Blood Cell Identification – Graded

Case History

This peripheral blood smear is from a 42-year-old woman with mild anemia and a clinical history of immunosuppression. Laboratory data includes: WBC = 6.5 x 10^9/L; RBC = 3.74 x 10^{12}/L; HGB = 11.2 g/dL; HCT = 33.0%; MCV = 84 fL; and PLT = 209 x 10^9/L. Identify the arrowed object(s) on each image.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

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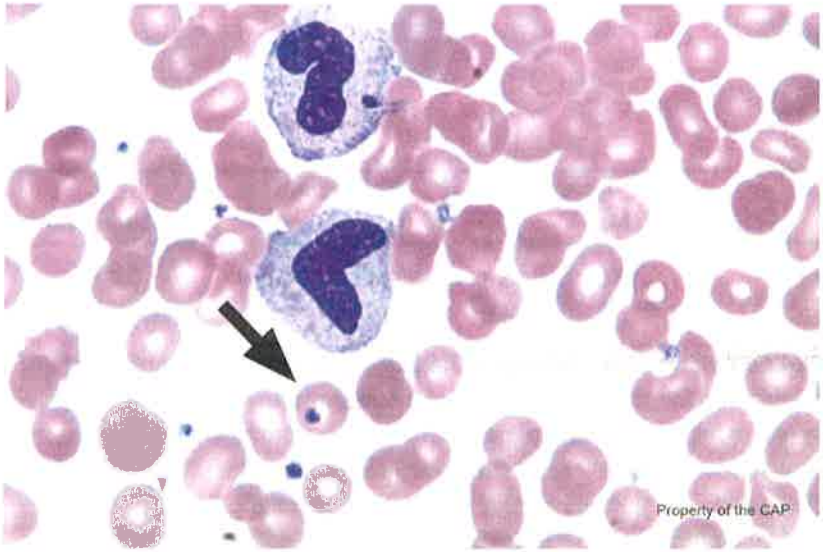
BCP-21

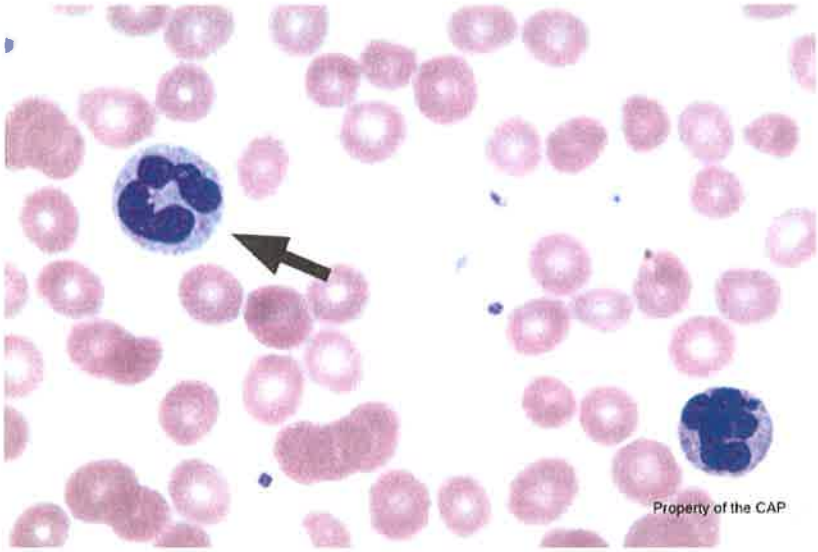


Identification	Referees No.	Referees %	Participants No.	Participants %	Evaluation
Erythrocyte with overlying platelet	108	99.1	5267	98.2	Good
Platelet Satellitism	1	0.9	1	0.1	Unacceptable

The arrowed cell is an erythrocyte with an overlying platelet, as correctly identified by 99.1% of referees and 98.2% of participants. When a blood smear is prepared, platelets may occasionally adhere to or overlap with red cells. Platelets overlying red cells should be distinguished from possible red cell inclusions or intracellular parasites. An overlying platelet will have a similar size, appearance and granularity to other platelets in the blood film. The overlying platelet may also have a thin clear zone or halo, as seen in this cell, which is not usually seen in association with red cell inclusions or parasites. You should also notice the band neutrophil near the top of the photo that contains a small, densely staining, round to oval inclusion in the cytoplasm. This inclusion resembles a Howell-Jolly body that is seen in red cells after splenectomy, and is termed a Howell-Jolly-like inclusion (HJLI). This is contrast to the band neutrophil located near the center of the photo that does not contain a cytoplasmic inclusion.

