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To view the blood cell images in more detail, click on the sample identification numbers underlined in the paragraphs below. This will open 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. Click on this link for the API ImageViewer™ Instructions.

Learning Outcomes

On completion of this activity, the participant should be able to:

- identify morphologic characteristics of normal peripheral blood granulocytes;
- describe morphologic features of immature granulocytes; and
- compare and contrast immature erythrocytes with normal lymphocytes.

Case Study

A 70-year-old male was seen by his physician for fatigue, night sweats, and weight loss. His CBC results are as follows: WBC=88.3 x 10^9/L, RBC=2.56 x 10^{12}/L, Hgb=8.2 g/dL, Hct=26.3%, MCV=102.5 fL, MCH=32.1, MCHC=31.3 g/dL, RDW=25.3 %, Platelet=412 x 10^9/L.

Educational Commentary

The patient presented in this testing event has been diagnosed as having chronic myelocytic (myelogenous) leukemia (CML). The images provided for review represent both normal and abnormal cells seen in his peripheral blood smear. The cell discussed in each is indicated by an arrow.

The cell in Image BCI-15 is a segmented neutrophil. Segmented neutrophils are typically medium-sized and characterized by two to five nuclear lobes. The lobes are separated by fine threads of chromatin. Note that this particular cell has only one clearly visible thin strand separating two of the lobes. Sometimes the threads of chromatin are not readily apparent, as multiple folding of the lobes may obscure filaments; such cells should still be classified as segmented neutrophils. The nuclear chromatin in segmented neutrophils
is dense and clumped. The cytoplasm contains many small granules that appear pink or sometimes tan or violet.

**Image BCI-16** is a nucleated red blood cell (NRBC). NRBCs are immature, have not yet expelled their nucleus, and, in adults, are normally seen only in the bone marrow. However, it is not unexpected to see NRBCs in the peripheral blood of a patient with CML, as in the current case. The bone marrow in someone with CML is stressed and releases not only immature leukocytes, but young erythrocytes as well. Although it is not necessary to identify the stage of maturation for NRBCs, this cell is characteristic of the type of nucleated RBC seen in the peripheral blood. The cell is small, with scanty, gray-blue cytoplasm and dense, clumped chromatin with no evidence of parachromatin visible. NRBCs, although not classified, must be quantitated and reported.

The arrow in **Image BCI-17** identifies an eosinophil. Eosinophils are approximately the same size as segmented neutrophils. They are typically bilobed, although it is difficult to visualize any distinct lobes in this cell. However, the distinguishing feature of eosinophils is seen in the numerous, red-orange granules that fill the cytoplasm. These granules are generally large and uniform in size and shape. The nuclear chromatin appears dense and clumped.

**Image BCI-18** shows a lymphocyte. Lymphocytes are variable in size and this is an example of a medium-sized cell. Nuclei are usually round or slightly indented with clumped and smooth chromatin. Nucleoli may be present, but are often not visible. Normal lymphocytes generally have a small amount of blue cytoplasm that rims the nucleus.

Sometimes lymphocytes and nucleated erythrocytes, such as the cell in Image BCI-16, may be confused. A careful review of cell size, nuclear features, and cytoplasmic characteristics can help differentiate these cells. In distinguishing lymphocytes and NRBCs, size is not the most useful feature. Although nucleated RBCs
are usually smaller than lymphocytes, at some stages they may be approximately the same size. The nucleus of lymphocytes is dense and smooth, with lighter and darker staining areas visible. Depending on the maturation stage, the chromatin of NRBCs appears more patchy or, as in the cell in Image BCI-16, so dense and clumped that no areas of parachromatin are visible. In general, lymphocytes have a scanty amount of truly blue cytoplasm. In contrast, the stages of nucleated erythrocytes usually seen in the peripheral blood may have a more moderate amount of cytoplasm that is typically blue-gray, a more faded blue, or even pink or pink-gray if some hemoglobin has been synthesized by the cell.

Editor's note: Some participants reported the lymphocyte shown in image BCI-18 to be reactive or immature. This cell is uniform in shape and has very little cytoplasm, while a reactive lymphocyte is often large with abundant, sprawling cytoplasm. Lymphoblasts characteristically have few nucleoli and often they are not prominent. This cell shows several clear areas in the nucleus that could be mistaken as nucleoli. Because there are several of these clear areas, instead of only a few, they should not be considered nucleoli. Also, the chromatin in this cell is still clumped and dense, which does not support classifying the cell as a blast.

Image BCI-19 is a basophil. Basophils are generally smaller than the other granulocytes, segmented neutrophils and eosinophils. However, this particular cell is unusually large. As is typical in basophils, it is difficult to view nuclear detail. Basophils characteristically have numerous deep purple or blue-black cytoplasmic granules. The granules are large, round, and so numerous that they often obscure the nucleus. It is important to keep in mind that basophilic granules are water soluble and may fade during the staining process.

The cell in Image BCI-20 is a metamyelocyte. Metamyelocytes are immature granulocytes that are not normally seen in the peripheral blood. However, it is not unusual to see them in a patient with CML. These cells are slightly larger or nearly the same size as the mature segmented neutrophil. The distinguishing morphologic feature in the metamyelocyte is the indented or kidney-shaped nucleus. The indentation is less than half the diameter of a hypothetical round nucleus. The chromatin is clumped. The
cytoplasm in the metamyelocyte contains many small pink or tan granules.

The last cell for identification in this testing event is a promyelocyte, in Image BCI-21. As with the metamyelocyte in Image BCI-20, promyelocytes should not be seen in the peripheral blood but it is not unusual to see them in a patient with leukemia. Promyelocytes are large cells with a high nuclear to cytoplasmic ratio. The nucleus is oval or round. Because this cell is only one stage removed from a myeloblast, the nuclear chromatin is loose and open and nucleoli are often visible, indicative of an immature cell. Likewise, the cytoplasm is still blue. However, promyelocytes are characterized by the presence of nonspecific, primary, or azurophilic granules. These granules may be numerous and appear violet or purple.

**Chronic Myelocytic (Myelogenous) Leukemia**

Chronic myelocytic (myelogenous) leukemia is usually insidious in onset and patients often initially complain of nonspecific symptoms such as fatigue and weight loss. It is classified as one of several disorders defined as the *chronic myeloproliferative neoplasms* (MPNs). These conditions all share a common etiology in that they are clonal and originate in a hematopoietic stem cell. The diseases also overlap in pathophysiology, clinical features, and some hematologic presentations. In CML, the neoplastic clone produces a spectrum of immature and mature granulocytes.

An important discovery in the investigation of patients with CML was a chromosomal translocation termed the *Philadelphia chromosome*. The Philadelphia chromosome, in turn, results in a fusion gene (*BCR/ABL*) that encodes for an abnormal protein with increased activity in pathways that regulate cellular proliferation and survival. The tangible benefit of this information is an effective therapy for CML that inhibits the enhanced activity of the *BCR/ABL* fusion product and induces remission of the cancer. Laboratory testing for the Philadelphia chromosome and the resulting *BCR/ABL* fusion gene are important confirmatory procedures to diagnose CML.

**Summary**

The patient’s peripheral blood smear in this testing event showed a variety of mature and immature cells that may be seen in CML, including NRBCs, neutrophils, eosinophils, and basophils. The medical laboratory professional, through a careful and systematic review and classification of cells, provides information crucial to the diagnosis of a malignant neoplasm such as CML.
EDUCATIONAL COMMENTARY – BLOOD CELL ID: IDENTIFYING MATURE AND IMMATURE GRANULOCYTES (cont.)

References


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