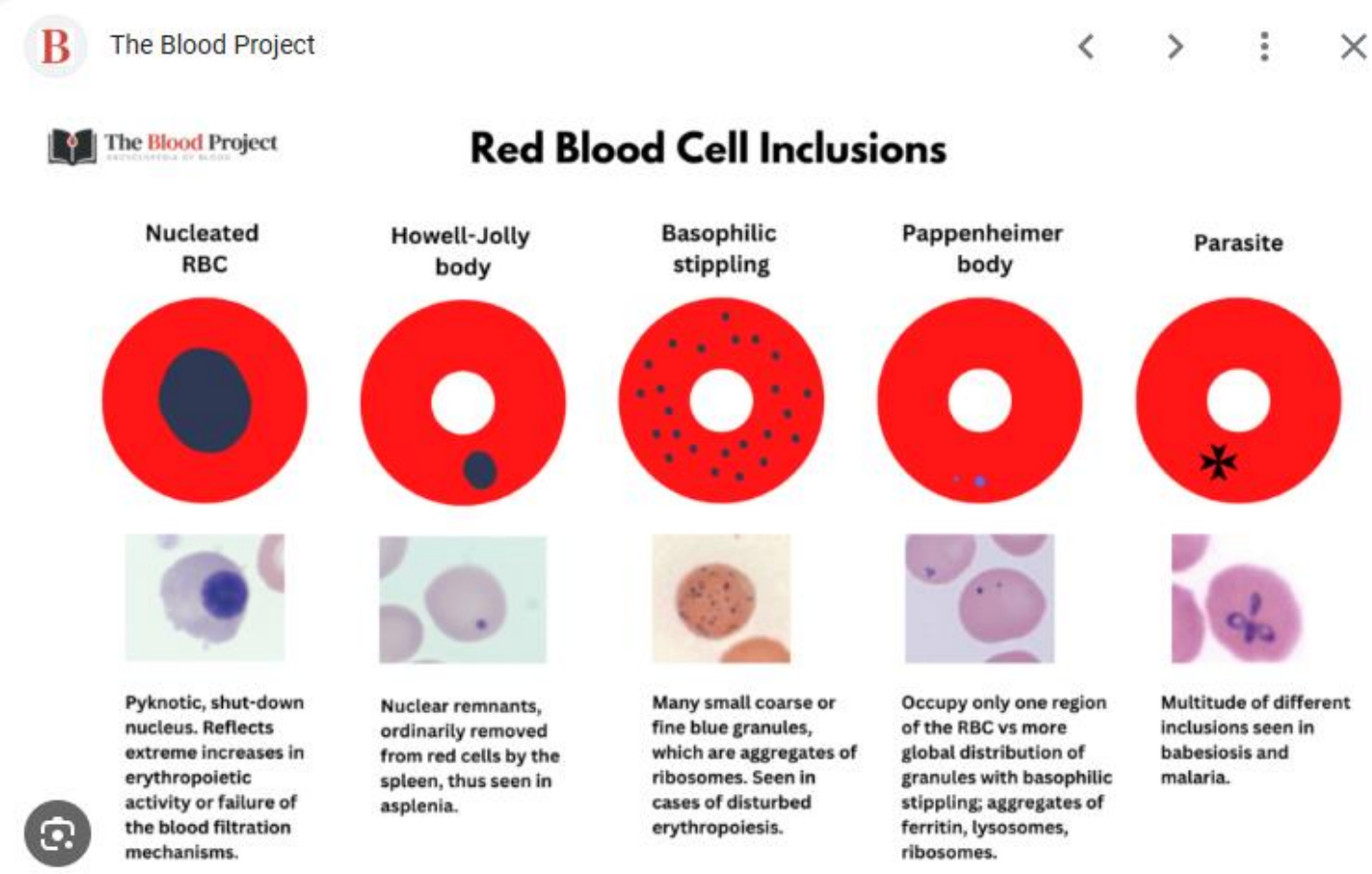
Welcome to the last education for 2024….in 2025!!!

