

61 - 65 Interpreting Peripheral Blood Smears

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Section 9 Hematologic Alterations Dan L. Longo

Interpreting Peripheral

Blood Smears Some of the relevant findings in peripheral blood, enlarged lymph nodes, and bone marrow are illustrated in this chapter. Systematic histologic examination of the bone marrow and lymph nodes is beyond the scope of a general medicine textbook. However, every internist should know how to examine a peripheral blood smear. The examination of a peripheral blood smear is one of the most informative exercises a physician can perform. Although advances in automated technology have made the examination of a peripheral blood smear by a physician seem less important, the technology is not a completely satisfactory replacement for a blood smear interpretation by a trained medical professional who also knows the patient's clinical history, family history, social history, and physical findings. It is useful to ask the laboratory to generate a Wright's-stained peripheral blood smear and examine it. A normal peripheral blood smear is shown in Figure 65-1. The best place to examine blood cell morphology is the feathered edge of the blood smear where red cells lie in a single layer, side by side, just barely touching one another but not overlapping. The author's approach is to look at the smallest cellular elements, the platelets, first and work his way up in size to red cells and then white cells. Using an oil immersion lens that magnifies the cells 100-fold, one counts the platelets in five to six fields, averages the number per field, and multiplies by 20,000 to get a rough estimate of the platelet count. The platelets are usually 1–2 μm in diameter and have a blue granulated appearance. There is usually 1 platelet for every 20 or so red cells. Of course, the automated counter is much more accurate, but gross disparities between the automated and manual counts should be assessed. Large platelets may be a sign of rapid platelet turnover, as young platelets are often larger than old ones; alternatively, certain rare inherited syndromes can produce large platelets. If the platelet count is low, the absence of large (young) platelets may be an indicator of marrow production problems. Platelet clumping visible on the smear can be associated with falsely low automated platelet counts. Clumping may be caused by the anticoagulant into which the blood is drawn. Similarly, neutrophil fragmentation can be a source of falsely elevated automated platelet counts. The absence of platelet granules may be an artifact of the handling of the blood or may indicate marrow disease or a rare congenital anomaly, gray platelet syndrome. Elevated platelet counts usually signify a myeloproliferative disorder or a reaction to systemic inflammation. Next one examines the red blood cells. One can gauge their size by comparing the red cell to the nucleus of a small

lymphocyte. Both are normally about 8- μ m wide. Red cells that are smaller than the small lymphocyte nucleus may be microcytic; those larger than the small lymphocyte nucleus may be macrocytic. Macrocytic cells also tend to be more oval than spherical in shape and are sometimes called macroovalocytes. The automated mean corpuscular volume (MCV) can assist in making a classification. However, some patients may have both iron and vitamin B12 deficiency, which will produce an MCV in the normal range but wide variation in red cell size. When the red cells vary greatly in size, anisocytosis is said to be present. When the red cells vary greatly in shape, poikilocytosis is said to be present. The electronic cell counter provides an independent assessment of variability in red cell size. It measures the range of red cell volumes and reports the results as "red cell distribution width" (RDW). This value is calculated from the MCV; thus, cell width is not being measured

but cell volume is. The term is derived from the curve displaying the frequency of cells at each volume, also called the distribution. The width of red cell volume distribution curve is what determines the RDW. The RDW is calculated as follows: $RDW = (\text{standard deviation of MCV} \div \text{mean MCV}) \times 100$. In the presence of morphologic anisocytosis, RDW (normally 11-14%) increases to 15-18%. The RDW is useful in at least two clinical settings. In patients with microcytic anemia, the differential diagnosis is generally between iron deficiency and thalassemia. In thalassemia, the small red cells are generally of uniform size with a normal small RDW. In iron deficiency, the size variability and the RDW are large. In addition, a large RDW can suggest a dimorphic anemia when a chronic atrophic gastritis can produce both vitamin B12 malabsorption to produce macrocytic anemia and blood loss to produce iron deficiency. In such settings, RDW is also large. An elevated RDW also has been reported as a risk factor for all-cause mortality in population-based studies, a finding that is unexplained currently.

