentially consist of supportive measures for asymptomatic essential thrombocytosis. The appearance of vasomotor phenomena must be monitored to initiate aspirin treatment. In the event of complications such as bleeding or thrombosis, acute platelet apheresis will be carried out in order to achieve rapid platelet reduction.

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REFERENCES

1. Dame C, Sutor AH. Primary and secondary thrombocytosis in childhood. Br J Haematol. 2005;129(2):165-77.
2. Barbui T, Thiele J, Tefferi A. Myeloproliferative neoplasms. N Engl J Med. 2017;377:894-5.
3. Arber DA, Orazi A, Hesperian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the

World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127:2391-405.
4. Putti MC, Bertozzi I, Randi ML. Essential Thrombocythemia in Children and Adolescents. Cancers (Basel). 2021;13(23):6147.
5. Yadav D, Chandra J, Sharma S, Singh V. Clinic hematological study of thrombocytosis. Indian J Pediatr. 2010;77:643-7.
6. Harrison CN, Donohoe S, Carr P, Dave M, Mackie I, Machin SJ. Patients with essential thrombocythaemia have an increased prevalence of antiphospholipid antibodies which may be associated with thrombosis. Thromb Haemost. 2002;87(5):802-7.
7. Monagle P, Cuello CA, Augustine C, Bonduel M, Brandão LR, Capman T, et al. American Society of Hematology 2018 Guidelines for management of venous thromboembolism: Treatment of pediatric venous thromboembolism. Blood Adv. 2018;2:3292-316.
8. Indolfi G, Catania P, Bartolini E, Azzari C, Massai C, Poggi GM, et al. Incidence and clinical significance of reactive thrombocytosis in children aged 1 to 24 months, hospitalized for community-acquired infections. Platelets. 2008;19:409-14.
9. Kaushansky K. Historical review: megakaryopoiesis and thrombopoiesis. Blood. 2008;111(3):981-6.
10. Ballmaier M, Germeshausen M, Schulze H, Cherkaoui K, Lang S, Gaudig A, et al. c-mpl mutations are the cause of congenital amegakaryocytic thrombocytopenia. Blood. 2001;97(1):139-46.
11. Wolber EM, Jelkmann W. Thrombopoietin: the novel hepatic hormone. News Physiol Sci. 2002;17:6-10.
12. Stockklausner C, Gehring N, Echner N, Mulla NAA, Kulozik AE. Autosomal recessive hereditary thrombocytosis: functional analysis of a novel C-Mpl mutation resulting in an unsual mode of constitutive receptor activation [abstract]. ASH Annual Meeting Abstracts. 2008;112(11).
13. Zhang B, Ng D, Jones C, Oh ST, Nolan GP, Salehi S, et al. A novel splice donor mutation in the thrombopoietin gene leads to exon 2 skipping in a Filipino family with hereditary thrombocythemia. Blood. 2011;118(26):6988-90.

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