

Managed Care Clinical Corner: Evaluation of Anemia

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A Word from the Editor

Ancillary services incur great cost to managed care organizations. The total expenditures for tests such as ambulatory laboratory evaluations may equal or exceed the costs associated with needless or medically inappropriate prolonged hospital admissions. A common source of overutilization is the laboratory assessment of anemia. Such a case is presented here.

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CASE

A 40-year-old Caucasian woman reported gradual progressive weakness and shortness of breath. She had a hemoglobin level of 4.2g/dL, but the total white cell count, white blood cell differential, and platelet count were normal. Her menarche began at age 12; she had had four term pregnancies and moderate to heavy menstrual flow beginning several years ago. She has been on no contraceptives after a tubal ligation rendered her infertile after her last delivery 3 years ago. She took no nutritional replacement during her pregnancies. She did not nurse, and her menses resumed quickly. During her last pregnancy, her obstetrician told her that her red blood cells were small, and that she was anemic because of her pregnancy. He suggested she may want to be screened for Mediterranean anemia or thalassemia. Her family is of Northern European ancestry, and her penultimate pregnancy was not complicated by anemia. She has no anemic siblings, offspring, or parents.

Initial laboratory studies revealed a mean corpuscular volume of 62 femtoliters (fL) and a red cell

distribution width (RDW) of 19. The technician reviewing the slide on reflex referral noted the presence of target cells and anisocytosis, but no other irregularities. The patient gave a history of recent craving for ice, but denied starch or other pica ingestion.

Physical examination was significant for pallor of skin, lips, palate, and nailbeds. She had no bruises or petechiae, nor was there enlargement of the lymph nodes, liver, or spleen. Further laboratory studies were ordered including serum iron and iron-binding capacity, serum ferritin, serum B₁₂ and red cell folic acid levels, hemoglobin electrophoresis, and direct Coombs test.

... MANAGED CARE PERSPECTIVE ...

Hemolytic states can be insidious and a difficult diagnosis to make. The differential diagnosis of microcytic anemia includes iron deficiency, anemia of chronic disease, thalassemia, hemolytic states, lead poisoning, and sideroblastic anemia.

The initial response to a patient presenting with weakness, fatigue, shortness of breath, and other symptoms of anemia, of course, is to make a physical examination and take a complete history. Just what the appropriate laboratory tests are depends on a number of factors, as demonstrated in the following analysis of the case.

Rationale for Substantial Laboratory Work-Up

Anemia in a multiparous woman at any age can never be taken for granted. Certain risk factors may be "red flags" for a congenital or serious form of hemolytic disease and thus may warrant comprehensive labo-

ratory analysis. In reviewing a patient's history, the physician needs to ask himself or herself:

- Is the patient on chronic iron supplementation?
- Did she undergo a hysterectomy?
- Has she been diagnosed with chronic anemia previously?
- Does the patient have a family history of anemia?
- Is she of Mediterranean, African, or Southeast Asian extraction?
- Do her preliminary laboratory results show an associated abnormality of the white cell count or differential or platelet count?
- Does her physical examination reveal lymphadenopathy, splenomegaly, or petechiae?
- Is the red cell size greater than 110 fL?
- Were schistocytes or sickle cells found on slide examination?

If the answer to any of these questions is yes, then further workup is warranted. On the other hand, if all answers are negative, as for the patient described here, then additional laboratory tests delay treatment unnecessarily and increase costs of care.

In this patient, in addition to the elevated RDW that indicates a high level of variety of the red cell sizes, and the lowered mean red cell size itself, a reticulocyte count, which is rapidly done and inexpensive, would show if the condition was one of underproduction (low reticulocyte count) or overconsumption (thalassemia, bleeding, Coombs-positive hemolysis, sickle cell disease, liver disease, or pernicious anemia). In the latter conditions as well, incidental measurement of the serum lactate dehydrogenase might show an elevation not seen in iron deficiency. A chemical examination of the stool for occult blood would provide an additional level of confidence in the diagnosis of simple iron deficiency anemia due to multiparity rather than gastrointestinal blood loss, particularly in view of the insidious onset of the moderately severe anemia.