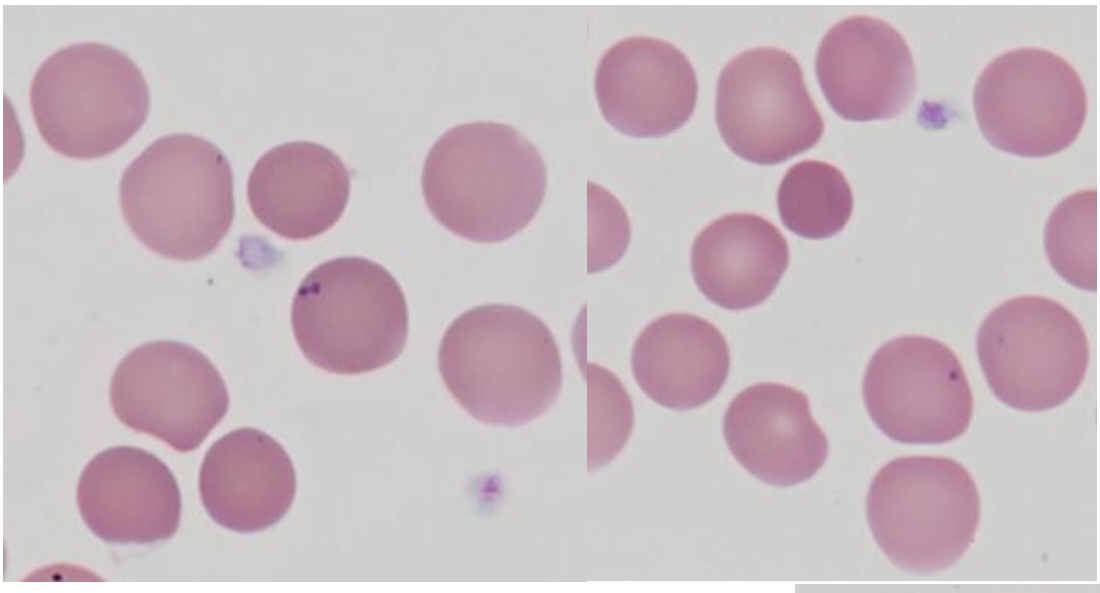
We're going to cover 3 things that were missed on hematology surveys in the second half of last year.

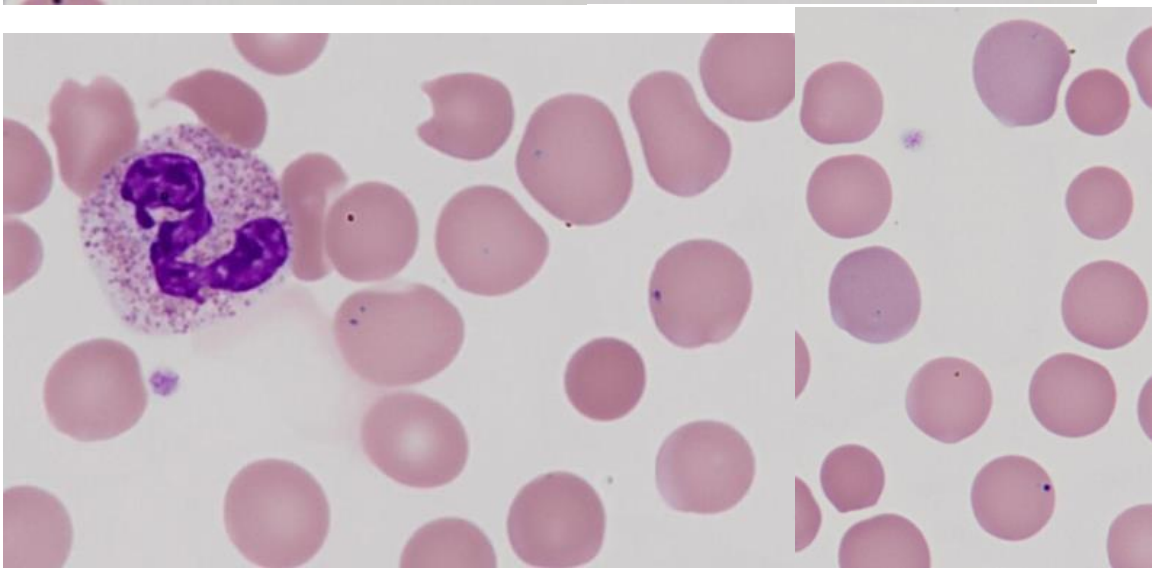
We'll try to make this quick but as painful as possible 😋.

First, there was an RBC morphology from the competency differentials that every one of us missed. Slide 5 had Pappenheimer bodies that none of us called, so here is a nice little refresher.

