Clinical History for VPBS-01 – VPBS-06

This peripheral blood smear is from a 58-year-old woman with a history of autoimmune hemolytic anemia and lupus. Laboratory data include: WBC = 7.0 x 10E9/L; RBC = 2.83 x 10E12/L; HGB = 8.6 g/dL; HCT = 27.4%; MCV = 97 fL; and PLT = 322 x 10E9/L. Identify the arrowed object(s) on each whole slide image.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

Please click on the hyperlink below to view the DigitalScope images for this case.
http://www.digitalscope.org/LinkHandler.axd?LinkId=42a395e0-9ddb-4cac-bd90-6deda0f397b2

To access the online Hematology Glossary, please click the hyperlink below:
http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution%20Folders/WebContent/pdf/hematology-glossary.pdf

Summary of Participant Survey Results

The following is a statistical summary of all results submitted by participating labs. These are provided to allow participants to see their responses in the context of their peers. These results may identify findings or topics for further education or review. Survey results are not intended to represent the correct or desired responses for proficiency testing purposes and the SD and CV should not be interpreted as acceptable reporting limits. Participants are encouraged to review discrepant results with their medical director.

WBC Differential – %

		No. Labs	Mean	S.D.	C.V.*	Median	Low Value	High Value
VPBS-01	Neutrophils (segs or bands)	1028	81.1	3.8	4.7	81	70	92
	Lymphocytes	1033	9.0	3.4	38.0	9	0	19
	Lymphocytes, reactive	469	0.3	0.7	*	0	0	3
	Monocytes	1019	8.3	3.4	40.7	8	0	18
	Eosinophils	662	0.8	0.8	*	1	0	3
	Basophils	438	0.0	0.0	0.0	0	0	0
	Metamyelocytes	504	0.4	0.6	*	0	0	2
	Myelocytes	493	0.4	0.6	*	0	0	2
	Promyelocytes	421	0.0	0.0	0.0	0	0	0
	Blasts	419	0.0	0.0	0.0	0	0	0
	nRBC/100 WBC	1029	14.5	6.8	46.5	14	0	34

WBC Differential – 10^9/L **Please see discussion on "Calculating Absolute Counts" that appears in this PSR.

		No. Labs	Mean	S.D.	C.V.*	Median	Low Value	High Value
VPBS-01	Neutrophils (segs or bands)	918	5.66	0.31	5.5	5.7	4.5	6.8
	Lymphocytes	914	0.63	0.24	38.2	0.6	0.0	1.4
	Lymphocytes, reactive	422	0.02	0.05	*	0.0	0.0	0.2
	Monocytes	905	0.58	0.24	42.1	0.6	0.0	1.3
	Eosinophils	594	0.06	0.05	90.8	0.1	0.0	0.2
	Basophils	394	0.00	0.00	0.0	0.0	0.0	0.0
	Metamyelocytes	446	0.03	0.04	*	0.0	0.0	0.1
	Myelocytes	442	0.03	0.04	*	0.0	0.0	0.1
	Promyelocytes	383	0.00	0.00	0.0	0.0	0.0	0.0
	Blasts	380	0.00	0.00	0.0	0.0	0.0	0.0

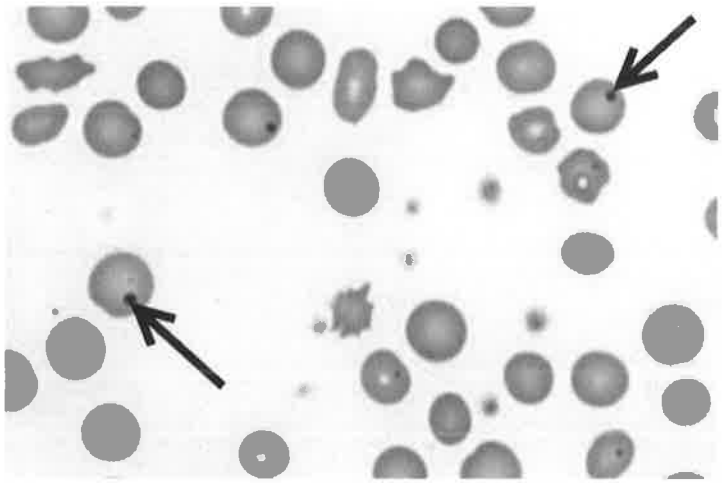
*When low results are reported on an analyte, a high coefficient of variance (CV) may result. When the mean value is very low, the CV may be exaggerated.

Committee Comments on the CBC and Blood Film

The CBC data are indicative of a moderate to marked normochromic, normocytic anemia in the context of normal WBC and platelet counts as well as generally unremarkable leukocyte and platelet morphology. Anisopoikilocytosis is significantly increased by fragmented red blood cells (eg. schistocytes), spherocytes, acanthocytes, and echinocytes. Polychromasia is present. Many red blood cells contain Howell-Jolly bodies.

Cell Identification

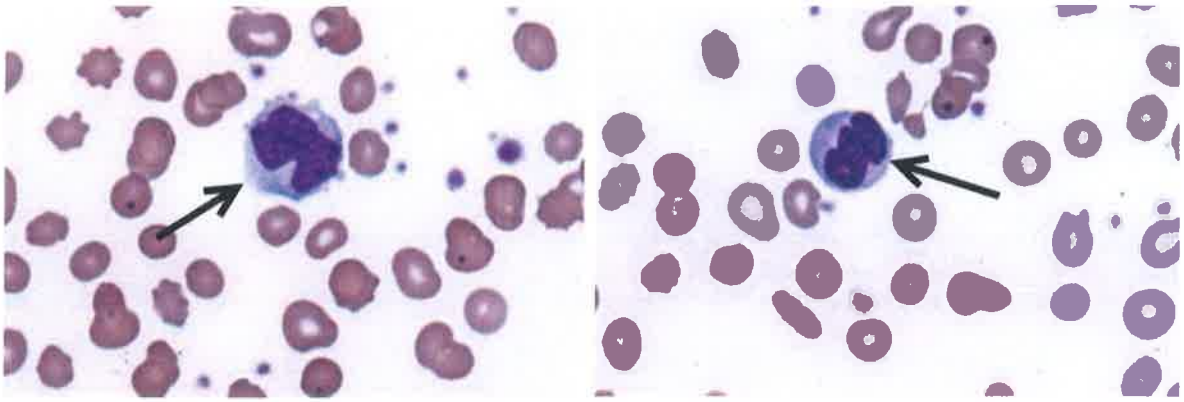
VPBS-02



Identification	Participants No.	Participants %	Evaluation
Howell-Jolly body	1037	99.5	Educational
Basophilic stippling	1	0.1	Educational
Erythrocyte with overlying platelet	1	0.1	Educational
Immature abnormal cell, would refer	1	0.1	Educational
Nucleated red blood cell, normal/abnormal morphology	1	0.1	Educational
Plasmodium spp.	1	0.1	Educational

The arrowed cells are red blood cells containing Howell-Jolly bodies, as correctly identified by 99.5% of participants. Howell-Jolly bodies are DNA remnants and appear as small (1 µm in diameter), round, peripherally located, dark purple homogeneous masses. They are DNA remnants that are left behind when the nucleus is extruded from the red cell as erythroid precursors undergo nuclear karyorrhexis or when an aberrant chromosome becomes separated from the mitotic spindle. Typically, Howell-Jolly bodies are not seen in the peripheral blood of normal individuals given the efficiency of the spleen in removing these remnant particles. However, the presence of Howell-Jolly bodies becomes prominent in patients with hypofunctional spleens or in those who have undergone a splenectomy.

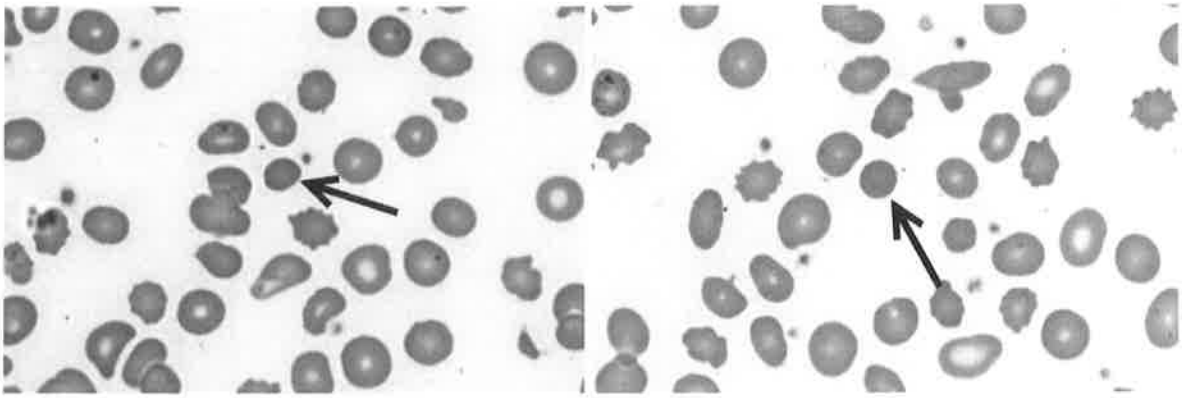
VPBS-03



Identification	Participants No.	%	Evaluation
Monocyte	981	94.2	Educational
Neutrophil, segmented or band	21	2.0	Educational
Monocyte, immature (promonocyte, monoblast)	14	1.3	Educational
Neutrophil, metamyelocyte	10	1.0	Educational
Lymphocyte, reactive	9	0.9	Educational
Lymphocyte	3	0.3	Educational
Neutrophil with dysplastic nucleu and/or hypogranular cytoplasm	2	0.3	Educational
Immature/abnormal cell, would refer	1	0.1	Educational
Malignant lymphoid cell	1	0.1	Educational

