Blood Cell Identification – Graded

Case History

This peripheral blood smear is from a 29-year-old woman with history of sickle cell disease, who presents with acute pain crisis. Laboratory data include: **Corrected** WBC = 18.6 × 10E9/L; RBC = 1.61 × 10E12/L; HGB = 5.6 g/dL; HCT = 16.3 %; MCV = 101 fL; MCHC = 34.1 g/dL; PLT = 184 × 10E9/L; and RDW = 20 %. Identify the arrowed object(s) on each image.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

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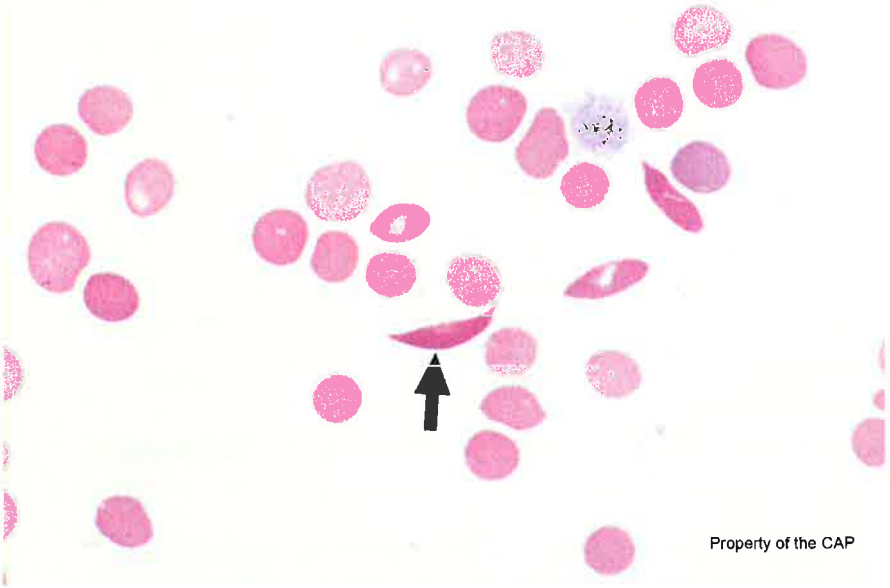
https://documents.cap.org/documents/2021-hematology-and-clinical-microscopy-glossary.pdf

BCP-11

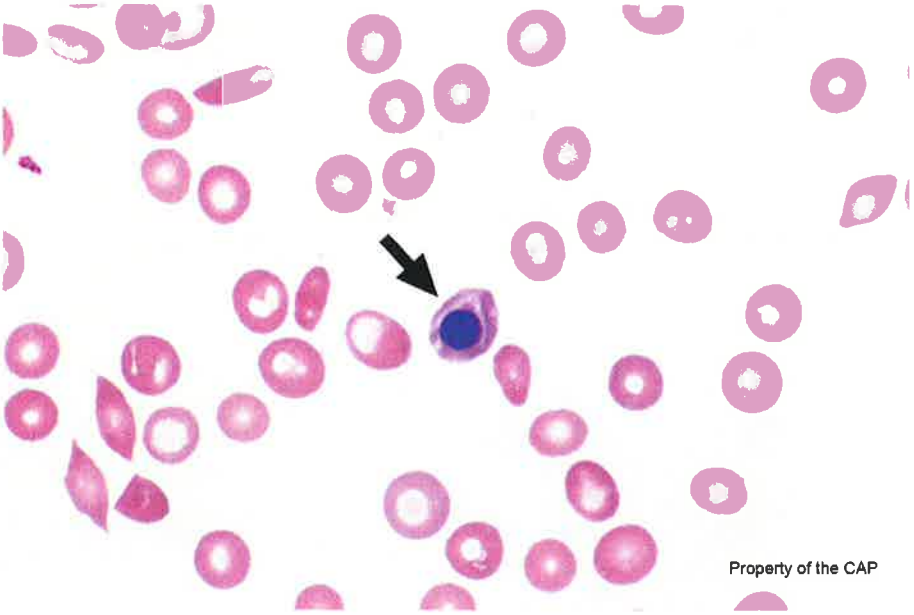


Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Sickle cell (drepanocyte)	185	100.0	5526	99.5	Good

The arrowed cell is a sickle cell (drepanocyte), as correctly identified by 100.0% of referees and 99.5% of participants. Red blood cells appearing in the shape of a thin crescent with two pointed ends are called sickle cells. The polymerization of deoxygenated hemoglobin S may cause red blood cells to appear in one or more of the following forms: crescent-shaped, boat-shaped, filament-shaped, holly-leaf form, or envelope cells. These cells usually lack central pallor. Sickle cells may be seen particularly in the absence of splenic function or after splenectomy in patients with the various forms of sickle cell disease including hemoglobin SS disease, SC disease, SD disease, and S-beta-thalassemia.

Blood Cell Identification – Graded

BCP-12

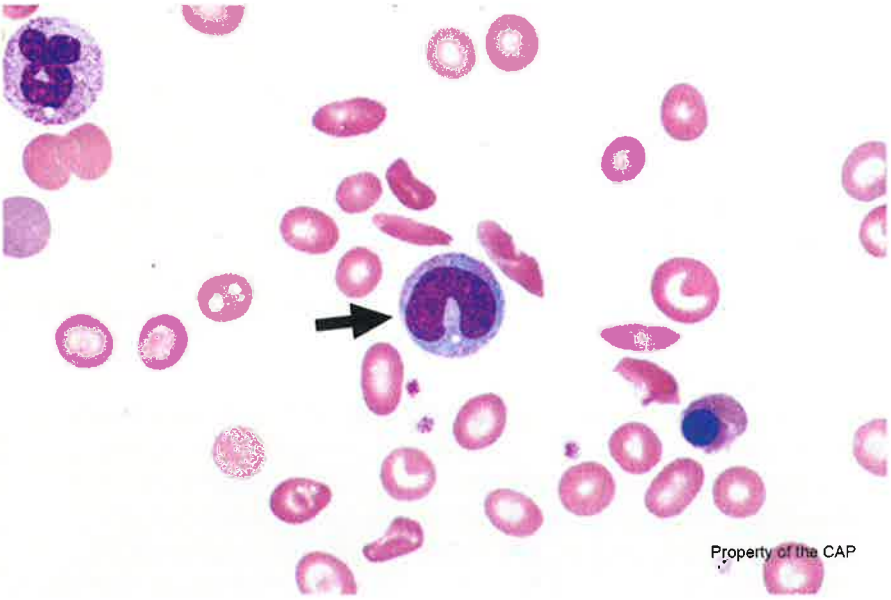


Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Nucleated red blood cell, normal or abnormal morphology	183	98.9	5519	99.4	Good
Immature or abnormal cell, would refer for identification	2	1.1	23	0.4	Unacceptable

The arrowed cell is a nucleated red blood cell, as correctly identified by 98.9% of referees and 99.4% of participants. The term nucleated red blood cell (nRBC) is used to state the presence of normoblasts in the peripheral blood and includes all normoblasts regardless of the stage of maturation. Typically, the circulating nucleated red blood cell is at the orthochromic stage of differentiation. Both megaloblastic and dysplastic changes can be seen in these circulating red blood cells, reflecting simultaneous erythroid maturation abnormalities present in the bone marrow. Caution should be used in classifying a circulating nucleated red blood cell as dysplastic on the basis of abnormal nuclear shape (lobated or fragmented), as these changes may occur during their egress from the marrow space and may not be present in the maturing erythroid precursors present in the marrow. For the purposes of proficiency testing, it is adequate to identify a cell as a nucleated red blood cell when it is present in the peripheral blood, be it normal or abnormal (ie, exhibits megaloblastic or dysplastic changes).