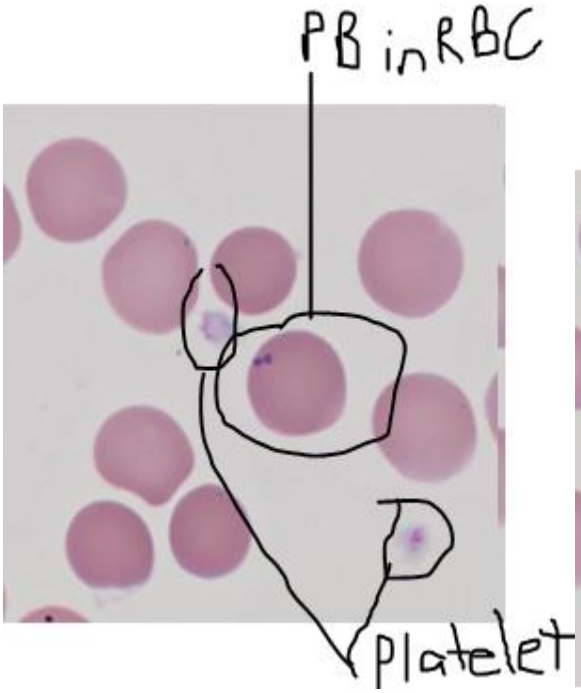


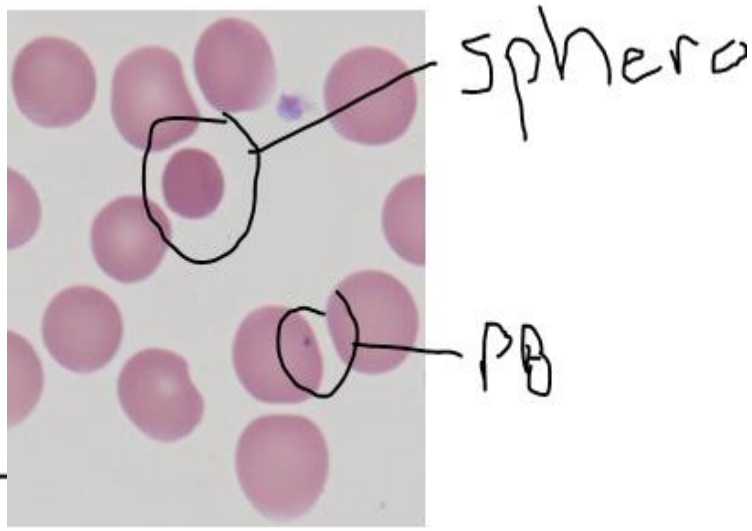
And here are some images from Slide 5 of QPR-C. See what you can find…..

