Case Report

Essential thrombocythemia in a child

Diagnostic and therapeutic dilemma

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ABSTRACT

We report an 11-year-old child with essential thrombocythemia (ET), a very rare myeloproliferative disorder among children. Essential thrombocythemia can be complicated by life-threatening thrombosis with a risk of converting into acute leukemia. Cytoreductive therapy may reduce the risk of thromboembolic complications. We usually recommend cytoreductive treatment for asymptomatic adult patients with platelet counts of more than 1.5 million/micro liter, but treatment remains obscure in children. Herein, we report the results of child with ET, treated successfully with hydroxuea.

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Essential thrombocythemia (ET) is a myeloproliferative disorder characterized by excessive proliferation of megakaryocytes and a sustained elevation of platelet count with a relatively benign chronic course.[1] While primary thrombocytosis is rare in children, secondary thrombocytosis occurs frequently.[2] The ET results in high platelet count or thrombocytosis, and is a myeloproliferative disorder with clonal mega-karyocytic proliferation. We can broadly categorize the causes of thrombocytosis as: 1. clonal, including ET and other myeloproliferative disorders; 2. familial; and 3. reactive or secondary.[3] Rarity of this condition obscures the real incidence and prevalence of ET in children. Therefore, application of Polycythemia Vera Study Group (PVSG) criterion, assigned mainly for adults, remains controversial among different authorities for children.[4] In addition to the PVSG criterion, the Thrombocythemia Vera Study Group (TVSG) also formulated a criterion, which, includes mainly the histopathological features of ET and is appropriate to diagnose ET with lower platelet counts in comparison with PVSG criteria.[5] However, the main stay of diagnosis is usually based on the exclusion of secondary causes and presence of persistently elevated platelets in patients' blood samples. Here, we describe an 11-year-old child with incidental finding of an extremely persistent elevation of platelets, diagnosed as ET. We considered both PVSG and TVSG criteria, and began a course of cytoreductive treatment with hydroxyurea (HU).

Case Report. An 11-year-old boy was admitted to the Emergency Room for pneumonia, his complete blood count was normal except for an extremely high platelet count (2,180,000/cc) (normal range [NR]: 150,000-450,000). Regardless, of the physician's advice for further diagnostic tests, his parents refused to take more laboratory tests. Two years later, he was readmitted with upper respiratory tract infection, and his high platelet count alerted the physician in charge, and he was

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referred to a specialist for a further investigation. He was an apparently healthy child, without any previous history of hospitalization, surgery, accident or allergies, or history of major thrombotic or hemorrhagic events. He was a well-nourished boy with normal outdoor activities and normal sleep pattern. His family history was unremarkable except for his father who died of cardiac arrest at age of 33, and had no prior health problem or thrombocytosis; his only younger brother and mother are alive and healthy. On physical examination, he suffers only from mild rhinorrhea which, recovered spontaneously in 3 days. His weight was 42 kg, and his height was 154 cm, which are normal for his age. There was no detectable evidence of mucosal bleeding, organomegaly, or neurological deficit on serial examinations. During the last 2 years his blood sample collections revealed persistently elevated platelet count (average=1,746,769/mm^3), we observed clumps of platelet on most of the blood slides. His blood sample analysis shows normal erythrocyte sedimentation rate, normal iron storage (iron=97 mcg/dl, total iron binding capacity [TIBC] =306 mcq/dl, ferritin=28 ng/ml), normal uric acid level, normal cholesterol, and leukocyte alkaline phosphatase score. However, there was mild elevation in his lactate dehydrogenase level (LDH= 537 IU/L) (NR: 250-500), and triglyceride. Abdominal sonography and echo for internal organs were normal. Bone marrow biopsy showed hypercellular marrow with increased megakaryocyte forming clusters of hyperploid cells. Reticulin staining did not show any significant fibrosis, and bone marrow revealed normal cellular maturation (**Figure 1**).

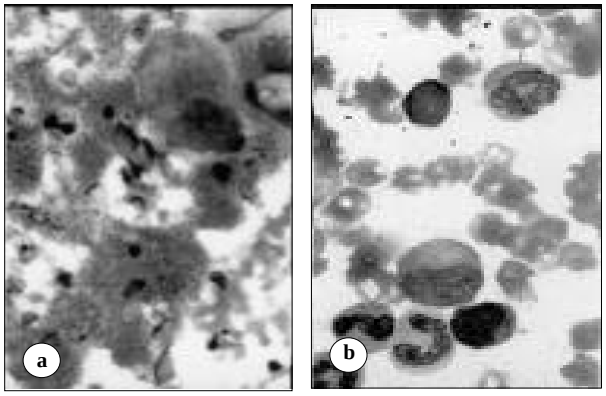

Figure 1 - Giemsa stain of bone marrow showing **(a)** multiple clusters of megakaryocytes with normal maturity, **(b)** Peripheral blood smear demonstrates different blood cells and many platelets in the background.

