73-Year-Old Asymptomatic Woman With Anemia

Claire Jansson-Knodell, MD, and C. Scott Collins, MD

A 73-year-old woman with a history of atrial fibrillation status post ablation who was receiving anticoagulation with warfarin presented to the general internal medicine clinic without symptoms or concerns for an annual physical examination. Her medical history included hypertension, hyperlipidemia with statin intolerance, osteopenia, osteoarthritis, impaired fasting glucose levels, fibrocystic breast changes, seasonal allergies, and a thyrocervical trunk aneurysm that was stable on serial ultrasonographic imaging. She had paroxysmal atrial fibrillation dating back to 2012, underwent ablation in 2014, and has remained in sinus rhythm since. Her medications included calcium, vitamin D, warfarin, sotalol, and metoprolol. Results of previous laboratory studies were notable for macrocytic anemia, dyslipidemia, and a therapeutic international normalized ratio. Review of her history revealed no obvious blood loss, including no hematochezia, melena, hematemesis, hematuria, epistaxis, gum bleeding, or hemoptysis. She was postmenopausal and was not a blood donor. No fevers, night sweats, or weight loss were reported. She had never been diagnosed as having cancer and had received all age-appropriate cancer screening, including mammograms every 1 to 2 years, regular Papanicolaou tests until age 65 years, and colonoscopies routinely starting in her 50s. She was not a vegetarian and was not following a special diet. No diarrhea, greasy stools, gastrointestinal tract symptoms, or history of bariatric operation were identified. She had no history of chronic medical conditions such as kidney disease, liver disease, or an inflammatory condition. She had no implanted devices or artificial valves. Her hemoglobin level had decreased from 13 to 11 g/dL over the preceding 4 years, with a baseline mean corpuscular volume (MCV) of 95 fL. She reported no symptoms such as fatigue, malaise, decreased exercise tolerance, dyspnea, or chest pain.

Vital signs included normal temperature, heart rate of 67 beats/min, and blood pressure of 114/63 mm Hg. Physical examination noted a well-nourished 73-year-old woman in no acute distress. She had anicteric sclera, normal conjunctiva, moist mucous membranes, and no blood in her nasal cavity or oropharynx. Cardiac examination revealed regular rate and rhythm and no murmurs. Results of pulmonary examination were unremarkable. Abdominal examination detected no abnormalities including no hepatosplenomegaly. Skin examination revealed no pallor, areas of ecchymosis, or petechiae. There was no evidence of lymphadenopathy, and results of neurologic examination were normal.

Laboratory evaluation revealed the following (reference ranges provided parenthetically): hemoglobin, 11.5 g/dL (12.0-15.5 g/dL); white blood cell count, 4.3×10^9/L ($3.5\text{-}10.5 \times 10^9$/L) with a normal differential; platelet count, 247×10^9/L ($150\text{-}450 \times 10^9$/L); electrolytes within normal limits; creatinine, 0.8 mg/dL (0.6-1.1 mg/dL); international normalized ratio, 2.4 (therapeutic while taking warfarin); MCV, 101.7 fL (81.6-98.3 fL); and red blood cell distribution width, 13.5% (11.9%-15.5%).

1. Which *one* of the following is the *most likely* cause of this patient's anemia?

a. Iron deficiency
b. Folate deficiency
c. Hypothyroidism
d. Anemia of chronic disease
e. Vitamin B_{12} deficiency

A reasonable way to begin to focus the differential diagnosis of anemia is consideration of MCV. This patient has macrocytic anemia because her MCV is elevated above the normal range.

Iron deficiency anemia classically manifests as a microcytic anemia with an MCV below the normal range, and the red blood

See end of article for correct answers to questions.