Blood Cell Identification – Graded

BCP-13



Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Monocyte	137	74.0	4161	75.0	Non-consensus
Neutrophil, segmented or band	42	22.7	1180	21.3	Non-consensus
Neutrophil, giant band or giant metamyelocyte	5	2.7	118	2.1	Non-consensus
Polychromatophilic (non-nucleated) red blood cell	1	0.5	1	0.0	Non-consensus

The arrowed cell is a monocyte, as correctly identified by 74% of referees and 75% of participants. Monocytes are slightly larger than neutrophils, ranging from 12 to 20 µm in diameter. Most monocytes are round with smooth edges, but some may have pseudopod-like cytoplasmic extensions. The cytoplasm is abundant, with a gray or gray-blue ground-glass appearance, and may contain vacuoles or fine, evenly distributed azurophilic granules. The N:C ratio ranges from 4:1 to 2:1. The nucleus is usually indented, often resembling a three-pointed hat, but it can also be folded or band-like. The chromatin is condensed but is usually less dense than that of a neutrophil or lymphocyte. Nucleoli are generally absent, but occasional monocytes may contain a small, inconspicuous nucleolus.

Approximately 22.7% of referees and 21.3% of participants identified the arrowed cell as a neutrophil, segmented/band. Segmented neutrophils and their immediate precursors, bands, constitute 12% to 25% of the nucleated cells in the bone marrow. Band neutrophils, also known as stabs, constitute 5% to 10% of the nucleated cells in the blood under normal conditions. The band is round-to-oval and 10 to 18 µm in diameter. The N:C ratio is 1:1.5 to 1:2 and the nuclear chromatin is condensed. The nucleus is indented to more than half the distance to the farthest nuclear margin, but the chromatin is not condensed to a single filament (as is the defining feature of the fully mature neutrophil). The nucleus can assume many shapes: it can be band- or sausage-like; S-, C-, or U-shaped; and twisted or folded on itself. The cytoplasm is similar to that of other post-mitotic

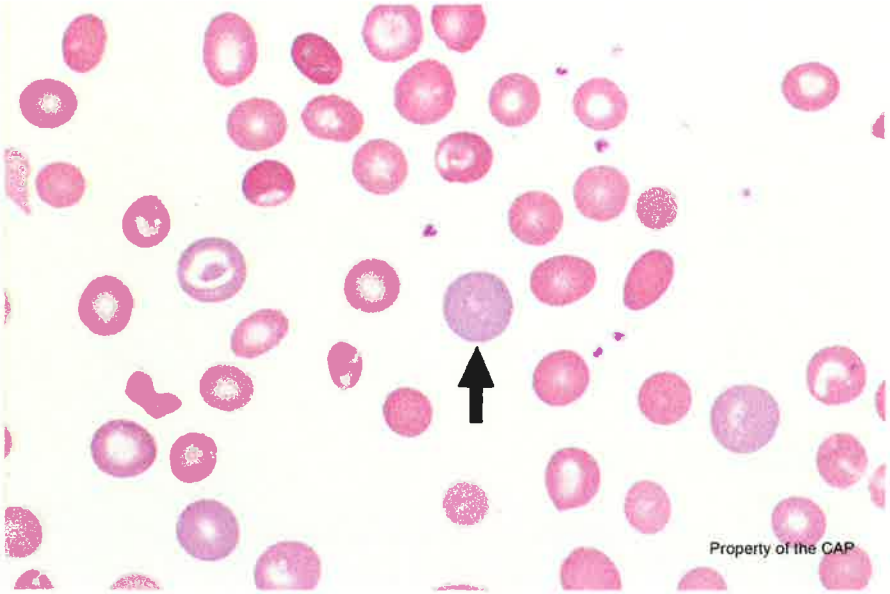
BCP-13, cont'd.

neutrophils, with specific granules predominating in an otherwise pale cytoplasm. The segmented neutrophil is the predominant blood leukocyte. It has a similar size to a band neutrophil (ie, 10 to 15 µm in diameter), as well as comparable shape (round to oval), and cytoplasmic appearance (pale pink cytoplasm with specific granules). The N:C ratio is 1:3 and the nuclear chromatin is highly condensed. The nucleus is segmented or lobated (with a normal range of three to five lobes). The lobes are connected by a thin filament that contains no internal chromatin, giving it the appearance of a solid, dark, thread-like line. The presence of these thread-like filaments is the basis for distinguishing the segmented neutrophil from the band neutrophil. The arrowed cell lacks the typical cytoplasmic appearance of neutrophils as its cytoplasm is not pale pink and specific granules are absent. Moreover, the chromatin pattern is finer than a typical neutrophil. Compare the arrowed cell in BCP-13 to the white blood cells in image BCP-15. In BCP-15, the white blood cells (ie, neutrophils) have coarser chromatin, pink cytoplasm, and specific granules. These features distinguish the arrowed monocyte in BCP-13 from neutrophils. Therefore, the choice of neutrophil, segmented/band is incorrect.

2.7% of referees and 2.1% of participants identified the arrowed cell as a neutrophil, giant band. Giant bands resulting from megaloblastic hematopoiesis show an increase in size, and they have nuclei that show aberrant maturation, whereby the nucleus appears less mature than the cytoplasm. These cells have diameters 1.5 times those of normal metamyelocytes or bands. The arrowed cell lacks the typical cytoplasmic appearance of neutrophils as its cytoplasm is not pale pink and specific granules are absent. Instead, the cytoplasm of the arrowed cell is gray-blue, and thereby consistent with a monocyte. Therefore, the choice of neutrophil, giant band is incorrect.

Blood Cell Identification – Graded

BCP-14



Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Polychromatophilic (non-nucleated) red blood cell	181	97.8	5431	97.9	Good
Spherocyte	2	1.1	43	0.8	Unacceptable
Macrocyte, oval or round (excluding polychromatophilic red blood cell)	1	0.5	62	1.1	Unacceptable

The arrowed cell is a polychromatophilic (non-nucleated) red blood cell, as correctly identified by 97.8% of referees and 97.9% of participants. A polychromatophilic red blood cell is a non-nucleated, round or ovoid red blood cell that represents the final stage of red blood cell maturation after exiting the bone marrow. It is larger than a mature erythrocyte and usually lacks central pallor. It primarily contains hemoglobin with a small amount of RNA, and thereby stains pale purple to pink-gray with Romanowsky or Wright-Giemsa stain. These cells can be stained as reticulocytes and enumerated by using supravital stains, such as new methylene blue. With supravital staining, reticulocytes reveal deep blue granular and/or filamentous structures. This reticulin network is called the "substantia reticulofilamentosa." The intensity of the polychromasia will vary with the amount of RNA and the age of the cell, with younger cells (ie, earlier polychromatophilic red cells) appearing more purple or blue and relatively more mature cells (i.e. later polychromatophilic red cells) appearing more pink-gray. Automated technologies for assessing reticulocytes improve the accuracy and precision of determining reticulocyte numbers.

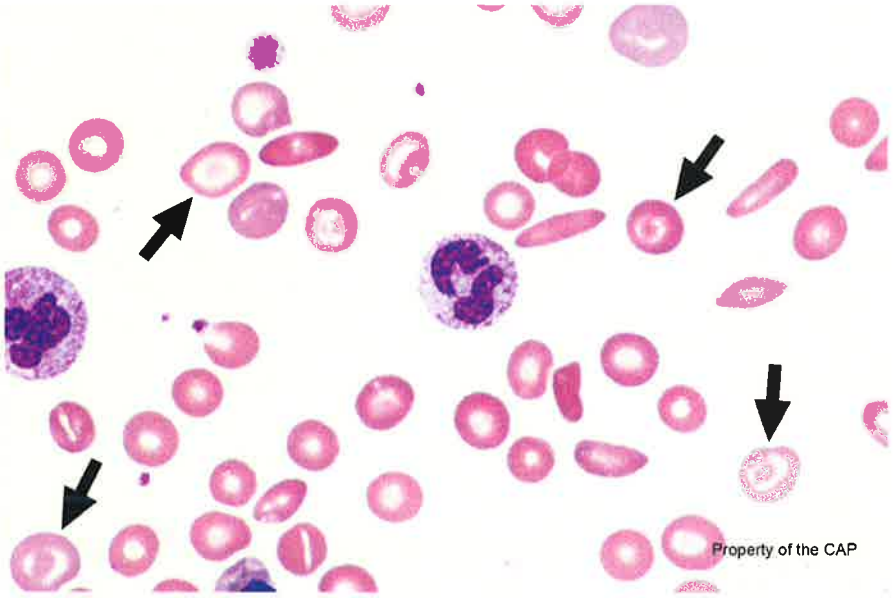
1.1% of participants identified the arrowed cell as macrocyte, oval/round. Macrocytes are abnormally large red blood cells (diameter > 8.5 µm). They are best detected by comparing to other red blood cells in a smear in the context of the MCV. They may be oval or round. The hemoglobin concentration is normal; these cells lack significant polychromasia. If polychromasia is readily identified, the term polychromatophilic red blood cell is

BCP-14, cont'd.

preferred for proficiency testing purposes. Therefore, given the overt presence of polychromasia in the arrowed cell (compare this arrowed cell to the mature spherocyte below it which lacks polychromasia), the choice of macrocyte, oval/round is incorrect.