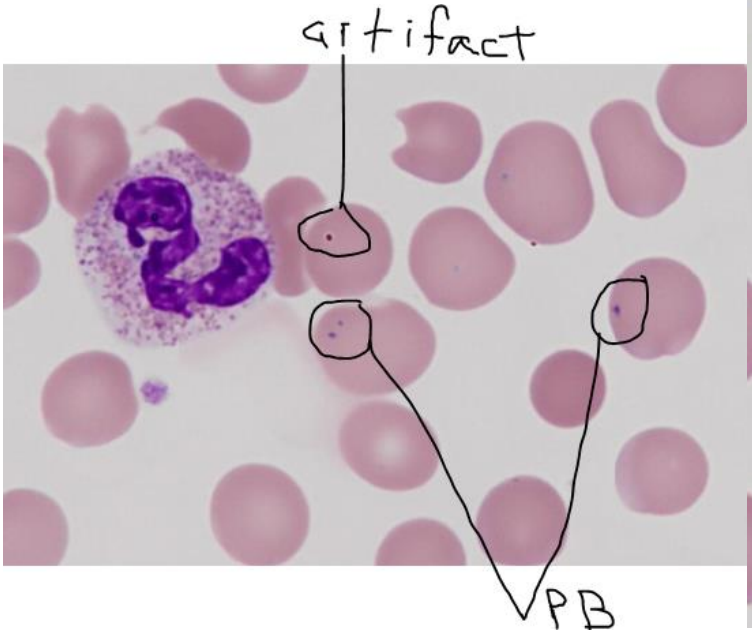


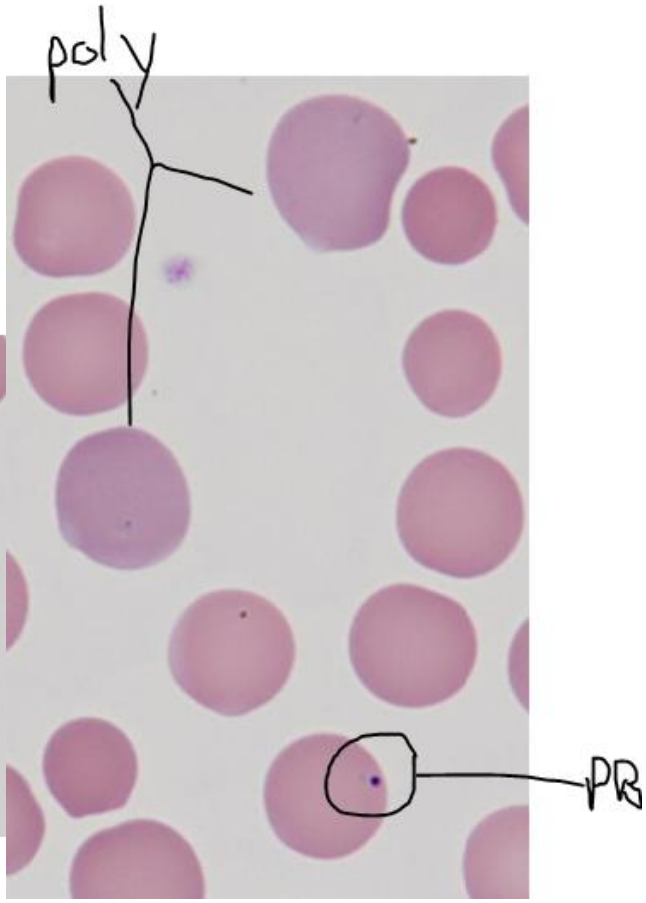


And here's the same images labeled (PB = Pappenheimer):





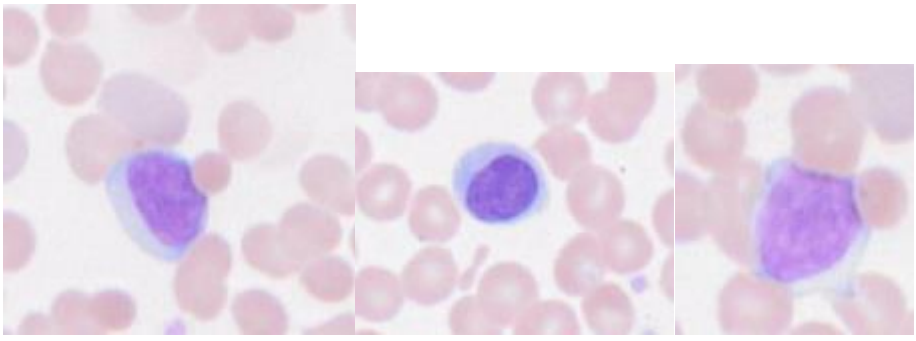


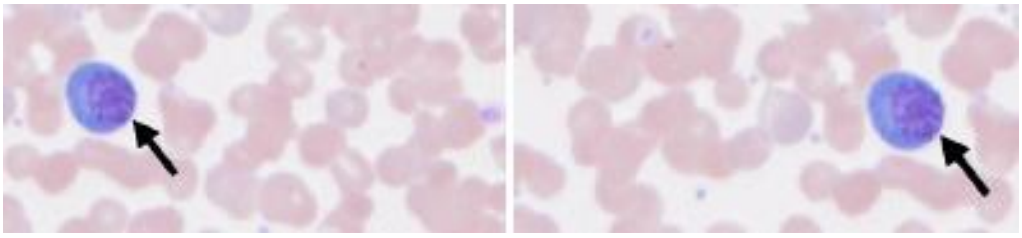


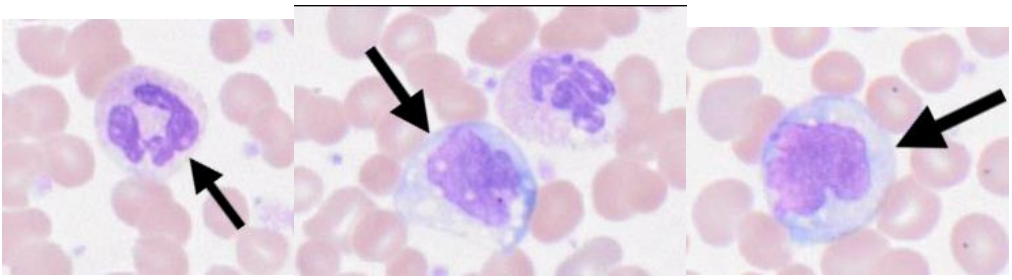
The next two we missed were all about immature cells.

