

EDUCATIONAL COMMENTARY – BLOOD CELL ID: IDENTIFYING ABNORMAL LYMPHOID CELLS

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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 leukocytes.
- describe morphologic features of immature granulocytes.
- differentiate among lymphoid cells with similar morphologic characteristics.

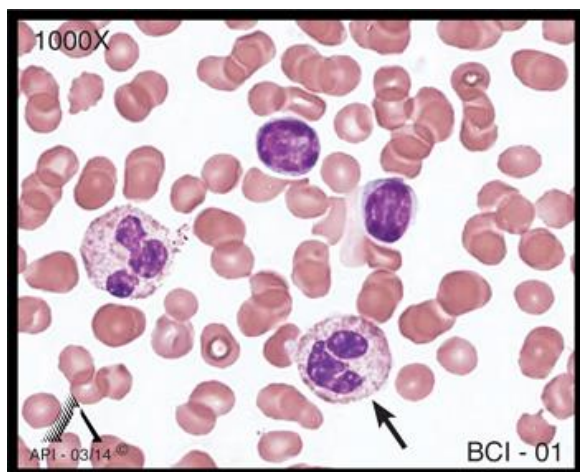
Case Study

A 57 year old male was seen by his physician for fatigue and abdominal discomfort. The CBC results are as follows: WBC=26.0 x 10⁹/L, RBC=4.33 x 10¹²/L, Hgb=13.4 g/dL, Hct=39.1%, MCV=90.2 fL, MCH=30.8 pg, MCHC=34.2 g/dL, RDW=16.1%, Platelet=88 x 10⁹/L.

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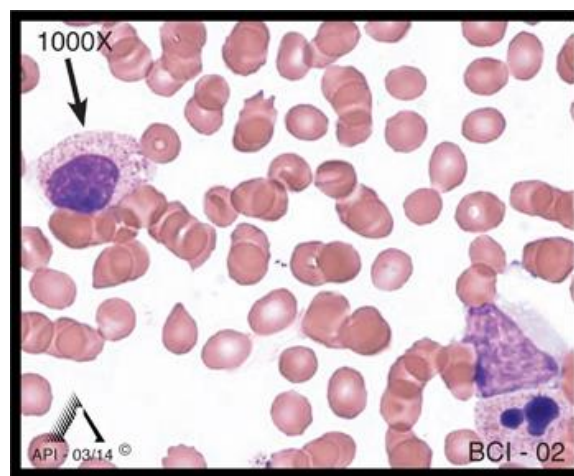
The images presented in this testing event represent normal and immature granulocytes as well as various abnormal lymphoid cells. The suggested diagnosis is hairy-cell leukemia or a possible variant of chronic lymphocytic leukemia (CLL). This case situation underscores the limitations of morphologic study in confirming a diagnosis when cells are present that show similarities in size, nuclear features, and cytoplasmic characteristics. If participants scan the whole smear using the API ImageViewer™, they can find additional examples of the abnormal cells from the same patient.

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[Image BCI-01](#) shows a normal segmented neutrophil. Segmented neutrophils are medium-sized cells that characteristically have from two to five nuclear lobes connected by thin strips of chromatin. Note the dense and clumped chromatin, with lighter areas of parachromatin. Numerous pink or pink-violet granules are typically seen in the cytoplasm.