Resident in Internal Medicine, Mayo School of Graduate Medical Education, Mayo Clinic, Rochester, MN (C.J.-K.); Advisor to Resident and Consultant in General Internal Medicine, Mayo Clinic, Rochester, MN (C.S.C.).

cell distribution width is elevated. A deficiency in folate is one possible cause of macrocytosis; however, since 1996, the US Food and Drug Administration has mandated that grain products be fortified with folate as a means of reducing the incidence of neural tube defects.[1] In this patient who is following a normal diet, folate deficiency is unlikely, and the prevalence in the United States is estimated at less than 0.1%.[2] Hypothyroidism can produce macrocytosis but is more often associated with milder disease (MCV <100 fL). It is a less common cause of macrocytic anemia, accounting for only 1% of cases.[3] Anemia of chronic disease usually presents as normocytic anemia and thus is unlikely in this patient. Vitamin B_{12} deficiency is the most likely cause of this patient's anemia. It is a relatively frequent cause of macrocytic anemia, particularly in older adults. In a large Dutch study examining the frequency of various etiologies of macrocytic anemia, vitamin B_{12} deficiency was the cause in 16.6% of cases, whereas folate deficiency was responsible in 5.8% of cases.[3]

Because the patient had no neurologic symptoms and no abnormalities on neurologic examination, further investigation was required.

2. Which *one* of the following is the *best* next step in the evaluation of this patient's macrocytic anemia?

a. Bone marrow biopsy
b. Upper and lower endoscopy
c. Peripheral blood smear
d. Obtain further history about alcohol and medication use
e. Pernicious anemia studies

An invasive test such as a bone marrow biopsy is premature at this phase in the work-up. Upper and lower endoscopy may be appropriate if there is concern that the patient is losing blood through her gastrointestinal system, eg, if she was exhibiting iron deficiency anemia or reticulocytosis. A peripheral blood smear would be an important step, and certainly a laboratory work-up is merited. This work-up ideally would initially focus on reticulocyte count, peripheral blood smear, vitamin B_{12}, folate, and thyroid and liver function, all of which can help elucidate the cause of macrocytic anemia. However, before a laboratory work-up is pursued, further history should be obtained in order to quickly eliminate prescription drugs and alcohol as a cause of her macrocytosis. There is a long list of medications that can cause macrocytosis including certain antibiotics, methotrexate, antacids, anticonvulsants, antiretrovirals for human immunodeficiency virus infection, and drugs that precipitate hemolysis.[4] A common cause of macrocytic anemia is alcohol use, which accounts for 11.2% of cases.[3] In order to cause this effect, a person must regularly ingest approximately 80 g of alcohol daily—the equivalent of one bottle of wine. Abstinence from alcohol can return MCV to normal levels within 2 to 4 months.[5] Obtaining further history is a cost-effective method to identify common causes of macrocytic anemia.

The patient reported drinking one glass of wine per day. Her medication list included a calcium with vitamin D supplement, warfarin, sotalol, and metoprolol succinate. Additionally, she took loratadine and fluticasone propionate nasal spray as needed for seasonal allergies. An agent that would lead to macrocytosis was absent from this list.

Pernicious anemia testing could be included as a part of laboratory testing later in the evaluation because it is an insidious cause of macrocytosis. It can cause macrocytic anemia due to vitamin B_{12} deficiency as absorption is impaired because the gastric parietal cells lack intrinsic factor. Measurement of vitamin B_{12} stores should be the first laboratory test performed. If the vitamin B_{12} level is less than 150 ng/L (180-914 ng/L), testing for intrinsic factor blocking antibody should be conducted, and if results are negative or indeterminate, the gastrin level should be measured. If the vitamin B_{12} level is 150 to 400 ng/L, a methylmalonic acid test is performed, and if results are greater than 0.40 nmol/mL, testing for intrinsic factor blocking antibody is performed. Again, a laboratory work-up should be completed in this patient after the medication and social history is complete.

