EDUCATIONAL COMMENTARY – MORPHOLOGIC CHARACTERISTICS OF PERIPHERAL BLOOD CELLS IN SICKLE CELL ANEMIA

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To view the blood cell images in more detail, participants enrolled in program #224 or 225 for Blood Cell Identification can click on the sample identification numbers underlined in the paragraphs below. After logging on with a Paperless Proficiency Testing user name and password, you will see a virtual image of the selected cell and the surrounding fields. If the image opens in the same window as the commentary, saving the commentary PDF and opening it outside your browser will allow you to switch between the commentary and the images more easily. To avoid the need to log in for each image, use the online tool to choose the cell you want to view. Click on this link for the API ImageViewer Instructions.

Learning Objectives

On completion of this exercise, the participant should be able to
- identify morphologic features of peripheral blood leukocytes;
- describe morphologic abnormalities in red blood cells associated with sickle cell anemia; and
- discuss the pathophysiologic process resulting in the formation of sickle cells.

Case History

A CBC was ordered on a 15-year-old African American male. His CBC results are as follows: WBC=7.9 x10^9/L, RBC=2.15 x 10^12/L, Hgb = 6.45 g/dL, Hct = 19.4%, MCV=90.2 fl, MCH=30.0 pg, MCHC=33.2 g/dL, RDW-CV= 25.1%, MPV= 9.6 fl, Platelet = 326 x 10^9/L.

Introduction

The patient presented in this testing event is a 15-year-old African-American boy diagnosed with the inherited hemoglobinopathy sickle cell anemia. The images for discussion include several normal peripheral blood leukocytes and abnormal erythrocytes that may be seen in this condition.

Educational Commentary

Image BCI-15 shows a neutrophil. Neutrophils are medium-sized cells distinguishable by their two to five nuclear lobes. The segmentations are usually separated by thin strands of chromatin. The chromatin in the nuclear lobes appears dense.
and clumped. The cytoplasm in neutrophils is typically pink, tan, or light violet because of numerous specific granules.

**Image BCI-16** is a sickle cell, also called a *drepanocyte*. These cells are common in sickle cell anemia, the disorder identified in this case study patient. This picture is a classic example of a sickle cell. Note the elongated crescent shape and pointed ends. The cell characteristically lacks any area of central pallor. Sickle cells contain an abnormal hemoglobin, hemoglobin S (HbS), which has reduced solubility when deoxygenated. Hemoglobin S is produced in an inherited manner when normal amino acids are substituted on the β hemoglobin chain. When HbS is deoxygenated, the molecules polymerize, forming tactoids or rods that distort the normal red blood cell (discocyte) into the sickle cell, or drepanocyte. When sickle cells are reoxygenated as they circulate, they can revert back to discocytes. But when deoxygenation occurs again, the cell will once again sickle. This sickling-nonsickling process can continue until the cell eventually deforms permanently as a sickle cell. This cell is now irreversibly sickled and remains in this shape even if reoxygenated. Sickle cells are not always classically shaped, but may resemble holly leaves, envelopes, cigars, filaments, or boats. They may have a less pronounced curvature, more tapering in their ends, and a broader center, sometimes with an area of central pallor. It is important to recognize that these other shapes are sickle cells too and not some other morphologic changes in erythrocytes, such as ovalocytes. When these other shapes are present on a peripheral blood smear, a careful review of the slide will usually also reveal several classic sickle cells. Note that in the field of view for Image BCI-16, the cell just above the classic sickle cell (identified by the arrow), is a sickle cell that is not in a classic shape. This sickle cell has ends that are more tapered and less pointed, with a slight area of central pallor.

**Image BCI-17** illustrates an eosinophil. Eosinophils are similar in size to neutrophils. In contrast to neutrophils, however, eosinophils usually only have two nuclear lobes. Also, the cytoplasmic granules are typically larger than the granules seen in neutrophils, are uniform in size, and are a distinctive, red-orange color. The nuclear chromatin, as with neutrophils, is condensed and clumped.
The cell in Image BCI-18 is a lymphocyte. Lymphocytes are variable in size; this is an example of a small cell. The nuclei in small lymphocytes are typically round or oval, with dense and clumped chromatin. Lighter areas of parachromatin are also visible in this cell, but are not unusual. Smaller lymphocytes generally have a high nuclear to cytoplasmic ratio, with scanty amounts of blue cytoplasm.