Cytogenetic-analysis on bone marrow cells showed normal male karyotype, absence of Philadelphia chromosome, and bcr/abl rearrangement. Family history of early sudden cardiac death and parent's concern about thromboembolic consequences of the disorder justified the starting dose of 25 mg/kg/day HU.[6] Dramatically reduced the platelet count to less than 601,000/ml from a high of 2,986,000/ml 5 months earlier just before initiation of the treatment, and then gradually declined to 445,000/ml, and remained stable thereafter in 9 months of follow-up. We checked the platelet count every week during the first month and every other week for the remaining 5 months, and then monthly afterward. We tried gradual reduction of HU after partial response (platelets=435,000) to establish the minimum required dosage. This drug reduction trial resulted in a rapid rises of platelet numbers up to 1,500,000 at point, when the dosage slumped to 15 mg/kg/day. After re-adjustment of drug dose to 20 mg/kg/day, the platelet count returned within normal range (445,000/ml), and remained stationary afterward (**Table 1**).

Discussion. Frequent inclusion of platelet counts in automated blood analysis, consequently, results in more detection of asymptomatic individuals, with incidental finding of thrombocytosis every day, consisting of a heterogeneous group of

Table 1 - Blood cell count profile during selected follow-up intervals.

Blood cell count profile	Normal ranges	Before treatment	After 5 months	After 9 months
Platelet count	150000-450000/ml	2986000/ml	601000/ml	445000/ml
Hemoglobin	13-18 gr/dl	13.2 gr/dl	10.3 gr/dl	11.2 gr/dl
Hematocrit	41.53%	44.3%	31.6%	32%
WBC count	4000-11000/ml	10500/ml	2600/ml	29000/ml
Hydroxyurea dosage		25 mg/kg/d	20 mg/kg/d	20 mg/kg/d

WBC - white blood cell

related disorders, including ET.[3] Essential thrombocytosis is one of the chronic myeloproliferative disorders similar to polycythemia vera, chronic myelogenous leukemia, and myelofibrosis with or without demonstrable myeloid metaplasia. Almost all the cases of thrombocytosis in children are secondary. The annual incidence of newly diagnosed primary thrombocytosis in childhood is approximately one per 10 million; 60 times lower than in adults.[7] Based on the criteria of the PVSG, approximately 75 children with essential thrombocytosis have been reported between 1966 and 2000.[8] In addition, the rarity of the condition, the higher proportion of thrombocytosis, and its unknown natural history put more uncertainties in accurate diagnosis of this condition in children. Randi et al,[9] earlier described children whose platelet numbers steadily declined in their adolescence, a condition that was named idiopathic thrombocytosis.

On the other hand, controversies exist in many aspects of treatment in children, and also in adults. Studies show that thrombosis is the most common complication. Whereas only a low number of children develop thrombosis or hemorrhages, many authors still recommend treatment with cell reducing agents on platelet count levels of more than 1-1.5 million platelets per cubic centimeter of blood samples.[10] In adults, HU is the mainstay of treatment and anagrelide (Agrylin) closely follows the former drug in application, however, studies concerning the usage of anagrelide have been performed only on adult patients, and the leukemogenic potential of HU in children is not known; and there is no specific information comparing anagrelide in children with its use in other age groups. Moreover, there is no study to show the efficacy of anagrelide in reducing the hemorrhagic or thrombotic complications of high platelet levels in children. Anagrelide is also more expensive than the former drug and therefore, its usage is limited in developing countries. A long term cohort study suggests that HU is more effective than anagrelide in preventing thrombosis in the young, apparently without an increase in leukemic risk.[10] There are theoretic reasons to support the superiority of HU as an anti-thrombotic drug, besides its platelet lowering effect. As a general myelosuppressive agent, HU also affects polymorphonuclear leukocytes (PMNs) and red blood cell counts, and there is growing evidence in the literature that these cells play a major role in the pathogenesis of thrombosis, also in ET patients.[11] However, recent studies reported no increased incidence of leukemic or neoplastic transformation after long-term treatment with HU in young adults (19–49 years) with primary thrombocytosis and in children with severe sickle cell disease.[12]

In conclusion, treatment with HU is a promising approach for children with ET. It should be considered as first line therapy due to its selective activity against platelet production, no side effect for 2 years, suspected negligible carcinogenic effect and low cost.

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