Blood Cell Identification – Graded

BCP-22

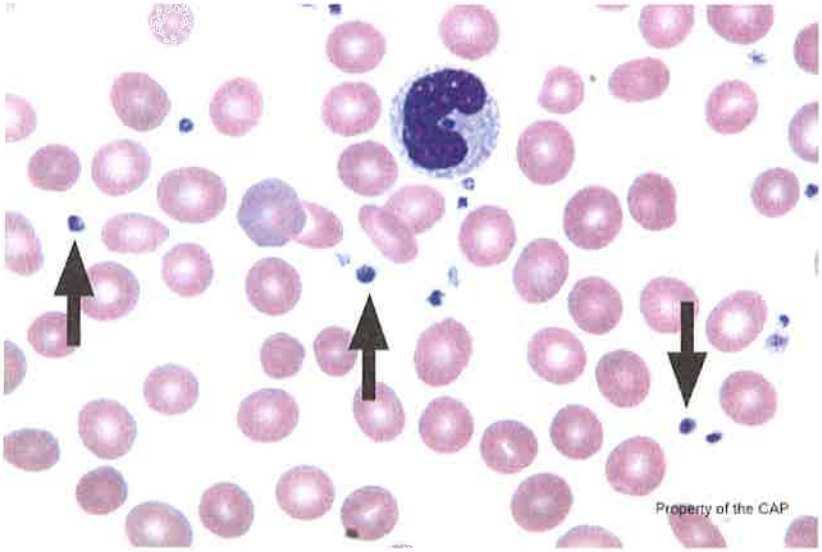


Identification	Referees No.	Referees %	Participants No.	Participants %	Evaluation
Neutrophil, segmented or band	104	95.4	5084	94.7	Good
Neutrophil, toxic	5	4.6	245	4.6	Unacceptable

The arrowed cell is a segmented neutrophil, as correctly identified by 95.4% of referees and 94.7% of participants. Segmented neutrophils are the most mature form of the myeloid lineage and are usually the most predominant white cells in adult blood. Sizes of neutrophils range from10 to 15 µm, with moderate amounts of pale pink cytoplasm containing specific (lilac-colored) granules. The N:C ratio is 1:3, with condensed nuclear chromatin. The nucleus usually has two to five segments (or "lobes") connected by a thin filament that contains no internal chromatin, giving it the appearance of a solid, thread-like dark line.

Blood Cell Identification – Graded

BCP-23

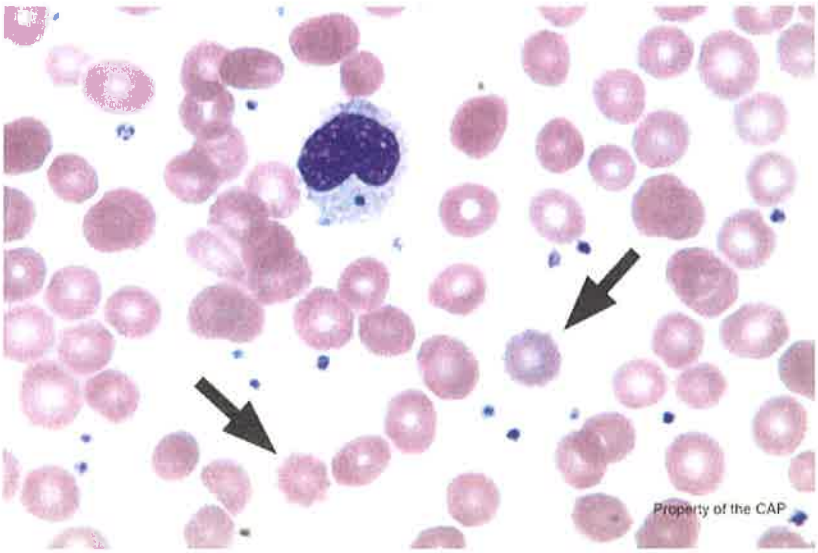


Identification	Referees No.	Referees %	Participants No.	Participants %	Evaluation
Platelet, normal	108	99.1	5279	98.3	Good
Platelet, giant	1	0.9	72	1.3	Unacceptable

The arrowed objects are platelets, as correctly identified by 99.1% of referees and 98.3% of participants. Platelets are circulating megakaryocyte fragments that function in blood clot formation and hemostasis. They are a normal constituent of the peripheral blood, occurring at a level of ~150,000-400,000/µL. They are normally small, ranging from ~1.5-3 µm in diameter and lack a nucleus. Also present in this image is a band neutrophil that contains a single, round, densely staining centrally placed cytoplasmic inclusion. This inclusion resembles a red cell Howell-Jolly body or Howell-Jolly-like inclusion (HJLI). This is believed to be a nuclear fragment and is seen in patients with immunosuppression.

