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Iron Deficiency Thrombocytopenia: A Case Report and Review of the Literature

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Abstract

Iron deficiency is a common cause of anemia in premenopausal women. Thrombocytopenia is rarely found in association with iron deficiency anemia (IDA), and its mechanism is not fully understood. Here, we present the case of a 41-year-old African-American woman who was found to have severe asymptomatic thrombocytopenia (platelet count 22,000/μL) in association with more moderate IDA (hemoglobin 8.5 g/dL). Both cytopenias resolved with oral iron replacement therapy in the absence of other therapeutics, such as corticosteroid therapy, and a diagnostic workup revealed no other cause for thrombocytopenia. We conclude that iron deficiency-associated thrombocytopenia should be considered in any case of thrombocytopenia accompanying IDA. Response of both anemia and thrombocytopenia to iron therapy should obviate the need for expensive evaluations and bone marrow examination.

Keywords: Blood platelets; Iron; Iron-deficiency anemia; Thrombocytopenia

Introduction

Iron deficiency is a common cause of anemia and occurs most commonly in premenopausal women, in which population the prevalence may reach as high as 11%. A normal to elevated platelet count is usually found in association with iron deficiency anemia (IDA); when present, thrombocytosis may result from the induction of thrombopoiesis by increased levels of erythropoietin [1]. Thrombocytopenia is far less frequently reported in IDA and its mechanism is not fully understood [2]. IDA patients with thrombocytopenia may be more severely iron deficient than those without thrombocytopenia [3].

Menorrhagia due to leiomyomata is a common cause of IDA in premenopausal women [4]. The presence of coexistent thrombocytopenia has been reported to accompany the IDA and menorrhagia in rare cases, and in all published cases the platelet count normalized with iron repletion [2,5-8].

Herein we present the case of a 41-year-old woman who with severe thrombocytopenia associated with asymptomatic and comparatively moderate IDA. Both anemia and thrombocytopenia resolved with iron replacement alone, as occurred in other published cases. Uniquely, the thrombocytopenia was quite slow to resolve in this case, lagging significantly behind improvement in the anemia.

Case Summary

A 41-year-old African-American woman presented to the primary care clinic to enroll in routine care. Her main complaints were unrelated to this case, but she did experience dull left lower quadrant pain that usually occurred at the time of her menses. She had had some laparoscopic myomectomy 14 years previously for fibroids with dysmenorrhea and bleeding; since then, her menses had occurred about every 28 days and lasted 2-3 days without excessive bleeding or metrorrhagia. She denied fatigue, shortness of breath, palpitations, neurologic deficits, and bleeding or bruising at any site. There was no personal or family history of bleeding disorders. She was not sexually active and did not drink alcohol, smoke cigarettes, or use illicit substances. She was a longtime vegetarian.

The physical examination revealed a blood pressure of 118/77 mmHg, a heart rate of 73 bpm, a respiratory rate of 18 per minute, oxygen saturation of 100% while breathing ambient air, a temperature of 98.8 degrees Fahrenheit, and a body mass index of 31. She was pleasant and somewhat anxious-appearing but in no distress. The exam was otherwise noteworthy for pale conjunctivae and mild left lower quadrant abdominal tenderness on deep palpation without mass, hepatosplenomegaly, rebound, or guarding noted. There were no petechiae, purpurae, or enlarged lymph nodes.

Initial laboratory data included platelet count 22,000/uL and hemoglobin 8.5 g/dL. Marked anisocytosis, microcytosis, and hypochromia were noted on the blood smear. Hematologic data are shown in the Table 1.

Serum iron and ferritin were diagnostic of iron deficiency (Table 1). Comprehensive metabolic panel, urinalysis, stool occult blood, pregnancy test, and serologic tests for human immunodeficiency virus (HIV), hepatitis C, hepatitis B, and syphilis, antinuclear antibody, tissue transglutaminase antibodies (IgA and IgG), quantitative immunoglobulins, and hemoglobin fractionation were negative or normal. Intrinsic factor and parietal cell antibodies were detected in the serum.