Blood Cell Identification – Graded

BCP-15



Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Target cell (codocyte)	185	100.0	5527	99.6	Good

The arrowed cells are target cells (codocytes), as correctly identified by 100.0% of referees and 99.6% of participants. Target cells are thin red blood cells with an increased surface membrane-to-volume ratio. They are often flattened out on the smears and may appear macrocytic. Target cells are believed to arise from disturbances in red blood cell membrane cholesterol and lecithin content or decreased cytoplasmic hemoglobin content. Target cells are characterized by a central hemoglobinized area within the surrounding area of pallor, which in turn is surrounded by a peripheral hemoglobinized zone giving target cells the appearance of a bull's-eye. Target cells associated with hemoglobin C may have a slightly reduced or normal MCV, whereas those associated with hemoglobin E disorders or hemoglobin H disease exhibit microcytosis of varying degree. Target cells are usually seen in thalassemias, iron deficiency anemia, following splenectomy or in patients who are jaundiced or who have chronic liver disease; in the latter two conditions, the MCV may be normal or increased. Target cells may also appear as artifacts from slow drying the slides in a humid environment or from specimens anticoagulated with excessive EDTA. The drying artifact results in the presence of numerous target cells in some fields, but none or few in other fields.

Clinical Presentation:

This peripheral blood smear is from a 29-year-old woman with history of sickle cell disease, who presents with acute pain crisis. Laboratory data include: Corrected WBC = 18.6 × 10E9/L; RBC = 1.61 × 10E12/L; HGB = 5.6 g/dL; HCT = 16.3 %; MCV = 101 fL; MCHC = 34.1 g/dL; PLT = 184 × 10E9/L; and RDW = 20 %.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

CASE DISCUSSION: SICKLE CELL DISEASE WITH ACUTE PAIN CRISIS

Sickle cell disease is a term that describes an inherited group of disorders that share the presence of abnormal, sickle-shaped RBCs. Sickle cell anemia is characterized by two copies of mutant hemoglobin S, whereas sickle cell disease is a broader term that includes sickle cell anemia and conditions characterized by one copy of mutant hemoglobin S and a second mutated hemoglobin (other than hemoglobin S). On the contrary, sickle cell trait is characterized by one copy of hemoglobin S and one normal copy of the beta globin gene. Sickle cell trait is a mostly benign carrier condition with normal CBC indices and peripheral blood appearance. This case focuses on sickle cell anemia, which is the most common monogenic disorder in the world, with approximately 300,000 people born each year with this disease.

Hemoglobin S results from a single point mutation in beta globin gene that changes the 6th amino acid in the protein, glutamine, to a valine. When both copies of the beta-globin gene carry this mutation (sickle cell anemia), this mutant beta globin protein combines with normal alpha globin to produce hemoglobin S. Hemoglobin S has reduced oxygen carrying capacity and polymerizes when deoxygenated, resulting in physical deformation of the red blood cell to a characteristic 'sickle' shape. 'Sickled' red blood cells have decreased deformability and are therefore predisposed to occlude small blood vessels, resulting in many of the clinical findings of sickle cell anemia including acute pain crisis.

The clinical manifestations of sickle cell disease are variable and affect many different organ systems; common and serious manifestations include acute painful episodes, acute chest syndrome, stroke, anemia, splenic infarcts predisposing to functional asplenia and sepsis from encapsulated organisms, and many others. Clinical symptoms predominantly arise as either acute or chronic sequelae of vaso-occlusion. Acute pain crisis, also known as acute pain episodes, are one of the most common complications of vaso-occlusion in sickle cell disease. The patient's assessment of their pain is the only measurement of this event; there is no correlation between pain and laboratory findings such as hemoglobin level or level of hemolysis. Treatment is individualized for each patient and variable. Importantly, acute pain episodes can co-occur with other life-threatening complications of sickle cell disease, and thorough evaluation for these complications is warranted in addition to treatment of pain.

The diagnosis of sickle cell anemia is typically made in adults by high performance liquid chromatography (HPLC). HPLC separates hemoglobin variants based on protein charge and is very effective at differentiating the majority of common hemoglobin variants. Newborn screening programs also exist in some jurisdictions and often employ HPLC-based methodology, potentially with confirmatory isoelectric focusing or DNA-based testing. High-voltage capillary electrophoresis and thin-layer isoelectric focusing are two additional methods that can be employed to identify hemoglobin S based on differences in protein charge. Metabisulfite or dithionite testing (reagents used to precipitate hemoglobin S *in vitro*) has largely been supplanted by HPLC and related methods and is generally not in routine clinical use in the hematology laboratory. However, these assays are routinely used in blood banks and transfusion services to determine which donors carry sickle cell trait so hemoglobin S-containing positive blood donations can be transfused to the appropriate patient population.

Review of the peripheral blood smear show characteristic findings in sickle cell anemia, including the presence of sickled red cells, anemia, and polychromasia due to a reticulocytosis in response to chronic hemolytic anemia. Other findings such as Howell-Jolly bodies and RBC anisocytosis are frequently present and are due to hyposplenism that has resulted from splenic auto-infarction secondary to repeated vaso-occlusion by sickle cells.

Philipp W. Raess, MD, PhD
Hematology and Clinical Microscopy Committee

References:

1. Azar S, Wong TE. Sickle cell disease: a brief update. *Med Clin North Am*. 2017;101(2):375-393.
2. McPherson RA, Pincus MR. *Henry's Clinical Diagnosis and Management by laboratory Methods*. 22nd ed. Saunders; 2011.
3. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. *N Engl J Med*. 2017;376(16):1561-1573.

Blood Cell Identification – Ungraded

Case History

This peripheral blood smear is from a 76-year-old Japanese woman diagnosed with bladder cancer and history of mature T-cell leukemia/lymphoma. Laboratory data include: WBC = 51.2 × 10E9/L; RBC = 3.69 × 10E12/L; HGB = 12.2 g/dL; HCT = 35.9 %; MCV = 97 fL; MCHC = 34.2 g/dL; PLT = 108 × 10E9/L; and RDW = 16 %. Identify the arrowed object(s) on each image.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