Blood Cell Identification – Graded

BCP-24

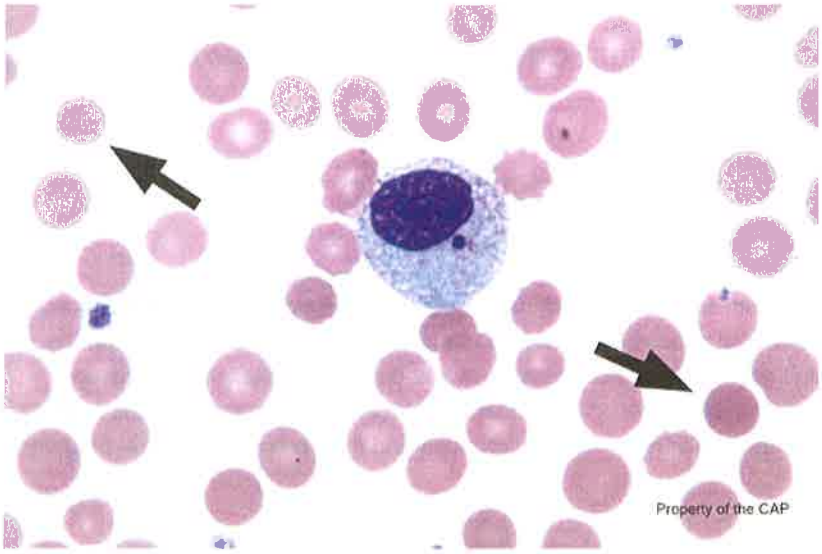


Identification	Referees No.	Referees %	Participants No.	Participants %	Evaluation
Echinocytes (burr cell, crenated cell)	107	98.2	5277	98.4	Good
Acanthocyte (spur cell)	2	1.8	77	1.4	Unacceptable

The arrowed cells are echinocytes or burr cells, as correctly identified by 98.2% of referees and 98.4% of participants. Echinocytes are red cells with 10-30 uniformly distributed, short, blunt projections that impart a serrated or spiky appearance to the red cell. Echinocytes are the same size or slightly smaller than a normal red cell and will have retention of central pallor. Echinocytes are often an artifact of smear preparation, but may also be increased in patients with uremia, certain red cell enzyme deficiencies and post-splenectomy. Note the metamyelocyte also present in photo, that contains a single, round, densely staining cytoplasmic inclusion (Howell-Jolly-like inclusion) resembling a red cell Howell-Jolly body.

Blood Cell Identification – Graded

BCP-25



Identification	Referees No.	Referees %	Participants No.	Participants %	Evaluation
Spherocyte	105	96.3	5212	97.2	Good
Microcyte (with increased central pallor)	4	3.7	58	1.1	Unacceptable

The arrowed cells are spherocytes, as correctly identified by 96.3% of referees and 97.2% of participants. Spherocytes are densely staining, spherically shaped red cells that lack central pallor and appear denser than normal red cells. Spherocytes have a decreased diameter compared to normal red cells. Spherocytes may be found in patients with the red cell membrane disorder, hereditary spherocytosis, or in patients with immune hemolytic anemia. Increased spherocytes may also be seen as an artifact in very thin areas of a blood film. Also seen in this photo is a myelocyte that contains a single, round, densely staining cytoplasmic inclusion (Howell-Jolly-like inclusion), similar to those seen in other myeloid cells associated with this patient.

Case Presentation:

This peripheral blood smear is from a 42-year-old woman with mild anemia and a clinical history of immunosuppression. Laboratory data includes: WBC = 6.5 × 10^9/L; RBC = 3.74 × 10^{12}/L; HGB = 11.2 g/dL; HCT = 33.0 %; MCV = 84 fL; and PLT= 209 × 10^9/L. Identify the arrowed object(s) on each image.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

Case discussion: Howell-Jolly like inclusions in immunosuppression

Cytoplasmic inclusions may be seen in both erythrocytes and leukocytes. These inclusions can be associated with a broad range of clinical conditions, and accurate characterization can guide both clinical care and/or further testing. In red cells, a number of inclusions may be seen. Pappenheimer bodies, for example, represent precipitated iron and appear as multiple, small, irregular, dark blue to violet granules in erythrocytes (**Figure 1**). Pappenheimer bodies can be seen in patients with hemoglobinopathies and thalassemia, after splenectomy, or associated with lead poisoning.

