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Severe Thrombocytopenia with Iron Deficiency Anemia

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Abstract

Objective—Although severe thrombocytopenia has been reported among children with iron deficiency anemia, the presence of both anemia and thrombocytopenia can suggest serious or malignant bone marrow dysfunction, requiring further work-up. This paper reviews the management and outcomes of patients with the diagnosis of iron deficiency anemia presenting with severe thrombocytopenia.

Methods—We present four pediatric patients with iron deficiency anemia and severe thrombocytopenia at initial presentation. Charts were reviewed after approval by the institutional review boards at both St. Jude Children's Research Hospital and LeBonheur Children's Medical Center in Memphis, Tennessee.

Results and Conclusions—All four patient's hemoglobin concentrations and platelet counts normalized within one to three weeks of initiating iron supplementation, suggesting that in such patients iron supplementation can obviate the need for invasive diagnostic procedures. In addition, these patients all had a platelet "overshoot" phenomenon during iron therapy prior to normalization of platelet counts, the mechanism of which is still unknown. The literature exploring the mechanism behind our clinical findings is reviewed.

Keywords

Anemia; iron deficiency; thrombocytopenia; children

Introduction

Iron deficiency is the most common etiology of anemia in children worldwide. Although the prevalence of iron deficiency has steadily declined among infants in the United States owing to a successful initiative to improve dietary iron intake [1], children from low-income families remain at high risk for developing anemia [2]. If left untreated, iron deficiency anemia can become severe [3] and cause lethargy, pallor, tachycardia, tachypnea, irritability, decreased appetite, failure to thrive, and congestive heart failure.

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Iron deficiency can also affect the platelet count. Most patients with iron deficiency will have normal or elevated platelet counts, some higher than $1,000 \times 10^9/L$ at diagnosis [3]; thrombocytopenia in association with iron deficiency is relatively rare. In a case series of 42 children with severe iron deficiency anemia, only 1 patient (2.4%) had a platelet count less than $100 \times 10^9/L$ [4]. Similarly, only 2 of 86 (2.3%) adult women with iron deficiency anemia had thrombocytopenia [5]. Although thrombocytopenia has been previously reported in association with iron deficiency [6,7], the frequency of this finding and the timing of platelet recovery after iron administration are unknown. We discuss four pediatric patients who presented with iron deficiency anemia and platelet counts $<50 \times 10^9/L$. Within a few weeks of iron supplementation, their platelet counts rose to elevated values before normalizing, coincident with recovery of the hemoglobin concentration.

Case Presentations

Patient 1 is an 18-month-old male referred for microcytic anemia 10 days after a tonsillectomy and adenoidectomy. He had a hemoglobin of 5.4 g/dL and a platelet count of $18 \times 10^9/L$ (for detailed data of all patients see Table 1). No postoperative bleeding had occurred to explain his anemia. He consumed a gallon of cow's milk daily, and had palmar and plantar pallor, angular stomatitis, and spoon shaped nails. He had no evidence of bone marrow failure or malignancy on physical examination or peripheral blood smear, so he was started on an oral iron polysaccharide to treat iron deficiency anemia.

Patient 2 is a 19-month-old male who presented with a 2-day history of worsening emesis, fever, and recent exposure to another child with a viral illness. The patient's sole source of nutrition was five 9-oz. bottles of cow's milk daily. He had been previously diagnosed with iron deficiency, but no iron supplementation had been initiated. On admission, the patient had pale mucous membranes, conjunctival pallor, a hemoglobin of 2.3 g/dL, and a platelet count of $48 \times 10^9/L$. He received packed red blood cells (PRBCs) and was orally supplemented with iron polysaccharide.

Patient 3 is a 16-year-old female who presented with a 3-week history of menorrhagia associated with worsening weakness and dizziness. She had been diagnosed with dysfunctional uterine bleeding and hospitalized for anemia associated with thrombocytopenia previously, which had responded to iron supplementation and oral contraceptive therapy. Her physical exam was unremarkable. She had a hemoglobin of 5.8 g/dL and a platelet count of $7 \times 10^9/L$. During hospitalization, she was transfused with PRBCs and platelets because of continued mucosal bleeding. She was restarted on iron polysaccharide supplementation before discharge.

Patient 4 is an 18-year-old African-American female who presented with dyspnea and a normal physical exam. She had a hemoglobin of 4.8 g/dL and a platelet count of $46 \times 10^9/L$ with a single abnormal cell on peripheral smear that was concerning for a blast. She was transfused with PRBCs because of her respiratory symptoms. During hospitalization, her bone marrow evaluation showed no evidence of malignancy but confirmed the diagnosis of severe iron deficiency anemia with thrombocytopenia (Figure 1).

All patients presented with hemoglobin concentrations below 6 g/dL and platelet counts below $50 \times 10^9/L$ (Table I). Only one patient had bleeding symptoms, and she did not have spontaneous bleeding, rather increased menstrual bleeding. No patients were thought to have idiopathic thrombocytopenic purpura (ITP) coincident with their iron deficiency presentation. No patient received steroids, intravenous gamma globulin, or anti-D antibody for platelet support. The timing of follow up blood counts varied, but all patients had a rapid rise in their platelet counts to elevated values before normalizing, coincident with increased

hemoglobin concentrations. Within three weeks of initiating oral iron supplementation, all patients had normal platelet counts.

