INDEX OF SUSPICION

Microcytic Anemia

Richard Zanetti, MD, MPH,* Brian Feldman, MD, MPH,† Timothy Porea, MD, MPH‡

*Walter Reed National Military Medical Center, Bethesda, MD
†Naval Medical Center Portsmouth, Portsmouth, VA
‡Texas Children's Hospital and Baylor College of Medicine, Houston, TX

PRESENTATIONS

Herein we present 3 different patient presentations with a common diagnosis.

Case 1: A 9-year-old boy with a normal diet presents for evaluation of fatigue. During review of systems, intermittent loose stools without hematochezia are reported. Screening laboratory values are obtained and reveal microcytic anemia (red blood cell [RBC] count, $4.6\times10^6/\mu L$ [4.6×10^{12}/L]; hemoglobin level, 9.6 g/dL [96 g/L]; mean cell volume [MCV], 66 fL; and RBC distribution width [RDW], 14.7%) and a low serum iron level (<9 μg/dL [1.61 μmol/L]). He is given a presumptive diagnosis of iron deficiency and is started on replacement therapy. Four weeks later, repeated laboratory tests show only mild improvement (RBC count, $4.91\times10^6/\mu L$ [4.91×10^{12}/L]; hemoglobin level, 10.3 g/dL [103 g/L]; MCV, 66 fL; RDW, 15.6%; ferritin level, 19 ng/mL). Additional laboratory values at this time reveal an elevated erythrocyte sedimentation rate (ESR) (32 mm/hr) and a decreased albumin level (2.6 g/dL [26 g/L]).

Case 2: A 14-year-old boy with a regular diet is found to have microcytic anemia (RBC count, $4.5\times10^6/\mu L$ [4.5×10^{12}/L]; hemoglobin level, 8.7 g/dL [87 g/L]; MCV, 60 fL; RDW, 15.6%) during evaluation for an acute febrile respiratory illness. At presentation he also reports a history of fatigue and 4 to 8 bowel movements per day with occasional episodes of hematochezia that predated his febrile illness. Further evaluation demonstrates occult blood in his stool on 3 separate samples, as well as a low albumin level (2.2 g/dL [22 g/L]) and an elevated ESR (55 mm/hr).

Case 3: A 15-year-old girl presents for evaluation of back pain and incidentally describes a 1-year history of eating ice consistent with pica. She reports intermittent fatigue but is otherwise active and healthy, with an iron-rich diet. She had menarche at age 13 years, and cycles were regular without menorrhagia or dysmenorrhea. Laboratory tests reveal mild microcytic anemia (RBC count, $4.2\times10^6/\mu L$ [4.2×10^{12}/L]; hemoglobin level, 10.6 g/dL [106 g/L]; MCV, 61 fL; RDW, 19.3%). Additional evaluation reveals a low ferritin level (5.54 ng/mL), negative inflammatory markers, a normal serum albumin level, negative stool occult blood test results, and negative celiac screening. Fecal calprotectin is also tested and is elevated (214 μg/g).

DISCUSSION

The most common diagnoses that result in microcytic anemia are iron deficiency, thalassemia trait, and anemia of inflammation. The patients in the previous case presentations were referred to pediatric hematology for further evaluation and

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management of iron deficiency anemia. The subtle findings of increased inflammatory markers and hypoalbuminemia in cases 1 and 2, the positive fecal occult blood in case 2, as well as the fecal calprotectin elevation in case 3 prompted referral to a pediatric gastroenterology clinic, where colonoscopy confirmed the diagnosis of underlying inflammatory bowel disease for each patient.

Iron deficiency is a relatively common condition, particularly in young children, with a prevalence of 9% in children younger than 2 years and 4.5% in children aged 3 to 5 years. (1)(2) Adolescent girls represent another population at risk for iron deficiency, with a prevalence of 15.6%. (3) The clinical presentation of iron deficiency is variable; most patients are asymptomatic, but potential presenting signs include fatigue, irritability, and pica. Identification of iron deficiency is important because early childhood iron deficiency is associated with poor cognitive achievement. (4) Common laboratory findings in iron deficiency anemia are listed in the Table. Serum ferritin is a measure of stored iron content in the reticuloendothelial system and, when low, is diagnostic of iron deficiency. (6) However, ferritin is an acute phase reactant and, thus, can be normal or even elevated in patients with coexisting iron deficiency and inflammation. The reticulocyte hemoglobin content reflects recent body iron stores; thus, a low reticulocyte hemoglobin content supports a diagnosis of iron deficiency anemia. (7) At the time of our cases, reticulocyte hemoglobin was not commonly used, but it is now becoming more readily available. Based on a thorough history and physical examination in at-risk populations, it is acceptable to make a presumptive diagnosis of iron deficiency in children with microcytic anemia and to treat empirically with supplemental iron; the diagnosis is confirmed on follow-up assessment by an increase in hemoglobin level, reticulocyte count, and MCV within 1 to 4 weeks of starting iron therapy.