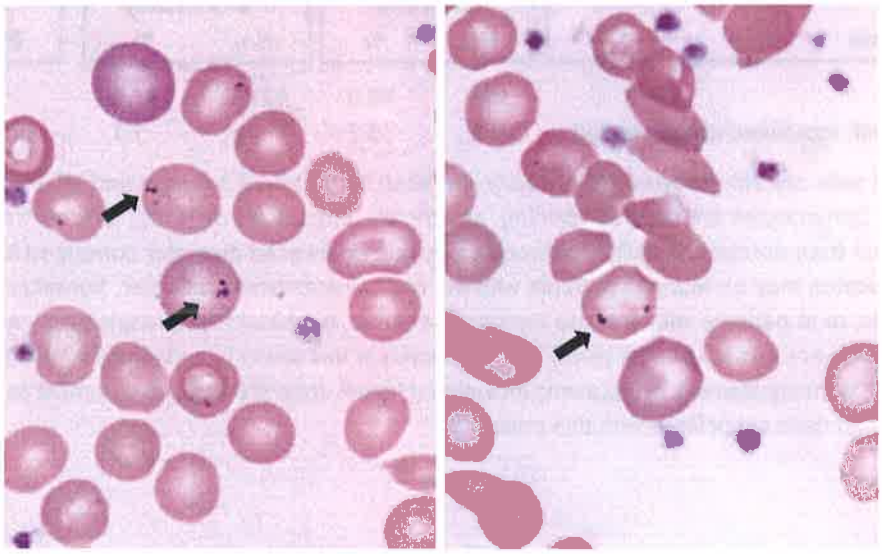


Figure 1: The arrows indicate red cells containing pappenheimer bodies, which are multiple, small, irregular, dark blue to violet granules representing precipitated iron. Wright-Giemsa stain, 1000X.

Classic Howell-Jolly (HJ) bodies, representing nuclear remnants in mature erythrocytes, appear as dense, round basophilic inclusions (**Figure 2**). As the spleen is normally responsible for removing such inclusions, HJ bodies can be seen in circulation following splenectomy, or in the context of hyposplenism (reduced splenic function), functional asplenia (absence of normal spleen function due to sickle cell disease, for example), or in some inherited or acquired defects in erythroid maturation (such as myelodysplastic syndrome). While some variation is possible, HJ bodies have reproducibly smooth borders and are localized at the red cell periphery. Most often they appear singly, and the rarely seen multiple HJ bodies in one red cell are associated with abnormal erythropoiesis. The size, shape, and distribution of the inclusions can help differentiate HJ from Pappenheimer bodies. Heinz bodies, representing denatured hemoglobin can also appear as single inclusions with similar distribution, but are not readily identified by routine Wright or Wright-Giemsa staining.

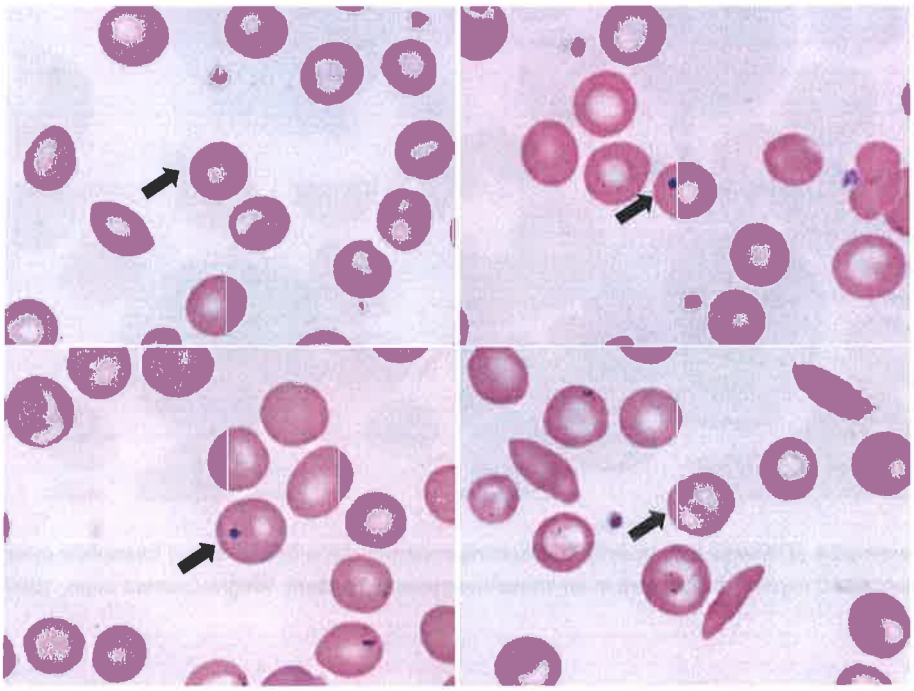


Figure 2: The arrowed red cells contain Howell-Jolly bodies or nuclear remnants in mature erythrocytes that appear as dense, round basophilic inclusions. Wright-Giemsa stain, 1000X.

Similar appearing dense, round basophilic inclusions, so called, "Howell-Jolly body-like" inclusions (HJBLI), can be uncommonly identified in neutrophils, as illustrated by the presented case. It is hypothesized that HJBLI arise due to nuclear fragmentation (**Figure 3**). Originally described in patients treated with immunosuppressive drugs or chemotherapy, HJBLI have been reported in other immunocompromised states including HIV infection and after solid organ transplantation.

