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Anemia in the Adult Patient

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Anemia, typically defined as a hemoglobin level of less than 13.0 g/dL in males and 12.0 g/dL in females,[1] is an indication of either dietary deficiency or an underlying pathologic process or disease. Iron deficiency, the most common nutritional deficiency in the world, is the most common cause of anemia.[2–4] Iron deficiency anemia is most prevalent among women of childbearing age and is more common in developing countries. Iron deficiency anemia can result either from nutritional deficiency or chronic blood loss. Other causes of anemia include chronic disease, renal failure, hemolysis, bone marrow disorders, and vitamin deficiencies. This article discusses the signs and symptoms associated with anemia in adults and reviews the laboratory evaluation of anemia, which is important in differentiating underlying causes.

SIGNS AND SYMPTOMS OF ANEMIA

Symptoms
Fatigue
Lightheadedness
Dyspnea

Signs
Pallor of:
- Conjunctivae
- Nail beds
- Palmar creases
- Face

ILLUSTRATIVE CASE

A 73-year-old man presents with a 3-week history of fatigue and dyspnea. He also reports episodes of melena (the passage of black or tarry stools) for the past 3 weeks. On physical examination, the patient appears pale but is in no apparent distress. His blood pressure is 100/50 mm Hg and his pulse is 110 bpm. The eye examination is remarkable for pale conjunctivae (**Figure 1**). The heart examination reveals regular rhythm with a systolic ejection murmur. The lungs are clear to auscultation. Epigastric tenderness is noted, and a stool sample is guaiac-positive. Laboratory examination reveals a blood hemoglobin level of 5 g/dL with a mean corpuscular volume (MCV) of 87 fl.

SYMPTOMS AND SIGNS OF ANEMIA

Table 1 lists items to consider in taking the history and performing the physical examination of a patient who may have anemia. Patients with anemia may present with fatigue, dizziness, and dyspnea; however, mild anemia may produce little in the way of clinical signs and symptoms. In the presence of congestive heart failure, mild anemia can worsen the dyspnea associated with the heart failure, and in patients with cardiovascular disease, it can cause a worsening of angina and claudication.[5] In severe cases (hemoglobin < 5 g/dL), high-output heart failure may develop.[6] Anemia leads to increased cardiac output in order to compensate for tissue hypoxia, and an associated systolic ejection murmur may occur as a result of increased aortic flow.

An unusual symptom of iron deficiency anemia is pica, which is defined as the compulsive eating of nonfood substances.[7] The exact prevalence of pica in patients with iron deficiency anemia is not known, and the etiology is poorly understood. A link to zinc deficiency has also been noted. Ice eating (pagophagia) is the most common form of pica in patients with iron deficiency anemia, although clay and dirt eating (geophagia) also occurs.

Patients with iron deficiency anemia may develop Plummer-Vinson syndrome, characterized by dysphagia and esophageal webs formed of thin mucosal membranes.[8] The dysphagia is believed to result from weakened esophageal muscle contractions rather than from the webs. The pathogenesis of the web formation is not known.

The signs of anemia include pallor of the conjunctivae,

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Figure 1. Pallor of the conjunctiva.

face, nailbeds, and palmar creases, although the absence of pallor does not rule out anemia.[9] The physical examination should focus on areas where capillaries are close to the surface (ie, conjunctivae, nailbeds). One study reported a sensitivity of 95% and a specificity of 68% for the detection of pallor in either the palms, nail beds, or conjunctivae for patients with moderate anemia (defined as hemoglobin level of 8 g/dL or less).[10] The interrater reliability in the detection of pallor was greatest for conjunctival pallor, but pallor of the nailbeds was the most sensitive detector of anemia. Another study found a statistically significant correlation between hemoglobin concentration and pallor of the conjunctivae, nail beds, and palmar creases.[11] The sensitivity of pallor of the conjunctiva, nailbeds, and palms increased as the hemoglobin concentration decreased. These signs of pallor were found to be quite specific because they were never present in the absence of anemia.[11]

Further physical examination can reveal clues to underlying diseases. Scleral icterus may indicate a hemolytic process or chronic liver disease. Urine color is also important. Dark urine in the setting of jaundice suggests an elevated conjugated bilirubin, indicative of liver disease. Normal urine color in the setting of jaundice would suggest an elevated unconjugated bilirubin (no bilirubin in the urine) thus pointing to a hemolytic process. Petechiae may indicate thrombocytopenia from a bone marrow disorder. Ecchymosis, lymphadenopathy, and splenomegaly may indicate a hematologic malignancy.