Iron homeostasis is tightly regulated in the human body. Iron is recycled from RBC breakdown or is absorbed in the duodenum and stored in the liver and reticuloendothelial system. The hepcidin-ferroportin pathway is responsible for iron balance. Ferroportin is the membrane transporter for iron found on hepatocytes, duodenal enterocytes, and macrophages. Hepcidin binds ferroportin on these cell surfaces and induces ferroportin internalization and degradation, which results in decreased gastrointestinal absorption as well as reduced release of iron from intracellular stores, which limits iron availability. (8) Hepcidin production is increased in the setting of iron overload and inflammation to limit free iron in the plasma. (6) Conversely, iron deficiency and erythropoiesis suppress hepcidin, which increases ferroportin expression and iron availability. (9)

Thalassemias are a group of disorders in which the normal ratio of α-globin to β-globin production is disrupted due to mutations or loss of 1 or more of the globin genes. α-Thalassemia trait, due to loss of 2 functioning α-globin alleles can present with a range of phenotypes to include mild chronic microcytic anemia. Silent carrier α-thalassemia, where only 1 α-globin allele is affected, often presents with microcytosis without anemia. Patients with β-thalassemia minor (with a heterozygous β-globin chain mutation) can also present with microcytic anemia. Unlike iron deficiency anemia, the RBC count is often normal or even elevated in these hemoglobinopathies. Other typical laboratory findings

Table. Common Laboratory Findings in the Differential Diagnosis of Microcytic Anemia

DIAGNOSIS	RBC COUNT	RDW	RETICULOCYTE HEMOGLOBIN	FERRITIN	TRANSFERRIN SATURATION	ESR/CRP	OTHER NOTES
Iron deficiency anemia	↓	↑	↓	↓	↓	N	Ferritin typically <30 ng/mL (5)
Anemia of inflammation	↓	N/↑	N/↓	↑	↓	↑	
Iron deficiency + anemia of inflammation	↓	N/↑	↓	↑	↓	↑	Ferritin <100 ng/mL suggests iron deficiency in inflammation (5)
α-Thalassemia trait	↑	N	↓	N	N	N	Newborn screen shows hemoglobin Barts (γ-tetramers produced only in infancy) Electrophoresis outside of infancy is normal
β-Thalassemia trait	↑	N	↓	N	N	N	Newborn screen normal Electrophoresis shows ↑ hemoglobin A2, ↑ hemoglobin F (electrophoresis should be interpreted in the setting of normal iron stores)

CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; N=normal; RBC=red blood cell; RDW=RBC distribution width.

and distinguishing features of thalassemia traits are included in the Table.

Anemia of inflammation can be difficult to distinguish from iron deficiency, and clinicians should obtain a thorough history and physical examination to screen for possible underlying chronic conditions. Because ferritin is an acute phase reactant, normal or high ferritin levels may be found in inflammatory conditions despite concurrent iron deficiency. (10) As detailed previously herein, a low serum iron level with an elevated hepcidin level would be consistent with anemia of inflammation. Unfortunately, hepcidin levels are not routinely available in clinical practice; however, a recent study established a normal range for hepcidin levels in a pediatric population, which may help in further development of this test for wider clinical use in the future. (11)

Inflammatory bowel disease often presents with diarrhea, rectal bleeding, and abdominal pain. Up to one-third of patients present with moderate symptoms, including occult hematochezia, abdominal cramping, fecal urgency, malaise, low-grade or intermittent fevers, anorexia, weight loss, elevated inflammatory markers (C-reactive protein and ESR), mild anemia, and hypoalbuminemia. In one study, the prevalence of anemia in inflammatory bowel disease at diagnosis was 75%; and up to 30% of patients remained anemic at follow-up 2 years later. (12) Evaluation for inflammatory bowel disease should include stool studies, which can reveal occult blood, fecal leukocytes, and elevated fecal calprotectin levels, and the diagnosis is confirmed via colonoscopy. Fecal calprotectin has been shown to have 96% sensitivity in detecting intestinal inflammation and is useful in the diagnosis of inflammatory bowel disease because it correlates with mucosal disease activity. (13)

The microcytic anemia that occurs in the setting of inflammatory bowel disease is caused by both iron deficiency and the effects of inflammation. Inadequate intake, blood loss, and poor absorption lead to iron deficiency in inflammatory bowel disease. (14) Patients often have a decreased appetite and avoid iron-containing foods due to chronic abdominal pain and diarrhea; one study showed approximately 20% decreased intake of dietary iron in patients with Crohn disease compared with a matched control population. (15) Local intestinal inflammation leads to secondary malabsorption and chronic blood loss, further exacerbating the iron-deficient state. (16) During inflammatory bowel disease flares, hepcidin levels have been shown to increase, which contributes to anemia by limiting the availability of the body iron stores. (17)

Lessons for the Clinician

- Iron deficiency is a common etiology of anemia in children younger than 3 years due to insufficient dietary intake and in adolescent girls due to menstruation. Outside of these 2 groups, microcytic anemia warrants additional evaluation.
- Evaluation of microcytic anemia should include iron studies (including ferritin) to assess iron stores and availability. If reticulocyte hemoglobin is available this can also provide insight into a patient's iron status. Additional studies may include fecal occult blood testing to evaluate for gastrointestinal blood loss as well as serum albumin and inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein.
- An elevated red blood cell number in the setting of microcytosis may suggest thalassemia trait. Newborn screen and hemoglobin electrophoresis results can aid in establishing this diagnosis.
- Testing for hepcidin levels is not routinely available for clinical use, but ongoing research is supporting its use in distinguishing anemia of inflammation from other forms of anemia. Inflammatory states lead to increased hepcidin levels and consequently decreased iron absorption and transport.

References for this article can be found at http://pedsinreview.aappublications.org/content/42/No. 1/41.

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