

# Educational Case: Nutrient Deprivation and Anemia

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*The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <http://journals.sagepub.com/doi/10.1177/2374289517715040>.<sup>1</sup>*

## Keywords

pathology competencies, diagnostic medicine, hematology, anemia, fatigue, peripheral neuropathy, iron, vitamin B<sub>12</sub>

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## Primary Objective

*Objective H3.2: Nutrients Required for Erythropoiesis:* Discuss the laboratory testing for specific nutrients including iron and vitamins to erythropoiesis.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic H: Hematology; Learning Goal 3: Mechanisms of Anemia.

## Patient Presentation

A previously healthy 38-year-old female presents to the clinic with 1 month history of dyspnea on exertion and increasing fatigue over the past 3 months. She does not report any abdominal pain or changes in bowel habits but reports a 10 pound weight loss over the past 3 months, which the patient attributes to decreased appetite. She does not have any prior medical history or surgeries. She takes a multivitamin and reports a healthy, varied diet without dietary restrictions. Her mother was diagnosed with Graves' disease at age 32.

On physical examination, she is in no acute distress. Vital signs are temperature of 98.7°F, pulse of 98/min, respirations of 17/min, and a blood pressure of 122/75 mm Hg. She is alert and oriented. The patient's tongue is smooth and erythematous without accompanying lesions to the oral mucosa. Cardiac examination is within normal

limits except for an increased heart rate as noted above, and lungs are clear to auscultation. Abdominal examination reveals the patient is mildly tender to palpation in all quadrants. Decreased vibratory sense is noted to both lower extremities. Proprioception is impaired at both great toes. Reflexes are 1+ on both lower extremities, 2+ on the upper extremities. Light touch is intact. Initial complete blood count (CBC) is ordered on the patient.

## Diagnostic Findings, Part I

A CBC and peripheral blood smear are performed and presented in Table 1.

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**Table 1.** Initial Laboratory Findings of the Complete Blood Count From Patient.\*

Test	Result	Reference Range
Hematocrit	29%	35.5%-44.9% (female)
Hemoglobin	9.8 g/dL	11.6-15 g/dL (female)
WBC	4740/ $\mu$ L	3400-9600/ $\mu$ L
Neutrophils, segmented	68%	40%-80%
Eosinophils	2%	1%-6%
Lymphocytes	24%	20%-40%
Monocytes	6%	2%-10%
Platelets	143 000/ $\mu$ L	157 000-371 000/ $\mu$ L

Abbreviation: WBC, white blood cell.

\* Microscopic review reveals macrocytic anemia with hypersegmented neutrophils.

## Questions/Discussion Points, Part I

### *Given the Clinical History, What Is a Broad Differential Diagnosis?*

The differential diagnosis includes anemias of multiple etiologies, with iron deficiency being most common especially in women who are menstruating. Other diagnoses in the differential will include inflammatory bowel disease and celiac disease. Other nutritional deficiencies, such as folate or vitamin B<sub>12</sub> deficiency, should be considered. Although less likely due to this patient's age, the nonspecific constitutional symptoms with accompanying weight loss are concerning for malignancy. In patients older than 50 years, colon adenocarcinoma must be strongly considered in the setting of chronic blood loss.<sup>2,3</sup>

### *What Is the Most Likely Diagnosis and Why? What Further Laboratory Tests Are Indicated?*

Given the patient's symptomatic anemia with peripheral neuropathy and the presence of megaloblasts on peripheral blood smear, vitamin B<sub>12</sub> deficiency must be considered very high on the differential. Megaloblastic anemia is most commonly due to vitamin B<sub>12</sub> or folate deficiency. Obtaining serum levels is the first diagnostic step in differentiating between them. The presence of peripheral neuropathy supports a diagnosis of vitamin B<sub>12</sub> deficiency, which may be secondary to chronic inadequate dietary intake or impaired absorption. In a patient consuming a regular diet with no diarrhea suggestive of malabsorption, pernicious anemia is much more likely.<sup>2</sup> Weakness, sore tongue, and paresthesias are the classic triad of pernicious anemia (attributable to anemia, glossitis, and peripheral neuropathy, respectively) and are highly suggestive if identified.<sup>3</sup>

## Diagnostic Findings, Part II

Additional serological studies are obtained and presented in Table 2.