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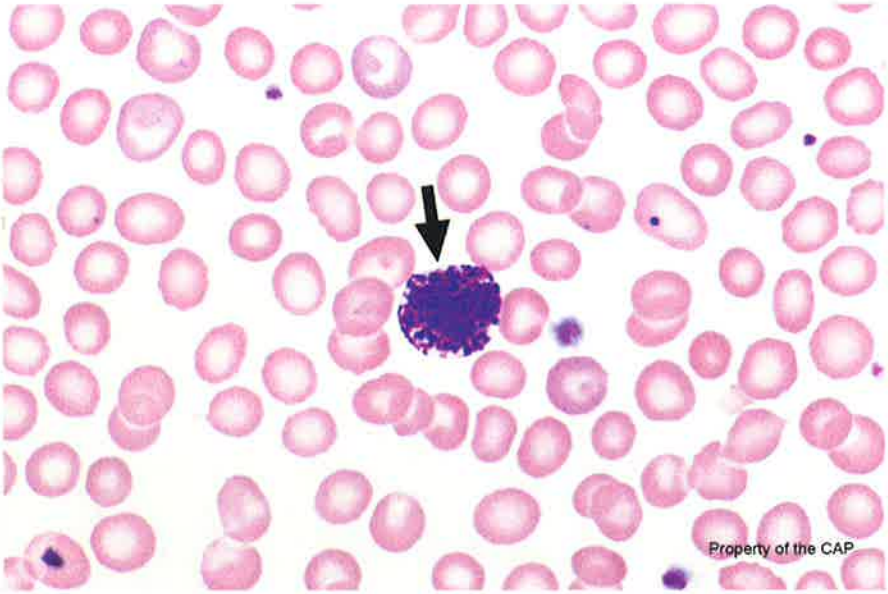
BCP-16

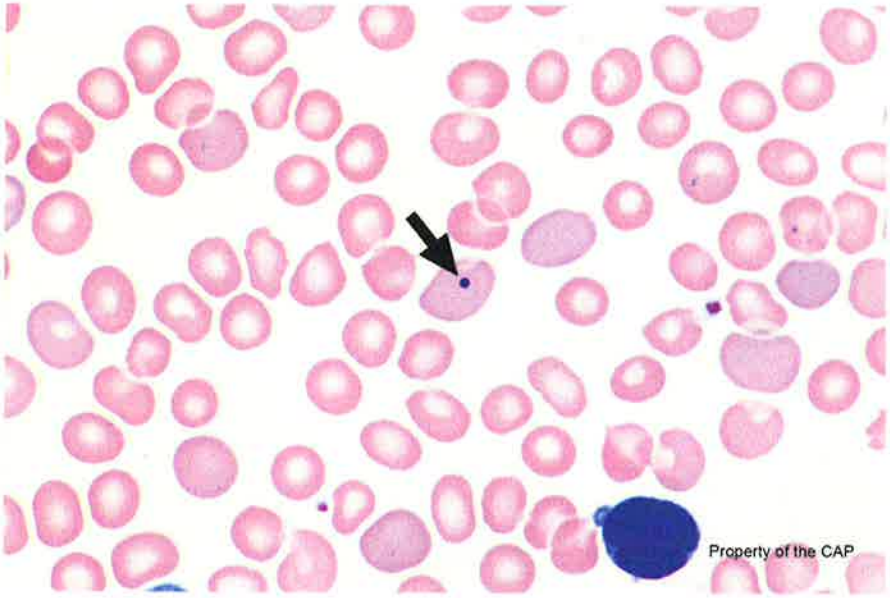


Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Basophil, any stage	183	98.9	5470	99.6	Educational
Basophilic stippling (coarse)	2	1.1	16	0.3	Educational

The arrowed cell is a basophil, as correctly identified by 98.9% of referees and 99.6% of participants. Basophils are characterized by the presence of numerous coarse and densely stained granules of varying sizes and shapes. The granules are larger than the granules of neutrophils, and most are roughly spherical. The granules are typically blue-black, but some may be purple-red when stained using Wright-Giemsa preparations. The granules are unevenly distributed and frequently overlay and obscure the nucleus. Basophils are comparable in size to neutrophils, ie, 10 to 15 µm in diameter, and the nuclear-to-cytoplasmic (N:C) ratio ranges from 1:2 to 1:3. Basophilia may be seen in several contexts, including in association with (but not limited to) myeloproliferative neoplasms, in hypersensitivity reactions, with hypothyroidism, iron deficiency, and renal disease.

Blood Cell Identification – Ungraded

BCP-17

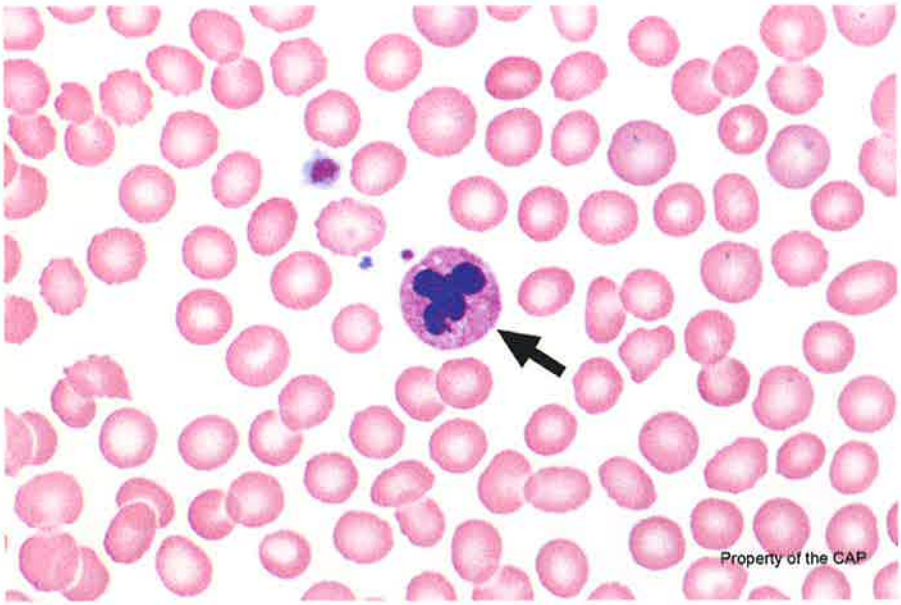


Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Howell-Jolly body	183	98.9	5350	98.6	Educational
Pappenheimer bodies (iron or Wright stain)	1	0.5	25	0.5	Educational
Platelet, normal	1	0.5	10	0.2	Educational

The arrowed object is a Howell-Jolly body, as correctly identified by 98.9% of referees and 98.6% of participants. Howell-Jolly bodies are small, round, dark purple homogeneous masses that measure about 1 µm in diameter. They are larger, more rounded and darker staining than Pappenheimer bodies and are composed of DNA. They are formed in the process of red blood cell nuclear karyorrhexis or when an aberrant chromosome becomes separated from the mitotic spindle and remains behind after the rest of the nucleus is extruded. Normally, the spleen is very efficient in removing Howell-Jolly bodies from red blood cells, but if the spleen is missing or hypofunctional, they may be readily found in the peripheral blood. Howell-Jolly bodies are usually present singly in a given red blood cell. Multiple Howell-Jolly bodies within a single red blood cell are less common and are typically seen in megaloblastic anemia.

Blood Cell Identification – Ungraded

BCP-18



Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Neutrophil, segmented or band	175	94.6	5010	92.4	Educational
Neutrophil, Toxic (to include toxic granulation and/or Döhle bodies, and/or toxic vacuolization)	8	4.3	236	4.3	Educational
Neutrophil with hypersegmented nucleus	1	0.5	56	1.0	Educational
Neutrophil necrobiosis (degenerated neutrophil)	1	0.5	21	0.4	Educational

The arrowed cell is a neutrophil, as correctly identified by 94.6% of referees and 92.4% of participants. Segmented neutrophils are the predominant blood leukocyte. They are about 10 to 15 µm in diameter, round to oval, and display pale pink cytoplasm with specific granules. The N:C ratio is 1:3, and the nuclear chromatin is highly condensed. The nucleus is segmented or lobated, with a normal range of three to five lobes. The lobes are connected by a thin filament that contains no internal chromatin, giving it the appearance of a solid, dark, thread-like line. For the purposes of proficiency testing, it is not required that segmented or band neutrophils be differentiated.