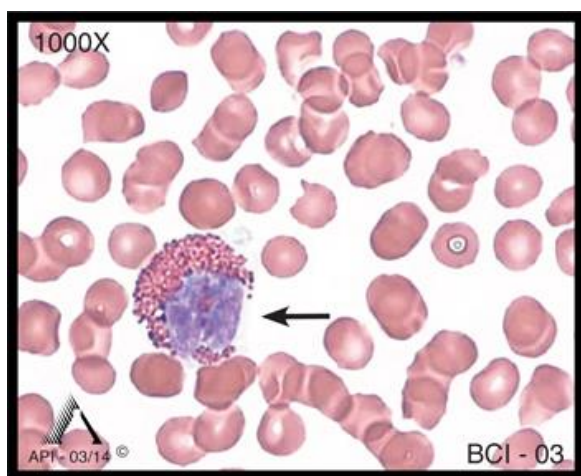
A myelocyte is identified in [Image BCI-02](#). Because they represent an immature stage of granulocyte development, myelocytes are not normally seen in the peripheral blood. Myelocytes are the earliest cells in the granulocytic series in which the pink or pink-violet specific (secondary) granules may be apparent. However, some darker, red-purple nonspecific (primary) granules are still retained and may be visible in the cytoplasm. Overall, the cell is medium-sized and may be round or slightly oval. The nucleus is often eccentrically located in the cytoplasm; no nucleoli are usually evident. The chromatin shows clumping, but lighter areas of parachromatin may be seen, as in this cell. Frequently, a clear zone, or *hof*, is present next to the nucleus. The *hof* in this particular cell is small and indistinct.



The next stage in granulocyte maturation, though not shown in the provided images, is the metamyelocyte. It is important to note similarities and differences between the myelocyte and the metamyelocyte. The myelocyte may be just slightly larger than the metamyelocyte. The cytoplasm of both cells is comparable with pink or pink-violet secondary granules, though sometimes the overall color of the cytoplasm may appear a pink-blue. Likewise, the chromatin pattern in these cells is fairly clumped with only a few areas of lighter staining parachromatin.

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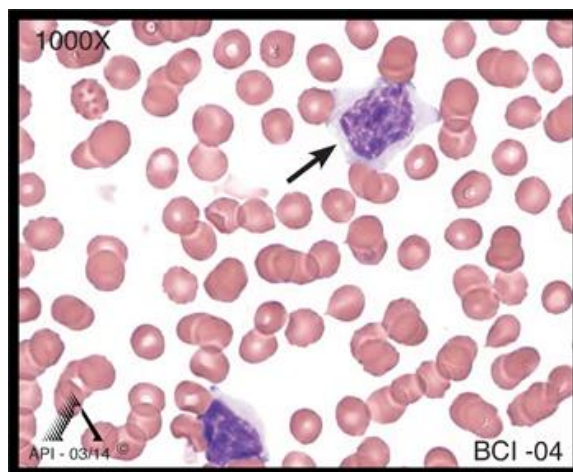
The major difference between the myelocyte and the metamyelocyte is the shape of the nucleus. Nuclei in myelocytes may be round or oval and are sometimes flattened on one side. In contrast, metamyelocytes have nuclei that are indented and resemble a kidney bean. This indentation is less than half the diameter of a hypothetically round or oval nucleus, such as the nucleus of the myelocyte, but is nevertheless showing a morphologic progression towards segmentation. The appearance of even a slight indentation in the nucleus is a characteristic feature that distinguishes the metamyelocyte from the myelocyte. Note that the nucleus in the myelocyte shown in BCI-02 has no evidence of indentation.



[Image BCI-03](#) is a nice example of an eosinophil. Generally, eosinophils are about the same size as segmented neutrophils or larger as seen in the cell in this image. However, the numerous, large, uniform, red-orange cytoplasmic granules are classic for an eosinophil. These granules have been compared to new copper pennies because of their brilliant color. The nuclei in eosinophils are often bi-lobed, but that is not the case in this cell. The nuclear chromatin is dense and clumped.

[Image BCI-04](#) shows an abnormal lymphocyte. This cell may be a reactive (*atypical* or *variant*) lymphocyte or a lymphoma cell; lymphomas are malignancies (tumors) of lymphoid tissue that sometimes involve the peripheral blood. It is often difficult to differentiate reactive lymphocytes from lymphoma cells.

Generally, both cell types may be large; however, lymphoma cells vary in size depending on the type of the lymphoma and may also appear as small as normal, mature lymphocytes. Likewise, lymphoma cells vary in shape, whereas reactive lymphocytes may be oval or round, with cytoplasm that often appears to “skirt” around adjacent red blood cells.



