Blood Cell Identification – Graded

Case History
This peripheral blood smear is from a 30-year-old man with untreated parasitic infection due to tropical filariasis. Laboratory data include: WBC = 19.1 x 10E9/L; RBC = 4.50 x 10E12/L; HGB = 13.7 g/dL; HCT = 41.0%; MCV = 88 fL; MCHC = 35.0 g/dL; PLT = 180 x 10E9/L; and RDW = 14%. Identify the arrowed object(s) on each image.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

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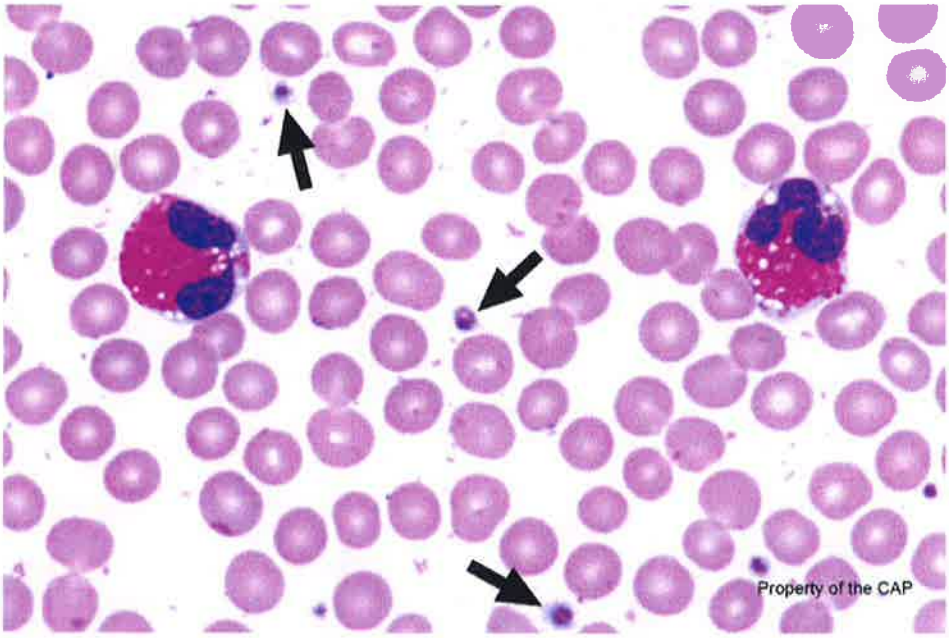
https://documents.cap.org/documents/2021-hematology-and-clinical-microscopy-glossary.pdf

BCP-01

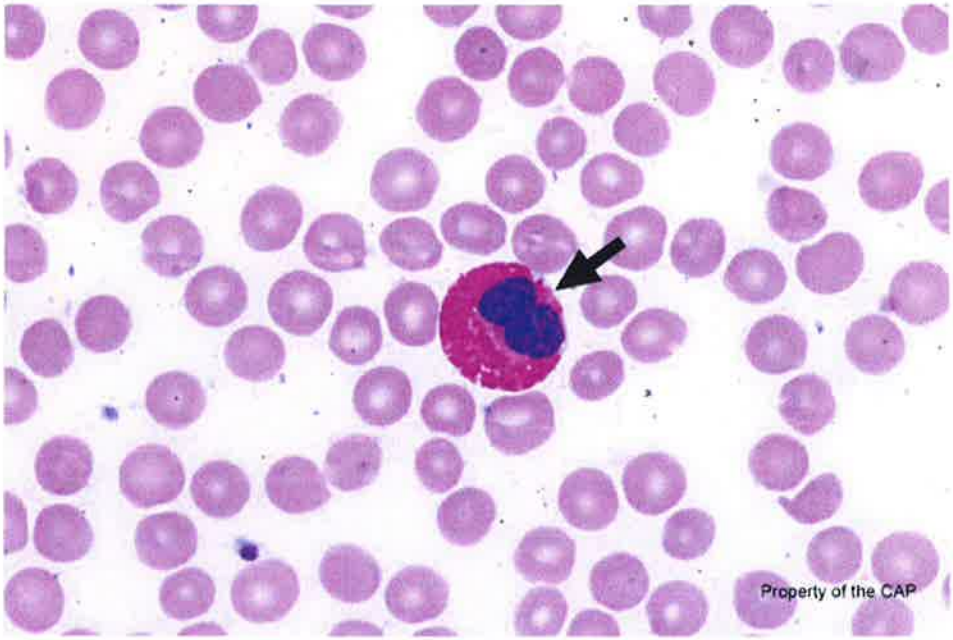


Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Platelet, normal	182	100.0	5394	99.4	Good

The arrowed cells are normal platelets, as correctly identified by 100.0% of referees and 99.4% of participants. Platelets are small, usually round or very slightly elliptical, blue-gray fragments of megakaryocytic cytoplasm. Normal-sized platelets, as in this case, typically measure 1.5 to 3 µm in diameter and are smaller than erythrocytes. Normal platelets contain fine, purple-red (alpha) granules dispersed throughout the cytoplasm or aggregated at the center.

