Residents' Clinic

22-Year-Old Woman With Severe Microcytic Anemia

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A 22-year-old woman who had no notable previous medical history reported increasing fatigue during the past few months. Her mother noticed that she looked pale and suggested she visit her family physician. Her family and personal histories were noncontributory. Findings on physical examination were remarkable only for pallor. In particular, she had no hepatosplenomegaly or lymphadenopathy.

Initial laboratory tests yielded the following results (reference ranges shown parenthetically): hemoglobin, 8.3 g/dL (12.0-15.5 g/dL); hematocrit, 26.2% (34.9%-44.5%); mean corpuscular volume (MCV), 65.3 fL (81.6-98.3 fL); red blood cell (RBC) count, 4.01 x 10¹²/L (3.90-5.03 x 10¹²/L); and reticulocyte count, 1.17% (0.60%-1.83%). Leukocyte and platelet counts were within normal limits. The peripheral blood smear is shown in Figure 1.

1. Which one of the following is the least likely diagnosis in this patient?
   a. Iron deficiency anemia (IDA)
   b. Thalassemia
   c. Anemia of chronic disease
   d. Sideroblastic anemia
   e. Hereditary spherocytosis

The peripheral blood smear showed hypochromic microcytic anemia with moderate anisocytosis and poikilocytosis. The differential diagnosis of microcytic anemia includes thalassemia, iron deficiency, chronic disease, and sideroblastic anemia. IDA is the most common cause of microcytic anemia. In adults, dietary deficiency is rare, and bleeding must always be excluded. Red cell distribution width (RDW), an index of anisocytosis, is usually increased in patients with iron deficiency. However, this is a nonspecific finding. Thalassemia consists of a heterogeneous group of disorders with defects in the synthesis of 1 or more globin chains of the hemoglobin. Target cells are evident in the peripheral blood smear. The RBC count is generally greater than 5 x 10¹²/L in thalassemia and lower than that in the other types of microcytic anemia. Anemia of chronic disease is predominantly a normocytic anemia, but microcytosis can be seen as well. Sideroblastic anemia is characterized by disrupted heme synthesis, resulting in iron accumulation in the mitochondria of RBC precursors. This is manifested by the presence of ringed sideroblast in the bone marrow after Prussian blue staining. The congenital form is most commonly X-linked, while the acquired form can be idiopathic (as in myelodysplastic syndrome) or due to toxins (alcohol) or drugs (isoniazid, chloramphenicol). The peripheral blood smear can show microcytosis, macrocytosis, or a combination of both. Hereditary spherocytosis is an autosomal dominant disorder that involves a defect in the RBC membrane proteins. Because of an abnormality in the exoskeleton, extravascular hemolysis occurs, producing spherocytes and accompanying reticulocytosis. Since this result in a normal MCV, hereditary spherocytosis would be the least likely diagnosis. In hereditary spherocytosis, the central pallor in the RBC is lost, and the mean corpuscular hemoglobin concentration (MCHC) is usually elevated. This is because of a reduction in the RBC surface area relative to the cell volume. The MCHC can be calculated by dividing the hemoglobin concentration (g/dL) by the hematocrit (%) multiplied by 100. The reference range for MCHC is 31 to 37 g/dL. Our patient's MCHC was 31.7 g/dL.

The patient did not appear to have a chronic disease or toxin exposure. A hemoglobin level obtained 7 years previously was normal. Therefore, a working diagnosis of IDA was made. Further laboratory results were as follows: ferritin, 222 µg/L (20-200 µg/L); iron, 13 µg/dL (35-145 µg/dL); total iron binding capacity (TIBC), 269 µg/dL (250-400 µg/dL); and transferrin saturation, 5% (14%-50%). The patient was empirically treated with iron tablets. After 3 months of iron replacement, follow-up laboratory tests yielded the following results: hemoglobin, 9.5 g/dL; MCV, 71.2 fL; RDW, 17.4%; ferritin, 555 µg/L; iron, 15 µg/dL; TIBC, 241 µg/dL; and transferrin saturation, 6%. She was then referred to the Mayo Clinic in Rochester, Minn., for further evaluation. At the time of the outpatient visit, she reported a 2-week history of drenching night sweats.
2. Which one of the following is the least appropriate next step?
   a. Continue iron supplementation
   b. Determine the erythrocyte sedimentation rate (ESR)
   c. Perform chest radiography
   d. Check heavy metal screen
   e. Perform a bone marrow biopsy

   The serum ferritin concentration reflects the size of the iron storage compartment. In uncomplicated anemia, a ferritin level of less than 12 µg/L is pathognomonic for iron deficiency. In the presence of an inflammatory state, a ferritin level greater than 100 µg/L makes iron deficiency unlikely.¹ Our patient did not respond to a therapeutic trial of iron supplementation. In a definitive case of IDA, the reticulocyte count is expected to increase within a few days after initiation of iron therapy. The hemoglobin level should be halfway back to normal in about a month and should certainly be normal by 2 months. Therefore, our patient does not have iron deficiency, and continuation of iron supplementation would be inappropriate. Furthermore, she has developed a new systemic symptom. An ESR can be determined, and if elevated, it could imply that the patient has an underlying inflammatory condition. Performing radiography is reasonable to search for an occult malignancy. Screening for heavy metals or performing a bone marrow biopsy could have been considered if the work-up had not revealed the cause of the anemia. Copper deficiency and lead poisoning are rare causes of microcytic anemia. A bone marrow biopsy can help in the assessment of iron stores and in searching for the presence of ringed sideroblasts, if necessary.