Table 1. History and Physical Examination for Anemia

Ask about:
Fatigue*
Dizziness*
Dyspnea*
Palpitations*
Stool color
Melena (suggests upper GI source)
Hematochezia (likely lower GI source)
Nausea and vomiting
Hematemesis (upper GI source)
Menstrual history
Nonsteroidal anti-inflammatory use (increases the risk for peptic ulcer)
Alcohol use (increases the risk for portal gastropathy)
Examine:
Conjunctivae†
Nailbeds†
Palms†
Rectal examination with stool guaiac testing
Sclera (for icterus) and skin (for jaundice) (hemolytic process or liver disease)

GI = gastrointestinal.

*These symptoms are more likely to occur with hemoglobin values < 8 g/dL.

†Pallor is more likely with hemoglobin values < 10 g/dL.

Table 2. Reference Laboratory Values for the Evaluation of Anemia in Adults

Parameter	Normal Value
Blood hemoglobin	Male: 13.0–17.0 g/dL
	Female: 12.0–16.0 g/dL
Mean corpuscular volume	80–100 fl
Red blood cell distribution width	11.5%–14.5%
Serum iron	50–175 μg/dL
Total iron-binding capacity	250–460 μg/dL
Serum ferritin	Male: 30–300 ng/mL
	Female: 10–200 ng/mL
Reticulocyte count	0.5%–2.5% of erythrocytes

LABORATORY EVALUATION

The clinical examination is important in detecting anemia, but it is the laboratory examination that is most useful in formulating a diagnostic approach in identifying an underlying cause of anemia. **Table 2** provides normal reference ranges for laboratory parameters