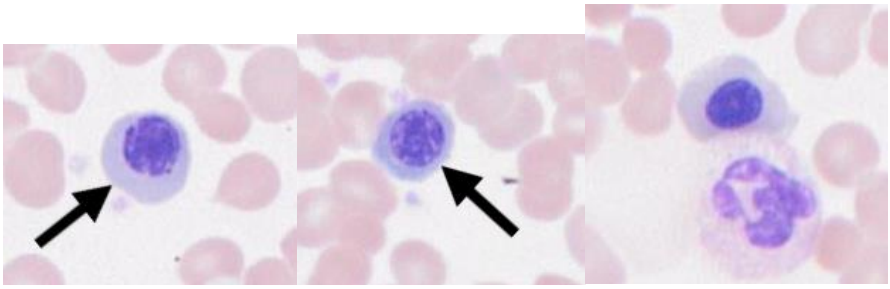
Case 1

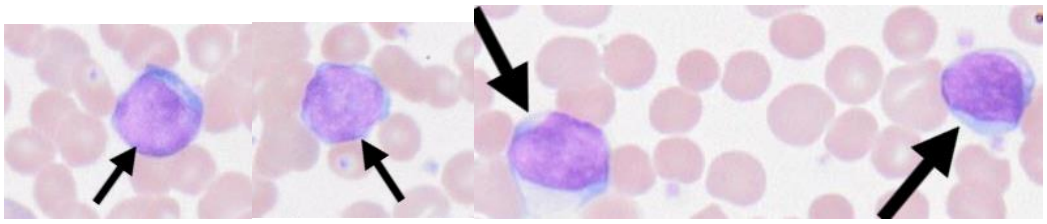
This peripheral blood smear is from a 3-year-old girl presenting with high fevers and diffuse skin rash, recently diagnosed with vasculitis. Laboratory data include: WBC = 26.3 x 10E9/L; RBC = 5.19 x 10E12/L; HGB = 16.2 g/dL; HCT = 48.2%; MCV = 93 fL; and PLT = 611 x 10E9/L.

Normal lymphocytes 

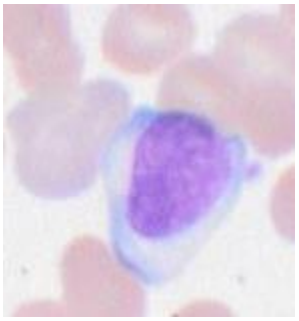
Plasma Cells 

Seg & Monocyte: 

Nucleated RBC's: 

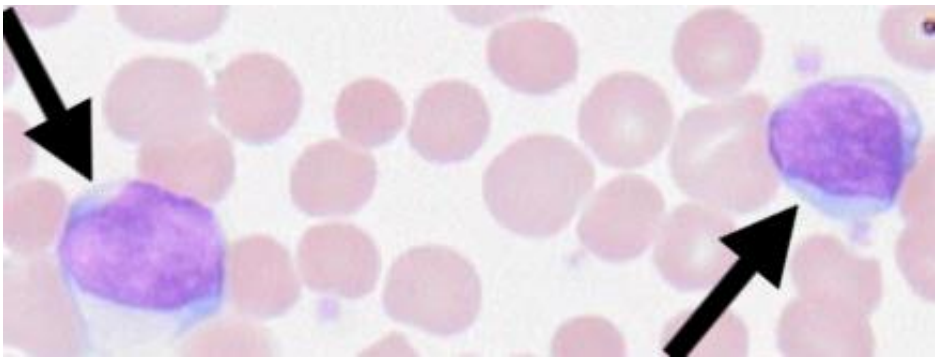
What are these? 

The person who answered knew it wasn't a leukemia or lymphoma starting, so didn't want to call those cells blasts. The nucleoli are quite evident, and you cannot see much cytoplasm, but what you can see looks pretty blue. The cells are not abnormally large, and are squished in the red cells. Also, there were some reactive lymphocytes around as well:



But the cells aren't quite like this either.

Well, CAP says they are myeloblasts. The patient has Kawasaki disease, which can sometimes have 2-6% circulating blast cells. The chromatin of the nucleus is too fine and lacy, and there is so little cytoplasm, and that cytoplasm is clearer and less dark blue than the reactive lymph above. 27% of participants got this right.



I think moving forward, we will likely start classifying cells like this as "Immature/Abnormal Cell, Would Refer." This will help us avoid missing cells like this with missing information or bad pictures, and it is also true and appropriate for our lab.