The patient was started on oral iron replacement therapy. Parenteral iron was not given. The hemoglobin and hematocrit showed good recovery by Day 73, while the platelet count remained low (45,000/μL) on Day 73, was still below normal on Day 148, and appeared to take between 6 and 15 months to normalize completely. She continued to feel well. Upper endoscopy revealed gastric mucosal erythema without masses or ulcerations; random biopsies demonstrated focal active chronic gastritis with no Helicobacter pylori on Giemsa stain.

Discussion

Thrombocytopenia is uncommonly associated with IDA, whereas reactive thrombocytosis is common [3], but both platelet abnormalities resolve with iron repletion unless there is another cause. In our case, both

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Laboratory	Reference Range	Day 1	Day 3	Day 22	Day 73	Day 148	Day 449
Hemoglobin (g/dl)	11.2-16	8.5	8.1	9.9	12	11.8	12.3
Hematocrit (%)	36.4-46.5	28.3	26.8	31.8	36.7	37.2	38.8
MCV (fL)	82.5-100.1	63.3	63.9	72.8	78.1	81.3	83.9
RDW (%)	11.4-15.6	20.8	20.9	31.6	21.6	15.7	14.5
Platelets (k/µL)	158-356	22	20	32	45	112	163
WBC (k/µL)	4.2-10.0	6.8	5.5	4.4	6.9	6.5	5.6
Reticulocytes (%)	0.4-2.4	-	1.9	-	-	-	-
Iron (µg/dL)	37-145	19	-	62	-	56	35
TIBC (µg/dL)	149-503	490	-	328	-	389	403
Ferritin (ng/mL)	-	6	-	467	-	34	23
Haptoglobin (mg/dL)	30-200	178	-	-	-	-	-
Vitamin B12 (pg/mL)	211-946	317	-	-	-	445	-
Folate (ng/mL)	2.8-20.0	8.2	-	-	-	16.1	-
LDH (U/mL)	135-214	200	-	-	-	-	-
Methylmalonic acid (nmol/L)	88-243	-	193	-	-	130	-

Table 1: Hematologic data.

anemia and thrombocytopenia resolved with oral iron replacement, albeit somewhat more slowly than in most reported cases. Uncertain compliance with oral iron therapy, lack of dietary assistance from a vegetarian diet, ongoing menstruation, and possibly subclinical or unreported excessive menstrual bleeding are all factors that could have contributed to slower resolution.

Immune-mediated thrombocytopenia (ITP) is a relatively common diagnosis, particularly in women in middle years, and may occur coincidentally with iron-deficiency anemia. Immunologic evaluations were negative in the cases of IDA-associated thrombocytopenia reported in the literature, except for one case in which ITP was identified later when thrombocytopenia recurred after an initial good response to iron replacement [9]. In contrast, in another case the authors described their initial impression of ITP, the marrow showing increased megakaryocytes, but they eventually considered ITP a misdiagnosis and cautioned against inappropriate corticosteroid therapy [10]. In our case, thrombocytopenia resolved without corticosteroids or other ITP therapies. The presence of intrinsic factor and parietal cell antibodies was probably incidental, because serum vitamin B12 and methylmalonic acid levels were normal, the anemia was microcytic and iron responsive, and the blood smear lacked findings typical for vitamin B12 deficiency.

The first cases of iron deficiency-associated thrombocytopenia in the literature were reported in 1964 by Gross et al. He described 17 severely anemic children and infants in whom the anemia was accompanied by thrombocytopenia; he concluded that the severity of iron depletion may be a factor in determining the direction of the platelet count [11]. Five similar cases were soon published in which the thrombocytopenia responded to iron therapy or blood transfusion in each, and the rise in platelet counts preceded the reticulocyte response [12]. Six more similar cases were published in a 2002 series of children aged 14 months to 17 years (mean 27 months). Bone marrow examinations were performed in three patients and showed increased numbers of megakaryocytes. All patient showed rapid increases in their platelet counts after treatment with therapeutic doses of oral iron [13].

