Laboratory Evaluation of Normocytic Anemia
Alexandra Harrington, MD
CAP Hematology and Clinical Microscopy Resource Committee

Anemias can be classified according to the mean corpuscular volume (MCV) into microcytic, normocytic and macrocytic. In normocytic anemias, the MCV is within the reference range, generally between 80-100 fL. Though anemia of chronic disease (ACD) is the most common cause of such anemias\(^1\), the differential diagnosis is extensive, including blood loss, hemolytic anemias, anemia of renal disease, nutritional anemias and primary bone marrow disorders. Multiple diagnostic algorithms are available\(^1-3\), a concise and clinically useful example is shown in the figure below.
Normocytic anemias can be initially categorized based on the reticulocyte count, into those characterized by effective erythropoiesis (elevated reticulocytes) or ineffective erythropoiesis (low to normal reticulocytes).\(^1\) Hemolytic anemias and anemias secondary to blood loss will have elevated reticulocyte counts in the days following episodes, as red cell production is not impaired. In contrast, nutritional anemias, ACD, anemia of renal disease and the anemias secondary to primary bone marrow disorders are examples of disorders of diminished red cell production and, therefore, have low to inappropriately normal reticulocyte counts.

Examination of the peripheral blood smear is as essential as reticulocyte enumeration in the initial work-up of a normocytic anemia. Attention must be paid to all three cell lineages, as abnormalities in each may provide diagnostic clues. For example, many of the hemolytic anemias have characteristic peripheral blood features, such as sickle cells in sickle cell disease, spherocytes in hereditary
spherocytosis (HS) and autoimmune hemolytic anemia (AIHA), schistocytes in microangiopathic hemolytic anemia (MAHA) and bite cells in glucose-6-phosphate dehydrogenase deficiency. Cytopenias, circulating immature precursors, including a leukoerythroblastic reaction, and dysplastic features suggest underlying bone marrow disorders and require bone marrow examination.\(^1\)\(^-\)\(^2\)

If hemolysis is suspected and supported by decreased haptoglobin with elevated indirect bilirubin and lactate dehydrogenase levels, further evaluation is needed. Because the hemolytic anemias encompass a wide variety of disorders—including AIHAs, MAHAs, hereditary and acquired red cell membrane defects, such as HS and paroxysmal nocturnal hemoglobinuria and hemoglobinopathies—additional work-up is tailored based on clinical suspicion and peripheral blood findings. For example, a direct antiglobulin test (Coombs test), which assesses immunoglobulin and/or complement bound to red cells, is requested to rule out an AIHA in a patient with spherocytes.

For normocytic anemias with decreased reticulocyte counts and fairly unremarkable blood smears, the differential diagnosis includes ACD, anemia of renal disease, nutritional anemias and red cell aplasia.\(^2\) In these cases, the clinical history may guide further laboratory evaluation, if needed. For example, in patients with chronic illness, iron studies are obtained to evaluate for ACD, with elevated serum ferritin levels, decreased serum iron levels and decreased total iron-binding capacity (TIBC) confirming the diagnosis. Likewise, in patients with poor diets, it may be appropriate to assess iron status and/or vitamin B\(_{12}\) and folate levels, as deficiencies of these nutrients may rarely present as normocytic anemias.\(^3\) Finally, bone marrow examination is required for evaluating the etiology of red cell aplasia.\(^2\)

In summary, the differential diagnosis of normocytic anemia is vast. Evaluation begins with reticulocyte enumeration and blood smear examination, with further work-up based on these findings and clinical history.

References