VPBS-19

Clinical History for VPBS-19 – VPBS-24

This peripheral blood smear is from a 3-year-old girl presenting with high fevers and diffuse skin rash, recently diagnosed with vasculitis. Laboratory data include: WBC = 26.3 x 10E9/L; RBC = 5.19 x 10E12/L; HGB = 16.2 g/dL; HCT = 48.2%; MCV = 93 fL; and PLT = 611 x 10E9/L.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

Please click on the hyperlink below to view the DigitalScope images for this case.
https://www.digitalscope.org/LinkHandler.axd?LinkId=a26478fd-dca8-4bdf-b5cb-407c47e345a9

To access the online Hematology Glossary, please click the hyperlink below:
https://documents.cap.org/documents/cap-hematology-and-clinical-microscopy-glossary.pdf

Summary of Participant Survey Results

The following is a statistical summary of all results submitted by participating laboratories. 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.

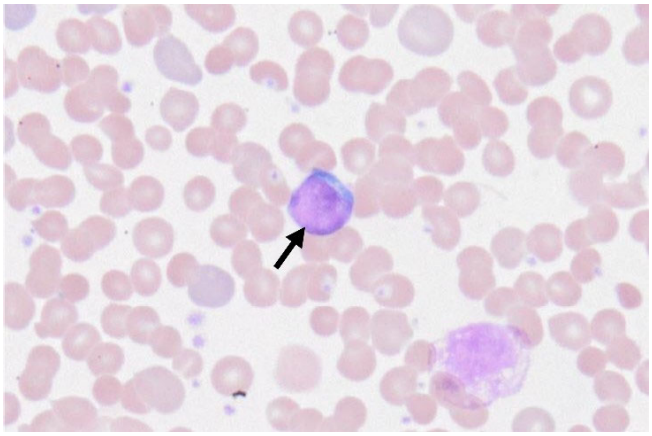
WBC Differential - %	N	MEAN	SD	CV%*	MEDIAN	MIN	MAX
Neutrophils (segmented or bands)	1294	75.4	4.2	5.6	76	63	88
Lymphocytes	1295	11.5	5.9	50.9	11	0	29
Lymphocytes, reactive	929	6.6	5.3	79.7	6	0	22
Monocytes	1278	5.5	2.3	42.6	5	0	12
Eosinophils	580	0.2	0.4	*	0	0	1
Basophils	529	0.0	0.0	0.0	0	0	0
Metamyelocytes	603	0.4	0.7	*	0	0	2
Myelocytes	620	0.4	0.7	*	0	0	2
Promyelocytes	489	0.0	0.0	0.0	0	0	0
Blasts	680	2.5	3.7	*	0	0	14
nRBC/100 WBC	1264	5.6	2.2	38.9	5	0	12

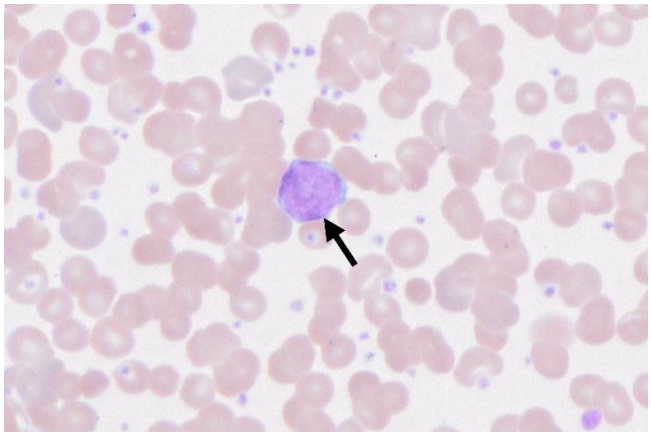
WBC Differential - 10E9/L**	N	MEAN	SD	CV%*	MEDIAN	MIN	MAX
Neutrophils (segmented or bands)	1205	19.797	1.140	5.8	19.73	16.00	23.14
Lymphocytes	1202	3.054	1.541	50.5	2.90	0.00	7.63
Lymphocytes, reactive	850	1.731	1.376	79.5	1.54	0.00	5.79
Monocytes	1189	1.448	0.614	42.4	1.32	0.00	3.20
Eosinophils	544	0.048	0.102	*	0.00	0.00	0.30
Basophils	496	0.000	0.000	0.0	0.00	0.00	0.00
Metamyelocytes	565	0.106	0.172	*	0.00	0.00	0.53
Myelocytes	586	0.115	0.175	*	0.00	0.00	0.72
Promyelocytes	463	0.000	0.000	0.0	0.00	0.00	0.00
Blasts	641	0.657	0.981	*	0.00	0.00	3.68

*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.