Berger and Brass collected 24 cases of iron deficiency with thrombocytopenia that had been published in the literature by 1987. In some, platelet counts were below 10,000/µL [6]. Menorrhagia was present in the majority, and multiparity in at least 3 cases. In the first reported adult case, published in 1974, a 31-year-old African-American woman presented with hematuria of one month's duration [14]. The second reported case, in 1978, concerned a woman with menorrhagia whose anemia and thrombocytopenia were responsive to iron therapy [5]. A case of severe anemia (hemoglobin of 3 g/dL) and severe thrombocytopenia (9000/uL) in a multiparous woman with menorrhagia was published in 1987; her symptoms, anemia, thrombocytopenia, and magakaryoctyopenia all resolved with iron replacement [6]. A fourth such case was then highlighted in the New England Journal of Medicine, in which discussions of the possible mechanism of thrombocytopenia were clouded by the possibility of drug-induced thrombocytopenia related to ranitidine therapy, and by the therapeutic withdrawal of ranitidine done in parallel to the initiation of iron replacement [2]. Since then, there have been several similar individual reports [1,4,9,10,12,15-17] and two series published, one of 3 [18] and the other of 10 [19] similar patients. Finally, in a large analysis of 615 consecutive IDA patients, thrombocytosis was found in 13% and thrombocytopenia in 2% (13 patients) of the population. Thrombocytopenia was more frequently noted in severe IDA (hemoglobin <7 g/dL) than in non-severe IDA [3].

The cause of IDA-associated thrombocytopenia is unclear. An inverse linear relationship between platelet count and iron saturation has usually been found—that is, platelets tend to increase as iron saturation decreases-and it has been hypothesized that iron may have an inhibitor effect on megakaryopoiesis [20]. However, a more complex relationship was demonstrated in a human model system when the effect of transferrin saturation on the ability of CD34+ cells to undergo erythro-, megakaryo-, and granulocytopoiesis was examined. Saturations ≥ 25% exhibited no effect on hematopoiesis. At 15% saturation, growth arrest was demonstrated only in the erythroid lineage. Most interestingly, the growth and viability of all three lineages was inhibited at saturations of ≤ 1.0%, [21]. The presence of erythropoietin is also known to affect platelet production. In a literature review on the relationship between erythropoietin and platelet production, the author concluded that moderate, short-term erythropoietin increases cause moderate elevations in platelet counts, whereas intense and prolonged erythropoietin stimulation, as produced by high doses of recombinant human erythropoietin, prolonged hypoxia or severe iron deficiency, causes some degree of thrombocytopenia. The author hypothesized that the latter phenomenon is due to stem-cell competition between erythroid and platelet precursors and may relate to the existence of a common erythrocytic and megkaryoctycic precursor [22].

We propose that the degree to which marrow thrombopoiesis may react to erythropoietin stimulation in the setting of iron-deficiency anemia is modulated by a few competing factors. Iron deficiency typically

leads to increased erythropoietin levels, which stimulates increases in platelet production and commonly results in thrombocytosis. However, severe, prolonged iron deficiency accompanied by intense and prolonged exposure of the bone marrow to high endogenous erythropoietin levels may lead to decreased platelet production through 1) marrow competition of platelet precursors with erythroid precursors for iron and other available substrates, 2) direct inhibition of thrombopoiesis, and 3) preferential differentiation of a common erythrocytic and megakaryoctytic precursor into erythroblasts, rather than megakaryoblasts, via unknown regulatory factors.

Conclusion

Iron deficiency-associated thrombocytopenia should be considered in any case of thrombocytopenia accompanying IDA. Response of both cytopenias to iron therapy should obviate the need for expensive evaluations and bone marrow examination.

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