Blood Cell Identification – Graded

BCP-02

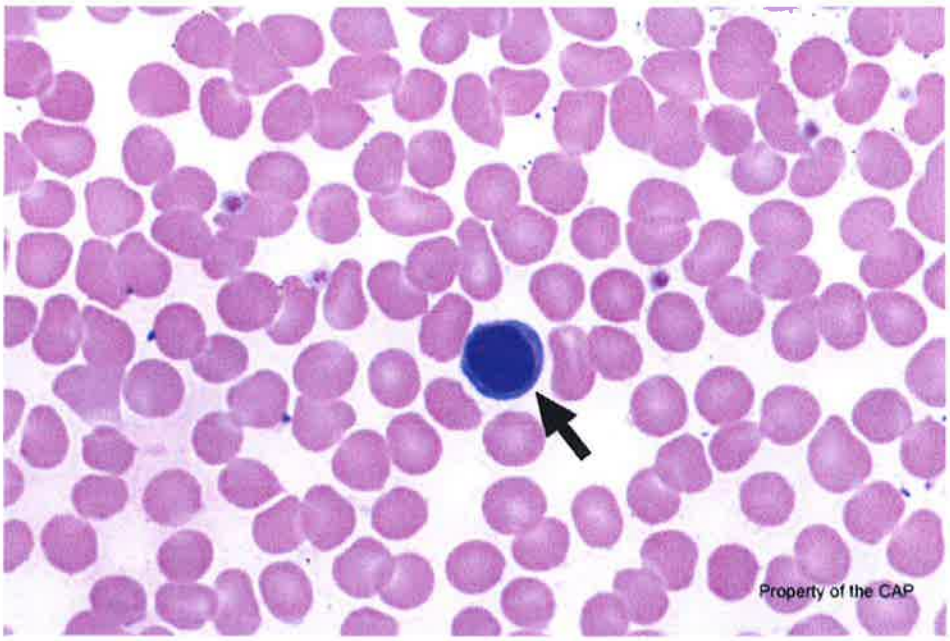


Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Eosinophil, any stage	182	100.0	5420	99.8	Good

The arrowed cell is an eosinophil, as correctly identified by 100.0% of referees and 99.9% of participants. Eosinophils are round-to-oval leukocytes that are recognizable by their characteristic coarse, orange-red granulation. They are comparable in size to neutrophils and exhibit similar nuclear characteristics and stages of development to neutrophils; in contrast to neutrophils, however, eosinophils typically exhibit a two-lobed nucleus (although a greater degree of nuclear lobation may occasionally be seen). Occasionally, eosinophils can become degranulated, with only a few orange-red granules remaining visible within the faint pink cytoplasm.

Blood Cell Identification – Graded

BCP-03

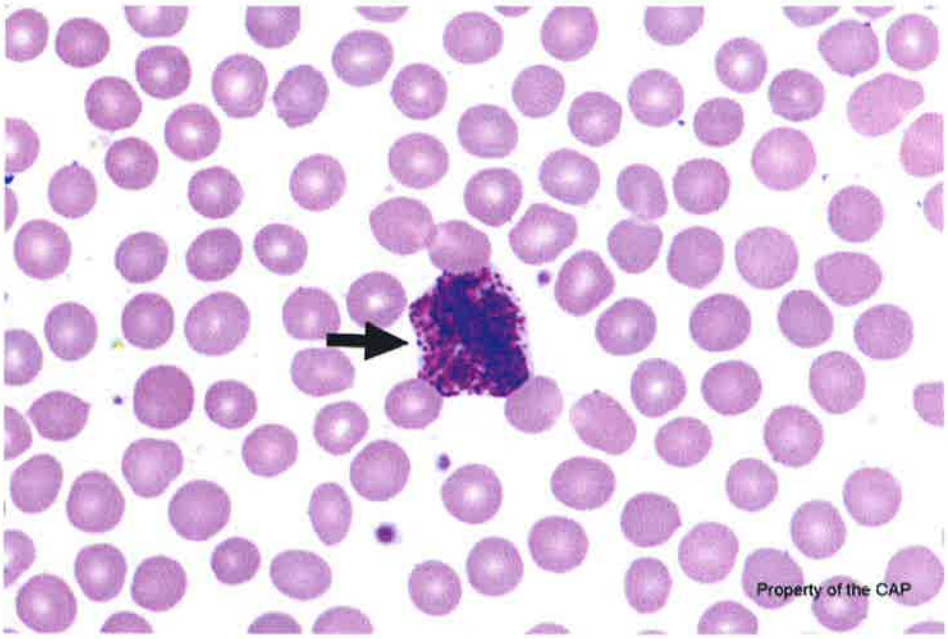


Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Lymphocyte	182	100.0	5317	98.0	Good

The arrowed cell is a lymphocyte, as correctly identified by 100.0% of referees and 98.0% of participants. Lymphocytes can exhibit a range of morphologic features; the lymphocyte pictured here is typical of a normal lymphocyte, with relatively small size (typically ranging from 7 to 15 µm), high N:C ratio, and a thin rim of agranular cytoplasm. In contrast to immature lymphocytes (lymphoblasts), the chromatin is dense and coarse; and in contrast to some malignant mature lymphocytes, the nuclear contours are regular and round.

Blood Cell Identification – Graded

BCP-04



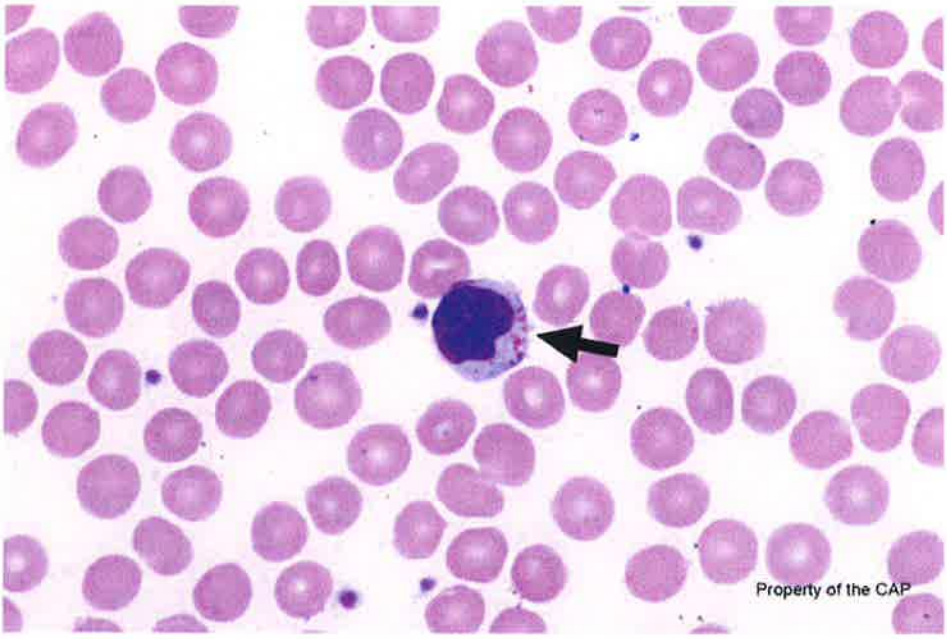
Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Basophil, any stage	178	97.8	5295	97.5	Good
Neutrophil, toxic (to include toxic granulation and/or Döhle bodies, and/or toxic vacuolization)	3	1.6	111	2.1	Unacceptable
Basophilic stippling (coarse)	1	0.6	10	0.2	Unacceptable

