Severe Thrombocytopenia Associated with Iron Deficiency

Mahendra K. Gupta, MD
Gardith Joseph, MD

Iron deficiency is well known to cause thrombocytosis. However, iron deficiency may also lead to thrombocytopenia. This has been described in both children and adults.[1–5] Although the exact mechanism of thrombocytopenia associated with iron deficiency is unknown, iron is postulated to have a role in the synthesis of platelets and in the regulation of thrombopoiesis. This article presents the case of a woman with severe iron deficiency anemia and thrombocytopenia. After blood transfusions and oral iron therapy, her platelet count rose to normal; it continued to rise and she developed thrombocytosis. This case demonstrates the effect of iron on thrombopoiesis and provides an insight into the pathogenesis of thrombocytopenia associated with iron deficiency.

CASE REPORT

Patient Presentation

A 50-year-old African American woman was admitted to our institution because of marked fatigue, dizziness, shortness of breath, and vaginal bleeding. She had a history of menorrhagia for more than 2 years resulting from uterine leiomyoma, for which she had not received any treatment. She was not taking any prescription or nonprescription medicines.

Physical Examination

Physical examination revealed a blood pressure of 110/60 mm Hg, a heart rate of 110 bpm, a respiratory rate of 20 breaths/min, and a temperature of 98°F. She was markedly pale and was not icteric. No petechiae, ecchymoses, or purpuric lesions were noted. She had no lymphadenopathy. Lungs were clear, and cardiac auscultation revealed a grade 2/6 to 3/6 systolic flow murmur. Abdominal examination revealed a uterus palpable at the level of the umbilicus. The liver and spleen were not palpable. Pelvic examination showed vaginal bleeding. No bleeding from any other site was observed.

Laboratory Evaluation

Initial laboratory data are summarized in **Table 1**. Her hemoglobin level was 1.6 g/dL (normal, 12–16 g/dL) and her platelet count was $23 \times 10^3/mm^3$ (normal, $150–450 \times 10^3/mm^3$). Results of iron studies were consistent with a diagnosis of iron deficiency anemia. There was no clinical or laboratory evidence of hemolysis. A peripheral blood smear showed marked microcytic hypochromic cells with decreased numbers of platelets.

Treatment and Clinical Course

The patient was treated with blood transfusions and received 5 units of packed erythrocytes over a period of several days. On day 1, she also received a transfusion of 6 units of platelets and was started on conjugated estrogens (Premarin) to control vaginal bleeding. Her symptoms improved, and over the next 4 days, her bleeding gradually resolved. She was started on oral iron supplementation (ferrous sulphate 325 mg 3 times daily) on day 2. On day 6, she was discharged home, was instructed to continue taking oral iron supplements, and was scheduled for hysterectomy at a later date.

Five days after she was discharged (day 11), the patient was readmitted because of continued vaginal bleeding. Her platelet count at this time was $502 \times 10^3/mm^3$. Her serial blood counts from the day of initial admission are shown in **Table 2**. She had been taking the iron supplements as instructed. A bone marrow aspiration and biopsy at this time showed hypercellular marrow and a decreased myeloid/erythroid (M/E) ratio, with increased numbers of erythroid cells and megakaryocytes. A Prussian blue stain of her bone marrow aspirate revealed that iron stores were markedly

Dr. Gupta is a Fellow and Dr. Joseph is the Fellowship Program Director, Department of Hematology-Oncology, Brookdale Hospital Medical Center, Brooklyn, NY.

Table 1. Laboratory Results for Case Patient on Admission to Hospital

Test	Result
Leukocyte count	$7.3 \times 10^3/mm^3$
Hemoglobin	1.6 g/dL
Hematocrit	6.7%
Platelet count	$23 \times 10^3/mm^3$
MCV	67 μm^3
Serum iron	27 µg/dL
TIBC	444 µg/dL
Serum ferritin	14.4 ng/mL
Serum vitamin B_{12}	442 pg/mL
Serum folate	5.1 ng/mL
Blood glucose	99 mg/dL
BUN	5 mg/dL
Creatinine	0.7 mg/dL
AST	28 U/L
ALT	25 U/L
Total protein	7.3 g/dL
Total bilirubin	1.4 mg/dL
LDH	549 U/L
ANA	Negative
Reticulocyte count	1.8% of erythrocytes

ALT = alanine aminotransferase; ANA = antinuclear antibody; AST = aspartate aminotransferase; BUN = blood urea nitrogen; LDH = lactate dehydrogenase; MCV = mean corpuscular volume; TIBC = total iron-binding capacity.

decreased. No other primary bone marrow abnormality was evident. She underwent hysterectomy on the following day (day 12) and was discharged home 5 days later. The patient continued to receive iron therapy (325 mg 3 times daily), and a repeat platelet count on day 28 was normal (Table 2).

DISCUSSION

Iron deficiency has been reported to cause both thrombocytosis and thrombocytopenia, although very few cases of thrombocytopenia have been reported. The mechanisms involved are not well understood, although iron has been said to have both synthetic and regulatory roles in thrombopoeisis.[6]

The patient described in this report initially had thrombocytopenia. Following blood transfusions and oral iron therapy for her anemia, she developed thrombocytosis (Table 2). No cause of thrombocytopenia other than iron deficiency was detected in this patient.