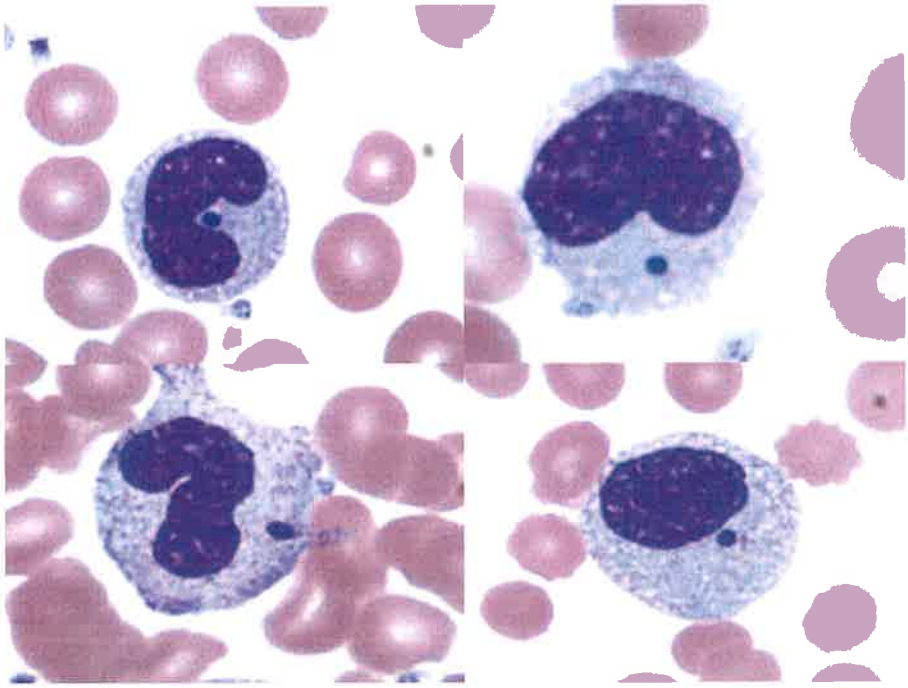


Figure 3: Several examples of Howell-Jolly body-like inclusions appearing as a dense, round basophilic cytopasmic inclusion in neutrophils and myeloid precursors in an immunosuppressed patient. Wright-Giemsa stain, 1000X.

HJBLI should be differentiated from other neutrophil inclusions including Döhle bodies,phagocytosed fungus, hemozoin pigment associated with malaria, and morulae of human granulocytic anaplasma. Inherited disorders including Chediak-Higashi syndrome and May-Hegglin anomaly are also associated with neutrophil inclusions. Döhle bodies are single or multiple, oval, blue inclusions found at the periphery of the neutrophil cytoplasm (**Figure 4**).

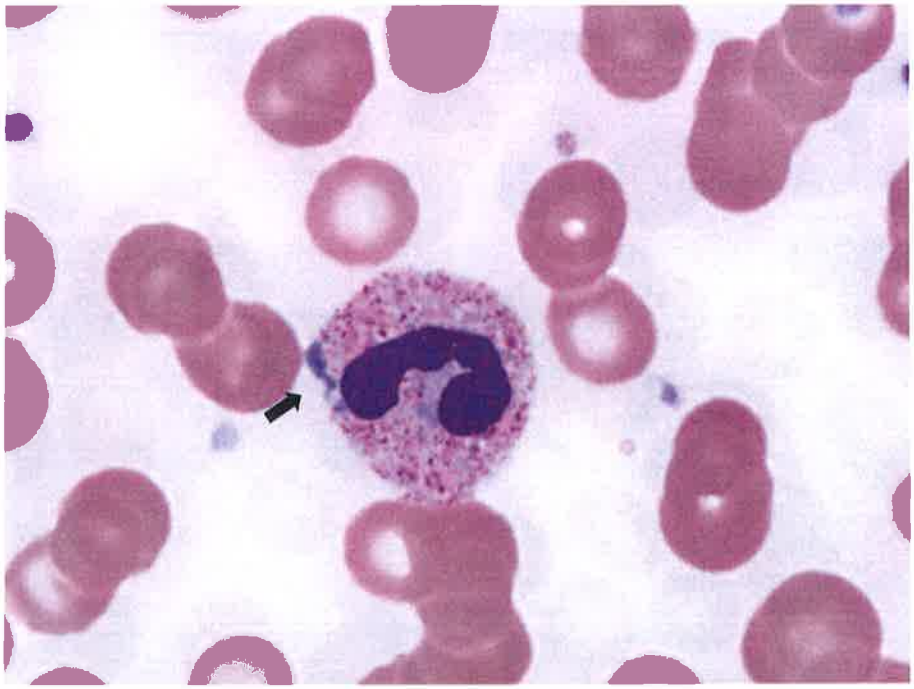


Figure 4: The arrowed cell is a band neutrophil containing a Döhle body. Döhle bodies are single or multiple, oval, blue inclusions found at the periphery of the neutrophil cytoplasm and are remnants of endoplasmic reticulum and ribosomes. They are usually seen in the context of acute infections and associated with other toxic changes, such as vacuolization and toxic granulation of the neutrophils. Wright-Giemsa stain, 1000X.