The arrowed cells are monocytes, as correctly identified by 94.2% of participants. Monocytes are slightly larger than neutrophils, with a nuclear to cytoplasmic ratio of 4:1 to 2:1. The nuclear contours can vary from reniform to indented to folded. The chromatin is condensed, but is more open (ie. less condensed) compared to the chromatin of neutrophils or lymphocytes. Monocytes typically have smooth cytoplasmic margins, though some have pseudopod-like cytoplasmic extensions; this is a helpful feature in identifying monocytes, as seen in one of the arrowed cells in this case. Finally, the cytoplasm is abundant and gray to gray-blue and may contain fine azurophilic granules or vacuoles.

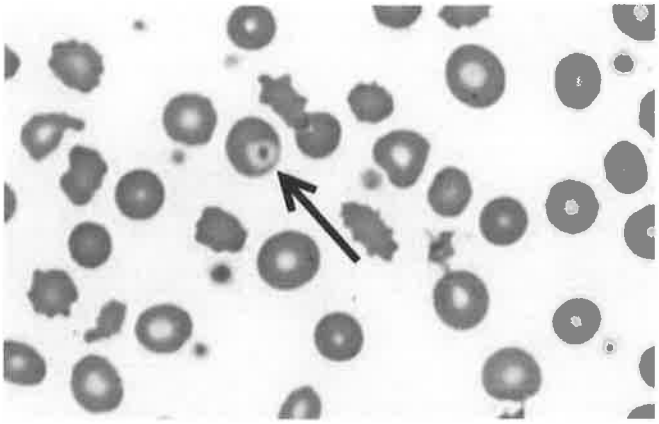
VPBS-04



Identification	Participants No.	%	Evaluation
Spherocyte	980	94.0	Educational
Microcyte (with increased central pallor)	31	3.0	Educational
Erythrocyte, normal	26	2.5	Educational
Polychromatophilic (non-nucleated) red blood cell	2	0.2	Educational
Immature/abnormal cell, would refer	1	0.1	Educational
Ovalocyte (elliptocyte)	1	0.1	Educational
Stomatocyte	1	0.1	Educational

The arrowed cells are spherocytes, as correctly identified by 94.0% of participants. Spherocytes are "rounded up", densely staining red blood cells that lack central pallor. The loss of the biconcave architecture of normal red blood cells imparts a spherical shape to these cells and the increased thickness results in their densely-staining appearance. The presence of spherocytes should alert one to the possibilities of hereditary spherocytosis, immune hemolytic anemia, severe burn, and microangiopathic hemolytic anemia. They can also sometimes be found in cases of oxidant injury in patients with glucose-6-phosphate dehydrogenase deficiency.

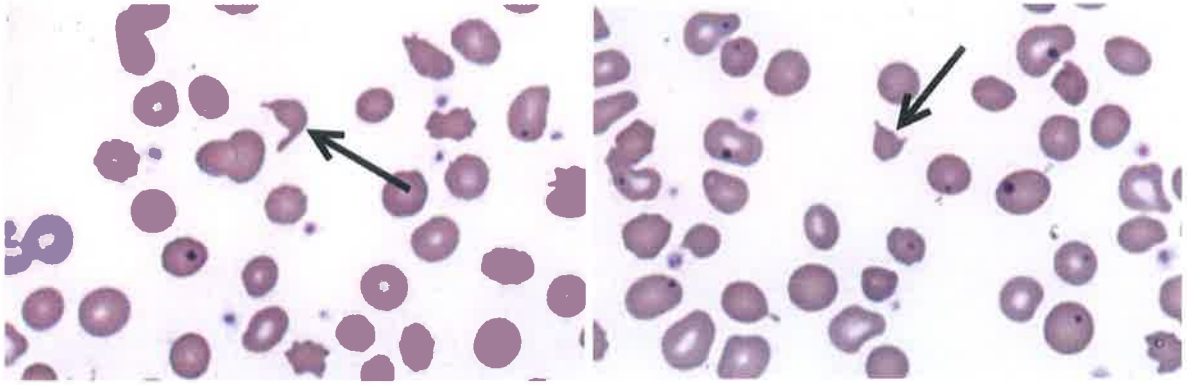
VPBS-05



Identification	Participants No.	%	Evaluation
Erythrocyte with overlying platelet	1019	97.8	Educational
Platelet, normal	9	0.9	Educational
Macrocyte oval/round	3	0.3	Educational
Blister cel/prekeratocyte	2	0.2	Educational
Target cell (codocyte)	2	0.2	Educational
Erythrocyte, normal	1	0.1	Educational
Fungi, extracellular	1	0.1	Educational
Hypochromasia	1	0.1	Educational
Mast cell	1	0.1	Educational
Microcyte (with increased central pallor)	1	0.1	Educational
Pappenheimer bodies	1	0.1	Educational
Platelet satellitism	1	0.1	Educational

The arrowed cell is an erythrocyte with an overlying platelet, as correctly identified by 97.8% of participants. Platelets overlying red blood cells are sometimes mistakenly classified as red blood cell inclusions or intraerythrocytic parasites. However, there are several clues to avoid such an error. Platelets overlying erythrocytes typically are surrounded by a thin clear zone or halo (as in the arrowed cell in this case). Another helpful feature is comparing the morphology of the platelet "pseudoinclusion" to other platelets in the same microscopic field. Recognizing that the size, staining quality, and granularity of the platelet overlying the red cell is similar (if not identical) to the other known platelets in the field can aid in the correct identification of this artifact.

VPBS-06



Identification	Participants No.	%	Evaluation
Fragmented red cell (schistocyte, helmet cell, keratocyte, triangular cell)	948	91.1	Educational
Acanthocyte (spur cell)	61	5.9	Educational
Bite cell	29	2.8	Educational
Blister cell/Prekeratocyte	2	0.2	Educational
Echinocyte (burr cell, crenated cell)	1	0.1	Educational

The arrowed cells are fragmented red blood cells, as correctly identified by 91.1% of participants. These red blood cells have undergone shearing and tearing, either by coming in contact with pathologically-formed fibrin strands in the microcirculation or by buffeting against unyielding structures in the macrocirculation (as occurs in severe cardiac valvular stenosis). This irregular erythrocyte fragmentation results in a spectrum of red blood cell poikilocyte morphology, with triangular shapes (triangulocytes) to others with horn-like projections (keratocytes) to cells simulating hats (helmet cells). The generic term "schistocyte" is sometimes used to refer to these fragmented red cells.

Clinical Presentation:
This peripheral blood smear is from a 58-year-old woman with a history of autoimmune hemolytic anemia and lupus. Laboratory data include: WBC = 7.0 x 10E9/L; RBC = 2.83 × 10E12/L; HGB = 8.6 g/dL; HCT = 27.4%; MCV = 97 fL; and PLT = 322 × 10E9/L.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

CASE DISCUSSION: Autoimmune hemolytic anemia and Systemic lupus erythematosus (SLE)

The CBC data in this case are indicative of a moderate to marked normochromic, normocytic anemia in the context of normal leukocyte and platelet counts. Anisopoikilocytosis is significantly increased by fragmented red blood cells (eg. schistocytes) and spherocytes, and occasional acanthocytes, elliptocytes, and echinocytes. Polychromasia is seen. Many red blood cells also contain Howell-Jolly bodies.

Systemic lupus erythematosus (SLE) is an autoimmune disease with multisystem involvement and a heterogeneous clinical presentation, which can range from mild to life threatening. Clinical manifestations include: fever, hepatomegaly, splenomegaly, cutaneous lesions (eg. malar rash, photosensitivity, cutaneous vasculitis, etc), arthritis, myositis, serositis, neuropsychiatric manifestations, nephritis, and hematologic abnormalities (including leukopenia, anemia, and/or thrombocytopenia).

Hemolytic anemias in SLE usually arise due to immune-mediated processes. In an isolated autoimmune hemolytic anemia (AIHA), typical peripheral blood smear abnormalities are confined to spherocytes admixed with normocytes and polychromatophilic cells. This case is unusual in the context of a patient with SLE because it additionally exhibits fragmented red cells and numerous Howell-Jolly bodies. The fragmented red cells suggest a concurrent microangiopathic hemolytic anemia, while the numerous Howell-Jolly bodies indicate a hypofunctional spleen or a post-splenectomy state. Howell-Jolly bodies may also be seen when there is rapid red cell turn-over, such as in hemolytic anemias, where splenic function is overwhelmed by the rapid rate of red cell production by the marrow. Additional laboratory investigation would likely yield increased levels of lactate dehydrogenase and indirect bilirubin, decreased haptoglobin, positive direct antiglobulin test, and increased reticulocyte counts.