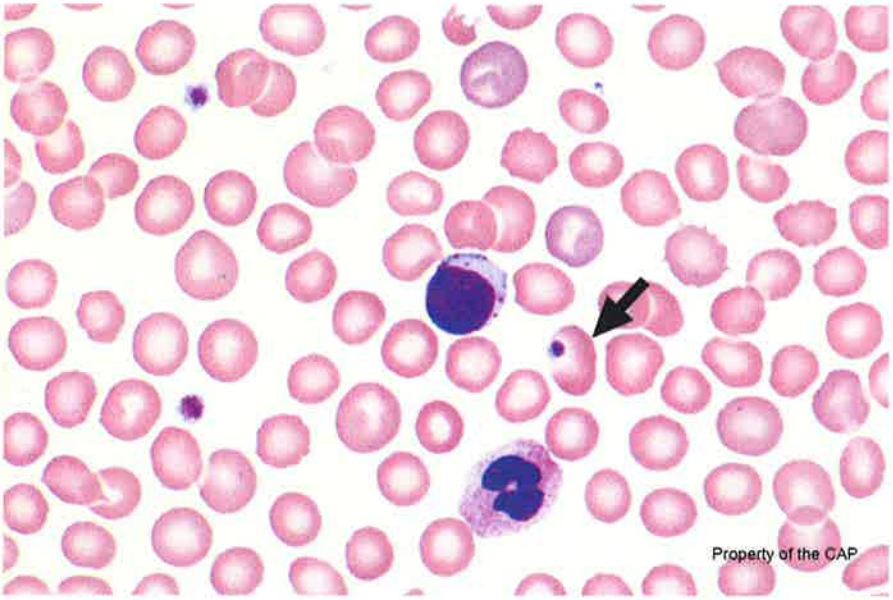
A minority of laboratories (4.3% of referees and 4.3% of participants) identified this cell as a toxic neutrophil. Toxic changes in neutrophils include toxic granulation, toxic vacuolization, and Döhle bodies. Toxic granulation and Döhle bodies each may be present in an individual cell without the other finding. Either change alone is sufficient to designate a neutrophil as toxic. Toxic granulation is defined by the presence of large, purple or dark blue cytoplasmic granules in neutrophils, bands, and metamyelocytes. In this cell ID, the vacuoles are not prominent and Döhle bodies are not seen. The granules here are not large, prominent, nor deeply stained enough to be considered toxic by the committee members. Admittedly, it can be challenging to make that determination on a single photomicrograph, and it is best to review the entire slide and assess the overall granulation of neutrophils.

BCP-18, cont'd.

Around 1.0% of participants responded with "neutrophil with hypersegmented nucleus." This is not the intended response and is not acceptable. Neutrophils qualify as hypersegmented when they contain six or more lobes. Hypersegmented neutrophils are uncommon unless there is megaloblastic hematopoiesis. In the clinical vignette, the MCV would not qualify as indicative of megaloblastic hematopoiesis, though it is at the upper limit of the normal reference range at 97 fL.

Blood Cell Identification – Ungraded

BCP-19



Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Erythrocyte with overlying platelet	175	94.6	5114	94.3	Educational
Ovalocyte (elliptocyte)	5	2.7	129	2.4	Educational
Erythrocyte, normal	2	1.1	30	0.6	Educational
Howell-Jolly body	2	1.1	53	1.0	Educational
Platelet, normal	1	0.5	39	0.7	Educational

The arrowed cell is an erythrocyte with an overlying platelet, as correctly identified by 94.6% of referees and 94.3% of participants. Platelets may adhere to or overlap red blood cells; this appearance may mimic a red blood cell inclusion (such as a Howell-Jolly body) or parasite. A correct interpretation depends on carefully examining the morphology of the platelet and comparing the size, staining characteristics, and granularity with known platelets in the same field, as well as determining whether the platelet is in the same plane of focus as the red blood cell. Many times, the platelet is surrounded by a thin clear zone or halo (as in this case), which is not a feature of most genuine red blood cell inclusions.

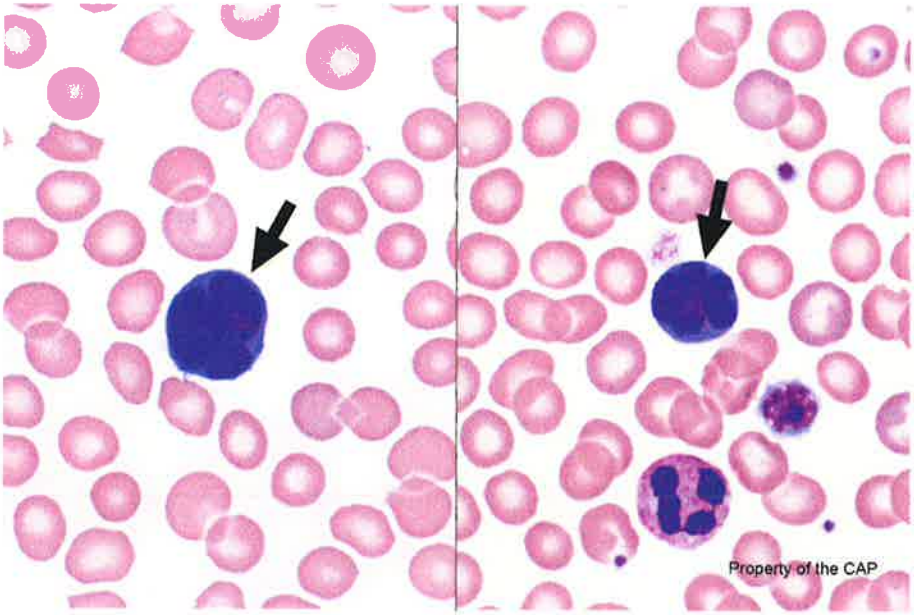
Several referees (2.7%) and participants (2.4%) incorrectly identified this cell as an ovalocyte or elliptocyte. These red cells appear in the shape of a pencil or a thin cigar, with blunt ends and parallel sides. Though the arrowed cell appears somewhat elongated, the hemoglobin is not concentrated at the ends, as it would be in the case of an elliptocyte/ovalocyte. Furthermore, elliptocytes/ovalocytes are commonly increased in cases of iron deficiency or hereditary elliptocytosis. The normal MCV and hemoglobin presented in the clinical vignette for this patient would not support iron deficiency anemia. Hereditary elliptocytosis would have normal red cell indices, but elliptocytes would represent a significant percentage of all red cells (>25% of red cells would be elliptocytes). In this photomicrograph, the red blood cells are predominantly normocytic and normochromic, with only a few poikilocytes.

BCP-19, cont'd.

Around 1.1 % of referees and 1.0% of participants erroneously identified this as a Howell-Jolly body. Howell-Jolly bodies are small (1 µm in diameter), round, dark purple homogeneous masses. They are composed of DNA, formed in the process of red blood cell nuclear karyorrhexis or when an aberrant chromosome becomes separated from the mitotic spindle and remains behind after the rest of the nucleus is extruded. As previously mentioned, red cell inclusions (like a Howell-Jolly body) can superficially resemble the intended response (ie, erythrocyte with an overlying platelet). This particular platelet overlying a red blood cell appears round and mostly homogeneous, mimicking a Howell-Jolly body. Upon closer inspection, however, the contours of the platelet are round, but ill-defined, and there is a hint of a pale blue clear peripheral region (ie, hyalomere) next to the darker central region (ie, granulomere) of the platelet. Lastly, the overlying platelet is surrounded by a clear zone or a halo (as in this case), which is not a feature of genuine red blood cell inclusions.

Blood Cell Identification – Ungraded

BCP-20



Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Malignant lymphoid cell (other than blast)	149	80.5	4212	77.7	Educational
Immature or abnormal cell, would refer for identification	14	7.6	307	5.7	Educational
Lymphocyte, reactive (includes plasmacytoid and immunoblastic forms)	11	6.0	366	6.8	Educational
Monocyte	3	1.6	54	1.0	Educational
Blast	2	1.1	159	2.9	Educational
Lymphocyte	2	1.1	131	2.4	Educational
Metastatic tumor cell	2	1.1	21	0.4	Educational
Megakaryocyte (normal, abnormal, or nuclear fragment)	1	0.5	31	0.6	Educational
Monocyte, immature (promonocyte, monoblast)	1	0.5	47	0.9	Educational

The arrowed cells are malignant lymphoid cells, as correctly identified by 80.5% of referees and 77.7% of participants. Lymphoma cells exhibit a variety of appearances depending on the lymphoma subtype, and definitive diagnosis can be difficult. Regarding the present case, however, these cells have such a characteristic morphology as to raise high suspicion for adult T-cell leukemia/lymphoma (ATLL). These so-called "flower cells" feature deeply convoluted nuclear contours which mimic flower petals or a clover-leaf pattern. The chromatin in these cells is coarsely clumped, with variably visible nucleoli. Some cells may display finely textured, blast-like chromatin. The cytoplasm is typically scant and basophilic. Supplemental studies, such as immunophenotyping, are necessary to arrive at a diagnosis.