They represent remnants of the endoplasmic reticulum and ribosomes. Döhle bodies are seen in neutrophils the context of acute systemic infection in association with toxic granulation. Döhle-body-like structures are also seen in association with the May-Hegglin anomaly. In May-Hegglin anomaly, which is inherited as an autosomal dominant disorder, the inclusions often resemble enlarged Döhle bodies and will be associated with thrombocytopenia with enlarged platelets (macrothrombocytopenia). In contrast to the Döhle bodies seen in the context of infection, the inclusions in May-Hegglin anomaly are typically adjacent to the nucleus (**Figure 5**).

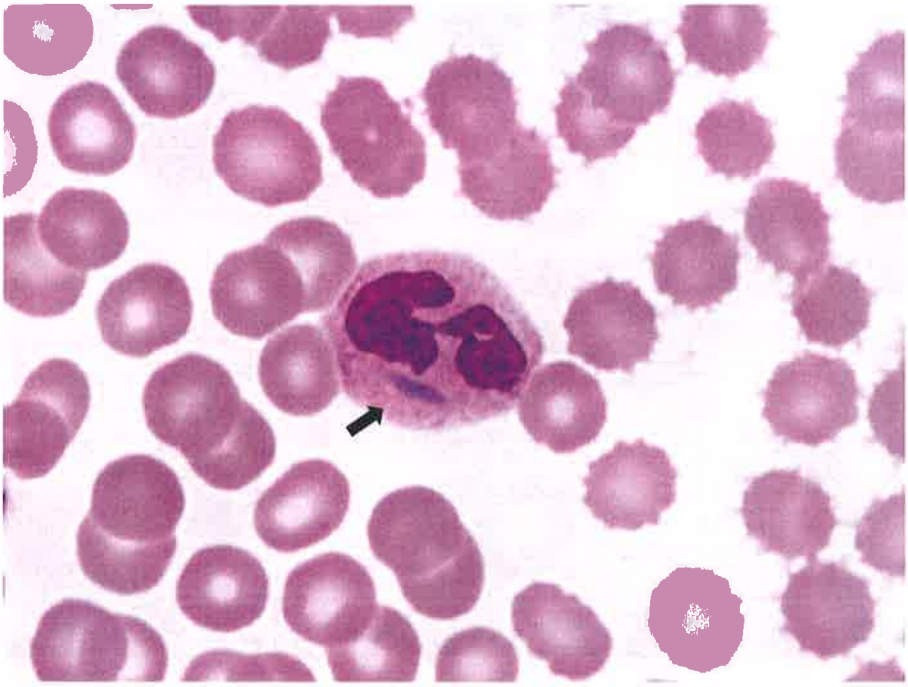


Figure 5: Döhle body-like inclusion in a patient with May-Hegglin anomaly. The arrowed neutrophil contains a prominent oval blue inclusion that is located near the nucleus (rather than the typical peripheral localization of Döhle bodies associated with infection) and is not associated with significant toxic changes. Wright-Giemsa stain, 1000X.

In Chediak-Higashi syndrome, a rare autosomal recessive disorder, the inclusions are large grey- green to pink-purple lysosomal granules (so called "giant granules") that are seen in neutrophils, monocytes and some lymphocytes (**Figure 6**). Other peripheral blood and clinical features, such as albinism, are often useful in identification of these cases.