Question 1. The following are different red blood cell findings typically seen in the context of a microangiopathic hemolytic anemia, EXCEPT:

A. Schistocytes
B. Rouleaux formation
C. Increased triangulocytes
D. Polychromatophilic cells

The different causes of hemolysis

The appropriate evaluation of anemia relies on assessment of the CBC data, careful examination of the peripheral blood smear for characteristic abnormalities, and a comprehensive review of pertinent clinical history, physical examination, and laboratory findings. Anemias can be classified based on red cell size (ie. microcytic, normocytic, and macrocytic). Then, anemias can be categorized broadly as either of two mechanisms: an underproduction/hypoproliferation problem (ie. insufficient or ineffective erythropoiesis) or as an issue of diminished red blood cell survival or blood loss leading to high output/RBC hyperproliferation. Thus, the reticulocyte count is an essential tool in discriminating between these two possibilities. An "underproduction/hypoproliferation" state would disclose a low reticulocyte count, while a "high output/hyperproliferation" state would reveal an elevated reticulocyte count.

If the reticulocyte count is high, recent hemorrhage (ie. blood loss) or hemolysis must be considered. Hemolytic anemia can be due to a broad range of etiologies, including intrinsic red cell defects, plasma factors, infections, and processes

that can lead to physical-mechanical disruption. Examples of intrinsic red cell defects include those seen in paroxysmal nocturnal hemoglobinuria (PNH), hereditary spherocytosis, hemoglobinopathies, and glucose-6-phosphate dehydrogenase (G6PD) deficiency. Plasma factors can include alloantibodies to the Rhesus or ABO blood group red cell antigens, as well as autoantibodies targeting red cells. Malarial infections and babesiosis can also lead to hemolytic anemia. Finally, hemolysis can be induced by physical-mechanical disruption of erythrocytes, such as in disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), severe valvular stenosis and thermal burns.

Question 2. Which of the following is NOT associated with hemolytic anemia?

A. Autoimmune conditions such as SLE
B. Red cell membrane defects
C. Decreased erythropoietin due to renal disease
D. Oxidant stress due to G6PD deficiency

The diagnosis and hematologic manifestations of systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease with multisystem involvement and heterogeneous clinical presentations. Two of the most widely used classification criteria were developed by the American College of Rheumatology (ACR 1997) and the Systemic Lupus International Collaborating Clinics (SLICC 2012). For example, to be classified as having SLE by the SLICC 2012 criteria, a patient must satisfy at least 4 of 17 criteria, including at least 1 of the 11 clinical criteria and one of the six immunologic criteria; OR that the patient has biopsy-proven nephritis compatible with SLE in the presence of antinuclear antibodies (ANA) or anti-double stranded DNA (dsDNA) antibodies. Although these classification criteria are useful, the diagnosis of SLE ultimately rests on the judgment of the clinician and his/her ability to distinguish abnormalities that occur as manifestations of SLE or as signs/symptoms of another disease.

Multiple causes of anemia have been reported in SLE. The most common of these is anemia of chronic disease. Presence of autoantibodies to erythropoietin leading to impaired erythropoietin response, as well as T-cell mediated inhibition of hematopoiesis are thought to contribute to the anemia in patients with SLE. Several other factors include: blood loss through menorrhagia and gastrointestinal loss, nutritional deficiencies (iron, folate, and B12), uremia, myelofibrosis, infection, drug-related/treatment-induced anemia. Microangiopathic hemolysis (such as in DIC and TTP) can also be observed.

Autoimmune hemolytic anemia (AIHA) is also a well-recognized condition seen in SLE, although it appears to be more prevalent in children than in adults. The anti-erythrocyte antibodies in SLE are mainly of the warm-type IgG, with antibody-induced damage of blood cells by complement dependent and independent mechanisms leading to AIHA.

Interestingly, SLE patients with AIHA show a frequent association with high levels of anticardiolipin antibodies or lupus anticoagulant, which in turn correlate with thrombotic episodes, thrombocytopenia, renal disease, and recurrent fetal loss – a sign/symptom complex called antiphospholipid syndrome (APLS) secondary to SLE. Thrombotic microangiopathic hemolytic anemia has been described in SLE patients with APLS. It is hypothesized that vasculitic changes seen within the spleen in APLS may lead to hyposplenism.

In this case of an SLE patient with a history of AIHA, she was initially admitted to the hospital with fatigue and acute renal failure. The CBC, peripheral blood smear findings, and laboratory studies supported a microangiopathic hemolytic anemia. The numerous Howell-Jolly bodies indicated an additional component of splenic hypofunction. Antiphospholipid antibodies were elevated. Her clinical course rapidly deteriorated with altered mental status due to cerebral infarcts, multiorgan failure, and death. Autopsy revealed widespread microvascular thrombi involving the kidney, pancreas, and brain, confirming the clinical diagnoses of thrombotic microangiopathic hemolytic anemia and catastrophic antiphospholipid syndrome.

Question 3. The following pathophysiologic causes of anemia are commonly described in patients with systemic lupus erythematosus, EXCEPT:

A. Anemia of chronic disease
B. Microangiopathic hemolytic anemia
C. Abnormal erythropoiesis due to genetic abnormalities
D. Iron deficiency anemia

Maria Vergara-Lluri, MD
Hematology and Clinical Microscopy Commitee

References:

Castellino G, Govoni M, Prandini N. Thrombocytosis in systemic lupus erythematosus: a possible clue to autosplenectomy? *J Rheumatol* 2007;34(7):1497-501.

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Gormezano NWS, Kern D, Pereira OL, et al. Autoimmune hemolytic anemia in systemic lupus erythematosus at diagnosis: differences between pediatric and adult patients. *Lupus* 2016;0:1-5.

Muscal E, Edwards RM, Kearney DL, et al. Thrombotic microangiopathic hemolytic anemia with reduction of ADAMTS13 activity: initial manifestations of childhood-onset systemic lupus erythematosus. *Am J Clin Pathol* 2011;135:406-416.

Wallace DJ. Diagnosis and differential diagnosis of systemic lupus erythematosus in adults. In: UpToDate, Pisetsky DS, Curtis MR (Eds), UpToDate, Waltham, MA. (Accessed on November 15, 2016.)

Wilson CS, Vergara-Lluri ME, Brynes RK. Evaluation of anemia, leukopenia, and thrombocytopenia. In: *Hematopathology*. 2nd edition. Philadelphia, PA: Elsevier; 2017:195-218.

ANSWERS:

Question 1: B. Rouleaux formation
Characteristic red blood cell findings seen in the peripheral blood smear of a patient with microangiopathic hemolytic anemia include fragmented red cells (ie. schistocytes, helmet cells, triangulocytes, horn cells), spherocytes, and polychromatophilic cells. Rouleaux formation is typically seen in infectious and inflammatory disorders with polyclonal increases in globulins and/or increased levels of fibrinogen, as well as monoclonal gammopathies (like multiple myeloma) and malignant lymphomas (such as Waldenstrom's macroglobulinemia). Rouleaux formation is not usually associated with microangiopathic hemolytic anemia.

Question 2: C. Decreased erythropoietin due to renal disease
Hemolytic anemia can be due to immune processes, such as autoimmune conditions (eg. SLE, cold autoimmune hemolytic anemia, drug-induced immune hemolysis) or alloimmune causes (eg. hemolytic anemia after transfusion of ABO-incompatible blood). Intrinsic red cell membrane defects may also lead to hemolysis. Examples of these would include hereditary spherocytosis, hereditary elliptocytosis, and hereditary pyropoikilocytosis. Red blood cell enzyme defects can also precipitate hemolysis, particularly when a patient is exposed to oxidant stress, such as occurs in G6PD deficiency. In contrast, decreased erythropoietin production secondary to renal disease is an issue of hypoproliferation or underproduction of erythroid precursors, which leads to anemia; this process does not induce hemolytic anemia.

Question 3: C. Abnormal erythropoiesis due to genetic abnormalities
SLE can present with a myriad of hematologic manifestations, with many different potential contributing factors of anemia. The most commonly cited form of anemia in SLE is anemia of chronic disease, found in approximately 50% of patients. Microangiopathic hemolytic anemias, such as DIC and TTP, have also been well described in SLE patients. Iron deficiency anemia, whether through nutritional deficiency or through gastrointestinal blood loss or menorrhagia, is also quite common. Genetic abnormalities are implicated in anemias associated with myelodysplastic syndrome but are not seen in autoimmune disorders such as SLE.