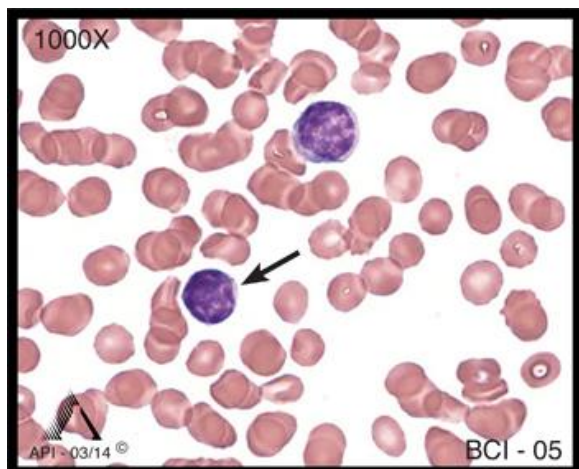
The nucleus in reactive lymphocytes tends to be oval, frequently with notches or indentations. The nuclei in lymphoma cells may also be round or oval with slight indentations, although some types of lymphoma

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demonstrate clefted and folded nuclei. Typically, neither reactive lymphocytes nor lymphoma cells have apparent nucleoli.

One feature that can help distinguish these two cell types is the nuclear to cytoplasmic ratio. Reactive lymphocytes have moderately abundant cytoplasm. In contrast, the cytoplasm in lymphoma cells is generally scanty or sometimes moderate in amount. The cytoplasm in both lymphoma cells and reactive lymphocytes may stain a deep blue. However, at times in reactive lymphocytes, only the periphery is basophilic, while most of the cytoplasm stains a pale blue. In cells that demonstrate a pale blue cytoplasm, radial striations of dark blue cytoplasm may be observed.

This image illustrates why several fields and multiple cells should be examined microscopically when trying to classify peripheral blood cells. A review of the whole peripheral smear can reveal whether the cells in question have a variety (heterogeneity) of morphologic appearances or are more homogeneous. There is no “typical” atypical lymphocyte. Within a given blood smear, reactive lymphocytes are characteristically variable in size, nuclear features, and cytoplasmic morphology. On the other hand, malignant cells, such as those in lymphoma, are more similar in their appearance within any blood slide or individual patient.



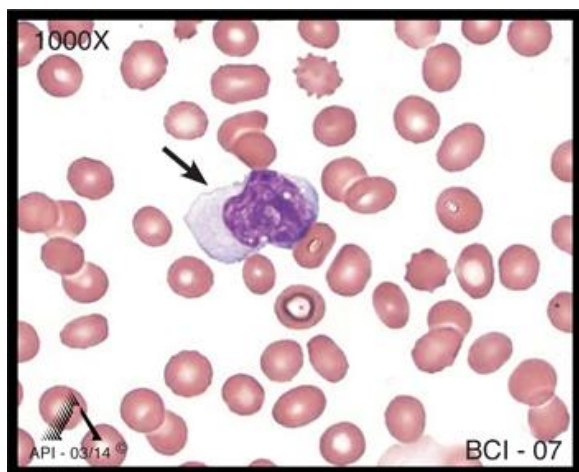
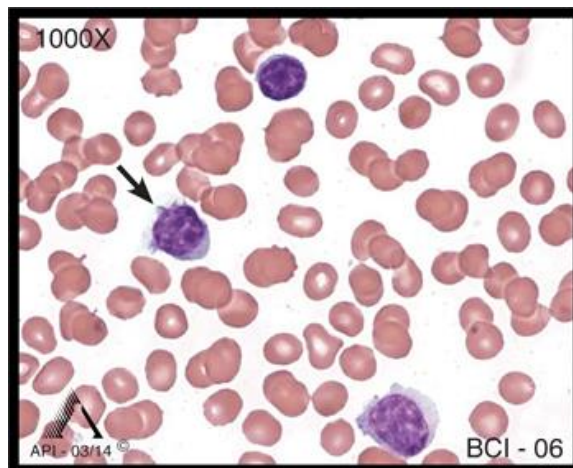
The cell in [Image BCI-05](#) appears to be a normal small lymphocyte. A scanty rim of pale blue cytoplasm is visible. The nuclear chromatin is clumped and dense, although the lighter areas of parachromatin are unusual. The nucleus in lymphocytes of this size is typically round, but may also be oval or slightly indented.