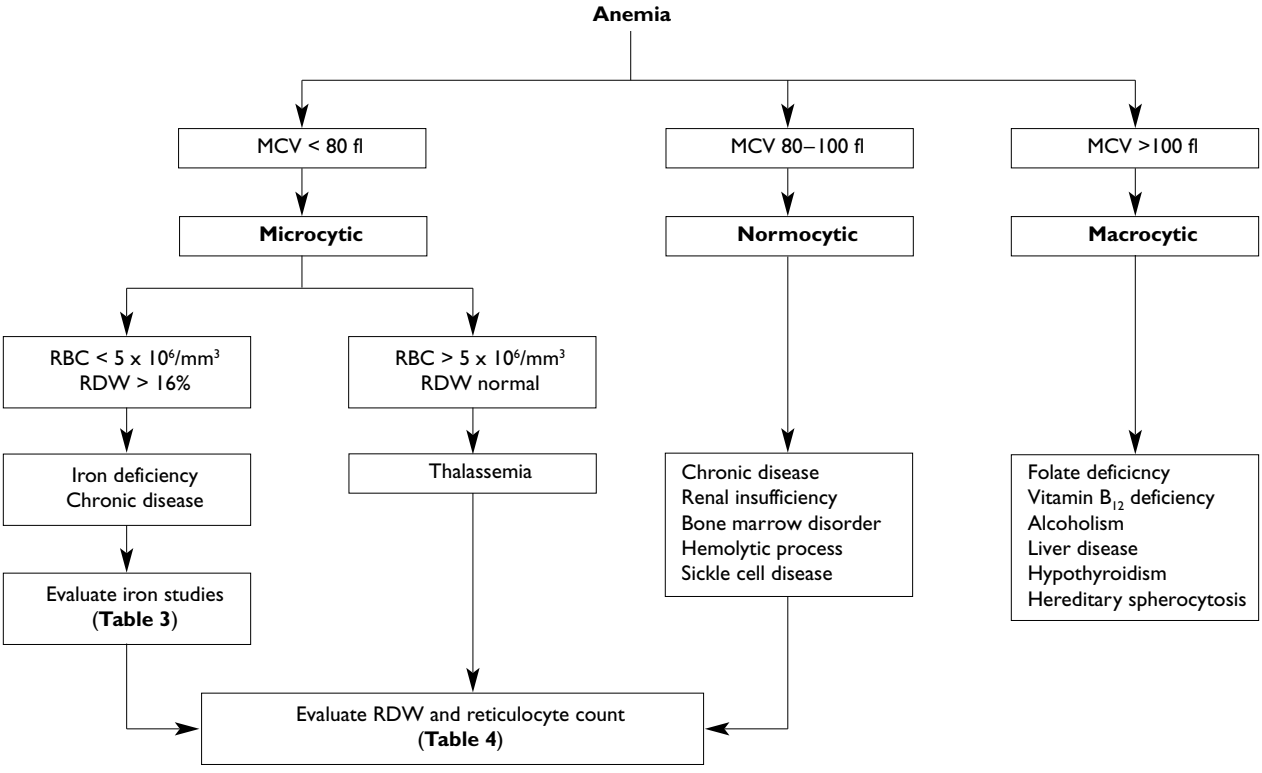

Figure 2. Approach to the laboratory evaluation of anemia. MCV = mean corpuscular volume; RBC = red blood cell count; RDW = red blood cell distribution width index.

Table 3. Differentiating Anemia of Chronic Disease and Iron Deficiency Based on Iron Studies

	Cause of Anemia	
Parameter	**Chronic Disease**	**Iron Deficiency**
Serum iron	↓	↓
Total iron-binding capacity	↓	↑
% Saturation of transferrin	Normal	↓
Serum ferritin	↑	↓

related to anemia. First, the MCV is used to classify the anemia as microcytic, normocytic, or macrocytic (**Figure 2**).[12,13] An iron panel is useful in differentiating anemia of chronic disease from iron deficiency as both may be microcytic (**Table 3**). Reticulocyte count is important as it indicates the response of the bone marrow to the anemia (**Table 4**). Reticulocytosis occurs in hemolysis as the bone marrow responds with increased erythrocyte production. The reticulocyte count is normal in anemia of chronic disease. The reticulocyte count is low in iron deficiency anemia and diseases that involve the bone marrow. The reticulocyte count will increase in response to therapy (eg, iron, folate, vitamin B_{12}). The red blood cell distribution width index (RDW) is also important in differentiating causes of anemia, being increased in iron deficiency and hemolytic anemias and normal in anemia of chronic disease (Table 4).

Microcytic and Normocytic Anemias

Iron deficiency is the most common cause of microcytic anemia. Anemia of chronic disease, however, is the most common cause of anemia in elderly patients[1] and may be either microcytic or normocytic. Serum iron studies are helpful in differentiating iron deficiency anemia from anemia of chronic disease (Table 3). Although iron depletion is the first stage in the development of iron deficiency anemia, a low serum ferritin level is the most reliable measure of iron deficiency versus chronic disease, where there is an increase in serum ferritin.[14] The total iron-binding capacity (TIBC) is increased when iron stores are diminished and decreased when they are elevated, as in anemia of chronic disease.

The anemia of chronic disease is a hypoproliferative anemia and may be multifactorial depending on the underlying condition (eg, hypersplenism in chronic liver

disease, diminished erythropoietin production in chronic renal disease, occult blood loss in chronic gastrointestinal disorders). The anemia of chronic disease typically resolves when the underlying disease is corrected.

Transferrin is a transport protein for iron; transferrin saturation falls once iron stores have been depleted. Iron deficiency, thus, is characterized by low serum iron, low ferritin, and low transferrin saturation levels in conjunction with an increased TIBC, whereas anemia of chronic disease is confirmed by findings of low serum iron, low TIBC, and normal or increased serum ferritin in the setting of a chronic disease.

Evaluation of kidney function is essential in evaluation of a normocytic anemia as mild-to-moderate renal insufficiency (serum creatinine, 1.5–3.0 mg/dL) can produce anemia.