Clinical History for VPBS-07 – VPBS-12

This peripheral blood smear is from a 30-year-old woman with a history of Hodgkin lymphoma. Laboratory data include: WBC = 7.1 x 10E9/L; RBC = 4.11 x 10E12/L; HGB = 10.8 g/dL; HCT = 34.0%; MCV = 83 fL; and PLT = 63 x 10E9/L. Identify the arrowed object(s) on each wholeslide image.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

Please click on the hyperlink below to view the DigitalScope images for this case.
http://www.digitalscope.org/LinkHandler.axd?LinkId=821b3ff5-18cf-4a46-9061-17b8348b3980

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Summary of Participant Survey Results

The following is a statistical summary of all results submitted by participating labs. These are provided to allow participants to see their responses in the context of their peers. These results may identify findings or topics for further education or review. Survey results are not intended to represent the correct or desired responses for proficiency testing purposes and the SD and CV should not be interpreted as acceptable reporting limits. Participants are encouraged to review discrepant results with their medical director.

WBC Differential – %

		No. Labs	Mean	S.D.	C.V.*	Median	Low Value	High Value
VPBS-07	Neutrophils (segs or bands)	1019	65.2	7.0	10.7	65	44	85
	Lymphocytes	994	4.3	2.3	52.5	4	0	11
	Lymphocytes, reactive	496	0.7	1.3	*	0	0	7
	Monocytes	994	5.0	2.5	50.0	5	0	12
	Eosinophils	491	0.2	0.5	*	0	0	2
	Basophils	428	0.0	0.0	0.0	0	0	0
	Metamyelocytes	959	9.5	5.1	53.8	9	0	25
	Myelocytes	954	8.1	4.3	53.4	8	0	21
	Promyelocytes	889	5.1	3.4	66.9	5	0	15
	Blasts	673	1.9	2.0	*	1	0	8
	nRBC/100 WBC	617	0.5	0.7	*	0	0	2

WBC Differential – 10^9/L **Please see discussion on "Calculating Absolute Counts" that appears in this PSR.

		No. Labs	Mean	S.D.	C.V.*	Median	Low Value	High Value
VPBS-07	Neutrophils (segs or bands)	906	4.56	0.61	13.4	4.6	2.3	6.3
	Lymphocytes	890	0.31	0.18	57.3	0.3	0.0	0.9
	Lymphocytes, reactive	446	0.05	0.09	*	0.0	0.0	0.5
	Monocytes	887	0.36	0.19	53.3	0.4	0.0	0.9
	Eosinophils	441	0.02	0.04	*	0.0	0.0	0.1
	Basophils	388	0.00	0.00	0.0	0.0	0.0	0.0
	Metamyelocytes	840	0.66	0.36	54.5	0.6	0.0	1.8
	Myelocytes	837	0.57	0.31	54.4	0.5	0.0	1.5
	Promyelocytes	774	0.36	0.25	68.4	0.4	0.0	1.1
	Blasts	595	0.12	0.13	*	0.1	0.0	0.5

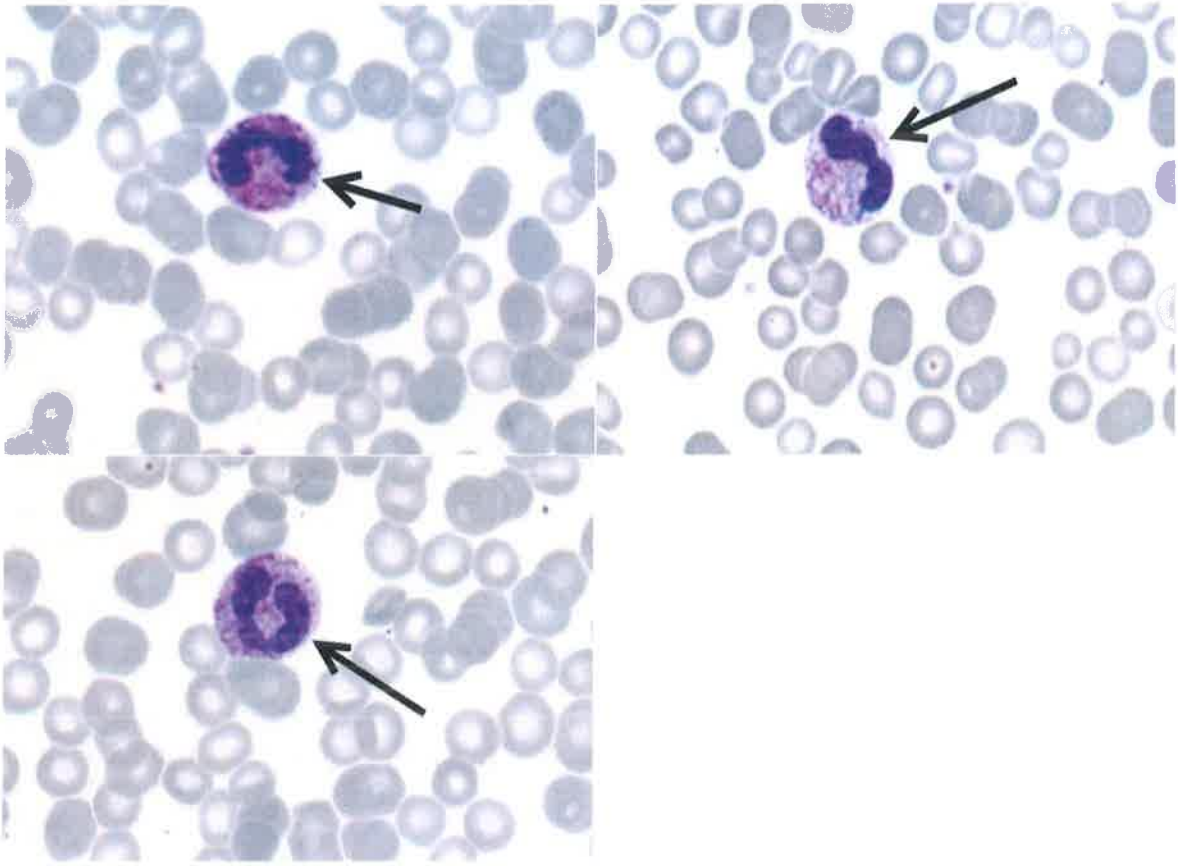
*When low results are reported on an analyte, a high coefficient of variance (CV) may result. When the mean value is very low, the CV may be exaggerated.

Committee Comments on Peripheral Blood Smear Whole Slide Image

The CBC data indicate a normocytic anemia and thrombocytopenia. The smear reflects this with an apparent decrease in number of erythrocytes and platelets compared to what should be seen in a blood smear from a normal patient. The leukocytes appear to be predominantly neutrophilic and many left shifted (immature) forms.

Cell Identification

VPBS-08

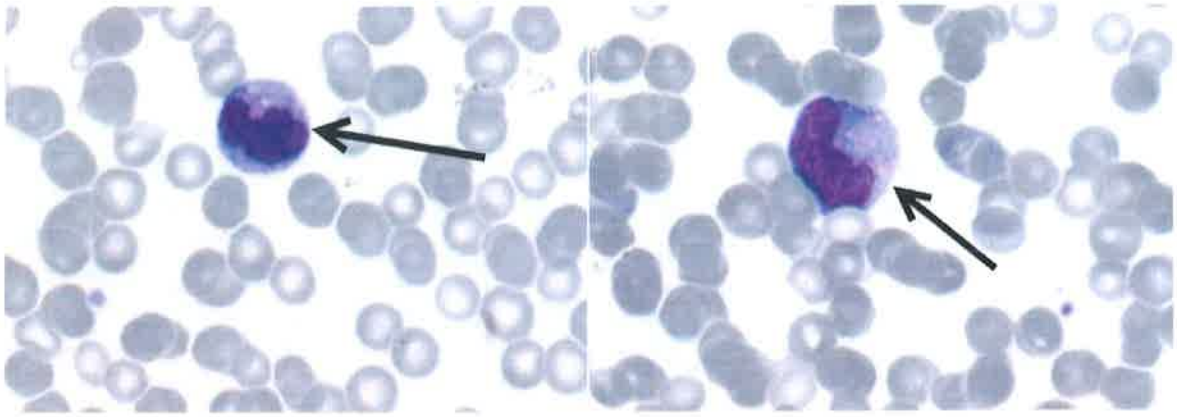


Identification	Participants No.	%	Evaluation
Neutrophil, toxic	846	81.3	Educational
Neutrophil, segmented or band	188	18.1	Educational
Neutrophil, giant band	3	0.3	Educational
Leukocyte with Alder-Reilly	2	0.2	Educational
Echinocyte (burr cell)	1	0.1	Educational
Eosinophil, any stage	1	0.1	Educational

VPBS-08 Discussion, Cont'd:

The arrowed cells are segmented neutrophils with toxic granulation, as correctly identified by 81.3% of laboratories. Segmented neutrophils are the most mature form of myeloid cell. They are round to oval cells, 10 - 15 µm in diameter, with lobated nuclei and condensed chromatin. Normally, there are 2 - 5 lobes that are connected by thin filaments of chromatin. The cytoplasm of a toxic neutrophil differs from a normal neutrophil and contains coarse purple or dark blue granules as opposed to the fine tan-orange specific neutrophil granules. Döhle bodies, amorphous light blue inclusions (0.5 - 5 µm) in the cytoplasm, are often present in subset of toxic granules, as shown in the image. They represent strands of rough endoplasmic reticulum. Toxic neutrophils may occur in the setting of infection, growth factor therapy (GM-CSF or G-CSF), or other stress such as burns or trauma.