Editor's note: *Chronic lymphocytic leukemia (CLL) cells may be the same size as normal lymphocytes and cannot be distinguished from a normal lymphocyte*

by morphology alone. Because this patient has a suggested diagnosis of CLL, the following responses were considered acceptable: "Lymphocyte, normal", "Lymphoma cell (malignant)", and "Immat/abnorm, send to ref lab."

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Another abnormal lymphocyte is depicted in [Image BCI-06](#). The strings of cytoplasm suggest a hairy cell. Hairy cells are malignant lymphocytes associated with hairy-cell leukemia. However, several morphologic features of this cell indicate that it may not be a hairy cell. Hairy cells may be round or oval, but are typically larger than a normal lymphocyte. The cytoplasm is generally pale blue with no granules. Although irregular, fine cytoplasmic projections are characteristic of hairy cells, they are usually present around the entire periphery of the cell, not on just one side, as in this example. Lymphocyte morphology may be easily altered through preparation of the blood smear or use of a blood sample that is too old. It is possible that the frayed margins of this cell are an artifact. However, because some lymphoma cells are associated with either eccentric or bipolar projections, a lymphoma cell may be considered as well. Nuclei in hairy cells may be round, oval, or slightly indented; sometimes they are eccentrically located in the cells. Nucleoli, if present, are usually inconspicuous. The chromatin is fine and may be described as “stippled.” This pattern distinctly contrasts with the dense and clumped chromatin associated with normal lymphocytes and further suggests that the cell in this image is not a hairy cell.



[Image BCI-07](#) shows what is most likely a prolymphocyte. Prolymphocytes are not normally seen in the peripheral blood. They most often appear, in small percentages, in cases of CLL. However, prolymphocytes are also associated with a prolymphocytic transformation of CLL and with prolymphocytic leukemia. These cells are generally large and round or oval. The chromatin is clumped and dense, but often more open than in a normal, mature lymphocyte. The nucleus is also round or oval. Distinctive to most prolymphocytes is a single,

prominent nucleolus. The cytoplasm is moderate in amount and dark to light blue.

Editor's note: Some participants reported this cell to be a monocyte or a reactive lymphocyte. There is an additional ASCP Educational Commentary available under Continuing Education on the main page of

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the API website. This commentary is titled “Comparing Mononuclear Cells” and it includes a table comparing monocytes, myelocytes, and reactive lymphocytes.

Summary

The images presented in this testing event represent a spectrum of blood cells including granulocytes, lymphocytes, and various abnormal lymphoid cells. The challenge of identifying and classifying the lymphoid cells in this case highlights the limitations of using only morphology to make a diagnosis. Several important considerations must be kept in mind. The preparation and staining of the blood smear must be completed in a timely manner with a quality reagent system to minimize alterations to cells, especially lymphocytes. Cells should be evaluated, in a good area of the slide, for overall size, nuclear features, and cytoplasmic characteristics. Note that in a “good” area of the smear, RBCs are barely touching or overlapping and defined areas of central pallor within the RBCs are visible. Likewise, several fields of view and multiple cells should be examined when trying to identify blood cells. Participants should note that the entire smear of this testing event can be scanned using the API ImageViewer™. Many more examples of the abnormal lymphoid cells described in this commentary can be seen.

Finally, the most important methods that can aid in classifying these lymphoid cells and confirming a diagnosis are immunophenotyping (using flow cytometry) and cytochemistry. For example, hairy cells have a specific immunophenotype and stain positive with tartrate-resistant acid phosphatase (TRAP).

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