Treatment might be undertaken with institution of low-dose oral contraceptives to reduce menstrual flow, and/or a trial of iron therapy. The reticulocyte count would be expected to begin to rise after a week or 10 days of therapy, serving as a reasonable indicator that the diagnosis (iron deficiency) was correct. This rise in the reticulocyte count occurs even before any rise in the measured hemoglobin. The latter may take as long as a month. Repeat testing should be done by fingerstick to prevent further iron depletion. No laboratory tests beyond the automated blood count and reticulocyte count and manual review of the blood smear would

be expected to change either the diagnosis or treatment in cases such as the one described above.

... CLINICIAN'S POINT OF VIEW ...

Making a Differential Diagnosis in Anemia

In the evaluation of anemias, as in all diagnostic encounters, a thorough history and physical examination are invaluable assets in determining the correct diagnosis. While the history and physical evaluation provided in this case are excellent, for the sake of completeness, we would have included the following:

- personal and family histories of bleeding, diathesis, and transfusions
- history of heart murmur or cardiac evaluation in the past
- cardiac examination with attention to heart murmurs
- history of rashes, petechia, or ecchymosis
- history of illicit drug or alcohol use
- history of lead ingestion or occupational exposure to lead
- history of gastrointestinal complaints
- history of constipation, dark, or bloody stools
- dietary history and nutritional status
- orthostatic blood pressures
- retinal examination
- rectal examination
- test for occult blood in the stool

However, with the ample information provided in this patient's history, we can explore the diagnostic possibilities and perhaps come to some conclusions with regard to the appropriateness of ordering further laboratory tests.

Iron deficiency is the most common cause of anemia in American adults. Iron loss due to menstrual bleeding is the most common cause of anemia in women of childbearing age, with iron loss due to gastrointestinal bleeding a close second in American adults. Gastrointestinal bleeding usually results from nonsteroidal anti-inflammatory medications prescribed for arthritis, which may be determined by history taking and which would be associated with an elevated, rather than a low, reticulocyte count. Our patient is a menstruating female, with a microcytic anemia and a wide red cell distribution width; iron deficiency should be considered in the differential diagnosis. The patient's history and physical examination are essentially normal, indicating that a diagnosis of the anemia of chronic disease is unlikely. While thalassemia is a possibility and is easily confused with iron deficiency anemia, the northern European ances-

try and absence of a family history for this make it less likely in this patient. The wide red cell distribution width and basophilic stippling of RBCs on the peripheral smear militate against the thalassemia diagnosis also. Finally, the history of normocytosis before the last pregnancy eliminates the diagnosis of thalassemia completely.

Red cell metabolic enzyme deficiency, hemoglobinopathies, red cell membrane defects, abnormal extrinsic stresses, and immune-mediated RBC destruction all can cause hemolysis. The first three diagnoses can be eliminated in this patient by the history of normal red cell morphology and red cell volume in the past. Extrinsic stresses such as microangiopathic hemolytic anemias and immune-mediated red cell destruction can be eliminated by the presence of a normal physical examination and the absence of schistocytes and helmet cells on the peripheral blood smear. Lead toxicity leading to anemia is unlikely, as there is no history of lead ingestion or occupational exposure to lead. Furthermore, there are no gastrointestinal, renal disease, or neurologic complaints, and no basophilic stippling or macrocytic red cells noted on the peripheral smear that would be characteristic of lead toxicity. The peripheral blood smear has no ringed sideroblasts, the sine qua non for sideroblastic anemia.

As the other diagnoses have been eliminated, we are left with the likely diagnosis of an iron deficiency anemia. What do the suggested additional laboratory tests add to our presumptive diagnosis? Let's see.