The arrowed cell is a basophil, as correctly identified by 97.8% of referees and 97.6% of participants. Basophils are similar in size to neutrophils (typically 10-15 µm in diameter) but contain characteristically dark blue-black coarse granules. These granules typically obscure the basophil nucleus. The basophil nucleus demonstrates segmentation similar to other granulocytes.

The arrowed cell was incorrectly identified as a toxic neutrophil by 1.6% of referees and 2.1% participants. While neutrophils and basophils do share similar features, and toxic neutrophils are characterized by increased blue-black granules, neutrophil secondary granules are absent in this case. Likewise, other features of toxic neutrophils such as prominent Döhle bodies and vacuoles are not present.

Blood Cell Identification – Graded

BCP-05



Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Lymphocyte, large granular	169	92.9	5008	92.3	Good
Lymphocyte, reactive (includes plasmacytoid and immunoblastic forms)	4	2.2	106	2.0	Acceptable
Monocyte	3	1.6	50	0.9	Unacceptable
Lymphocyte	2	1.1	122	2.3	Unacceptable
Leukocyte with intracellular *Anaplasma/Ehrlichia*	1	0.6	2	0.0	Unacceptable
Neutrophil with dysplastic nucleus and/or hypogranular cytoplasm	1	0.6	3	0.1	Unacceptable
Neutrophil, metamyelocyte	1	0.6	10	0.2	Unacceptable
Neutrophil, toxic (to include toxic granulation and/or Döhle bodies, and/or toxic vacuolization)	1	0.6	8	0.1	Unacceptable

The arrowed cell is a large granular lymphocyte, as correctly identified by 92.9% of referees and 92.3% of participants. Identification of the arrowed cell as a reactive lymphocyte, identified by 2.2% of referees and 1.9% of participants, is also considered acceptable. Large granular lymphocytes are medium to large cells with round nuclei, dense chromatin, and no visible nucleoli. The cytoplasm is moderate to abundant, clear and lightly basophilic, and contains several coarse, unevenly distributed, small azurophilic granules. The nuclear contours of large granular lymphocytes (as in this case) may be irregular; however, the chromatin pattern is mature, characteristically dense and coarse. While similar size and nuclear features may be seen in reactive lymphocytes, these do not generally contain coarse cytoplasmic granules and often have a relatively more basophilic cytoplasmic coloration.

BCP-05, cont'd.

1.1% of referees and 2.3% of participants incorrectly identified the arrowed cell as a lymphocyte. Large granular lymphocytes are larger than normal lymphocytes, with much more abundant lightly basophilic cytoplasm. Also, in contrast to normal lymphocytes, the cytoplasmic granules of large granular lymphocytes should be readily apparent. In this case, the identification of the arrowed cell as "lymphocyte" is insufficiently specific and is therefore considered unacceptable for the purposes of proficiency testing.

Clinical Presentation:

This peripheral blood smear is from a 30-year-old man with untreated parasitic infection due to tropical filariasis. Laboratory data include: WBC = 19.1 × 10E9/L; RBC = 4.50 × 10E12/L; HGB = 13.7 g/dL; HCT = 41.0%; MCV = 88 fL; MCHC = 35.0 g/dL; PLT = 180 × 10E9/L; and RDW = 14%.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

CASE DISCUSSION: Eosinophilia (secondary to history of tropical filariasis)

Eosinophilia refers to the identification of excess eosinophils. In the blood this typically refers to eosinophil counts in excess of 0.4 x 10E9/L, although the upper limit of normal may vary from laboratory to laboratory. Eosinophilia can be primary (ie, the eosinophils are neoplastic) or secondary (ie, the increase in eosinophils is reactive and can be attributed to another cause) and short-lived or prolonged. In most cases, short-lived eosinophilia is attributable to a myriad of potential secondary causes. In cases of prolonged eosinophilia (typically months), especially at high levels (typically in excess of 1.5 x 10E9/L), consideration of potential primary eosinophilia disorders (or recalcitrant secondary causes) is warranted.

A lengthy list of potential secondary causes of eosinophilia should be considered. These include allergic states (asthma, rhinitis, dermatitis and others) and drug reactions; infectious causes (especially involving parasites); and autoimmune disease (including as diverse entities as lupus, inflammatory bowel disease and vasculitides). There are a small number of malignant conditions in which secondary eosinophilia may occur; these include myeloid neoplasms (eg, acute myeloid leukemia with inv(16), chronic myelomonocytic leukemia, and systemic mastocytosis), certain lymphomas (most notably Hodgkin lymphoma and occasional T-cell lymphomas) and certain solid tumors (including some colon and lung cancers).

In this case, a history of tropical filariasis was provided. Filariasis refers to illness caused by filariae species of parasitic nematodes (round-worms). In humans, filariasis is most commonly caused by *Wuchereria bancrofti*, transmitted by mosquito and endemic to tropical regions. Although filarial worms can occasional be seen on peripheral smears, modern detection methods rely on serological testing.