Discussion

Iron deficiency anemia is a common condition that rapidly improves with oral iron supplementation. The diagnosis is made by taking the nutritional history, performing a physical examination, and identifying hypochromic, microcytic anemia on peripheral blood smear. Treatment with oral iron usually increases the hemoglobin concentration by at least 1 g/dL within 1 month of starting iron supplementation [2]. Often, iron deficiency is associated with normal or elevated platelet counts [8].

In contrast, anemia that occurs in combination with severe thrombocytopenia is unusual and may suggest other diagnoses such as bone marrow failure, Evan's syndrome, aplastic anemia, or malignancy. Over 40 years ago, Gross and colleagues [9] reported thrombocytopenia in association with iron deficiency anemia, but no patients had platelet counts $<50 \times 10^9/L$. Lopas et al also identified two in a series of five patients with platelet counts $<50 \times 10^9/L$ with iron deficiency, both with bone marrow aspirates showing a decreased number of megakaryocytes. Both the platelet counts and megakaryocytes on bone marrow aspiration increased in response to iron therapy in these two children. This was the first time the combination of iron deficiency and severe thrombocytopenia was described in detail in children [6]. Most recently, Perlman et al. [7] described six children with iron deficiency and thrombocytopenia, two of whom had platelet counts $<50 \times 10^9/L$. Both of these patients had bone marrow aspiration showing an increase in the number of megakaryocytes. When these two patients were treated with iron therapy, both responded by increasing their platelet counts by at least tripling their initial value within the first 24 hours of treatment [7].

Each of our four patients presented with low hemoglobin concentrations due to iron deficiency and had severe thrombocytopenia, but only one had symptoms or signs suggestive of aplastic anemia or leukemia. In all patients, oral iron supplementation was initiated and their peripheral blood counts normalized rapidly.

Classically, an increasing reticulocyte count is a reliable way to confirm iron responsiveness during the initial period of observation and supplementation. In patients with concomitant thrombocytopenia, a rapid rise in the platelet count also can serve as evidence of an appropriate hematological response to iron replenishment [6,7]. Figure 1 shows the changes in hemoglobin concentration and platelet count for Patient 4 during oral iron supplementation. After initiation of iron therapy, a "rebound" thrombocytosis to a maximum platelet count of $1497 \times 10^9/L$ occurred. This increase to supra-normal levels occurred in Patients 1, 3 and 4, in whom platelet counts increased by more than $700 \times 10^9/L$ within 2 weeks of initiating oral iron treatment, with a peak of approximately $1500 \times 10^9/L$ transiently in Patients 1 and 4. A platelet count was unavailable for Patient 2 until day 24 of treatment, at which time it was normal. No clinical evidence of thrombosis was seen in any of these patients despite the very elevated platelet counts during this time.

In iron-deficient mice, thrombocytosis is thought to occur because of an increase in EPO activity and secondary stimulation of megakaryopoiesis [10]. As iron stores become replete, competition for iron between erythrocyte and megakaryocyte precursors seems to favor the former, and platelet counts return to baseline values. Bilic and Bilic have suggested reactive thrombocytosis occurs in humans since EPO and thrombopoietin (TPO) have strong sequence homology, and renal failure patients receiving recombinant erythropoietin often develop elevated platelet counts [11]. This hypothesis has been debated by several authors,

however, who note that some patients with iron deficiency anemia have normal or low platelet counts, while patients with conditions associated with high EPO levels, such as thalassemia, do not routinely have elevated platelet counts [12, 13]. Furthermore, Broudy et al have shown that EPO and TPO display no cross competition for receptor binding despite their structural and functional similarity [14]. Our initially thrombocytopenic patients developed thrombocytosis within 2 weeks of initiating iron therapy, when EPO levels are expected to decrease as the hemoglobin concentration increases. This platelet response to EPO level suggests that complex and potentially undiscovered mechanisms underlie this process, which could result from a “resetting” of the erythrocyte and platelet producing systems in the bone marrow in the face of iron repletion. Clinically, the platelet count normalization with iron therapy can eliminate the need for further diagnostic evaluation of thrombocytopenia in cases of severe iron deficiency anemia.

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Figure 1. Time to hemoglobin and platelet recovery after initiation of iron

This graph depicts the rise in hemoglobin concentration and platelet counts from the initiation of iron supplementation (day 0) in Patient 4.

Table 1
Characteristics of patients presenting with severe iron deficiency anemia and thrombocytopenia

Patient	Age	Gender	Hemoglobin (g/dL)		Platelet count ($\times 10^9/L$)		Initial white blood cell count ($\times 10^3$)	Initial MCV (fL)	Initial ferritin (ng/mL)
			Initial	During Iron Therapy (day)	Initial	Maximum value during iron therapy (day)			
1	18 months	Male	5.4	7.1 (day 13)	18	1538 (day 13)	14.2	53	17.7
2	19 months	Male	2.3	10.3 ^a (day 24)	48	446 (day 24)	7.5	53	2.9
3	16 years	Female	5.8	8.9 ^a (day 10)	7 ^b	802 (day 10)	6.0	60	*
4	18 years	Female	4.8	7.7 ^a (day 10)	46	1497 (day 10)	4.7	57	2

MCV, mean corpuscular volume.

* Serum iron 18 mcg/dL (normal: 24–154); transferrin 371 mg/dL (168–336); iron saturation 3% (20–50%); total iron binding capacity 553 mcg/dL (250–501).

^aReceived packed red blood cell transfusion.

^bReceived platelet transfusion.