Serum iron, iron binding capacity, and serum ferritin. These tests give us an indication of the patient's iron stores. If stores were high, we could rule out iron deficiency anemia, but high stores would be consistent with sideroblastic anemia, a diagnosis that is eliminated by red cell morphology on peripheral blood smears. Also, in a menstruating female with a history of a heavy flow and no iron supplementation, the likelihood is that iron stores would be low. Low iron stores would tend to confirm the diagnosis of iron deficiency anemia, but not eliminate other possibilities. These tests would not confirm our diagnosis if stores were low; if stores were normal or high, it would provide data in conflict with our presumptive diagnosis drawn from the history, physical, and examination of the peripheral smear. The results of this test would not help us make a clinical decision.

Serum B₁₂ and red cell folic acid levels. This is an appropriate test when a macrocytic anemia is being evaluated and/or hypersegmented polymorphonucleocytes are noted on the peripheral smear. In this case, it would be inappropriate.

Hemoglobin electrophoresis. When evaluating hemoglobinopathies such as alpha and beta thalassemia and sickle cell disease, this test can be confirmatory. In the present case, the history of normocytosis in the past and the absence of relevant family or personal history of sickle cell disease or other hemoglobinopathy eliminate these possibilities.

Direct Coombs test. When evaluating the cause of a hemolytic anemia, a Coombs test is very helpful in sorting out the immune-mediated etiologies. Our patient has no history of jaundice, light stools, or dark urine. Her physical examination revealed no heart murmurs or hepatosplenomegaly. Finally, her peripheral smear gives no evidence of spherocytes, schistocytes, or helmet cells. To perform this test on a patient without clinical or laboratory indications would only provide the clinician with useless, or worse, confusing data. This test would not be indicated in this patient.

The Costs of Testing

The number of laboratory tests available to physicians has increased, as has their reliability and the speed with which they can be performed. The tests are objective and the results are reported in easily quantifiable terms; because of this, the results appear authoritative. Furthermore, a third-party insurer usually covers these tests, so the patient is apparently "protected" from their costs. Operating in this environment, physicians may give little thought to the expense of tests and may come to rely on them for the solution of clinical problems. However, physicians must keep in mind that these test results are as flawed (or as accurate) as the people who sample, analyze, and interpret them and the tolerances of the instruments used to determine them.

Admittedly, the financial cost of an individual test is small. Based on the size and volume of commercial tests, the cost of an individual test to the managed care organization is minimally more than the reagents. The only effect that managed care has had on the cost of laboratory tests is through these organizations' capitation of the costs. In reality, the larger costs associated with inappropriate testing are the cost to the patient in missed or delayed diagnoses and the risks involved in the evaluation of false-positive results.

When it comes to changing physician behavior, managed care organizations have not effectively changed the quantitative or qualitative use of the clinical laboratory by the physicians in their networks. Ultimately, physicians are responsible to their patients for the risks and expense involved in the laboratory procedures ordered. Before ordering each test, physicians should ask themselves the question, "How

will the results of this test change my diagnosis or treatment?" If the answer is "It won't," the test should not be ordered.

Afterword

The authors feel comfortable with a secondary and minimal use of the laboratory. They agree that the evaluation of anemia hinges on a thorough history and physical examination (which includes checking the stool for occult blood) and a "look" at the peripheral smear for RBC and other cell line morphology. Both authors caution against a "shotgun" approach of ordering scans and panels of laboratory tests that previously were called (facetiously) the "anemia one" work-up.

Cost-effective use of the laboratory to diagnose the cause of anemia was not borne of managed care. It is a holdover from the "good old days," showcasing the individual physician's bedside skills as he/she approaches a single patient with a hematological problem.

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To Our Readers

If you would like to submit a case or if there is a condition you would like to see covered in a future column, please send your suggestions to:

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Suggested Reading

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