   The ESR was 110 mm/1 h (0-29 mm/1 h). Chest radiography revealed a paratracheal mass. Subsequently, chest computed tomography (CT) was performed (Figure 2).

3. Which one of the following tumors is least likely to represent the abnormality seen on chest CT?
   a. Neurogenic tumor
   b. Thymoma
   c. Hodgkin disease (HD)
   d. Germ cell tumor
   e. Thyroid neoplasm

   The CT scan revealed a mass in the anterior mediastinum. All the abnormalities mentioned are included in the differential diagnosis except a neurogenic tumor, which occurs almost exclusively in the posterior mediastinum. Metastatic tumors are the most common tumors to involve the mediastinum. Among the primary mediastinal tumors, thymoma and lymphoma predominate.² The former is occasionally associated with pure red cell aplasia. Thymoma is a tumor seen in older adults (median age, 55 years), while HD and germ cell tumor are noted in younger adults (median age, 30 years). Extragonadal germ cell tumors are predominantly detected in male patients (90%). A thyroid neoplasm frequently presents as a retrosternal mass in women during the fourth decade of life.

   A biopsy specimen of the right paratracheal node showed Reed-Sternberg cells, diagnostic of HD, nodular sclerosis type.

4. In pursuing the staging work-up of this patient, which one of the following statements is not true?
   a. Exploratory laparotomy and splenectomy are necessary
   b. A gallium scan rarely yields additional information
   c. Bone marrow involvement is uncommon
   d. Lymphangiography is not routinely used in evaluating retroperitoneal and pelvic lymph nodes
   e. CT of the abdomen and pelvis is recommended

   In the past, exploratory laparotomy with splenectomy was an integral component of HD staging. However, with the advent of CT, it is no longer considered necessary. Exploratory laparotomy is indicated to provide pathological staging when radiation is contemplated as the sole therapy, but it is unnecessary when chemotherapy is part of the treatment plan. Although a baseline gallium scan is frequently obtained, it is generally not used as a staging procedure; usually it is utilized for predicting viability of residual mass after therapy by comparing the pretreatment and posttreatment scans. Bone marrow involvement by HD at presentation is uncommon (about 7%). Advanced stage of the disease (stages III and IV), presence of “B” symptoms (temperature >38°C, drenching sweats, or at least a 10% weight loss in the past 6 months), peripheral blood cytopenias, and bulky tumor all increase the risk of the bone marrow being involved. Lymphangiography is highly dependent on the skills and experience of the inter-
preting radiologist and is an uncomfortable test for patients. Therefore, it is not used at most medical centers. A CT scan of the abdomen and pelvis is now the preferred method for evaluating retroperitoneal and pelvic lymph nodes.

The bone marrow biopsy revealed normal hematopoiesis in all 3 cell lineages. There was no lymphoma. Stainable iron on aspirate was normal, and ringed sideroblasts were not seen. In general, bone marrow iron stores should be absent before microcytic anemia of iron deficiency is evident. This suggests that a disease process other than iron deficiency is responsible for the anemia. In contrast, bone marrow iron content in chronic disease is usually normal or increased. These findings are consistent with anemia of chronic disease. Findings on CT of the abdomen and pelvis were normal. The patient had HD stage IB disease. Because of the presence of a B symptom as an unfavorable prognostic factor, the decision was made to initiate chemotherapy.

5. If chemotherapy is the sole treatment modality, which one of the following late treatment-related complications will most likely be a relevant issue?
   a. Acute myelogenous leukemia
   b. Breast cancer
   c. Hypothyroidism
   d. Premature coronary artery disease
   e. Pneumococcal sepsis

A curable disease, HD has the best prognosis among all hematologic malignancies. The most recent estimate of overall 5-year relative survival is 82%. In patients with advanced disease, 66% are alive and disease free at 4 years. Late therapeutic complications are a major concern and should always be considered in management discussions. Second treatment-related malignancies are the most serious late complications of HD therapy. The more common malignancies include acute myelogenous leukemia, non-Hodgkin lymphoma, lung cancer, and breast cancer. While both chemotherapy and radiation therapy most likely increase the risk of many second malignancies, breast carcinoma is almost completely restricted to women who had radiotherapy to the chest before age 30 years. Hypothyroidism or premature coronary artery disease may result when the thyroid gland or the heart is included within the radiation treatment field. Pneumococcal sepsis is a concern in patients who have undergone splenectomy or splenic irradiation.