BCP-20, cont'd.

Although these "flower-like cells" are technically lymphocytes (as classified by 1.1% of referees and 2.4% of participants), the best response is "malignant lymphoid cells." In reviewing the clinical vignette that was provided, this patient of Japanese ancestry has a history of mature T-cell leukemia/lymphoma. In the context of these abnormal cells, this clinical history provided should raise one's suspicion for a particular lymphoma (see the Continuing Education material for further discussion). The designation of "lymphocyte" or "lymphocyte, reactive (includes plasmacytoid and immunoblastic forms)" [erroneously identified by 6.0% of referees and 6.8% of participants presumes that such cells are non-neoplastic. The key distinguishing feature of reactive lymphocytes is their wide range of cellular sizes and shapes, as well as nuclear sizes, shapes, and chromatin patterns. This feature is a reflection of lymphocytes reacting to an immune stimulus and are frequently increased in viral illnesses. In contrast, while lymphoma cells can exhibit a wide range of morphologic appearances, any individual case tends to show a more monotonous population of abnormal cells. In this photomicrograph, although the 2 lymphoma cells vary in size (the one on the left is larger than the one on the right), the Committee contends that the two cells are actually strikingly similar in their flower-like nuclear contours, coarsely clumped chromatin, and scant basophilic cytoplasm. Another important distinction between a reactive lymphocyte versus lymphoma cell is the difference in their N:C ratios. The N:C ratio tends to be low in reactive lymphocytes, while it is high in lymphoma cells.

Around 7.6% of referees and 5.7% of participants responded with "immature or abnormal cell, would refer", indicating that this necessitates a pathology consultation. This is an acceptable response, given the challenging identification.

Approximately 1.1% of referees and 2.9% incorrectly identified these cells as blasts. Lymphoblasts, in particular, can exhibit a spectrum of chromatin quality, from finely dispersed to dense chromatin. On the other hand, a case of acute lymphoblastic leukemia with occasionally dense chromatin, will almost always feature blasts with finely textured chromatin. In this particular mature T-cell leukemia/lymphoma (information provided in the clinical vignette), blast-like cells can sometimes be observed, however, the arrowed cells shown here uniformly display mature, coarsely clumped chromatin. In addition, the deep flower-petal nuclear convolutions observed here are quite unusual for lymphoblasts.

Lastly, 1.6% of referees and 1.0% of participants mistakenly identified these lymphoma cells as monocytes. Although monocyte nuclear contours can be variable (from looking like a three-pointed hat to being folded or band-like), they are never as deeply convoluted as these lymphoma cells. Monocytic chromatin is condensed and cytoplasm is gray or gray-blue, and abundant; in contrast, these lymphoma cells have coarsely clumped chromatin and only sparse cytoplasm.

Actions Laboratories Should Take when a PT Result is Not Graded

The CAP uses exception reason codes that signify the proficiency testing (PT) for an analyte has not been graded. The exception reason code is located on the evaluation report in brackets to the right of the result. Your laboratory must identify all analytes with an exception reason code, review, and document the acceptability of performance as outlined below and retain documentation of review for at least 2 years. The actions laboratories should take include, but are not limited to:

Code	***Exception Reason Code Description***	***Action Required***
11	Unable to analyze	Document why the specimens were not analyzed (eg, instrument not functioning or reagents not available). Perform and document alternative assessment (ie, split samples) for the period that commercial PT was not tested to the same level and extent that would have been tested.
20	Response was not formally graded due to insufficient peer group data. Please see the participant summary for additional information.	Applies to a response that is not formally evaluated when a peer group is not established due to fewer than 10 laboratories reporting. Document that the laboratory performed a self-evaluation using the data presented in the participant summary and compared its results to a similar method, all method, all participant statistics, or data tables for groups of 3-9 laboratories, if provided. Perform and document the corrective action of any unacceptable results. If self-evaluation is not possible, it is up to the laboratory director/designee to determine an alternative performance assessment.
21	Specimen problem	Document that the laboratory has reviewed the proper statistics supplied in the participant summary. Perform and document alternative assessment for the period that commercial PT was not tested to the same level and extent that would have been tested. Credit is not awarded in these cases.
22	Result is outside the method/ instrument reportable range	Document the comparison of results to the proper statistics supplied in the participant summary. Verify detection limits. Perform and document the corrective action of any unacceptable results.
24	Incorrect response due to failure to provide a valid response code	Document the laboratory's self-evaluation against the proper statistics and evaluation criteria supplied in the participant summary. Perform and document the corrective action of any unacceptable results. Document corrective action to prevent future failures.
25	Inappropriate use of antimicrobial	Document the investigation of the results as if they were unacceptable and review the proper reference documents to gain knowledge of the reason your response is not appropriate.
26	Educational challenge	Review participant summary for comparative results and document performance accordingly. Evaluation criteria are not established for educational challenges. Laboratories should determine their own evaluation criteria approved by their laboratory director for self-evaluation.
27,31	Lack of participant or referee consensus	Document that the laboratory performed a self-evaluation and compared its results to the intended response when provided in the participant summary. If comparison is not available, perform and document alternative assessment (ie, split samples) for the period that commercial PT reached non-consensus to the same level and extent that would have been tested.
28	Response qualified with a greater than or less than sign; unable to quantitate	Applies to a response that is not formally evaluated when a less than or greater than sign is reported. Document that the laboratory performed a self-evaluation and compared its results to the proper statistics supplied in the participant summary. Verify detection limits. Perform and document the corrective action of any unacceptable results.
30	Scientific committee decision	Applies to a response that is not penalized based on scientific committee decision. Document that the laboratory has reviewed the proper statistics supplied in the participant summary.

Actions Laboratories Should Take when a PT Result is Not Graded

The CAP uses exception reason codes that signify the proficiency testing (PT) for an analyte has not been graded. The exception reason code is located on the evaluation report in brackets to the right of the result. Your laboratory must identify all analytes with an exception reason code, review and document the acceptability of performance as outlined below and retain documentation of review for at least 2 years. The actions laboratories should take include but are not limited to:

Code	***Exception Reason Code Description***	***Action Required***
33	Specimen determined to be unsatisfactory after contacting the CAP	Document that the laboratory has contacted the CAP and no replacements specimens were available. Perform and document alternative assessment (ie, split samples) for the period that commercial PT was not tested to the same level and extent that would have been tested.
40 41	Results for this kit were not received. Results for this kit were received past the evaluation cut-off date.	Document why results were not received, corrective action to prevent recurrence and the laboratory's self-evaluation of the results by comparing results to the proper statistics and evaluation criteria supplied in the participant summary. If PT specimens were not analyzed, perform and document alternative assessment (ie, split samples) for the period that commercial PT was not tested to the same level and extent that would have been tested.
42	No credit assigned due to absence of response	The participant summary indicates which tests are graded (see evaluation criteria) and which tests are not evaluated/educational. Updates to grading will also be noted. If a test is educational, the laboratory is not penalized for leaving a result(s) blank. If a test is graded (regulated and non-regulated analytes) and your laboratory performs that test, results cannot be left blank. The laboratory is required to submit results for **all** challenges within that test or use an appropriate exception code or indicate test not performed/not applicable/not indicated. Exceptions may be noted in the kit instructions and/or the result form. Document corrective actions to prevent future failures.
44	This drug is not included in our test menu. Use of this code counts as a correct response.	Verify that the drug is not tested on patient samples and document to ensure proper future reporting.
45	Antimicrobial agent is likely ineffective for this organism or site of infection	Document that the laboratory performed a self-evaluation of written protocols and practices for routine reporting of antimicrobial susceptibility reports to patient medical records. Document that routine reporting of this result to clinicians for patient care is compliant with specific recommendations of relevant medical staff and committees (eg, infectious diseases, pharmacy and therapeutics, infection control).
77	Improper use of the exception code for this mailing	Document the identification of the correct code to use for future mailings.
91	There was an insufficient number of contributing challenges to establish a composite grade.	Document the investigation of the result as if it were an unacceptable result. Perform and document the corrective action if required.
35, 43, 46, 88, 92	Various codes	No action required.