The diagnosis of primary eosinophilia is quite rare and is typically arrived at after exclusion of an extensive number of potential secondary causes. Primary eosinophilia can be further subclassified into idiopathic hypereosinophilic syndrome, myeloid/lymphoid neoplasms with eosinophilia (usually characterized by certain specific molecular genetic changes) and chronic eosinophilic leukemia, not otherwise specified. In addition to an extensive clinical work-up, these cases typically require bone marrow studies with additional cytogenetic and molecular investigations to exclude underlying clonal processes.

Notwithstanding the potential clinical implications of the underlying etiologies in secondary eosinophilia, prolonged eosinophilia is a risk factor for tissue damage (owing to tissue infiltration and commensurate tissue damage), especially of cardiac and pulmonary tissues, as well as thromboembolic disease.

Etienne Mahé, MD, MSc, FRCPC, FCAP
Hematology and Clinical Microscopy Committee

References:

1. Butt NM, Lambert J, Ali S, et al. Guideline for the investigation and management of eosinophilia. *Br J Haematol.* 2017;176(4):553-572. doi: 10.1111/bjh.14488.
2. Kovalszki A, Weller PF. Eosinophilia. *Primary Care*. 2016;43(4):607-617. doi: 10.1016/j.pop.2016.07.010.
3. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H and Thiele J, eds. *WHO Classification of Tumours of Haematopietic and Lymphoid Tissues*. Revised 4th ed. International Agency for Research on Cancer, 2017.
4. Leggat P, Melrose W, Dürrheim DN. Could it be lymphatic filariasis? *J Travel Med.* 2004;11(1):56-60. doi: 10.2310/7060.2004.13636.

Blood Cell Identification – Ungraded

Case History
This peripheral blood smear is from a 76-year-old Japanese woman diagnosed with bladder cancer and with a history of T-cell lymphoproliferation. 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%. Identify the arrowed object(s) on each image.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

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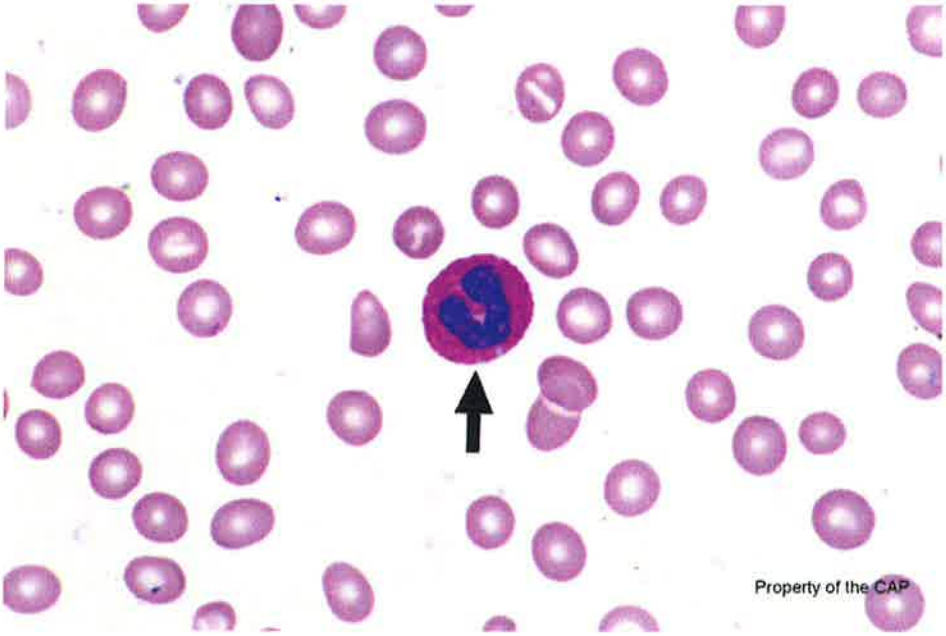
BCP-06



Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Eosinophil, any stage	177	97.3	5248	97.7	Educational
Neutrophil, segmented or band	4	2.2	107	2.0	Educational
Basophil, any stage	1	0.6	13	0.2	Educational

The arrowed cell is a mature eosinophil, as correctly identified by 97.3% of referees and 97.8% of participants. Eosinophils are round-to-oval leukocytes that are recognizable by their characteristic coarse, orange-red granulation. They are comparable in size to neutrophils, ie, 10 to 15 µm in diameter in their mature forms, and 10 to 18 µm in diameter in immature forms. The eosinophil N:C ratio ranges from 1:3 for mature forms to 2:1 for immature forms. The eosinophil cytoplasm is evenly filled with numerous coarse, orange-red granules of uniform size. These granules rarely overlie the nucleus and are refractile by light microscopy due to their crystalline

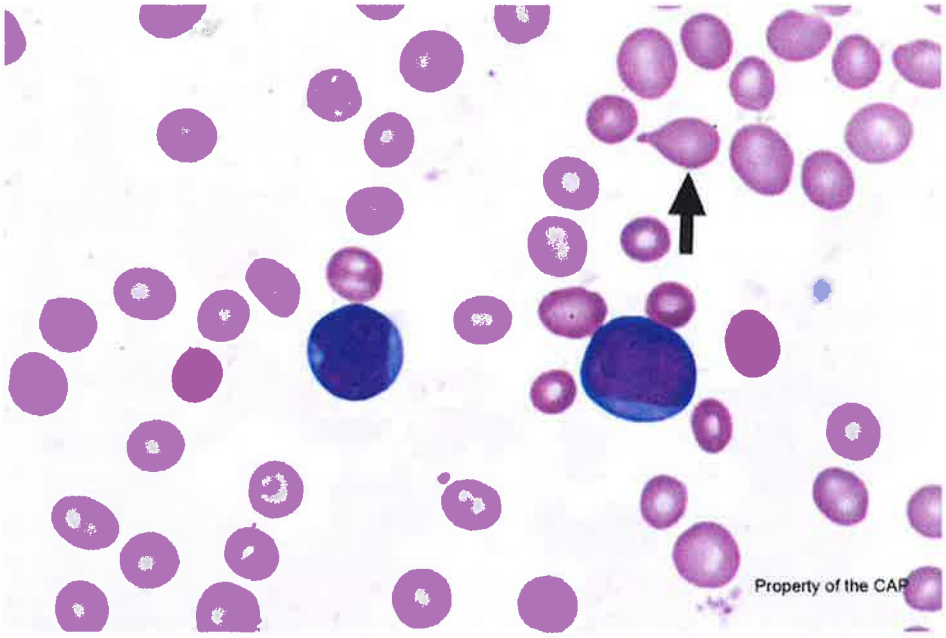
BCP-06, cont'd.

