Laboratory Evaluation of Macrocytic Anemia
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Anemias can be classified, according to the mean corpuscular volume (MCV), into microcytic, normocytic and macrocytic anemias. Macrocytic anemia is defined by a MCV of greater than 100 fl. Nutritional deficiencies, medications and alcohol use are among the most common causes of macrocytosis. Bone marrow diseases, such as myelodysplastic syndrome (MDS) and aplastic anemia, may present with a macrocytic anemia. Chronic liver disease and hypothyroidism may also have an associated macrocytic anemia.

Initial evaluation, of any anemia, should begin with examination of the peripheral blood smear, where diagnostic clues may be revealed. For example, oval macrocytes are seen with certain medications, nutritional deficiencies and MDS, while round macrocytes are seen with chronic alcohol use, liver disease and hypothyroidism. Hypersegmented neutrophils are characteristic of vitamin B₁₂ and/or folate deficiency. Peripheral blood cytopenias, occasional circulating blasts and dysplastic morphologic features, such as giant and/or hypogranular platelets and pelgeroid (bi-lobed nucleus) and/or hypogranular neutrophils, raise suspicion for MDS. (See algorithm below.)
Prior to additional laboratory work-up, it is important to consider medications and/or alcohol as the cause of macrocytosis.\textsuperscript{1} Hydroxyurea, methotrexate, trimethoprim, and nucleotide analogs, including those prescribed for HIV infection and chemotherapy, are common causes of macrocytosis, sometimes associated with an anemia. Alcohol use is another common cause of mild macrocytosis, though usually without anemia.\textsuperscript{2}

Next, deficiencies of folate and vitamin B\textsubscript{12} need to be ruled out. Although recommendations differ, initial investigation usually begins with serum vitamin B\textsubscript{12} and serum/red cell folate levels.\textsuperscript{3} Some authors recommend using homocystine along with serum vitamin B\textsubscript{12} levels as the initial screen, because of its higher sensitivity.\textsuperscript{1} Of note, homocystine levels will not help differentiate between the two vitamin deficiencies, as elevated levels are seen in both states.

Serum vitamin B\textsubscript{12} is used as a screening test. A low level of vitamin B\textsubscript{12} is expected in deficient states, but is also seen in pregnant, elderly and folate
deficient patients. A subset of vitamin B\textsubscript{12} deficient patients (3–5%) will have a normal vitamin B\textsubscript{12} level. When the vitamin B\textsubscript{12} level is equivocal, confirmatory testing with methylmalonic acid (MMA) is performed, with elevated MMA expected in vitamin B\textsubscript{12} deficiency. Once the diagnosis is confirmed, evaluation for pernicious anemia and malabsorption occurs.

The folate assays also have limitations. A low level of serum/red cell folate is expected in folate deficiency, but approximately 60% of vitamin B\textsubscript{12} deficient patients will also have a low red cell folate level. Folate deficiency is presumed when a low serum/red cell folate level is obtained in the presence of a normal vitamin B\textsubscript{12} level.

If nutritional deficiencies are excluded, primary bone marrow disorders must be considered. MDS, aplastic anemia and large granular lymphocyte leukemia are bone marrow disorders most commonly associated with a macrocytic anemia. A bone marrow examination is required for diagnosis of these entities.

In summary, laboratory investigation of a macrocytic anemia is done in concert with a thorough clinical history, including medication and drug use history. Assessment begins with peripheral blood review and serum chemistries, including folate, vitamin B\textsubscript{12} and possibly homocystine and MMA levels. Bone marrow evaluation also may be clinically warranted.

References