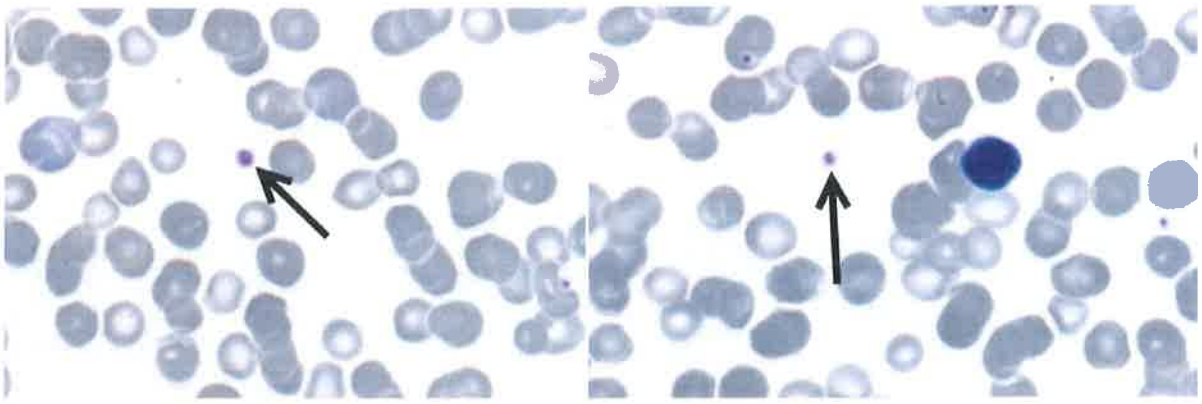
VPBS-09



Identification	Participants No.	%	Evaluation
Monocyte	909	87.3	Educational
Monocyte, immature (promonocyte, monoblast)	43	4.1	Educational
Neutrophil, metamyelocyte	39	3.8	Educational
Lymphocyte, reactive	13	1.3	Educational
Malignant lymphoid cell	11	1.1	Educational
Neutrophil, segmented or band	5	0.5	Educational
Neutrophil, giant band	4	0.4	Educational
Neutrophil, myelocyte	4	0.4	Educational
Neutrophil with dysplastic nucleus and/or hypugranular cytoplasm	3	0.3	Educational
Blast cell	2	0.2	Educational
Immature abnormal cell, would refer	2	0.2	Educational
Lymphocyte	2	0.2	Educational
Neutrophil, toxic	2	0.2	Educational
Myeloblast with Auer rod	1	0.1	Educational
Neutrophil, promyelocyte	1	0.2	Educational

The arrowed cells are monocytes, as correctly identified by 87.3% of laboratories. Monocytes are leukocytes that are slightly larger than neutrophils (12 - 20 µm in diameter). They are found to be oval with an indented or folded nucleus with mildly condensed chromatin (less than that of a neutrophil or lymphocyte) and relatively abundant cytoplasm. The N:C ratio is 1:2 to 1:4. An occasional small nucleolus can be seen. The cytoplasm may show pseudopods or bulbous extensions at the periphery of the cell. The cytoplasm is gray-blue and may contain sparse fine azurophilic granules and scattered vacuoles.

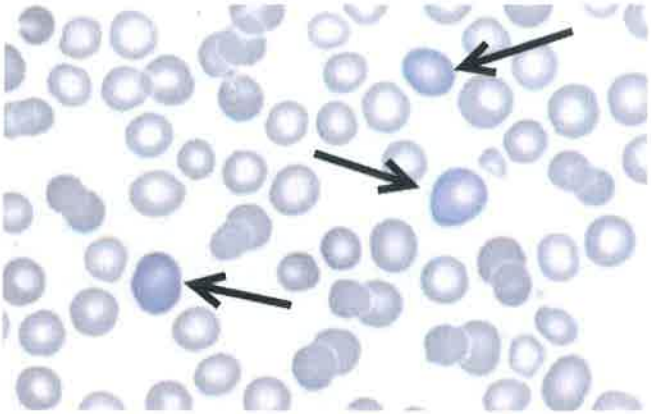
VPBS-10



Identification	Participants No.	%	Evaluation
Platelet, normal	1033	99.2	Educational
Platelet, giant	7	0.7	Educational
Neutrophil, myelocyte	1	0.1	Educational

The arrowed objects are platelets, as correctly identified by 99.2% of laboratories. Platelets are variably shaped 1.5 - 3.0 µm fragments of megakaryocyte cytoplasm. They are blue-gray and have fine purple-red granules. These are alpha granules. Delta granules are also present but cannot be seen by light microscopy. The granules contain a variety of chemical mediators and factors involved in platelet function.

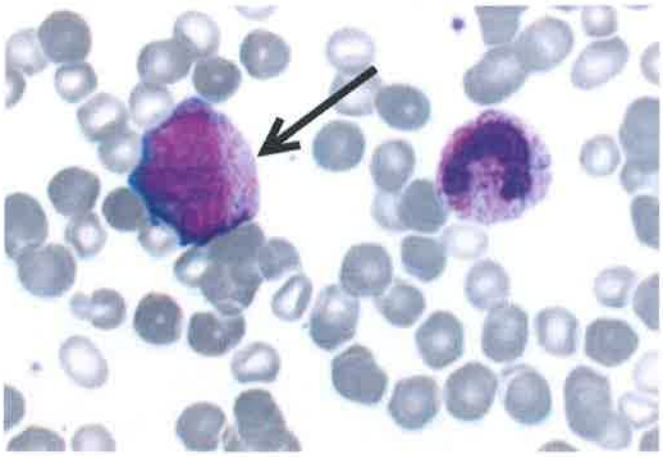
VPBS-11



Identification	Participants No.	%	Evaluation
Polychromatophilic (non-nucleated) red blood cell	1001	96.3	Educational
Macrocyte oval/round	28	2.7	Educational
Erythrocyte, normal	8	0.8	Educational
Ovalocyte (elliptocyte)	3	0.3	Educational

The arrowed cells are polychromatophilic (non-nucleated) red blood cells, as correctly identified by 96.3% of laboratories. Erythrocytes are mature, nonnucleated red cells with a biconcave shape and are approximately 7 µm in diameter. They contain hemoglobin and stain pink-red with a zone of central pallor due to the biconcavity. Polychromatophilic erythrocytes are the youngest of the anucleate erythrocytes and thus are slightly larger than a typical mature erythrocyte and since they contain more RNA appear slightly pink-blue on a Wright stain. Thus, they are recognizable and separable from mature erythrocytes. They are seen normally at low numbers (<1% of erythrocytes) but can be increased when there is increased red cell production such as in response to anemia or in the setting of growth factor therapy with erythropoietin.

VPBS-12



Identification	Participants No.	%	Evaluation
Neutrophil, promyelocyte	575	55.3	Educational
Neutrophil, myelocyte	299	28.8	Educational
Blast cell	44	4.2	Educational
Neutrophil promyelocyte abnormal with/without Auer rods	33	3.2	Educational
Lymphocyte, reactive	30	2.9	Educational
Neutrophil, metamyelocyte	19	1.8	Educational
Lymphocyte, large granular	13	1.3	Educational
Maligant lymphoid cell	9	0.9	Educational
Monocyte, immature (promonocyte, monoblast)	6	0.6	Educational
Immature abnormal cell, would refer	4	0.4	Educational
Myeloblast with Auer rod	3	0.3	Educational
Monocyte	2	0.2	Educational
Basophil, any stage	1	0.1	Educational
Hypochromasia	1	0.1	Educational
Megakaryocyte	1	0.1	Educational

The arrowed cell is a neutrophil, myelocyte, as correctly identified by 28.8% of laboratories. The transition from promyelocyte to myelocyte occurs with the end of production of azurophilic (primary) granules and the beginning of production of lilac or pale orange/pink (specific) granules. Myelocytes are usually confined to the marrow where they constitute approximately 10% of the nucleated cells. In pathologic states, myelocytes are seen in blood. The myelocyte is smaller than the earlier precursors, usually 10 to 18 µm. The cells are round to oval in shape and have a N:C ratio of 2:1 to 1:1. The nucleus is slightly eccentric, lacks a nucleolus, and begins to demonstrate chromatin clumping; one side often shows slight flattening. Sometimes a clear space or hof is seen adjacent to the nucleus, indicating the location of the Golgi apparatus. The cytoplasm is relatively more abundant than in earlier precursors and is amphophilic. Both azurophilic and specific granules are present in the cytoplasm with specific granules coming to predominate as maturation progresses.