**Table 2.** Additional Studies to Determine the Cause of the Anemia in the Patient.<sup>3</sup>

Test	Result	Reference Range
Vitamin B <sub>12</sub>	138 pg/mL	(200-900 pg/mL)
Folate	12 ng/mL	(2.5-20 ng/mL)
Methylmalonic acid (MMA)	Elevated	
Homocysteine	Elevated	

## Questions/Discussion Points, Part II

### *How Can You Make a Diagnosis of Pernicious Anemia? What Is the Schilling Test?*

The diagnosis of a vitamin B<sub>12</sub> deficiency is first made with a CBC, peripheral blood smear, and vitamin B<sub>12</sub> and folate levels, demonstrating a megaloblastic macrocytic anemia and low serum vitamin B<sub>12</sub> (<200 pg/mL), but a normal folate level (necessary to rule out folate deficiency, which may be comorbid). Elevated methylmalonic acid (MMA) and homocysteine levels are also supportive of vitamin B<sub>12</sub> deficiency (MMA will be normal in folate deficiency).<sup>3</sup>

To diagnose pernicious anemia as the etiology of a vitamin B<sub>12</sub> deficiency, additional testing for antibodies against intrinsic factor is needed. Although rarely performed today, the Schilling test can be useful diagnostically. This test consists of giving radiolabeled vitamin B<sub>12</sub> orally, followed 1 to 6 hours later by parenteral vitamin B<sub>12</sub>, and measuring the urine excretion of the radiolabeled vitamin B<sub>12</sub>. Inadequate absorption (<5% radiolabeled vitamin B<sub>12</sub> in urine) indicates malabsorption along the pathway, but improvement (to >9%) with subsequent administration of intrinsic factor on a repeat test is specific to pernicious anemia.<sup>3</sup>

### *How Is Vitamin B<sub>12</sub> Obtained and Absorbed?*

Vitamin B<sub>12</sub> (cobalamin) is a water-soluble vitamin normally sourced from dietary meat and dairy, which is then stored in the liver for several years. For this reason, vitamin B<sub>12</sub> deficiency from lack of dietary intake is very rare and usually only occurs after years of strict adherence to a vegan diet without supplementation.<sup>4,5</sup>

Once ingested and chemically isolated via gastric acid, vitamin B<sub>12</sub> is bound in the stomach by R protein (haptocorrin). The parietal cells in the stomach produce intrinsic factor, which becomes the second bound-carrier of vitamin B<sub>12</sub> in the small intestine, after pancreatic enzymes cleave vitamin B<sub>12</sub> from the R protein. The vitamin B<sub>12</sub>-intrinsic factor complex is then absorbed in the terminal ileum.<sup>4,5</sup>

Thus, vitamin B<sub>12</sub> deficiency may result from the disruption of any of these mucosal surfaces as a result of malabsorption, most commonly affecting either the production/binding of intrinsic factor (destruction of the gastric mucosa as in chronic gastritis) or the absorption in the terminal ileum (chronic inflammatory bowel disease or bowel resections affecting the terminal ileum).<sup>4</sup>

### **How Is Folate Obtained and Absorbed?**

Dietary folate is naturally sourced in green leafy vegetables, citrus fruits, and animal products. In the United States and Canada, products such as cereals and grains are also typically folate-enriched for greater bioavailability. Folate is absorbed in the duodenum and upper jejunum and is ultimately (once metabolized to the biologically active form tetrahydrofolic acid) required for nucleic acid synthesis (a process which also requires vitamin B<sub>12</sub>). Folate is available from so many dietary sources that deficiencies only typically result from severe malnutrition (such as chronic alcoholism, which also independently interferes with folate absorption and metabolism), increased demand (to include pregnancy), or impaired absorption in the small intestine (such as celiac disease). A number of medications are folic acid antagonists, such as methotrexate, and may clinically mimic a folate deficiency.<sup>4,6</sup>

### **How Is Iron Obtained and Absorbed?**

Iron is found in a variety of dietary sources but is most readily absorbed from meats as a preformed heme complex. The main sites of absorption are in the duodenum and upper jejunum, where iron is then bound to transferrin (an iron-transport protein) within the intestinal mucosal cells. From there, iron may be transported throughout the body as needed (i.e., to the liver for storage as ferritin or to the bone marrow for erythropoiesis). Iron absorption is regulated in part by hepcidin, which is secreted by the liver when intrahepatic iron is high, and can be suppressed in order to increase intestinal iron absorption as needed. The ability to regulate the absorption, storage, and redistribution of iron within the body is important for protection against uncontrolled elimination, particularly in the setting of blood loss.<sup>4,5</sup>