The patient subsequently received a total of 6 cycles of ABVD (Adriamycin [doxorubicin], bleomycin, vinblastine, dacarbazine) combination chemotherapy, resulting in a complete remission. Her microcytic anemia resolved during treatment.

DISCUSSION
Anemia of chronic disease is frequently associated with inflammatory, infectious, or neoplastic diseases. The degree of anemia is usually mild to moderate, with the hematocrit generally in the 30% to 40% range. Red blood cells are characteristically normocytic. Microcytosis is common, however. One series reported an incidence of microcytosis of 21% in a group of hospitalized patients with anemia of chronic disease. Central to the pathology of the disease is the production of inflammatory cytokines that inhibit proliferation of erythroid precursors, limit erythropoietin secretion by the kidneys, and impair mobilization of iron from reticuloendothelial cells. When the defect in iron utilization is severe, microcytosis ensues.

The differential diagnosis of microcytic anemia is usually straightforward. The more common causes are IDA, thalassemia, and anemia of chronic disease. One approach to distinguish among these disorders is to analyze the RBC count, RDW, and results of iron studies. An increased RBC count with a normal RDW suggests thalassemia. When the RBC count is normal or decreased and the RDW is increased, IDA is likely. The presence of iron deficiency should be further assessed by measuring iron indices. Typically, the levels of ferritin, iron, and transferrin saturation (<10%-15%) are low, while the TIBC is high. In anemia of chronic disease, the RBC count is either normal or decreased, but the RDW is normal. Results of iron studies are the converse of those for IDA (high ferritin and transferrin saturation, low TIBC), except for a low serum iron level. When a discrepancy exists between the ferritin level and iron to the TIBC ratio (transferrin saturation), the ferritin level should be monitored because it is a more sensitive test. During the onset of anemia of chronic disease, the level of decline of transferrin (as measured by TIBC) lags behind that of iron. As a result, the transferrin saturation may decrease within the range of that in IDA.
As our case illustrates, distinguishing microcytic anemia due to chronic disease from IDA may be difficult when the history and physical examination findings are not helpful and the results of serum iron studies are atypical for either disease. When iron studies are not helpful, further tests are warranted to exclude IDA or inflammatory disease. The presence of any systemic symptom or the absence of response to iron supplementation should prompt a thorough evaluation for a potentially serious illness. Besides malignancy, several benign conditions can also present simultaneously with mediastinal lymphadenopathy and anemia of chronic disease. Mycobacterial and fungal (especially histoplasmosis) infections tend to be insidious. When a patient is clinically asymptomatic, the diagnosis may be overlooked and treatment delayed.

Hodgkin disease is a relatively common malignancy but is one of the most curable. In 2000, approximately 7400 new cases will be diagnosed. This figure is about 4% and 6% of the total projected new cases of lung and colorectal cancers, respectively. Most patients with HD present with lymphadenopathy. In our patient, microcytic anemia was the only initial manifestation. Microcytic anemia is a common finding in HD. In 1 retrospective study of 162 patients with HD, microcytic anemia of chronic disease was present at diagnosis and at disease recurrence in 15% and 6% of the patients, respectively. The MCV level returned to normal in all the patients who responded to the treatment of HD, and the recurrence of microcytic anemia signaled a relapse.

The treatment focus of HD has changed over the years. With the success of treatment, the initial attention on the risk of death due to disease shifted to the risk associated with staging. Chemotherapy is now being used in the early stages of disease. Thus, staging laparotomy is seldom used, and splenectomy is avoided because of the risk of infection. Current emphasis is on reducing the risk of therapy, ie, the prevention and early detection of late treatment complications including second malignancies. Alkylating agents are avoided in the chemotherapeutic regimens, and radiation doses are minimized. In general, the risk of hematologic malignancies increases immediately within the first year of treatment and declines over time, while the risk of solid tumors may not be substantially increased after several years yet steadily increases with follow-up. For example, in 1 study, all cases of breast cancer appeared after 15 years of observation. Internists responsible for the care of HD survivors should be aware of the risk of second cancers in their patients. During follow-up, thorough attention should be given to new signs or symptoms that may suggest lymphoma. Women who were treated with chest irradiation before age 30 should be taught to perform regular breast self-examinations. Although there is no consensus regarding initiation of mammographic screening, yearly mammography at 5 to 10 years after radiation therapy is reasonable, in addition to a yearly examination by a physician. Smoking should be strongly discouraged to reduce the risk of lung cancer. Some new treatment strategies are being evaluated in clinical trials, and the results should be available soon.

REFERENCES