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None

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Learning Objectives

1. Describe the diagnostic criteria of adult T-cell leukemia/lymphoma (ATLL), including the classification of clinical subtypes.
2. Identify the clinical, morphologic, and common laboratory features of ATLL.
3. Recognize the essential role of HTLV-1 infection in the pathogenesis of ATLL.
4. Describe the utility of common laboratory tests used to confirm and further investigate cases of ATLL, including flow cytometry, cytogenetics, and molecular sequencing.

FH (1-4, 6, 9-10, 13, 16)-B 2021: Adult T-Cell Leukemia/Lymphoma

Case Presentation

This peripheral blood smear is from a 76-year-old Japanese woman diagnosed with bladder cancer and history of mature T-cell leukemia/lymphoma. Laboratory data include: WBC = 51.2 x 10E9/L; RBC = 3.69 x 10E12/L; HGB = 12.2 g/dL; HCT = 35.9%; MCV = 97 fL; MCHC = 34.2 g/dL; PLT = 108 x 10E9/L; and RDW = 16%.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

INTRODUCTION

Adult T-cell leukemia/lymphoma (ATLL) is a rare, mature T-cell lymphoma that is associated with infection by human T-cell lymphotropic virus type 1 (HTLV-1). It displays protean clinical presentations, and its severity and prognosis depend on these clinical variants. Unfortunately, most cases (around 80%) demonstrate poor clinical behavior with few therapeutic interventions. Patients suffer from opportunistic infections, suggesting a component of immunodeficiency in this lymphoma.

Epidemiology

HTLV-1 infection plays an essential role in the development of ATLL. As many as 10 million people worldwide are affected by the retrovirus in Japan, the Caribbean Basin, Africa, Central and South America, Romania, and northern Iran. The incidence of HTLV-1 infection is highest in Japan, with 27 persons infected per 100,000 individuals. Notably, only 1% to 5% of those with HTLV-1 infection will eventually develop ATLL. In contrast, in the United States, ATLL is observed mostly in individuals who have immigrated from endemic regions, with an approximate incidence of five persons with ATLL per 10 million individuals. A slight male predominance is observed in ATLL (male-to-female ratio of 1.5:1.0).

Pathogenesis

Transmission of the HTLV-1 retrovirus is thought to occur through breastmilk (from mother to child), sexual intercourse, and blood transfusion. Carriers of the HTLV-1 infection do not uniformly progress to malignancy; as previously mentioned, only 1% to 5% of carriers go on to develop ATLL. Thus, the virus itself is insufficient to produce malignant transformation. However, the long duration of HTLV-1 infection promotes other molecular events to induce tumor growth.

Interestingly, HTLV-1 infection can also lead to other non-neoplastic disorders, including HTLV-1 associated myelopathy (tropical spastic paraparesis), HTLV-1 associated infective dermatitis, and other HTLV-1 inflammatory disorders (eg, uveitis, thyroiditis, pneumonitis, myositis).

Clinical Features

Four clinical variants or subtypes are recognized. The aggressive variants are the acute and lymphomatous subtypes, while the more favorable variants are chronic and smoldering. Most cases of ATLL (60%) present as the acute variant, followed by lymphomatous (20%), chronic (15%), and smoldering (5%). Opportunistic infections are common in all types of ATLL, and include infections with *Pneumocystis carinii, Strongyloides stercoralis*, *Cryptococcus neoformans*, and other bacterial and fungal organisms. Cutaneous lesions are frequent and can range from a diffuse, red rash to papules or larger nodules. Some nodules may ulcerate.

The **acute subtype** is characterized by overt peripheral blood leukemic involvement with marked lymphocytosis and the presence of abnormal circulating lymphoma cells. Patients experience constitutional symptoms and display many cutaneous lesions, including nodules and papules. Disseminated lymphoma in multiple organ sites can lead to infiltration of bone marrow, liver, spleen, lung, and other sites; thus, manifestations such as hepatosplenomegaly and cytopenias are common with this variant. Central nervous system (CNS) involvement can be observed. Significant laboratory abnormalities include high levels of serum calcium and lactate dehydrogenase (LDH). The hypercalcemia can be severe. Increased bone osteoclastic activity, evidenced by lytic bone lesions on imaging, can be seen in this subtype.

The **lymphomatous subtype** is typified by extensive lymphadenopathy without significant blood involvement by abnormal lymphocytes. Constitutional symptoms due to widespread lymphomatous involvement in both nodal and extranodal sites (including CNS) can be observed. As with the acute variant, this subtype is clinically aggressive.

The **chronic subtype** is considered one of the less aggressive variants, with mild disease manifestations. While lymphocytosis and circulating lymphoma cells can be seen, and while serum LDH is elevated, the increase is slight in comparison with the acute subtype. Hepatosplenomegaly and lymphadenopathy may be observed, yet these occur only to a mild degree when compared to the lymphomatous subtype. A widespread redness, scaling, and even peeling of the skin over large areas of the body (ie, exfoliative rash) is common in this subtype.

Finally, the **smoldering subtype**, which is the least frequent ATLL clinical subtype, is also categorized as less aggressive. It can be recognized by the presence of circulating lymphoma cells that are greater than 5% of the WBC count, yet is not accompanied by an absolute lymphocytosis. Cutaneous lesions (erythema and papules) and lung involvement are frequent. However, there is no associated hypercalcemia, bone marrow infiltration, lymphadenopathy, or hepatosplenomegaly. Table 1 provides a summary of the findings that are associated with the clinical variants of ATLL.

Table 1. Comparison of the presentation and findings in the clinical variants of ATLL.

		CLINICAL VARIANTS			
Presentation and Findings		**Acute**	**Lymphomatous**	**Chronic**	**Smoldering**
History, Physical Examination, and Imaging Findings	**Systemic symptoms**	+++	+++	+	-
	Skin manifestations (cutaneous lesions)	++	+++	++ exfoliative skin rash	Erythema, papules
	Lymphadenopathy	++	+++	+	-
	Hepatosplenomegaly	++	++	+	-
	Extranodal involvement (eg, lungs, liver, GI tract, CNS)	++	++	+	+/-

		CLINICAL VARIANTS			
Presentation and Findings		**Acute**	**Lymphomatous**	**Chronic**	**Smoldering**
Pertinent Laboratory and Pathology Studies	**Increased absolute lymphocyte count**	+++	-	++	-
	Circulating lymphoma cells	+++ (marked atypia)	< 1% circulating lymphoma cells	+++ (mild atypia)	> 5% circulating lymphoma cells (mild atypia)
	Hypercalcemia	+++	++	-	-
	Increased lactate dehydrogenase	+++	+++	+	-
	Bone marrow findings	+/- involvement Bone remodeling	+/-	No BM infiltration	No BM infiltration
Clinical Behavior	**Prognosis**	Aggressive	Aggressive	Protracted; better survival compared to acute and lymphomatous phases	Protracted; better survival compared to acute and lymphomatous phases

Symbols: -, condition or feature is absent; +/-, condition or feature is observed to a variable degree; +, present to a mild degree or in a minor subset (< 10%) of cases; ++, present to a moderate degree or in a moderately high percentage (10% - 50%) of cases; +++, seen to marked degree or in a high percentage (≥ 50%) of cases.