structure. In the most mature eosinophil form, the nucleus segments into two or more lobes connected by a thin filament. About 80% of segmented eosinophils will have the classic two-lobed appearance (as seen on the photomicrograph). Typically, these lobes are of equal size and round to ovoid or potato-shaped with dense, compact chromatin. The remainder of segmented eosinophils will have three lobes, and an occasional cell will exhibit four to five lobes.

2.2% of referees and 1.9% of participant incorrectly identified the cell as a segmented or band neutrophil. Although the nucleus of a mature eosinophil may resemble the nucleus of a mature neutrophil, the cytoplasm of the latter is pale containing specific fine granules.

Blood Cell Identification – Ungraded

BCP-07

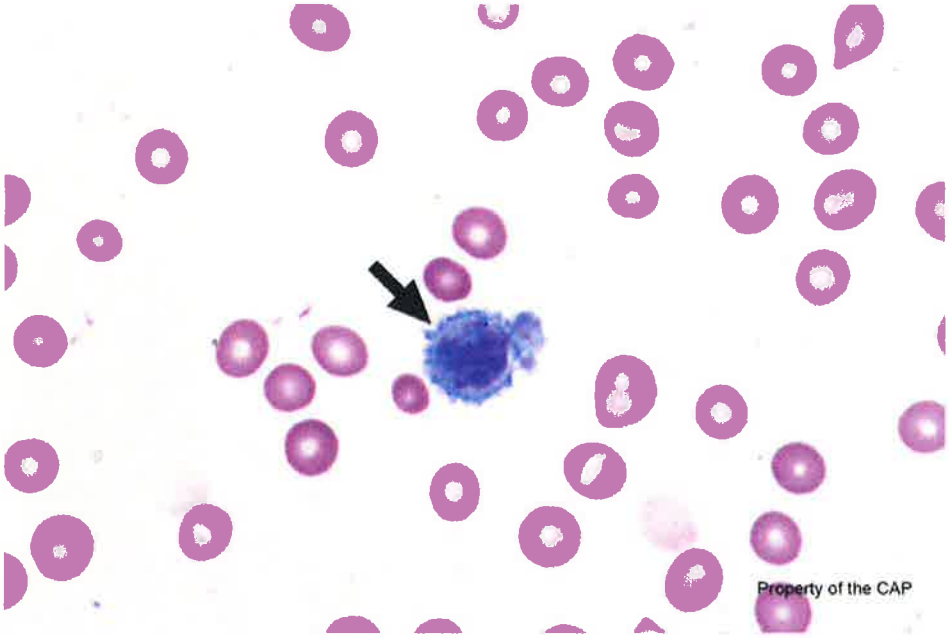


Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Teardrop cell (dacrocyte)	181	99.5	5291	99.6	Educational
Papenheimer bodies (iron or Wright stain)	1	0.6	2	0.0	Educational

The arrowed cell is a teardrop cell (dacrocyte), as correctly identified by 99.5% of referees and 99.6% of participants. Red blood cells appearing in the shape of a teardrop or a pear with a single, short or long, often blunted or rounded end are called teardrop cells. These are commonly seen in patients with bone marrow fibrosis but may also be seen in pernicious anemia, anemia of renal disease, hemolytic anemias, and other forms of severe anemia. These cells are often associated with an abnormal spleen or bone marrow. Bone marrow infiltration with hematologic and non-hematologic malignancies may also be accompanied by dacrocytosis. Teardrop cells may be seen as an artifact of slide preparation; such dacrocytes are usually easily recognized due to the fact that their "tails" all point in the same direction.

Blood Cell Identification – Ungraded

BCP-08



Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Platelet, giant (macrothrombocyte)	168	92.3	4921	92.7	Educational
Megakaryocyte	9	5.0	214	4.0	Educational
Malignant lymphoid cell (other than blast)	4	2.2	74	1.4	Educational
Immature or abnormal cell, would refer for identification	1	0.6	39	0.7	Educational