Interpreting Peripheral Blood Smears CHAPTER 65 After red cell size is assessed, one examines the hemoglobin content of the cells. They are either normal in color (normochromic) or pale in color (hypochromic). They are never "hyperchromic." If more than the normal amount of hemoglobin is made, the cells get larger—they do not become darker. In addition to hemoglobin content, the red cells are examined for inclusions. Red cell inclusions are the following:

1. Basophilic stippling—diffuse fine or coarse blue dots in the red cell usually representing RNA residue—especially common in lead poisoning
2. Howell-Jolly bodies—dense blue circular inclusions that represent nuclear remnants—their presence implies defective splenic function
3. Nuclei—red cells may be released or pushed out of the marrow prematurely before nuclear extrusion—often implies a myelophthitic process or a vigorous marrow response to anemia, usually hemolytic anemia
4. Parasites—red cell parasites include malaria and babesia (Chaps. A2 and A6)
5. Polychromatophilia—the red cell cytoplasm has a bluish hue, reflecting the persistence of ribosomes still actively making hemoglobin in a young red cell. Vital stains are necessary to see precipitated hemoglobin called Heinz bodies. Red cells can take on a variety of different shapes. All abnormally shaped red cells are poikilocytes. Small red cells without the central pallor are spherocytes; they can be seen in hereditary spherocytosis, hemolytic anemias of other causes, and clostridial sepsis. Dacrocytes are teardrop-shaped cells that can be seen in hemolytic anemias, severe iron deficiency, thalassemias,

myelofibrosis, and myelodysplastic syndromes. Schistocytes are helmet-shaped cells that reflect microangiopathic hemolytic anemia or fragmentation on an artificial heart valve. Echinocytes are spiculated red cells with the spikes evenly spaced; they can represent an artifact of abnormal drying of the blood smear or reflect changes in stored blood. They also can be seen in renal failure and malnutrition and are often reversible. Acanthocytes are spiculated red cells with the spikes irregularly distributed. This process tends to be irreversible and reflects underlying renal disease, abetalipoproteinemia, or splenectomy. Elliptocytes are elliptical-shaped red cells that can reflect an inherited defect in the red cell membrane, but they also are seen in iron deficiency, myelodysplastic syndromes, megaloblastic anemia, and thalassemias. Stomatocytes are red cells in which the area of central pallor takes on the morphology of a slit instead of the usual round shape. Stomatocytes can indicate an inherited red cell membrane defect and also can be seen in alcoholism. Target cells have an area of central pallor that contains a dense center, or bull's eye. These cells are seen classically in thalassemia, but they are also present in iron deficiency, cholestatic liver disease, and some hemoglobinopathies. They also can be generated artifactually by improper slide making.

PART 2 Cardinal Manifestations and Presentation of Diseases FIGURE 65-1 Normal peripheral blood smear. Small lymphocyte in center of field. Note that the diameter of the red blood cell is similar to the diameter of the small lymphocyte nucleus. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault, Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-2 Reticulocyte count preparation. This new methylene blue-stained blood smear shows large numbers of heavily stained reticulocytes (the cells containing the dark blue-staining RNA precipitates). (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-3 Hypochromic microcytic anemia of iron deficiency. Small lymphocyte in field helps assess the red blood cell size. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.)

FIGURE 65-4 Iron deficiency anemia next to normal red blood cells. Microcytes (right panel) are smaller than normal red blood cells (cell diameter $<7\ \mu\text{m}$) and may or may not be poorly hemoglobinized (hypochromic). (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault, Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-5 Polychromatophilia. Note large red cells with light purple coloring. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-6 Macrocytosis. These cells are both larger than normal (mean corpuscular volume >100) and somewhat oval in shape. Some morphologists call these cells macroovalocytes. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.)

FIGURE 65-7 Hypersegmented neutrophils. Hypersegmented neutrophils (multilobed polymorphonuclear leukocytes) are larger than normal neutrophils with five or more segmented nuclear lobes. They are commonly seen with folic acid or vitamin B12 deficiency. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA

Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-8 Spherocytosis. Note small hyperchromatic cells without the usual clear area in the center. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-9 Rouleaux formation. Small lymphocyte in center of field. These red cells align themselves in stacks and are related to increased serum protein levels. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.)