Bone marrow biopsies performed while a patient is thrombocytopenic usually show decreased numbers of megakaryocytes and an increased M/E ratio.[2] In the present case, a bone marrow biopsy was not performed at this stage. However, a bone marrow biopsy performed after approximately 10 days of oral iron therapy and after her thrombocytopenia had resolved showed erythroid hyperplasia, an increase in the number of megakaryocytes, and a decreased M/E ratio. These findings are consistent with findings from other case reports.[2,7]

These bone marrow findings may reflect a stimulatory effect of iron on erythroid and megakaryocytic cells. Using experimental animal models, Karpatkin and colleagues[6] described a dual role of iron in thrombopoiesis. The researchers phlebotomized guinea pigs and found that chronic blood loss resulted in a 1.4-fold increase in platelet count, whereas chronic blood loss and concomitant iron therapy resulted in a 2.5-fold increase in platelet count through a significant increase in megakaryocyte number. They also found that in animals that were acutely bled while on an iron-deficient diet, megakaryocyte count decreased, indicating that iron is required for platelet production.

After the role of iron was demonstrated, Kiem et al[7] showed that iron is present in platelets in a concentration of approximately 12.28 µg/g, further supporting the hypothesis of Karpatkin and colleagues that iron may have a functional role in controlling platelet production. Karpatkin and Freedman[8] showed that iron is required for platelet protein synthesis. Based on their observations, they proposed a 2-compartment model for the role of iron in maintaining platelet counts and in the changes leading to reactive thrombocytosis.

In the "inhibitor" compartment of the model, iron either directly or indirectly inhibits the rise in platelet count above steady state levels via an unknown mechanism. This postulated mechanism accounts for the thrombocytosis that often occurs after iron removal via blood loss or after adherence to an iron-deficient diet. In the "essential component" compartment of the model, iron is required for the synthesis or production of platelets. Thus, when iron deprivation occurs, it first affects the inhibitor compartment, leading to thrombocytosis; once the iron deficiency is severe enough to deplete the iron in the essential component compartment, thrombocytopenia occurs.

The case patient had severe iron deficiency, as manifested by a hemoglobin level of 1.6 g/dL and abnormal iron study results. Therefore, at the time of her initial

Table 2. Serial Blood Test Results for Case Patient

Day	Hemoglobin (g/dL)	Hematocrit (%)	Platelet Count (cells/mm^3)	Leukocyte Count (cells/mm^3)	MCV (μm^3)	Reticulocyte Count (% of erythrocytes)
1	1.6	6.7	23×10^3	7.3×10^3	67.0	1.8
3	6.5	19.4	52×10^3	11.0×10^3	79.6	2.6
5	7.9	23.4	192×10^3	10.5×10^3	80.1	N/A
6	10.0	30.1	316×10^3	10.2×10^3	81.9	N/A
11	8.1	26.6	502×10^3	7.8×10^3	86.3	N/A
14	8.8	27.9	832×10^3	9.8×10^3	84.4	6.1
28	9.2	32.0	410×10^3	8.4×10^3	86.2	N/A

MCV = mean corpuscular volume; N/A = data not available.

Day 1 is the day of admission to the hospital.

presentation, the iron store of the essential component compartment was exhausted and thrombocytopenia ensued. When iron was replaced in the form of packed erythrocyte transfusions and oral iron supplementation, thrombopoiesis occurred and the platelet count returned to normal by day 6 (Table 2). Because she continued to bleed while on oral iron replacement therapy, however, the patient progressed to thrombocytosis owing to secondary overshoot resulting from the function of iron in the inhibitor compartment.

The level of iron deficiency at which these two aspects of the model exist has not been determined. Review of prior reported cases of thrombocytopenia associated with iron deficiency indicates that patients with thrombocytopenia had severe anemia, with hemoglobin levels ranging from 1.75 to 5.6 g/dL. (**Table 3**). The patient presented in the current report had an initial hemoglobin level of 1.6 g/dL. Thus, the previous case reports and our case support the 2-compartment model of thrombopoiesis.

CONCLUSION

The case presented, in which iron deficiency–associated thrombocytopenia was followed by thrombocytosis following administration of iron therapy, supports the 2-compartment model of the role of iron in maintaining platelet counts. Based on our report and others (Table 3), we propose that iron deficiency–associated thrombocytopenia occurs only in the presence of severe iron deficiency, as evidenced by very low hemoglobin levels. Careful observation of platelet levels following treatment for iron deficiency may lead to detection of more cases. **HP**

Table 3. Hemoglobin Levels and Platelet Counts in Case Reports of Thrombocytopenia due to Iron Deficiency

Report	Hemoglobin (g/dL)	Platelet Count (cells/mm^3)
Lopas and Rabiner* (5 cases)	2.1	42×10^3
	3.2	100×10^3
	3.8	197×10^3
	1.75	38×10^3
	4.0	50×10^3
Berger and Brass†	3.0	33×10^3
Sonneborn‡	5.2	40×10^3
Beard and Johnson§	5.6	77×10^3
Gross et al¶	4.0	120×10^3
Present case	1.6	23×10^3

*Data from Lopas H, Rabiner SF. Thrombocytopenia associated with iron deficiency anemia. A report of five cases. Clin Pediatr (Phila) 1966;5:609–16.

†Data from Berger M, Brass LF. Severe thrombocytopenia in iron deficiency anemia. Am J Hematol 1987;24:425–8.

‡Data from Sonneborn D. Letter: Thrombocytopenia and iron deficiency. Ann Intern Med 1974;80:111.

§Data from Beard ME, Johnson SA. Thrombocytopenia and iron deficiency anaemia in a patient with alpha1-thalassemia trait. Response to iron therapy. Case report. Acta Haematol 1978;59:114–8.

¶Data from Gross S, Keefer V, Newman AJ. The platelet in iron deficiency anemia. The response to oral and parentral iron. Pediatrics 1964;34:315–23.

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