**Please see discussion on "Calculating Absolute Counts" that appears in this PSR.

VPBS-23





Identification	Participants Freq	%	Evaluation
Blast cell	359	27.3	Educational
Lymphocyte, reactive (includes plasmacytoid and immunoblastic forms)	688	52.4	Educational
Lymphocyte	186	14.2	Educational
Immature or abnormal cell, would refer for identification	31	2.4	Educational
Malignant lymphoid cell (other than blast)	26	2.0	Educational
Lymphocyte, large granular	10	0.8	Educational
Monocyte, immature (promonocyte, monoblast)	8	0.6	Educational
Monocyte	2	0.2	Educational
Plasma cell, morphologically mature/abnormal/containing inclusion (eg, Dutcher body, Russell body)	2	0.2	Educational
Neutrophil, metamyelocyte	1	0.1	Educational
Neutrophil, myelocyte	1	0.1	Educational

The arrowed cells are blasts, specifically myeloblasts, as correctly identified by 27.3% of participants. Myeloblasts are the most immature cells in the myeloid series. They are normally confined to the bone marrow, where they normally constitute less than 3% of the nucleated cells. They may be present in the blood in leukemic states, in myelodysplastic syndromes, in myeloproliferative neoplasms, and, very rarely, in leukemoid reactions. Leukemic myeloblasts may also exhibit a few delicate granules and/or Auer rods. Distinguishing one type of abnormal blast cell from another is not always possible using Wright-Giemsa stains alone. Additional testing such as cytochemical staining (eg, using myeloperoxidase or Sudan black) or immunophenotyping by flow cytometry may be required to further define the lineage of a given blast population.

2.4% of participants selected the response of immature/abnormal cell, would refer for identification. This is considered an acceptable answer if your laboratory routinely sends the cells in question to an outside laboratory with another CLIA number.

VPBS-23, cont'd

52.4% of participants incorrectly identified the arrowed cells as reactive lymphocytes. Reactive lymphocytes show a range of cellular shapes, sizes and chromatin patterns. The most common type of reactive lymphocyte (Downey type II) are larger lymphocytes with round to oval nuclei, moderately condensed chromatin, and abundant blue-gray cytoplasm. Immunoblasts and immunoblastic-like reactive lymphocytes (Downey type III cells) are large cells with deeply basophilic cytoplasm and round to oval nuclei with moderately to finely dispersed chromatin and abundant parachromatin. The arrowed cells have more homogeneously fine chromatin, a higher N:C ratio, and less basophilic cytoplasm than is typical of Downey type III cells.

14.2% of participants incorrectly identified the arrowed cells as lymphocytes. Normal lymphocytes are small, round to ovoid cells with high N:C ratios and diffusely dense or coarsely clumped chromatin. The arrowed cells are larger and have more open chromatin than lymphocytes.

2.0% of participants incorrectly identified the arrowed cells as malignant lymphoid cells other than blasts. Lymphoma cells can exhibit a variety of appearances based on the lymphoma subtype. Cell size ranges from 8 - 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. Some types of lymphoma cells, including large cell lymphoma, Burkitt lymphoma, and blastoid mantle cell lymphoma, may be difficult to distinguish from blasts, and immunophenotyping studies may be required to make the correct diagnosis.

Case Presentation:

This peripheral blood smear is from a 3-year-old girl presenting with high fevers and diffuse skin rash, recently diagnosed with vasculitis. Laboratory data include: WBC = 26.3 x 10E9/L; RBC = 5.19 x 10E12/L; HGB = 16.2 g/dL; HCT = 48.2%; MCV = 93 fL; and PLT = 611 x 10E9/L.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