After gathering further history, a laboratory work-up was initiated in a stepwise fashion. The following values reflect her laboratory results from a series of sequential testing:

Mayo Clin Proc. ■ June 2017;92(6):e89-e93 ■ http://dx.doi.org/10.1016/j.mayocp.2016.09.016
www.mayoclinicproceedings.org

reticulocyte count, 1.98% (0.77%-2.36%); vitamin B_{12}, 350 ng/L; methylmalonic acid, 0.17 nmol/mL (<0.40 nmol/mL); folate, >20.0 μg/L (≥4.0 μg/L); peripheral blood smear, macrocytosis without other diagnostic abnormalities; total bilirubin, 1.1 mg/dL (≤1.2 mg/dL); thyrotropin, 2.6 mIU/L (0.3-4.2 mIU/L); iron, 106 μg/dL (35-145 μg/dL); ferritin, 108 μg/L (11-307 μg/L); erythrocyte sedimentation rate, 22 mm/h (0-29 mm/h); C-reactive protein, <3.0 mg/L (≤8.0 mg/L); human immunodeficiency virus types 1/2 antigen and antibody screen, negative; lactate dehydrogenase, 167 U/L (122-222 U/L); haptoglobin, 123 mg/dL (30-200 mg/dL); Coombs test for autoimmune hemolysis, negative; and serum protein electrophoresis and urine protein electrophoresis, normal.

No obvious cause of her macrocytic anemia is evident from her laboratory studies. Importantly, hemolysis was ruled out with a normal reticulocyte count and peripheral blood smear lacking schistocytes, bite cells, or other abnormalities. Given the level of diagnostic uncertainty and the patient's desire to continue the evaluation, invasive testing was the next consideration. A bone marrow biopsy of the right posterior iliac crest was performed. It revealed refractory cytopenia with multilineage dysplasia and blasts that were not increased. The bone marrow was normocellular with slightly megaloblastoid erythroid maturation and prominent dysmegakaryopoiesis.

3. Which *one* of the following diagnoses is *most likely* in this patient?

a. Myelofibrosis
b. Myelodysplastic syndrome (MDS)
c. Idiopathic aplastic anemia
d. Acute myeloid leukemia (AML)
e. Polycythemia vera

Bone marrow biopsy findings consistent with myelofibrosis would include hypercellular marrow with increased fibrosis and focal infiltration of mast cell granulomas. Our patient's normocellular marrow and lack of fibrosis make myelofibrosis unlikely. Pathologic examination of her biopsy specimen revealed cytopenia and dysplasia consistent with a diagnosis of MDS. The appearance of the disruption of normal architecture and loss of cellular differentiation are hallmarks of MDS. This patient's marrow also included immature red blood cell and platelet precursors, which are typical features of MDS. Idiopathic aplastic anemia would appear as hypocellular bone marrow combined with pancytopenia. In AML, the marrow would exhibit excessive blasts. Polycythemia vera would manifest as hypercellular marrow with neoplastic proliferation of erythroid cells on biopsy specimens.

With the diagnosis of MDS, coordination of care was continued with hematology. Cytogenetic testing was performed and revealed a 3q inversion and 5q deletion.

4. Which *one* of the following is the *most appropriate* treatment for this patient?

a. Hematopoietic stem cell transplant
b. Corticosteroids
c. Observation
d. Erythropoietin
e. Chemotherapy

There are a number of possible treatment pathways for a patient with MDS. Patients are most commonly risk stratified using the Revised International Prognostic Scoring System. This scoring system groups patients into risk categories: very low risk (≤1.5), low risk (>1.5 to 3.0), intermediate risk (>3 to 4.5), high risk (>4.5 to 6), and very high risk (>6). The prognostic variables used to calculate the score include cytogenetics, bone marrow blast percentage, hemoglobin level, platelet count, and absolute neutrophil count.[6] This patient received a score of 3 points, all for her cytogenetic findings, which were on the poor end of the spectrum in which 0 to 4 points are available; she had less than 2% bone marrow blasts, hemoglobin level of greater than 10 g/dL, platelet count of more than 100×10^9/L, and absolute neutrophil count of more than 0.8×10^9/L, for all of which she received 0 points. These risk categories help clinicians identify appropriate treatment options for patients. A stem cell transplant is reserved for patients with point values of 4.5 or greater only if they have good performance status; it would not be an appropriate treatment choice for this patient. This option is the only potentially curative treatment for MDS, but not all patients are candidates. Corticosteroids are not used for treatment for MDS. Observation is the appropriate

treatment course for low-risk patients with a point value of 3 or less and thus is the best choice for this patient. Erythropoietin can be used for patients with symptomatic anemia who have a low serum erythropoietin level and is usually the initial therapy when patients are symptomatic. This patient reported no symptoms, and her erythropoietin level was 14.9 mIU/mL (2.6-18.5 mIU/mL). Chemotherapy with medications such as azacitidine, decitabine, or lenalidomide are sometimes used in low- and intermediate-risk patients.