The arrow in Image BCI-19 identifies a typical monocyte. Monocytes are the largest normal cell that can be seen in the peripheral blood. The nuclei in monocytes vary in shape and may be oval, round, lobulated, or, as in this particular cell, indented. The chromatin is usually fine, showing minimal clumping, and appears a lighter purple. Monocytes have abundant, blue-gray cytoplasm. There may be a few pink or red-purple granules and often, as in this example, cytoplasmic vacuoles. The cellular margins of monocytes are frequently irregular, as also seen in this cell, and cytoplasmic projections are sometimes present. The cytoplasm generally looks uneven or as if it has grains of sand.

The red blood cell featured in Image BCI-20 is an echinocyte. Echinocytes may also be referred to as crenated or burr cells. Echinocytes are usually the same size as normal erythrocytes, although sometimes they appear slightly smaller. They characteristically have 10 to 30 short, blunt, evenly spaced projections around their surface. Echinocytes have a well-defined area of central pallor. Red blood cells are sensitive to several environmental and physiological factors that can alter their shape. Therefore, echinocytes are commonly seen on a peripheral blood slide as an artifact if the smear dries too slowly, the slide is made too thick, or old blood is used to prepare the smear. Changes in pH on the glass slide also often result in the formation of echinocytes. Echinocytes have rarely been associated with renal disease and in cases of patients with severe burns. These cells are not typically seen in patients who have sickle cell anemia and are most likely artifacts.
The final cell, Image BCI-21, is a target cell, or codocyte. In contrast to echinocytes, it is expected that these cells will be seen in a case of sickle cell anemia. Target cells are red blood cells that have a central dense area of hemoglobin surrounded by a white circle and then a final rim of more hemoglobin. Codocytes actually circulate in the peripheral blood as “bells” or “Mexican hats.” They acquire the target appearance when flattened on the glass slide during preparation of the blood smear. Three primary mechanisms result in target cell formation. When excess lipid accumulates on the red blood cell membrane, as may occur in liver disease, an increase in erythrocyte membrane surface area relative to the hemoglobin content forms codocytes. Target cells will be seen as artifacts from the process of slide preparation if a wet smear is dried too slowly (blown dry rather than fan dried) or if the slide is made in a humid environment. In these situations, hemoglobin puddles and precipitates in the perimeter and center of the red blood cells. Finally, some anemias result in less hemoglobin within the red blood cells, although the same membrane surface area is maintained. This again causes excessive membrane relative to cell surface area and codocytes can form. Anemias commonly associated with the presence of target cells include iron deficiency, thalassemia, and, as in this case study patient, hemoglobinopathies such as sickle cell disease.

Sickle Cell Anemia

Sickle cell anemia, also called sickle cell disease, is a common, worldwide disorder affecting primarily individuals of sub-Saharan African descent. It is a severe, inherited abnormality of the hemoglobin molecule. Patients homozygous for this condition do not produce any normal hemoglobin. Individuals with the heterozygous state inherit one normal and one abnormal hemoglobin-producing gene and therefore make some normal hemoglobin. These persons have sickle cell trait. It is rare to see sickle cells in the peripheral blood of individuals with heterozygous sickle cell trait. Only severe physiologic stress could cause sickling in these people. Sickle cell trait does not cause any symptoms. However, patients with sickle cell anemia experience severe symptoms directly related to the abnormal hemoglobin. Sickle cells are rigid and cannot circulate easily in blood vessels, especially through capillaries. They aggregate, eventually occluding the microvasculature. This blockage prevents normal red blood cells from passing through the vessels and delivering oxygen to tissues. Tissue necrosis can result, and further deoxygenation causes more sickling to occur. Patients experience many effects of this disease, including signs and symptoms of anemia and vaso-occlusive crises that trigger extreme bone and joint pain. Hematologic findings are also abnormal. In addition to the presence of sickle and target cells on
the peripheral blood smear, the lysis of erythrocytes results in a hemolytic anemia, with hemoglobin and hematocrit values decreased, as seen in the complete blood cell count reported in this case study patient.

It should be noted that less common conditions, in which patients are doubly heterozygous for HbS and another qualitative or quantitative hemoglobin defect, can also result in the presence of sickle cells on a peripheral blood smear. These disorders include HbSC disease and HbS–β-thalassemia. Therefore, although sickle cells seen on a peripheral blood smear are most often indicative of sickle cell disease, clinical laboratories still use different methods, such as hemoglobin electrophoresis, to identify the presence of HbS as well as other abnormal hemoglobins.

**Summary**

The young man presented in this testing event has sickle cell anemia, an inherited disorder affecting the production of hemoglobin. The images provided for identification and commentary include normal white blood cells as well as abnormal red blood cells that may be seen in the peripheral blood in this condition. Sickle cells, in particular, are diagnostic for this abnormality and must be recognized and reported when present. The ability to identify changes in red blood cells, such as sickle cells, underscores the significant contribution the laboratory professional makes to quality patient care.

**Bibliography**


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