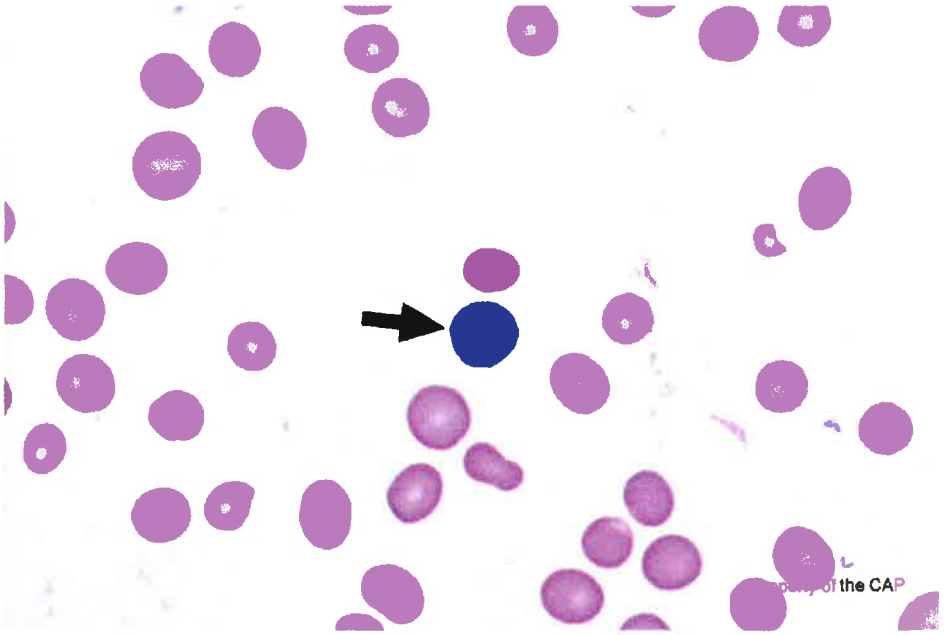
The arrowed cell is a giant platelet (macrothrombocyte), as correctly identified by 92.3% of referees and 92.7% of participants. Giant platelets are larger than 7 µm, usually measuring 10 to 20 µm in diameter. For proficiency testing purposes, the term *giant platelet* is used when the platelet is larger than the size of the average red blood cell in the field, assuming a normal MCV. The periphery of the giant platelet may be round, scalloped, or stellate. The cytoplasm may contain a normal complement of fine azurophilic granules, or the granules may fuse into giant forms. Giant platelets are a rare finding in normal peripheral blood, but may be seen in many different reactive, neoplastic, and inherited conditions. Reactive causes include conditions in which platelet turnover is markedly increased, such as immune thrombocytopenia or severe leukemoid reactions. Giant platelets are most often seen in myeloproliferative neoplasms and myelodysplastic syndromes. The inherited conditions associated with giant platelets are rare and also have associated thrombocytopenia. This group of disorders is termed congenital macrothrombocytopenias and includes May-Hegglin anomaly and Bernard-Soulier syndrome.

BCP-08, cont'd.

5.0% of referees and 4.0% of the participants incorrectly identified the cell as a megakaryocyte. While megakaryocyte nuclei and micromegakaryocytes may infrequently be seen, normal mature megakaryocytes are not found in the peripheral blood. Megakaryocytes are the largest bone marrow hematopoietic cells, measuring at least 25 to 50 µm in diameter. The numerous nuclear lobes are of various sizes, connected by large bands or fine chromatin threads. The chromatin is coarse and clumped to pyknotic. The abundant cytoplasm stains pink or wine-red and contains fine azurophilic granules that may be clustered, producing a checkered pattern.

Blood Cell Identification – Ungraded

BCP-09



Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Lymphocyte	180	98.9	5160	97.2	Educational
Nucleated red blood cell, normal or abnormal morphology	0	0.0	94	1.8	Educational
Malignant lymphoid cell (other than blast)	1	0.6	6	0.1	Educational
Plasma cell, morphologically mature/abnormal/containing inclusions (eg, Dutcher body, Russel body)	1	0.6	3	0.1	Educational

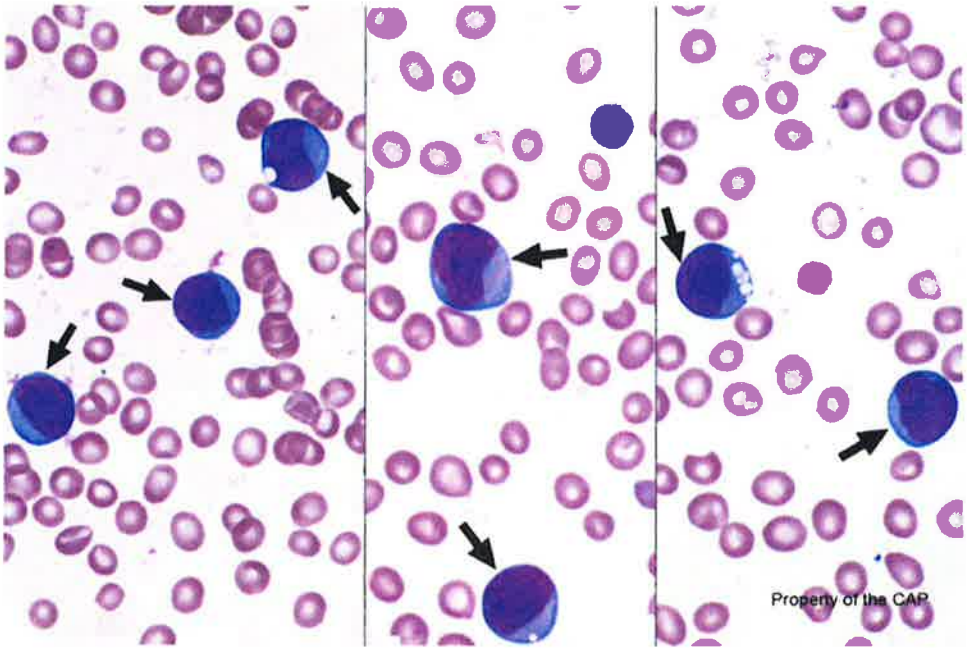
The arrowed cell is a normal lymphocyte, as correctly identified by 98.9% of referees and 97.2% of participants. Lymphocytes are small, round to ovoid cells ranging in size from 7 to 15 µm with an N:C ratio ranging from 5:1 to 2:1. Most lymphocytes have round to oval nuclei that may be slightly indented or notched. The chromatin is diffusely dense or coarse and clumped. Nucleoli are not visible, although some cells may exhibit a small, pale chromocenter that may be mistaken for a nucleolus. Most lymphocytes have a scant amount of pale blue to moderately basophilic, agranular cytoplasm. Occasionally, the edges may be slightly frayed or pointed due to artifacts induced during smear preparation. Occasional lymphocytes will have a small clear zone, or hof, adjacent to one side of the nucleus. While most normal lymphocytes are fairly homogeneous, they do exhibit a range of normal morphology.

BCP-09, cont'd.

1.8% of participants incorrectly identified the cell as a nucleated red blood cell (nRBC). The term 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. Unlike lymphocytes, nRBC demonstrate a round central nucleus with clumped chromatin often with open spaces with moderate amounts of cytoplasm, which depending on the maturation stage ranges from deeply basophilic to pink. Mature lymphocytes have a thin rim of blue cytoplasm, a nucleus with dark chromatin without open spaces that takes up almost the entire cell.