Asymptomatic patients can be managed expectantly with serial physical examinations and laboratory tests with the purpose of evaluating disease tempo. In most patients with MDS, the main goal of therapy is to control symptoms, which ideally should improve their quality of life. There is no evidence that treating asymptomatic patients improves long-term survival. Because our patient had no symptoms, observation was recommended at this time.

5. Which *one* of the following is the *best* next step in this patient's care?

a. Ensure proper vaccination against influenza and pneumonia
b. Provide prophylactic antibiotics against opportunistic infections
c. Frequent hemoglobin checks and transfusion as needed
d. Periodic bone marrow biopsies to monitor for transformation to AML
e. Prioritize advanced care planning

Supportive care is a central component of MDS management. This patient has a low Revised International Prognostic Scoring System score of 3, which corresponds to a median survival of 5.3 years and a median time to AML development, in 1 in 4 patients, of 10.8 years.[6] The most appropriate first step is to prevent infection. The principal cause of death in patients with MDS is infection, primarily bacterial infections, and incidence rates are high. Those with MDS should be given appropriate vaccinations including influenza yearly and a pneumococcal vaccine every 5 years. Prophylactic antibiotics are not a helpful strategy and may endanger the patient through antibiotic resistance. Periodic hemoglobin checks and transfusions as needed certainly would occur for this patient as a part of her care plan, but it is not the most immediate next step. Routine laboratory monitoring with complete blood cell counts should be performed, and when cell counts deteriorate more rapidly than anticipated, a bone marrow biopsy may be performed to evaluate for transformation to AML. This option is not routinely performed because patients with MDS are more likely to die of bone marrow failure than AML. Advanced care planning is an important component of care for any older patient and should certainly be addressed; however, this discussion of end-of-life wishes can occur at any time. Being aware of this patient's health priorities is an important aspect of her care. Our patient is up-to-date on her vaccinations, remains anemic yet asymptomatic, and continues to receive care in both the general internal medicine and hematology departments, which includes monitoring of her complete blood cell count and observation.

DISCUSSION

Unexplained anemia in an elderly patient merits further evaluation. Myelodysplastic syndrome is one of many possible etiologies for anemia in older adults and the ultimate diagnosis in approximately 2.5% of patients who present with macrocytic anemia.[4] Myelodysplastic syndrome is not a distinct illness but rather a heterogeneous group of hematopoietic stem cell malignancies involving dysplastic and inadequate blood cell production, which carries a range of risk for transformation to an acute leukemia. The pathogenesis of this constellation of disorders is incompletely understood. Like most other cancers, it is driven by the stepwise acquisition of mutations that are oncogenic; in this case, the cause is thought to be a single hematopoietic progenitor cell that is transformed and spawns a clonal process resulting in ineffective hematopoiesis.[7]

The incidence of MDS in the United States is estimated at approximately 10,000 cases per year.[8] An estimated 3 to 4 individuals per 100,000 are affected by this disease.[9] It is seen most commonly in the geriatric population, with a median age at diagnosis of older than 65 years. Older age, previous radiation therapy, chemical exposure (eg, benzene), tobacco use, chemotherapy, a benign hematologic disease, and inherited genetic abnormalities

Mayo Clin Proc. ■ June 2017;92(6):e89-e93 ■ http://dx.doi.org/10.1016/j.mayocp.2016.09.016
www.mayoclinicproceedings.org

(Fanconi anemia or trisomy 21) have all been associated with increased risk of MDS.[10] Therapy-related MDS is caused by mutational events induced by cytotoxic agents given for preexisting conditions and historically has poorer outcomes than de novo MDS. With a growing population of long-term cancer survivors, this form of MDS is on the rise and is an important clinical consideration.