If iron deficiency and anemia of chronic disease are ruled out in a patient with microcytic anemia, thalassemia must be considered. A group of inherited hemolytic anemias, the thalassemias are characterized by microcytosis out of proportion to the degree of anemia. The erythrocyte count is helpful in differentiating iron deficiency anemia from a thalassemia. The erythrocyte count is less than $5.0 \times 10^6/mm^3$ in iron deficiency anemia versus greater than $5.0 \times 10^6/mm^3$ in thalassemia. Hemoglobin electrophoresis is helpful in diagnosing thalassemias.

Macrocytic Anemia

Causes of macrocytic anemia include drugs (eg, hydroxyurea, methotrexate, trimethoprim, zidovudine, and chemotherapeutic agents), alcohol abuse, liver disease, hypothyroidism, vitamin B_{12} deficiency, and folate deficiency. Liver and thyroid function testing and vitamin B_{12} and folate levels are essential in evaluation. If laboratory evaluation shows elevated unconjugated bilirubin and lactate dehydrogenase levels, a hemolytic process should be considered. The classic hemolytic process causing a macrocytic anemia is hereditary spherocytosis. (Most hemolytic processes produce a normocytic anemia.)

CASE DISCUSSION

The patient in the illustrative case had severe anemia from gastrointestinal blood loss, and the signs and symptoms were quite obvious. Although iron deficiency anemia is typically microcytic, the anemia in this case was normocytic owing to a relatively acute onset of blood loss. Pallor of the conjunctivae was easily noted. In the study by Strobach and colleagues, pallor of the nailbeds and conjunctivae was not detectable unless the hemoglobin level was less than 10 g/dL.[11] The report of melena makes an upper gastrointestinal source of bleeding more likely, although melena is not a specific indication of an upper gastrointestinal bleed and thus small bowel bleeding or a right-sided colonic lesion would be possible. Blood must remain in the gastrointestinal tract for at least 14 hours before melena develops.[15]

Table 4. Differentiating Anemias Based on Reticulocyte Count and RDW

Reticulocyte Count	Normal RDW	Increased RDW
> 2%	Thalassemia	Hemolytic anemia
≤ 2%	Chronic disease	Iron deficiency

RDW = Red blood cell distribution width index.

Although the case patient's stool was guaiac positive, the nasogastric aspiration was negative. Esophagogastroduodenoscopy revealed a duodenal ulcer and colonoscopy revealed a 3-cm mass in the cecum, the cytology of which was positive for adenocarcinoma.

IRON DEFICIENCY ANEMIA CAUSED BY GASTROINTESTINAL BLEEDING

Iron deficiency anemia in the absence of an obvious cause of blood loss (eg, menorrhagia) is likely to be of gastrointestinal origin. One study found a gastrointestinal cause of iron deficiency anemia in 85% of patients with anemia.[16] A prospective study of 151 elderly patients with iron deficiency anemia found an upper gastrointestinal tract lesion in 49% of cases and a lower gastrointestinal tract lesion in 32% of cases. Cancer was the most common lesion in the colon.[17] A retrospective review of 98 cases of iron deficiency anemia found similar results, with an upper gastrointestinal source of bleeding in 54% of cases and a lower gastrointestinal source of bleeding in 37% of cases.[18] Thus, in adult men and postmenopausal women, a gastrointestinal source of bleeding is often the cause of iron-deficiency anemia.

For patients with a suspected upper gastrointestinal source of bleeding, aspiration of gastric contents via nasogastric tube is a useful screening test. According to one study, patients with positive aspirates (defined by the presence of blood or guaiac-positive material) were found to have a site of bleeding as determined by upper gastrointestinal endoscopy in 93% of cases. Patients with negative aspirates were found to have a lower gastrointestinal lesion in 60% of cases.[19] For this reason, patients whose nasogastric aspirate is negative should undergo both upper and lower gastrointestinal endoscopy.

CONCLUSION

Clinical signs and symptoms of anemia are readily evident at hemoglobin levels of less than 10 g/dL. Iron deficiency anemia is the most common form of anemia. In the absence of nutritional deficiency or an obvious source of blood loss, gastrointestinal tract pathology should be investigated as a cause of iron deficiency anemia. Other causes of anemia include chronic disease, renal failure, hemolysis, bone marrow disorders, and vitamin deficiencies. Laboratory evaluation is important in differentiating underlying causes of anemia. **HP**

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