Diagnosis

Complete blood count and peripheral blood smear evaluation.

The degree of absolute lymphocytosis and/or the presence of the characteristic "flower cells" depend on the clinical subtype. In the acute variant, an absolute lymphocytosis exceeding 4,000/µL is seen in 88% of cases, with half displaying overt lymphocytosis beyond 15,000/µL. Cytologic atypia in the so-called ATLL "flower cells" is striking. Their deeply convoluted nuclear contours are reminiscent of flower petals or a clover-leaf pattern. Chromatin is coarsely clumped with variably visible nucleoli. A subset of cells can display finely textured, blast-like chromatin. The cytoplasm is typically scant and intensely basophilic.

The lymphomatous variant, on the other hand, is defined by extensive lymphadenopathy coupled with the absence of lymphocytosis and scarcity of circulating lymphoma cells (< 1%). Of the more favorable variants, the chronic subtype is the one that displays lymphocytosis as well as greater numbers of circulating lymphoma cells. Lymphocytosis is not observed in the smoldering subtype, though circulating lymphoma cells can account for > 5% of WBCs. The degree of cytologic atypia in both the chronic and smoldering variants is mild, mimicking the appearance of normal lymphocytes.

Ancillary Studies in the Diagnostic Work-up

Flow cytometry is essential in uncovering the distinctive lymphoma immunophenotype. The lymphoma cells are T cells whose closest normal counterpart are T-regulatory cells, which are CD4+, CD25+ T cells. The typical ATLL lymphoma immunophenotype includes expression of T-cell markers CD3, CD2, CD4, and CD5; CD7 expression is typically lost. Though the typical phenotype is that of a CD4+ T cell, other cases may display a double negative (ie, CD4-/CD8-) or double positive (ie, CD4+/CD8+) phenotype. Most exhibit high expression of CD25 (a characteristic but not specific marker for Treg cells), and a significant subset are positive for CD30. On tissue sections, **immunohistochemistry** can be employed to demonstrate T-cell lineage and FOXP3 expression (a transcription factor characteristic of Treg cells).

Regarding other ancillary studies, such as **cytogenetic analysis**, there is no specific karyotypic abnormality ascribed to ATLL. Clonal peaks in PCR studies for T-cell receptor gene rearrangements are invariably present, as they are in most other T-cell lymphomas.

To summarize the diagnostic work-up, the combination of overt lymphocytosis with circulating "flower cells" with a T-regulatory immunophenotype as above, severe systemic manifestations (ie, constitutional symptoms, adenopathy, organomegaly, etc), and positive HTLV-1 serology in an individual from an endemic region are diagnostic of ATLL (particularly the acute subtype).

Table 2 shows some of the salient diagnostic features during the laboratory and pathology work-up for the acute subtype of ATLL.

Table 2. Selected features in the diagnostic laboratory and pathology work-up of acute subtype of ATLL.

Test	Typical Features
CBC with differential	Absolute lymphocytosis; leukemic presentation of lymphoma
Peripheral blood smear	Lymphoma cells with flower-like cytology
HTLV-1 serology	Positive in all cases
Flow cytometry	T-cell marker expression: positive for CD2, CD3, CD4 (typically CD4+/CD8-), CD5, and CD25. Usually negative for CD7. Other cases may have double negative (ie, CD4-/CD8-) or double positive (ie, CD4+/CD8+) T cells.
Skin pathology	Epidermal infiltration with Pautrier-like microabscesses common, mimicking mycosis fungoides
Lymph node pathology	Variable morphology can mimic other lymphoma types. Some cases show paracortical expansion with highly pleomorphic lymphoma cells with Hodgkin-like cytology. Some resemble angioimmunoblastic T-cell lymphoma with EBV+ B-cells.
Bone marrow pathology	Variable lymphomatous infiltration, from sparse to moderate patchy involvement Osteoclastic bone activity
Immunohistochemistry	T-cell marker expression (as in flow cytometry). Also, markers of T-regulatory cells are evident, such as CD25 and FOXP3.
Cytogenetics	No associated pathognomonic karyotypic abnormalities
Molecular	Demonstration of abnormalities is not essential for diagnosis (see text for further discussion)

Molecular Sequencing

The demonstration of **molecular abnormalities** is not necessary for the diagnosis of ATLL. However, research studies have shown that the gene, *HBZ* (HTLV-1 basic leucine zipper), is consistently expressed in high levels on all ATLL cases, while *CCR4* mutations are detected in 25%. A large number of other recurrently mutated genes have been discovered, some of them involved in T-cell receptor signaling and regulation of the NF-kappa-B pathway. Other significant abnormalities point to inactivation of the tumor suppressor gene *TP73* (a *TP53* homologue) and aberrations in mechanisms that control genes for important immune system activities; these abnormalities ultimately lead to tumor cells successfully evading the immune system.

Differential Diagnosis

Despite the seemingly characteristic features, not all cases of ATLL "read the textbook." Some ATLL cases can display cytologic, histomorphologic, and immunophenotypic features that are practically indistinguishable from other T-cell lymphomas, such as Sézary syndrome, angioimmunoblastic T-cell lymphoma and other lymphomas of T-follicular helper cell origin, and peripheral T-cell lymphoma. As an example, a widespread erythrodermic skin rash and numerous circulating lymphoma cells with cerebriform morphology in ATLL could clinically and pathologically mimic a case of Sézary syndrome. The key is in recognizing that the patient is from an endemic region and to evaluate for the presence of HTLV-1 infection through serology.

Therapy and Prognosis

As discussed previously, the acute and lymphomatous variants behave aggressively, while the chronic and smoldering variants have a more protracted disease course.

For the aggressive variants, several combination chemotherapy regimens have been employed; these can vary geographically and with hematologists' preferences. For example, a specific protocol called VCAP-AMP-VECP is widely adopted in Japan, while other providers prefer CHOP, DA-EPOCH, or other etoposide-based regimens. Other more intensive regimens are being tested in clinical trials. Despite these interventions, ultimately 90% of patients will experience disease recurrence within months of concluding treatment. Patients may die within weeks to months of diagnosis, with only a very few surviving beyond one year. Because of these dismal outcomes, allogeneic stem cell transplantation at first complete remission is an essential consideration for the hematologist/oncologist.

In Japan, a relatively new antibody drug targeted against *CCR4* (an antigen that can be found in T-regulatory cells), mogamulizumab, has been approved for use in the setting of relapsed or persistent ATLL with some promising results. Additional studies using this drug in combination with conventional chemotherapy are underway. Other novel drugs are also being investigated in clinical trials, such as the anti-CD30 monoclonal antibody brentuximab vedotin and checkpoint inhibitors (eg, nivolumab).

Antiviral therapies have been employed with some success in the chronic and smoldering subtypes. Another approach by some practitioners is to monitor these patients and employ watchful waiting. Unfortunately, though typically less aggressive, the chronic and smoldering subtypes do carry a 25% risk for progression to the acute variant.

References

1. Cook LB, Phillips AA. How I treat adult T-cell leukemia/lymphoma. *Blood* 2021; 137(4):459-470. doi:10.1182/blood.2019004045.
2. Glassy EF, ed. *Color Atlas of Hematology: An Illustrated Field Guide Based on Proficiency Testing*. 2nd ed. College of American Pathologists; 2018.
3. Khanlari M, Ramos JC, Sanchez SP, et al. Adult T-cell leukemia/lymphoma can be indistinguishable from other more common T-cell lymphomas. The University of Miami experience with a large cohort of cases. *Mod Pathol.* 2018;31(7):1046-1063.
4. Mehta-Shah N, Ratner L, Horwitz SM. Adult T-cell leukemia/lymphoma. *J Oncol Pract.* 2017;13(8):487-492.
5. Shimoyama M, Lymphoma Study Group members. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma: a report from the Lymphoma Study Group (1984-87). *Br J Haematol.* 1991;79(3):428-437.
6. Swerdlow SH, Campo E, Harris NL, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Revised 4th ed. IARC Press; 2017.

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