The clinical presentation of MDS is nonspecific. Most patients are asymptomatic, and MDS is discovered by the presence of abnormalities on routine blood cell counts. Patients may complain of fatigue, malaise, weakness, angina, exercise intolerance, or dyspnea on exertion when they are anemic, which is the most common cytopenia in MDS. Almost all patients with MDS have anemia, about half exhibit leukopenia, and a quarter have thrombocytopenia.[11] The diagnostic work-up includes a complete blood cell count, peripheral blood smear, and bone marrow biopsy. The peripheral blood smear often reveals macrocytosis and can include basophilic stippling, Howell-Jolly bodies, and nucleated red blood cells, which indicate that red blood cells are leaving the bone marrow prematurely. The bone marrow biopsy specimen features dysplasia. Samples are evaluated for cytogenetic abnormalities in order to aid in prognosis. Diagnosis of MDS requires both unexplained qualitative changes in the blood or bone marrow of one or more cell lines and morphological evidence of dysplasia on visual inspection of peripheral blood or bone marrow specimens.[12] The level of blasts must be less than 20%, otherwise the disorder is considered to be AML. Treatment for MDS varies widely on the basis of symptoms and risk stratification, ranging from observation to chemotherapy and stem cell transplant.

Myelodysplastic syndrome is a condition that disproportionately affects older adults and often presents asymptomatically or nonspecifically. Because of the spectrum of severity and variability of prognosis, macrocytic anemia warrants further evaluation.

Correspondence: Address to C. Scott Collins, MD, Division of General Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (collins.charles@mayo.edu).

REFERENCES

1. Czeizel AE, Dudás I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med*. 1992;327(26):1832-1835.
2. Odewole OA, Williamson RS, Zakai NA, et al. Near-elimination of folate-deficiency anemia by mandatory folic acid fortification in older US adults: Reasons for Geographic and Racial Differences in Stroke study 2003-2007. *Am J Clin Nutr*. 2013;98(4):1042-1047.
3. Stouten K, Riedl JA, Droogendijk J. Prevalence of potential underlying aetiology of macrocytic anaemia in Dutch general practice. *BMC Fam Pract*. 2016;17(1):113.
4. Hesdorffer CS, Longo DL. Drug-induced megaloblastic anemia. *N Engl J Med*. 2015;373(17):1649-1658.
5. Hoffbrand V, Provan D. ABC of clinical haematology: macrocytic anaemias. *BMJ*. 1997;314(7078):430-433.
6. Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System for myelodysplastic syndromes. *Blood*. 2012;120(12):2454-2465.
7. Will B, Zhou L, Vogler TO, et al. Stem and progenitor cells in myelodysplastic syndromes show aberrant stage-specific expansion and harbor genetic and epigenetic alterations. *Blood*. 2012;120(10):2076-2086.
8. Ma X, Does M, Raza A, Mayne ST. Myelodysplastic syndromes: incidence and survival in the United States. *Cancer*. 2007;109(8):1536-1542.
9. Rollison DE, Howlader N, Smith MT, et al. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004, using data from the NAACCR and SEER programs. *Blood*. 2008;112(1):45-52.
10. Ma X, Lim U, Park Y, et al. Obesity, lifestyle factors, and risk of myelodysplastic syndromes in a large US cohort. *Am J Epidemiol*. 2009;169(12):1492-1499.
11. Groupe Francais de Morphologie Hematologique. French registry of acute leukemia and myelodysplastic syndromes: age distribution and hemogram analysis of the 4496 cases recorded during 1982-1983 and classified according to FAB criteria. *Cancer*. 1987;60(6):1385-1394.
12. Swerdlow SH, Campo E, Harris NL, et al., eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: International Agency for Research on Cancer; 2008.

CORRECT ANSWERS: 1. e. 2. d. 3. b. 4. c. 5. a