55.3 % of participants incorrectly identified this cell as a promyelocyte. Promyelocytes are round to oval cells that are generally slightly larger than myeloblasts, with a diameter of 12 to 24 µm. They are normally confined to bone marrow, where they constitute less than 2% of nucleated cells. However, like myeloblasts, promyelocytes can be seen in the blood in pathologic states. The N:C ratio usually ranges from 5:1 to 3:1. The nucleus is round-to-oval, has fine chromatin, and contains distinct nucleoli. The cytoplasm is basophilic, more plentiful than in a myeloblast, and contains multiple distinct azurophilic (primary) granules. A paranuclear hof or cleared space is typically present.

Clinical presentation:

This peripheral blood smear is from a 30-year-old woman with a history of Hodgkin lymphoma. Laboratory data include: WBC = 7.1 x 10E9/L; RBC = 4.11 x 10E12/L; HGB = 10.8 g/dL; HCT = 34.0%; MCV = 83 fL; and PLT = 63 x 10E9/L. Identify the arrowed object(s) on each whole slide image.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

Case Discussion: Neutrophilic left shift

The CBC data indicate a normocytic anemia and thrombocytopenia. Erythrocytes appear relatively normal and an occasional polychromatophilic cell is seen. The white cell count is normal but scan of the smear shows a neutrophilic left shift. All myeloid forms from promyelocytes to neutrophils are present. In addition, closer inspection of the neutrophilic cells shows toxic granulation with unusually coarse granules, many of which are blue-purple. Furthermore, bodies are present. These neutrophilic series findings indicate a stressor resulting in activation of these cells and a regenerative response by the bone marrow. Neutrophilic left shift is a non-specific finding that can be seen in a variety of reactive conditions but can also be part of a neoplastic process. While the presence of blasts can be alarming and raise concern for an acute leukemia, a left shift to the blast stage can be seen in reactive processes but blasts are usually low in percentage.

Question 1:

The following conditions can be associated with neutrophilic left shift as the dominant finding EXCEPT:

A. Systemic bacterial infection
B. Epstein-Barr virus infection
C. Granulocyte colony stimulating factor (GCSF) therapy
D. Chronic myelogenous leukemia (CML)
E. Early regeneration after myeloablative chemotherapy

Many conditions may result in a neutrophilic left shift. Bacterial infection with resulting neutrophilic response and left shift with toxic changes is a common scenario. Viral infections typically do not elicit this response but may be associated with a reactive lymphocytosis. The classical example of this is Epstein Barr virus and associated infectious mononucleosis in which a lymphocytosis occurs with many reactive lymphocytes. Regenerative changes after myeloablative chemotherapy or growth factor (GCSF) therapy also can result in left shift with toxic change. Neoplastic processes such as CML will manifest as neutrophilia with left shift but toxic changes are usually not present.

Question 2:

Döhle bodies are inclusions that:

A. are only visible by electron microscopy
B. are normal variants
C. are present in monocytes in sepsis due to bacteria
D. are usually present in next to nuclei
E. are composed of rough endoplasmic reticulum

The blood smear shows that neutrophils contain Döhle bodies. These structures are cytoplasmic inclusions consisting of rough endoplasmic reticulum and are light blue on Wright staining. They are located near the cell membrane and limited to neutrophils in toxic reactions. Döhle-like bodies are seen in May-Hegglin disease, an autosomal dominantly inherited disorder with thrombocytopenia, bleeding tendency, large macrothrombocytes and other anomalies due to mutations in *MYH9*. In this disorder, the Döhle-like bodies are present without associated toxic granulation and can be seen in other cells such as monocytes.

Question 3:
Polychromatophilic erythrocytes are:

A. increased in myelodysplastic syndrome
B. increased in aplastic anemia
C. are smaller than normal erythrocytes
D. are erythrocytes recently released from the bone marrow
E. are culled from circulation by the spleen

This case shows an anemia with polychromasia. Polychromatophilic erythrocytes are slightly larger than typical erythrocytes and are younger cells recently released from the bone marrow. They contain greater amounts of RNA than more mature red cells and this imparts a slightly pink-blue color on Wright stain that can be recognized and differentiated from mature erythrocytes. They represent less than 1% of erythrocytes in normal smears and increase in regenerative situations, correlating with the reticulocyte count.

In summary, this blood smear shows anemia, thrombocytopenia and a neutrophilic left shift in a patient with Hodgkin lymphoma. The findings are not specific but are likely reactive.

Eric D. Hsi, MD
Hematology and Clinical Microscopy Resource Committee

References:

1. Mathur SC, Schexneider KI and Hutchison RE. Hematopoiesis, Chapter 31 in *Henry's Clinical Diagnosis and Mangement by Laboratory Methods,* 22 ed. McPherson and Pincus, eds. Philadelphia, PA: Elsevier Saunders, 2011: 547-8.
2. Hutchison RE and Schexneider KI. Leukocytic Disoders, Chapter 33 in *Henry's Clinical Diagnosis and Mangement by Laboratory Methods,* 22 ed. McPherson and Pincus, eds. Philadelphia, PA: Elsevier Saunders, 2011: 602-615.

Answers:

Question 1: B. Epstein-Barr virus infection
EBV virus infection in the acute phase in associated with a lymphocytosis and many reactive lymphocytes that have enlarge nuclei, small nucleoli and abundant basophilic cytoplasm. Neutrophilia and toxic changes are not seen.

Question 2: E. are composed of rough endoplasmic reticulum

Döhle bodies are collection of rough endoplasmic reticulum seen in toxic cells. They are not present in other cell types. They are located within the cytoplasm and oftentimes closely opposed to the inner cell membrane. Similar inclusions can be seen in the May-Hegglin anomaly. In such cases, there are macrothrombocytes and bleeding tendency. The Döhle-like bodies can be found in cells other than neutrophils such as monocytes.

Question 3: D. are erythrocytes recently released from the bone marrow

Polychromatophilic red cells are young erythrocytes, having been recently released form the bone marrow. Reticulocytes should correlate with polychromatophilc red cells. Increased numbers in the setting of anemia suggest the bone marrow response is in intact and that the marrow is attempting to compensate for the anemia. Thus, when present, they argue against marrow failure processes such as aplastic anemia and myelodysplastic syndromes.

Clinical History for VPBS-13 – VPBS-18

This peripheral blood smear is from an 18-year-old male college student presenting with a sore throat and fatigue. Laboratory data include: WBC = 14.2 x 10E9/L; RBC = 4.87 x 10E12/L; HGB = 13.9 g/dL; HCT = 41.7%; MCV = 86 fL; and PLT = 232 x 10E9/L. Monospot test is positive. Identify the arrowed object(s) on each whole slide image.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

Please click on the hyperlink below to view the DigitalScope images for this case.
http://www.digitalscope.org/LinkHandler.axd?LinkId=3a94b991-5bed-4ce7-99c6-f531349bbd0c

To access the online Hematology Glossary, please click the hyperlink below:
http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution%20Folders/WebContent/pdf/hematology-glossary.pdf

Summary of Participant Survey Results

The following is a statistical summary of all results submitted by participating labs. These are provided to allow participants to see their responses in the context of their peers. These results may identify findings or topics for further education or review. Survey results are not intended to represent the correct or desired responses for proficiency testing purposes and the SD and CV should not be interpreted as acceptable reporting limits. Participants are encouraged to review discrepant results with their medical director.

WBC Differential – %

		No. Labs	Mean	S.D.	C.V.	Median	Low Value	High Value
VPBS-13	Neutrophils (segs or bands)	1037	24.6	4.9	19.8	24	12	38
	Lymphocytes	1027	33.6	19.6	58.3	30	0	82
	Lymphocytes, reactive	931	37.8	17.2	45.5	39	0	79
	Monocytes	1004	6.9	3.5	51.8	6	0	18
	Eosinophils	814	1.2	0.8	66.0	1	0	3
	Basophils	420	0.0	0.0	0.0	0	0	0
	Metamyelocytes	407	0.0	0.0	0.0	0	0	0
	Myelocytes	411	0.0	0.0	0.0	0	0	0
	Promyelocytes	417	0.0	0.0	0.0	0	0	0
	Blasts	416	0.0	0.0	0.0	0	0	0
	nRBC/100 WBC	497	0.0	0.0	0.0	0	0	0

WBC Differential –10^9/L **Please see discussion on "Calculating Absolute Counts" that appears in this PSR.