Blood Cell Identification – Ungraded

BCP-10



Identification	Referees		Participants		Evaluation
	No.	%	No.	%	
Blast cell	53	29.1	1762	33.2	Educational
Malignant lymphoid cell (other than blast)	77	42.3	1820	34.3	Educational
Lymphocyte, reactive (includes plasmacytoid and immunoblastic forms)	29	15.9	1011	19.0	Educational
Immature or abnormal cell, would refer for identification	13	7.1	272	5.1	Educational
Plasma cell, morphologically mature/abnormal/containing inclusions (eg, Dutcher body, Russel body)	5	2.8	144	2.7	Educational
Monocyte, immature (promonocyte, monoblast)	2	1.1	58	1.1	Educational
Lymphocyte, large granular	1	0.6	15	0.3	Educational
Monocyte	1	0.6	67	1.3	Educational
Neutrophil, metamyelocyte	1	0.6	7	0.1	Educational
Lymphocyte	0	0.0	112	2.1	Educational

There was no consensus for the identification of the neoplastic cells. The targeted response was "blast", as correctly identified by 29.1 % of referees and 33.4% of participants. However, more referees and participants (42.3% of referees and 34.3% of participants) identified the cells as "malignant lymphoid cells", likely given the clinical history of T-cell lymphoproliferation. This is a morphologically challenging case that in clinical practice will require ancillary studies, such as flow cytometry immunophenotyping, to arrive at a correct cell identification and diagnosis.

Blasts are divided into myeloid (myeloblast) and lymphoid (lymphoblast) lineages.

BCP-10, cont'd.

The myeloblast is usually a fairly large cell, 15 to 20 µm in diameter, with a high N:C ratio, usually 7:1 to 5:1, and typically basophilic cytoplasm. Myeloblasts may occasionally be smaller, similar to the size of a mature myeloid cell. The cell and nucleus are usually round, although irregularly shaped or folded nuclei may be present. The myeloblast nucleus has a characteristically finely reticulated chromatin pattern with distinct nucleoli present. Leukemic myeloblasts may also exhibit a few delicate granules and/or Auer rods, which are absent in the cells on the image.

Lymphoblasts are round to oval cells that range in size from 10 to 20 µm. The N:C ratio varies from 7:1 to 4:1. Morphologically, lymphoblasts are variable in appearance, at times within a single case. At one end of the spectrum are small lymphoblasts (previously called L1 subtype) with dense but not clumped chromatin, inconspicuous or absent nucleoli, and extremely scanty cytoplasm. At the other end are large lymphoblasts (previously called L2 subtype) with finely dispersed chromatin, variable numbers of distinct nucleoli, and moderate amounts of cytoplasm, closely resembling myeloblasts. The nuclear contours of lymphoblasts range from round to convoluted. The cytoplasm is typically slightly to moderately basophilic and is usually agranular. Auer rods are absent.

One arrowed cell is larger with an oval nucleus, fine chromatin, distinct nucleoli and more cytoplasm, with a paranuclear cleared space reminiscent of promyelocyte. However, unlike promyelocytes, this cell does not contain distinct azurophilic (primary) granules, nor overlapping Auer rods as seen in atypical promyelocytic blasts of acute promyelocytic leukemia.

Distinguishing one type of abnormal blast cell from another, especially in the absence of Auer rods, is not always possible using Wright-Giemsa stains alone. Additional testing such as cytochemical staining (eg, using myeloperoxidase or Sudan black for myeloblasts), or immunophenotyping by flow cytometry may be required to further define the lineage of a given blast population. For purposes of proficiency testing, one should identify individual cells exhibiting this immature type of morphology as blast cells.

Lymphoma cells can exhibit a variety of appearances depending on the lymphoma subtype, and definitive diagnosis can be difficult. These cells can exhibit a variety of sizes, shapes, and nuclear and cytoplasmic characteristics. Cell size ranges from 8 to 30 µm and the N:C ratio varies from 7:1 to 3:1. It is critical to obtain an accurate clinical history, since knowledge of a previous diagnosis of lymphoma greatly aids in the identification of these cells.

7.1% of referees and 5.0% of participants identified the cells as the "immature/abnormal cells", which is an acceptable answer.

15.9% of referees and 19.0% of participants incorrectly identified the cells as reactive lymphocytes. A variety of reactive lymphocyte forms have been described and they are often seen concurrently in the same blood film. The reactive lymphocytes that may resemble lymphoma cells or blasts are immunoblasts and immunoblastic-like reactive lymphocytes. These are large cells (15 to 20 µm) with round to oval nuclei. They have finely to moderately dispersed chromatin with abundant parachromatin and one or more prominent nucleoli. Their cytoplasm is moderately abundant and stains deeply basophilic. The N:C ratio is high (3:1 to 2:1). These reactive lymphocytes correspond to Downey type III cells. Despite some similarities, the arrowed cells lack morphologic variations and demonstrate irregular nuclei and scant to moderate amounts of basophilic cytoplasm with cytoplasmic vacuoles.

BCP-10, cont'd.

2.8% of referees and 2.7% of participants incorrectly identified the cells as plasma cells. Plasma cells range in size from 10 to 20 µm, and they are often oval shaped with relatively abundant cytoplasm and eccentrically located nuclei. The N:C ratio is 1:2. Their nuclei are usually round to ovoid with prominently coarse and clumped chromatin that is often arranged in a cartwheel-like or clock-face pattern. Nucleoli are absent. The cytoplasm stains gray-blue to deeply basophilic. A prominent hof or perinuclear zone of pale or lighter staining cytoplasm is typically seen adjacent to one side of the nucleus. This area corresponds to the Golgi zone, which is prominent in cells that produce large amounts of protein, such as immunoglobulin in the case of plasma cells. Cytoplasmic granules are absent, and scattered vacuoles of varying size may be seen. Despite the present of cytoplasmic vacuoles, none other features of plasma cells are present in the arrowed cells.