Interpreting Peripheral Blood Smears CHAPTER 65 FIGURE 65-10 Red cell agglutination. Small lymphocyte and segmented neutrophil in upper left center. Note irregular collections of aggregated red cells. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGrawHill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-11 Fragmented red cells. Heart valve hemolysis. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-12 Sickle cells. Homozygous sickle cell disease. A nucleated red cell and neutrophil are also in the field. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.)

PART 2 Cardinal Manifestations and Presentation of Diseases FIGURE 65-13 Target cells. Target cells are recognized by the bull's-eye appearance of the cell. Small numbers of target cells are seen with liver disease and thalassemia. Larger numbers are typical of hemoglobin C disease. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-14 Elliptocytosis. Small lymphocyte in center of field. Elliptical shape of red cells related to weakened membrane structure, usually due to mutations in spectrin. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-15 Stomatocytosis. Red cells characterized by a wide transverse slit or stoma. This often is seen as an artifact in a dehydrated blood smear. These cells can be seen in hemolytic anemias and in conditions in which the red cell is overhydrated or dehydrated. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.)

FIGURE 65-16 Acanthocytosis. Spiculated red cells are of two types: acanthocytes are contracted dense cells with irregular membrane projections that vary in length and width; echinocytes have small, uniform, and evenly spaced membrane projections. Acanthocytes are present in severe liver disease, in patients with abetalipoproteinemia, and in rare patients with McLeod blood group. Echinocytes are found in patients with severe uremia, in glycolytic red cell enzyme defects, and in microangiopathic hemolytic anemia. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-17 Howell-Jolly bodies. Howell-Jolly bodies are tiny nuclear remnants that normally are removed by the spleen. They appear in the blood after splenectomy (defect in removal) and with maturation/dysplastic disorders (excess production). (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005;

RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-18 Teardrop cells and nucleated red blood cells characteristic of myelofibrosis. A teardrop-shaped red blood cell (left panel) and a nucleated red blood cell (right panel) as typically seen with myelofibrosis and extramedullary hematopoiesis. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.)

FIGURE 65-19 Myelofibrosis of the bone marrow. Total replacement of marrow precursors and fat cells by a dense infiltrate of reticulin fibers and collagen (hematoxylin and eosin stain). (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-20 Reticulin stain of marrow myelofibrosis. Silver stain of a myelofibrotic marrow showing an increase in reticulin fibers (black-staining threads). (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-21 Stippled red cell in lead poisoning. Mild hypochromia. Coarsely stippled red cell. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.)

Interpreting Peripheral Blood Smears CHAPTER 65 FIGURE 65-22 Heinz bodies. Blood mixed with hypotonic solution of crystal violet. The stained material is precipitates of denatured hemoglobin within cells. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-23 Giant platelets. Giant platelets, together with a marked increase in the platelet count, are seen in myeloproliferative disorders, especially primary thrombocythemia. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-24 Normal granulocytes. The normal granulocyte has a segmented nucleus with heavy, clumped chromatin; fine neutrophilic granules are dispersed throughout the cytoplasm. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.)

PART 2 Cardinal Manifestations and Presentation of Diseases FIGURE 65-25 Normal monocytes. The film was prepared from the buffy coat of the blood from a normal donor. L, lymphocyte; M, monocyte; N, neutrophil. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-26 Normal eosinophils. The film was prepared from the buffy coat of the blood from a normal donor. E, eosinophil; L, lymphocyte; N, neutrophil. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-27 Normal basophil. The film was prepared from the buffy coat of the blood from a normal donor. B, basophil; L, lymphocyte. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.)

FIGURE 65-28 Pelger-Huet anomaly. In this benign disorder, the majority of granulocytes are bilobed. The nucleus frequently has a spectacle-like, or "pince-nez," configuration. (Source: From M

Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-29 Döhle body. Neutrophil band with Döhle body. The neutrophil with a sausage-shaped nucleus in the center of the field is a band form. Döhle bodies are discrete, blue-staining nongranular areas found in the periphery of the cytoplasm of the neutrophil in infections and other toxic states. They represent aggregates of rough endoplasmic reticulum. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGraw-Hill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.) FIGURE 65-30 Chédiak-Higashi disease. Note giant granules in neutrophil. (Source: From M Lichtman et al (eds): Williams Hematology, 7th ed. New York, McGrawHill, 2005; RS Hillman, KA Ault: Hematology in General Practice, 4th ed. New York, McGraw-Hill, 2005.)

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