		No. Labs	Mean	S.D.	C.V.*	Median	Low Value	High Value
VPBS-13	Neutrophils (segs or bands)	918	3.49	0.70	20.1	3.4	1.4	5.4
	Lymphocytes	909	4.79	2.84	59.2	4.3	0.0	11.5
	Lymphocytes, reactive	814	5.37	2.47	45.9	5.5	0.0	11.2
	Monocytes	888	0.96	0.49	51.3	0.9	0.0	2.6
	Eosinophils	725	0.15	0.12	81.6	0.1	0.0	0.5
	Basophils	381	0.00	0.00	0.0	0.0	0.0	0.0
	Metamyelocytes	379	0.00	0.02	*	0.0	0.0	0.1
	Myelocytes	376	0.00	0.01	*	0.0	0.0	0.1
	Promyelocytes	379	0.00	0.00	0.0	0.0	0.0	0.0
	Blasts	379	0.00	0.00	0.0	0.0	0.0	0.0

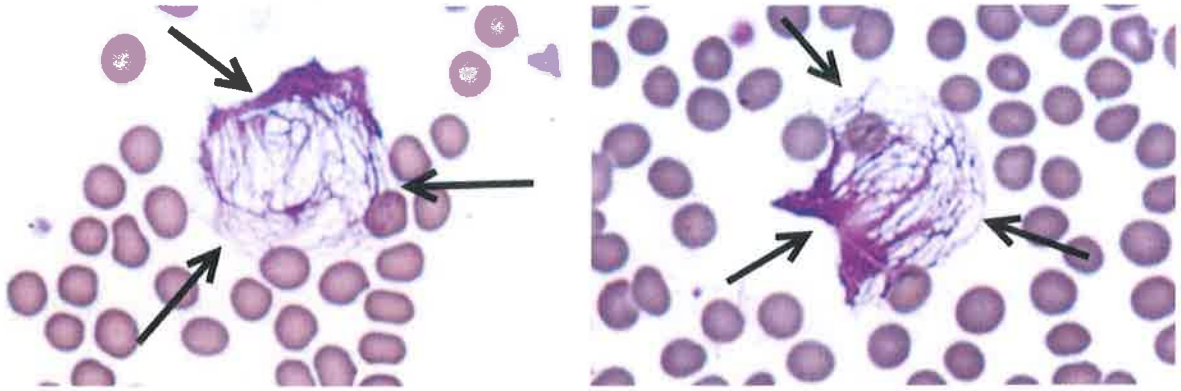
*When low results are reported on an analyte, a high coefficient of variance (CV) may result. When the mean value is very low, the CV may be exaggerated.

Committee Comments on the CBC and Blood Film

The CBC data are indicative of isolated leukocytosis. The hemoglobin concentration is at the lower limit of normal, and red blood cells are normocytic and normochromic. Mild anisopoikilocytosis in the form of rare ovalocytes and elliptocytes is noted. Platelets are normal in number and morphologically unremarkable. There is a lymphocytosis, with atypical lymphocytes noted. The atypical lymphocytes have variably abundant basophilic cytoplasm and some appear to "hug" adjacent red blood cells. Occasional eosinophils and monocytes are noted.

Cell Identification

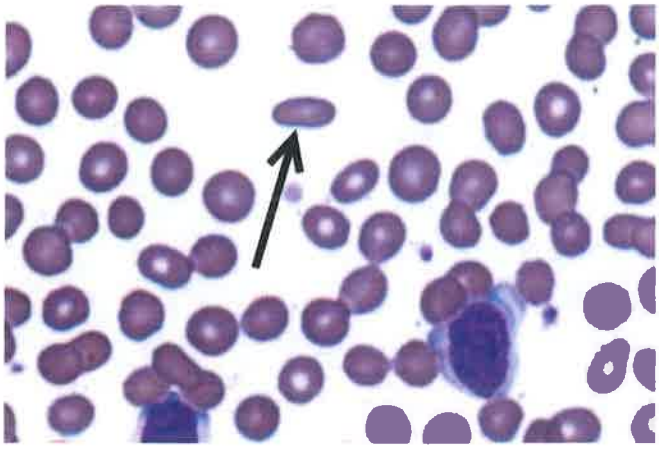
VPBS-14



Identification	Participants No.	%	Evaluation
Basket cell/smudge cell	1016	97.3	Educational
Stain precipitate	26	2.5	Educational
Blast cell	1	0.1	Educational
Immature/abnormal cell, would refer	1	0.1	Educational

The arrowed cells are basket/smudge cells, as correctly identified by 97.3% of participants. Basket/smudge cells are artifacts produced when fragile cells, typically lymphocytes, are subjected to the shearing forces of the peripheral smear production process. The "basket" appearance results when chromatin strands are spread-out from a condensed nuclear remnant. Basket/smudge cells are most commonly encountered in disorders of increased lymphocyte fragility such as infectious mononucleosis or chronic lymphocytic leukemia.

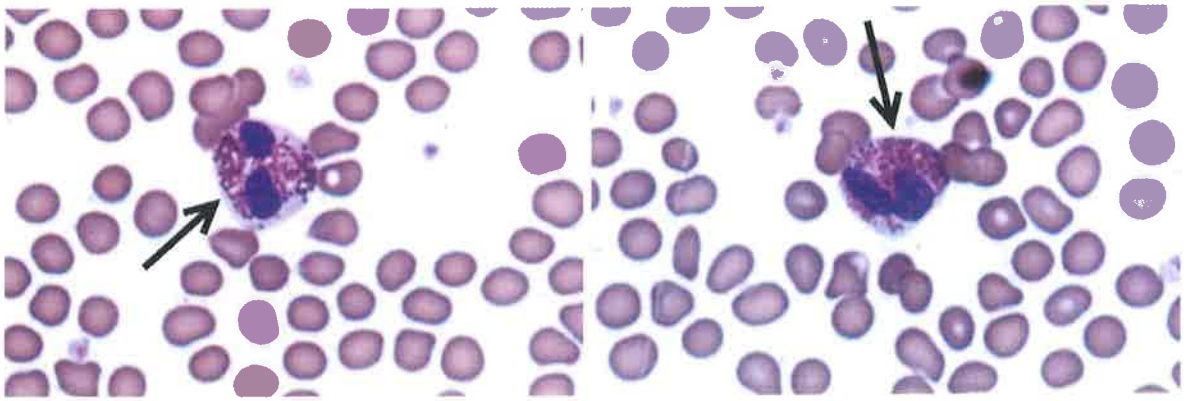
VPBS-15



Identification	Participants No.	%	Evaluation
Ovalocyte (elliptocyte)	1037	99.3	Educational
Erythrocyte, normal	6	0.6	Educational
Lymphocyte, reactive	1	0.1	Educational

The arrowed cell is an ovalocyte (elliptocyte), as correctly identified by 99.3% of participants. An ovalocyte is a red cell with an oval shape; the term elliptocyte is often used to described a red cell having a shape more akin to that of a cigar or pencil. Ovalocytes and elliptocytes may be seen in the peripheral smears of normal individuals in low numbers (<1% of red cells). When seen in very large numbers (>25%), consideration of an abnormality of red cell membrane proteins is warranted. Elliptocytes may also be increased in patients with iron deficiency anemia.

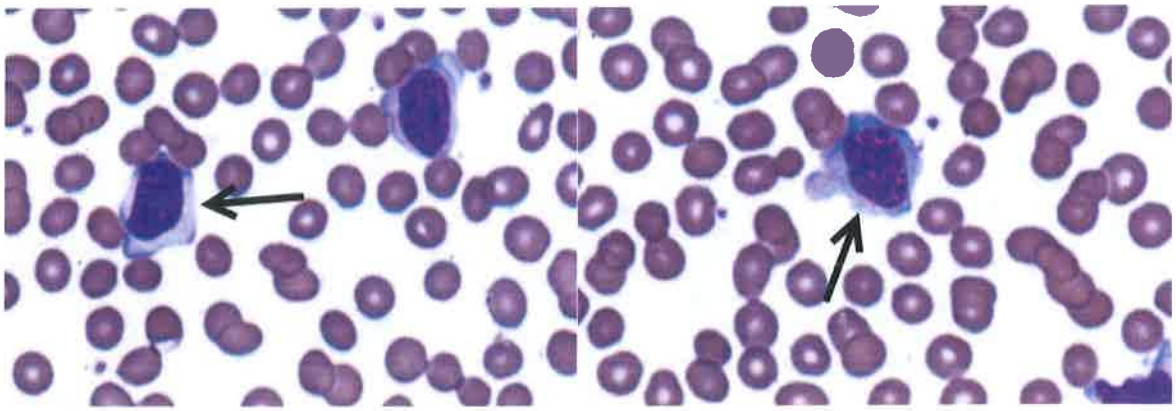
VPBS-16



Identification	Participants No.	%	Evaluation
Eosinophil, any stage	1034	99.0	Educational
Basophil, any stage	3	0.3	Educational
Neutrophil, toxic	3	0.3	Educational
Neutrophil with Pelger-Huët nucleus (acquired or congenital)	3	0.3	Educational
Cryoglobulin	1	0.1	Educational

The arrowed cells are eosinophils, as correctly identified by 99.0% of participants. Eosinophils are leukocytes that are easily recognizable by their abundant cytoplasmic orange-red granulation. These granules often have a refractile appearance by light microscopy that is not well-represented in photomicrographs. The eosinophil nucleus segments into two or more lobes with approximately 80% of cells bearing the typical bilobed appearance. The mature eosinophil nucleus has a characteristic coarse chromatin, similar to that seen in mature neutrophils.