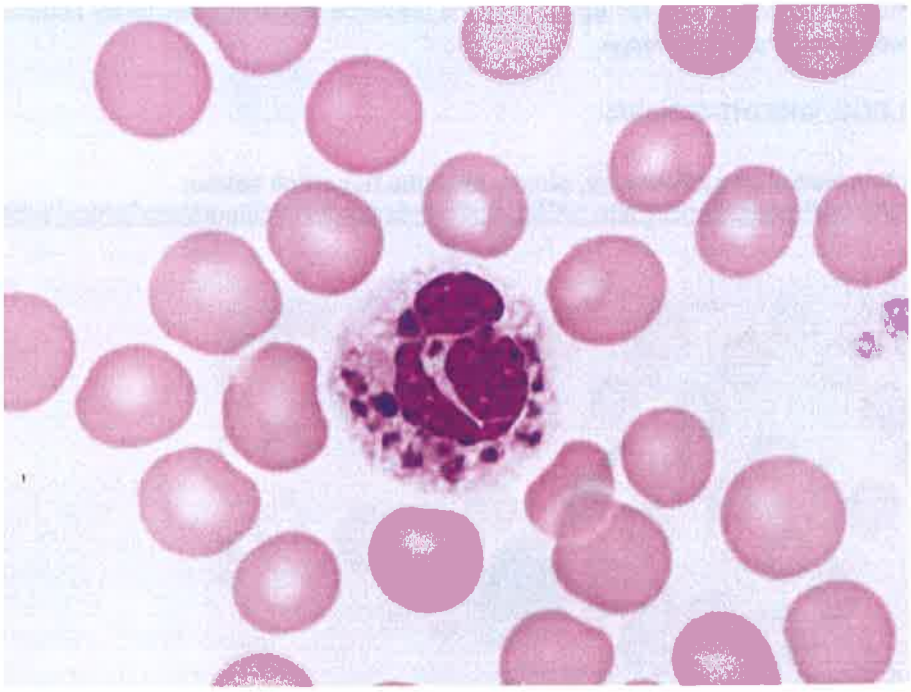


Figure 6: Neutrophil in a patient with Chediak-Higashi syndrome containing large pink-purple inclusions that appear as "giant granules", representing abnormal lysozomal structures. Wright-Giemsa stain, 1000X.

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Sherrie L. Perkins MD, PhD
Hematology and Clinical Microscopy Resource Committee

References:

1. Glassy EF, Agosti SJ. College of American Pathologists. Atlas Subcommittee, College of American Pathologists. *Color Atlas of Hematology: An Illustrated Field Guide Based On Proficiency Testing.* Northfield, Ill.: College of American Patholgists; 1998.
2. Ford J. Red blood cell morphology. *International Journal of Laboratory Hematology.* Jun 2013;35(3):351-357.
3. Abdel-Monem H, Prakasam A, Thiagarajan P. Howell-jolly body-like inclusions in neutrophils of a transplant recipient in association with ganciclovir therapy. *Archives of Pathology & Laboratory Medicine.* Jun 2010;134(6):809-810.
4. Kahwash E, Gewirtz AS. Howell-Jolly body-like inclusions in neutrophils. *Archives of Pathology & Laboratory Medicine.* Oct 2003;127(10):1389-1390.

Blood Cell Identification – Ungraded

Case History

This peripheral blood smear is from an 82-year-old woman with an eight-month history of increasing fatigue and pallor. Laboratory data includes: WBC = 2.8 x 10^9/L; RBC = 2.98 x 10^{12}/L; HGB = 7.9 g/dL; HCT = 29.2%; MCV = 121 fL; MCHC = 34.1 g.dL; RDW = 26; and PLT = 120 x 10^9/L. Additional testing showed a vitamin B_{12} level of <150 pg/mL (normal range 240-930 pg/mL) and the presence of anti-intrinsic factor autoantibodies. Identify the arrowed object(s) on each image.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

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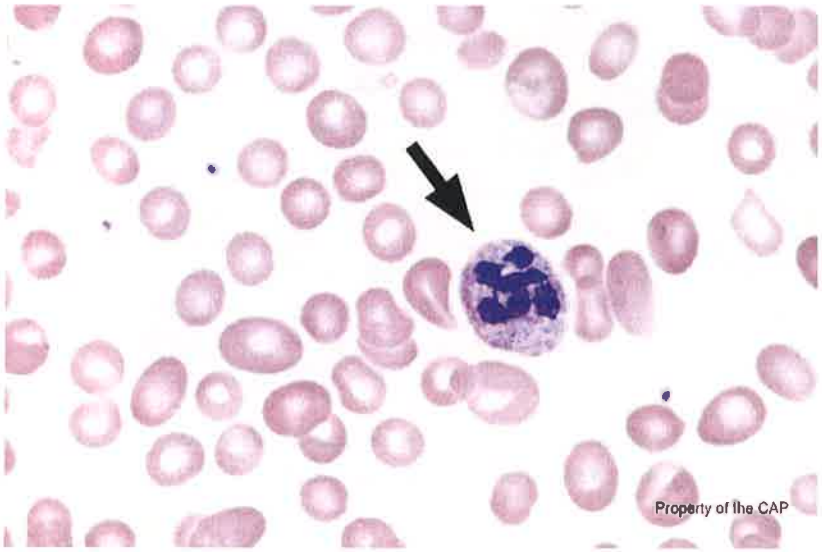
BCP-26