### **What Are Possible Treatments of Pernicious Anemia?**

Patients with pernicious anemia have severely impaired absorption of vitamin B<sub>12</sub>, and so regular supplementation is required, usually with intramuscular injections. Patients with severe deficiencies at their initial presentation will receive vitamin B<sub>12</sub> anywhere from 1 to 4 times per week until their macrocytosis resolves (an initial increase of reticulocytes is the first indication of a response, followed by increased hemoglobin). Then the frequency of supplementation can be reduced to once per month. As the pathophysiology of pernicious anemia is immune-mediated, treatment is expected to be lifelong.<sup>3</sup>

### **What Are Possible Treatments of Folic Acid Deficiency and Iron Deficiency?**

Folate and iron deficiencies are usually treated with daily oral supplementation. The recommended folate dose for nonpregnant patients is 400 to 1000 µg daily. For pregnant patients, a dose of 600 µg folate daily is recommended beginning 1 month prior to conception (if possible) to prevent neural tube defects in the fetus. For the patient presenting with megaloblastic

anemia, serology to test both vitamin B<sub>12</sub> and folate levels is required prior to empiric treatment. As mentioned, folate and vitamin B<sub>12</sub> deficiencies each cause a megaloblastic anemia, often comorbidly, and folic acid supplementation alone in these settings will appear to resolve the megaloblastic anemia while worsening the neurologic sequelae of the vitamin B<sub>12</sub> deficiency.<sup>6</sup>

Iron supplementation is also given orally, with a recommended initial dose of 325 mg ferrous sulfate daily or every other day. Gastrointestinal (GI) upset is the most common side effect. Empiric supplementation in the setting of suspected iron deficiency anemia is an appropriate first step; however, as mentioned, the most common etiology for iron deficiency is chronic blood loss. A workup to find the source for the patient's blood loss should begin immediately. In premenopausal women, menstrual blood loss is the most common etiology. In men and postmenopausal women, occult GI bleeding is most common, to include peptic ulcer disease and malignancy.<sup>4,7</sup>

### **What Are the Other Possible Complications of Long-Standing Pernicious Anemia?**

These patients are at elevated risk for gastric carcinoma, and periodic monitoring is indicated. Folic acid deficiency and iron deficiency are not associated with an increased risk of gastric carcinoma.<sup>3</sup>

### **Teaching Points**

- Most anemias present with nonspecific symptoms of fatigue and dyspnea on exertion. Consider vitamin B<sub>12</sub> deficiency when peripheral neuropathy is present, a CBC reveals a macrocytosis, or the history suggests malabsorptive pathology or extreme dietary deficiency (as in long-term vegans or chronic alcoholics).<sup>2,3</sup>
- Consider pernicious anemia in a patient without symptoms of malabsorption or dietary deficiencies, particularly in a young female with a personal or family history of autoimmune diseases.<sup>3</sup>
- A diagnosis of pernicious anemia can be made with a CBC, peripheral blood smear, and vitamin B<sub>12</sub> and folate levels. Methylmalonic acid and homocysteine levels may be ordered if necessary. Antibody titers against intrinsic factors are very specific.<sup>3</sup>
- Vitamin B<sub>12</sub> is obtained via animal products (meat and dairy) and requires healthy mucosa in the stomach and terminal ileum for adequate absorption. Patients on strict vegan diets, with inflammatory bowel disease, chronic gastritis, or who have undergone small bowel resection may require oral supplementation.<sup>4</sup>
- Patients with pernicious anemia produce antibodies against the intrinsic factor required for adequate vitamin B<sub>12</sub> absorption. These patients will require monthly intramuscular injections for lifelong treatment.<sup>3</sup>
- Iron is obtained from meats and absorbed in the proximal small intestine. It is bound to transferrin for

transport throughout the body and stored in the liver as ferritin. The body is so efficient at retaining and recycling its iron that the most common mechanism for iron deficiency is through chronic blood loss.<sup>4</sup>

- Iron deficiency anemia is treated with oral supplementation while the etiology (most likely a source of chronic occult bleeding) is investigated.<sup>4</sup>
- Folate is widely available in leafy greens, citrus fruits, animal products, and enriched grains. It is absorbed in the proximal small intestine and required for nucleic acid synthesis.<sup>6</sup>
- Folate deficiency is also treated with oral supplementation, with a higher dose for patients who are anticipating or are currently pregnant.<sup>7</sup>
- Patients with a megaloblastic anemia must be tested for both folate and vitamin B<sub>12</sub> deficiencies prior to beginning treatment. Empiric folic acid supplementation will mask a comorbid vitamin B<sub>12</sub> deficiency while neurologic symptoms worsen.<sup>3,6</sup>

#### Authors' Note

The views expressed in this educational case report are those of the author and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or US Government.

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