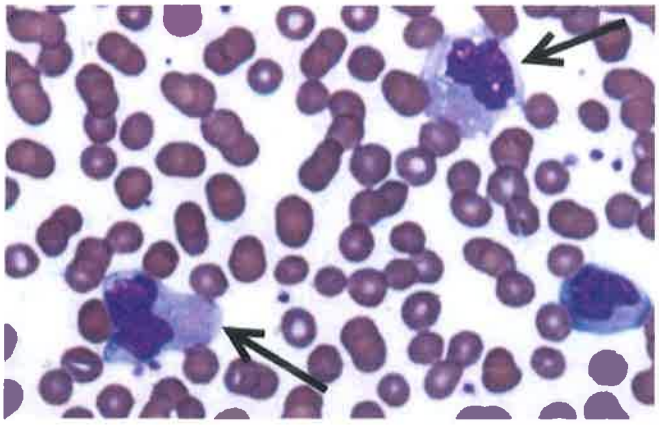
VPBS-17



Identification	Participants No.	%	Evaluation
Lymphocyte, reactive	1011	96.8	Educational
Lymphocyte	30	2.9	Educational
Lymphocyte, large granular	2	0.2	Educational
Immature/abnormal cell, would refer	1	0.1	Educational

The arrowed cells are reactive lymphocytes, as correctly identified by 96.8% of participants. Reactive lymphocytes can have a wide variety of cellular shapes and sizes. The classic reactive lymphocyte is that seen in association with EBV infection (mononucleosis), although reactive lymphocytes may be seen in a variety of other immunologically-stimulated states. Reactive lymphocytes typically have abundant pale gray-blue cytoplasm, often characterized by amoeboid extensions partially surrounding adjacent red cells. The nuclei of reactive lymphocytes are larger than normal lymphocytes, but without the extremes of high N:C ratios that are typical of blasts. Also, the chromatin of reactive lymphocytes is typically coarse or smeared with absent or indistinct nucleoli.

VPBS-18



Identification	Participants No.	%	Evaluation
Monocyte	1017	97.5	Educational
Monocyte, immature (promonocyte, monoblast)	14	1.3	Educational
Lymphocyte, reactive	9	0.9	Educational
Neutrophil, metamyelocyte	1	0.1	Educational
Neutrophil, toxic	1	0.1	Educational
Neutrophil with dysplastic nucleus and/or hypogranular cytoplasm	1	0.1	Educational

The arrowed cells are monocytes, as correctly identified by 97.5% of participants. Monocytes are relatively large leukocytes, typically round with smooth edges, and some may have pseudopod-like extensions. The monocyte cytoplasm is abundant, with a typically gray-blue appearance, many containing fine granules, and often containing a variable number of vacuoles. The monocyte nucleus is often indented and may be twisted, folded or band-like, and the nuclear chromatin is condensed, generally with absent or inconspicuous nucleoli.

Distinguishing monocytes from reactive lymphocytes may be challenging on occasion. These two cell types can often be distinguished on the basis of their cytoplasmic features, with granules and/or vacuoles more characteristic of monocytes. The reactive lymphocyte nucleus has a much more regular contour than that of the monocyte, twisting or an elongated or band-like shape. Finally, the reactive lymphocyte chromatin has a much more characteristically smeared appearance than that of the monocyte.

Clinical Presentation:

This peripheral blood smear is from an 18-year-old male college student presenting with a sore throat and fatigue. Laboratory data include: WBC = 14.2 x 10E9/L; RBC = 4.87 x 10E12/L; HGB = 13.9 g/dL; HCT = 41.7%; MCV = 86 fL; and Platelet = 232 x 10E9/L. Monospot test is positive.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

CASE DISCUSSION: Infectious mononucleosis

The CBC data are indicative of isolated leukocytosis. The hemoglobin concentration is at the lower limit of normal, and red blood cells are normocytic and normochromic. Mild anisopoikilocytosis in the form of rare ovalocytes and elliptocytes is noted. Platelets are normal in number and morphologically unremarkable. There is a peripheral lymphocytosis, with atypical lymphocytes noted. The atypical lymphocytes have variably abundant basophilic cytoplasm and some appear to "hug" adjacent red blood cells. Occasional eosinophils and monocytes are noted.

The peripheral smear in this case originates from an 18-year-old man with complaints of sore throat and fatigue. The triad of young age, sore throat and fatigue, while not specific, should raise the prospect of Epstein - Barr virus related mononucleosis in the clinical differential diagnosis. In the out-patient setting, this diagnosis can be quickly and reliably confirmed with a monospot test. Occasionally, peripheral blood analyses may also be requested; the CBC data for this case are typical of uncomplicated mononucleosis, notable for leukocytosis, resulting from lymphocytosis with reactive morphologic features.

Question 1: Which statement about mononucleosis is the most correct?

a. Mononucleosis is caused by viral infection by HIV
b. Mononucleosis produces a characteristically uniform small-sized atypical cell population on peripheral smear
c. Atypical or reactive lymphocytes are not specific to mononucleosis
d. Patients with mononucleosis almost never have overt clinical symptoms

Occasional nonspecific morphologic changes may also be seen in the red cells, such as ovalocytes or elliptocytes. When present in large numbers, these types of changes in red cell morphology may raise suspicion for red cell membrane disorders or iron deficiency, but these are non-specific findings when present in small numbers.

Question 2: Which statement is the most correct?

a. Ovalocytes are very specific for mononucleosis
b. Ovalocytes/Elliptocytes are only seen in patients with erythrocyte membrane disorders
c. Elliptocytes may be seen in patients with iron deficiency
d. Ovalocytes/Elliptocytes are never seen in normal healthy patients

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The lymphocytes encountered in peripheral smears of patients with mononucleosis, as well as other infectious (eg. cytomegalovirus, adenovirus, acute HIV infection, etc.) and reactive conditions, may raise potential alarms out of concern that they may represent a neoplastic process. Basket/smudge cells may be encountered in cases of mononucleosis, as well as in other disorders characterized by increased lymphocyte fragility such as chronic lymphocytic leukemia. Most reactive lymphocytes are easily recognizable as such given their variation in size (unlike neoplastic lymphoid cells which are more characteristically uniform in appearance), ample cytoplasm, mature chromatin and, typically, inconspicuous nucleoli. Lymphocytes that deviate from this prototype, especially when numerous, deserve careful evaluation. Indeed, extreme cases of "reactive" lymphocytosis may require ancillary studies such as flow cytometric evaluation to exclude a monoclonal process.

Question 3: Basket/smudge cells are most commonly seen with:

a. Acute lymphoblastic leukemia
b. Mononucleosis
c. Acute myeloid leukemia
d. Autoimmune hemolytic anemia

The Epstein-Barr virus may infect a number of cell types, although mononucleosis arises from acute infection of B-cells, typically followed by a cytotoxic T-cell immune response and a humoral immune response. It is these cytotoxic T-cells that are manifest as atypical lymphocytes on peripheral smears of patients with mononucleosis and it is the humoral response that is exploited by the monospot test. This test, also called a heterophile antibody test, relies on the identification of antibodies presumably to EBV-viral antigens. While the monospot test is attractive as a rapid point-of-care test, problems relating to sensitivity should be highlighted (owing to the frequent identification of heterophile antibodies in the general otherwise healthy population).

Etienne Mahe, MD, MSc
Hematology & Clinical Microscopy Committee

References:

1. Gross, TG. Chapter 66: Infectious Mononucleosis and Other Epstein-Barr Virus-Related Disorders, In: *Wintrobe's Clinical Hematology*. 12th Edition. Wolters Kluwer, 2009.
2. Mazur, LJ, Costello, M. Viral Infections, In: *Henry's Clinical Diagnosis and Management by Laboratory Methods*. 23rd Edition. Elsevier, 2016.

ANSWERS

Question 1: C. Atypical Mononucleosis is caused by acute Epstein-Barr virus infection
Although some cases may not manifest with clinical symptoms, studies suggest that most known/diagnosed cases have an associated symptomatology that includes malaise/fatigue, adenopathy and sore throat. In contrast to many malignant processes, which are often characterized by uniform atypical cells, the atypical lymphocytes of mononucleosis are often widely in size and shape. Atypical lymphocytes such as those seen in mononucleosis are not specific to mononucleosis and may be seen in association with a wide variety of infectious conditions, hypersensitivity reactions and other conditions.

Question 2: C. Elliptocytes may be seen in patients with iron deficiency
Ovalocytes/Elliptocytes are not specific to any particular condition and may be seen in small numbers in otherwise healthy patients. Ovalocytes and elliptocytes may be seen in iron deficiency and red cell membrane abnormalities manifest as profound elliptocytosis may occur.

Question 3: B. Mononucleosis
While basket/smudge cells may be seen in a number of conditions in which fragile lymphocyte membranes occur, they are most frequently seen in the benign context with mononucleosis and in the malignant context with chronic lymphocytic leukemia/ small lymphocytic lymphoma. Lymphoblastic leukemias are less frequently known for frequent smudge cells but these may occur within this context.