2.1% of participants incorrectly identified the cells as lymphocytes. Lymphocytes are small, round to ovoid cells ranging in size from 7 to 15 µm with an N:C ratio ranging from 5:1 to 2:1. Most lymphocytes have round to oval nuclei that may be slightly indented or notched. The chromatin is diffusely dense or coarse and clumped. Nucleoli are not visible, although some cells may exhibit a small, pale chromocenter that may be mistaken for a nucleolus. Most lymphocytes have a scant amount of pale blue to moderately basophilic, agranular cytoplasm. None of these features are present in the arrowed cells.

Clinical Presentation:

This peripheral blood smear is from a 76-year-old Japanese woman diagnosed with bladder cancer and with a history of T-cell lymphoproliferation. 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%.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

CASE DISCUSSION: Therapy-related acute myeloid leukemia

Therapy-related acute myeloid leukemia (AML), as the name implies, is AML that occurs in patients previously treated with chemo/radiation therapy. In the World Health Organization (WHO) Classification, therapy-related AML is included in a broader therapy-related myeloid neoplasm (t-MN) category that encompasses cases morphologically diagnosed as AML, myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), or overlap MDS/MPN. This WHO category accounts for 10 - 20% of all cases of AML, MDS, and MDS/MPN.

The median age at diagnosis is 61 years; however, patients of any age can be affected. More than 80% of t-MNs are associated with treatment for a prior malignancy; it has been estimated that 70% of prior malignancies are solid tumors and 30% are hematologic malignancies. A small percent (5 - 20%) occurs in patients treated with cytotoxic therapy for a non-neoplastic disorder or who underwent autologous hematopoietic cell transplantation (HCT) for a non-myeloid neoplasm. Therapy-related MNs, including therapy-related AML, are associated with a wide variety of therapeutic agents with different mechanisms of action and varying interval (latency) following treatment; in addition, the clinical presentation varies according to the type of therapy.

Cytotoxic agents implicated in therapy-related AML include the following:

- Alkylating agents: Melphalan, cyclophosphamide, nitrogen mustard, chlorambucil, busulfan, carboplatin, cisplatin, dacarbazine, procarbazine, carmustine, mitomycin, thiotepa, lomustine
- Topoisomerase II inhibitors: Etoposide, teniposide, doxorubicin, daunorubicin, mitoxantrone, amsacrine, actinomycin
- Radiation therapy (alone or as combined modality treatment): Typically associated with large fields that encompass active bone marrow
- Other agents (usually in combination with agents listed above): antimetabolites (eg, thiopurines, mycophenolate mofetil, methotrexate, fludarabine) or antitubulin agents (eg, vincristine, vinblastine, vindesine, paclitaxel, docetaxel); the role of other agents such as hydroxyurea, L-asparaginase, and radioisotopes is unclear
- Growth factors, such as filgrastim, may play a role in the emergence of a t-MN clone

Therapy-related AML may develop at any time following the chemo/radiation treatment; however, cases with shorter latency (1 - 3 years post-treatment) are usually associated with topoisomerase II inhibitors therapy, while cases with longer latency (5 - 7 years post-treatment) are more commonly associated with alkylating agents. The risk of AML increases with age in the latter group.

The clinical presentation and morphologic and genetic findings of therapy-related AML closely resemble those of *de novo* AML. The diagnosis of therapy-related AML should be suspected in all patients with prior exposure to chemo/radiation therapy presenting with leukocytosis or pancytopenia. Therapy-related AML associated with alkylating agents and longer latency typically present with peripheral blood cytopenia(s), macrocytosis with

poikilocytosis of red blood cells, and granulocytic dysplasia. The latter includes hypogranular neutrophils and neutrophils with abnormal nuclear lobation (ie, pseudo-Pelger-Huët cells). Multilineage dysplasia is also present in the bone marrow, and fibrosis is commonly seen. In contrast, AML associated with topoisomerase II inhibitors and shorter latency do not demonstrate dysplastic hematopoiesis and usually exhibit morphologic features of AML with maturation or AML with monocytic differentiation (acute myelomonocytic leukemia and acute monocytic leukemia).

Similar to *de novo* AML, the diagnosis of therapy-related AML requires the presence of ≥ 20% blasts with myeloid and/or monocytic differentiation in bone marrow or peripheral blood, or, in cases with < 20% blasts, the presence of one of the following balanced translocations: t(8;21); *RUNX1-RUNX1T1*, inv(16) or t(16;16); *CBF-MYH11*, and t(15;17); *PML-RARA*. Greater than 90% of therapy-related AML cases demonstrate clonal chromosomal abnormalities, which vary depending on the prior treatment and latency duration. AML associated with topoisomerase II inhibitors and shorter latency often exhibit a balanced chromosomal translocation that involves 11q23 *(KMT2A)* or 21q22 *(RUNX1)*. AML associated with alkylating agents and longer latency often shows deletion of chromosomes 5 or 7 and complex karyotype. Approximately 50% of cases have *TP53* mutations, a much higher incidence than is seen in *de novo* AML cases. Other commonly mutated genes include *TET2*, *PNTP11*, *IDH1/2*, and *FLT3*.

The prognosis of therapy-related AML is generally poor, with a reported overall survival of less than 10%. Therapy-related AML with monosomy 5 or 7 has a particularly poor prognosis of less than one year. In contrast, some studies suggest that therapy-related AML with t(15;17) or inv(16) have a much better prognosis, which is similar to their *de novo* counterparts. The poor prognosis is due to dose-limiting toxicities of the prior treatments as well as development of drug resistance in the neoplastic cells. Therapeutic options are limited for this group of patients owing to the high rate of treatment-related mortality, high rate of treatment failure, and early disease recurrence.

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