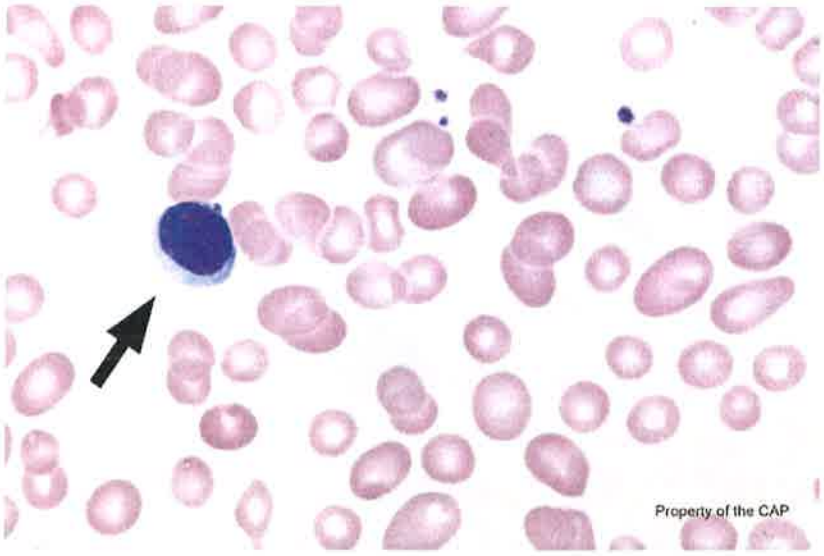


Identification	Referees No.	Referees %	Participants No.	Participants %	Evaluation
Neutrophil with hypersegmented nucleus	98	89.9	4730	89.1	Educational
Neutrophil, segmented or band	8	7.3	398	7.5	Educational
Neutrophil, toxic	3	2.8	168	3.2	Educational

The arrowed cell is a neutrophil with hypersegmented nucleus, as correctly identified by 89.9% of referees and 89.1% of participants. Although not the best response, neutrophil, segmented or band is an acceptable answer as identified by 7.3% of referees and 7.5% of participants. Hypersegmented neutrophils are a result of megaloblastic myelopoiesis and are characterized by increased size compared to normal neutrophils (reflecting the smaller number of cell divisions of these cells in the bone marrow) and increased numbers of nuclear lobes, generally at least six or more. The increase in nuclear lobes reflects the impaired DNA synthesis that is typical of megaloblastic anemias. Outside of megaloblastic anemia, hypersegmented neutrophils are rare, although they may be uncommonly encountered as a congenital anomaly or occasionally in sepsis, renal disease, myeloproliferative neoplasms, myelodysplasia, and alcoholism. Hypersegmented neutrophils often appear earlier than macrocytosis and anemia as granulocytic changes often precede megaloblastic erythropoiesis.

Blood Cell Identification – Ungraded

BCP-27

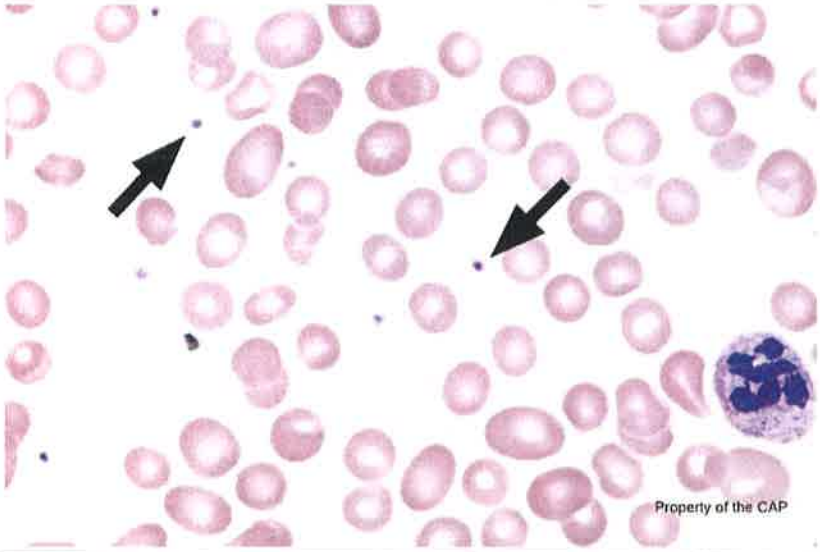


Identification	Referees No.	Referees %	Participants No.	Participants %	Evaluation
Lymphocyte	108	99.1	5203	98.0	Educational
Lymphocyte, large granular	1	0.9	54	1.0	Educational

The arrowed cell is a lymphocyte, as correctly identified by 99.1% of referees and 98.0% of participants. Mature lymphocytes are normally encountered in the peripheral blood and are small to medium sized with high nuclear: cytoplasmic ratio, variable amounts of weakly basophilic cytoplasm, and round nuclei with variably clumped nuclear chromatin. Nucleoli are absent. Some mature lymphocytes are slightly larger, with more abundant cytoplasm and variable amounts of azurophilic granules and usually represent circulating natural killer cells.

Blood Cell Identification – Ungraded

BCP-28



Identification	Referees No.	Referees %	Participants No.	Participants %	Evaluation
Platelet, normal	106	97.3	5188	97.7	Educational
Platelet, hypogranular	3	2.7	83	1.6	Educational

The arrowed objects are platelets, as correctly identified by 97.3% of referees and 97.7% of participants. Platelets are circulating megakaryocyte fragments. They are a normal constituent of the peripheral blood, occurring at a level of ~150,000-400,000/µL. They are normally small, ranging from ~1.5-3 µm in diameter. In good Wright-Giemsa preparations, the zonal morphology of platelets is evident; they have a central granular region termed a granulomere with a peripheral agranular region called a hyalomere.