Case Discussion: Leukemoid reaction in a patient with Kawasaki disease

Kawasaki disease (KD) is an acute, self-limited vasculitis of unknown etiology with a preferential involvement of the coronary arteries of infants and young children. The diagnosis of classic KD requires the presence of fever lasting more than five days and must have 4 of 5 principal physical signs. The features include: polymorphous erythematous skin rash; bilateral conjunctival injection; cervical lymphadenopathy (> 15mm in diameter, often unilateral); and oral mucosal changes, including diffuse oropharyngeal hyperemia, strawberry tongue, lip swelling, fissuring, erythema, or bleeding. In very young children, diagnosis can be very challenging, since the disease course is often incomplete and more difficult to recognize, with subsequent delay of appropriate therapy and increased risk of coronary artery aneurysms. The diagnosis of KD is usually based on clinical findings, but the American Heart Association has also recommended laboratory evaluation[1-2]. Suggested laboratory studies include complete blood count (CBC), serum alanine aminotransferase, serum albumin, ESR, CRP, and urinalysis. Laboratory findings suggestive of KD include the following: elevated acute-phase reactants (CRP ≥ 3 mg/dL (≥ 30 mg/L) or ESR ≥ 40 mm/hour), WBC count ≥ 15.0 x 10E9/L, normocytic, normochromic anemia, platelet count ≥ 450 x 10E9/L, non-neutrophilic (sterile) pyuria due to urethritis in KD (≥ 10 WBCs/high-power field), serum alanine aminotransferase level > 50 units/L, and serum albumin ≤ 3 g/dL. After a clinical diagnosis of KD, an echocardiogram is usually performed due to an increased risk of coronary artery aneurysm.

Question 1. Patients with KD typically do not show which of the following laboratory findings?

A. ESR ≥ 40 mm/hour
B. Normocytic, normochromic anemia
C. Platelet cell count ≥ 450 x 10E9/L
D. WBC count < 1.0 x 10E9/L

Leukocytosis is typical during the acute stage of KD. A leukemoid reaction occurs in KD when the leukocyte count exceeds 25.0 x 10E9/L, with more than 2% immature white blood cells. The presence of less mature myelocytes and metamyelocytes in the peripheral blood results in the so-called “left shift” in the WBC differential.[3] It is an extreme neutrophilia that may superficially resemble leukemia due to the level of leukocytosis. The granulocytes may show toxic changes including toxic granulation, Döhle bodies, and/or cytoplasmic vacuolization. Leukemoid reactions may be the result of increased demargination (from causes such as strenuous exercise, trauma, medications, or hypoxia), a shift from the bone marrow storage pool (from causes such as significant stress or infection), increased marrow production (from causes such as infection, tissue necrosis, granulocyte colony-stimulating factor (G-CSF) therapy, or chemokine producing tumors), or decreased egress from circulation (from causes such as pregnancy, asplenia, or steroids). Some cases may show an erythroblastosis where immature granulocytes are accompanied by circulating nucleated red blood cells. Erythroblastosis raises a differential of severe infection, significant trauma, prematurity, exuberant marrow regeneration, or a marrow replacing process such as granulomata, hematopoietic neoplasms, and metastasis.

Question 2. Which of the following best describes a leukemoid reaction in a peripheral blood smear?

A. Leukocytosis with > 20% blasts
B. Leukocytosis with increased segmented neutrophils and more than 2% immature myeloid cells including myelocytes and metamyelocytes
C. Leukocytosis with lymphocytosis and normal levels of segmented neutrophils
D. Leukocytosis with mature segmented neutrophils and no immature cells

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A leukemoid reaction may prompt an extensive workup to rule out a broad but concerning differential. Clinical evaluation, peripheral smears, culture studies, and radiologic imaging may be necessary to exclude other causes of leukemoid reaction.[4] This must be distinguished from acute leukemia, which is defined as an increase in blast cells (generally > 20%) and immature WBCs rather than mature neutrophils seen in a leukemoid reaction. Increased blasts are rarely seen in leukemoid reactions unless the patient is a neonate or receiving G-CSF therapy. Leukemoid reactions with more significant granulocyte left shift more closely mimic chronic myeloid leukemia, *BCR*::*ABL1* positive (CML). Moreover, eosinophilia and most notably basophilia are not typical in a leukemoid reaction, aiding in distinguishing CML from a leukemoid reaction. Moreover, the clinical scenario greatly aids in the distinction of the two. However, in more challenging cases, FISH analysis for *BCR*::*ABL1* fusion gene can be performed to exclude CML. The cause of leukemoid reaction in KD is unknown due to a lack of an etiologic agent.[5] However, it is likely due to the combination of an over-productive and reactive bone marrow in an inflammatory state.[6] Additionally, if corticosteroids are included in the patient management, leukemoid reaction may be associated with steroid-related demargination. Notably, unlike CML, a leukemoid reaction is reversible and often resolves, typically after the acute phase.

Question 3. An abnormal *BCR*::*ABL1* fusion gene will differentiate leukemoid reaction due to Kawasaki disease from the following?

A. Chronic myeloid leukemia
B. G-CSF therapy
C. Infection
D. Strenuous exercise

Ifeyinwa Obiorah, MD, FCAP
Hematology and Clinical Microscopy Committee

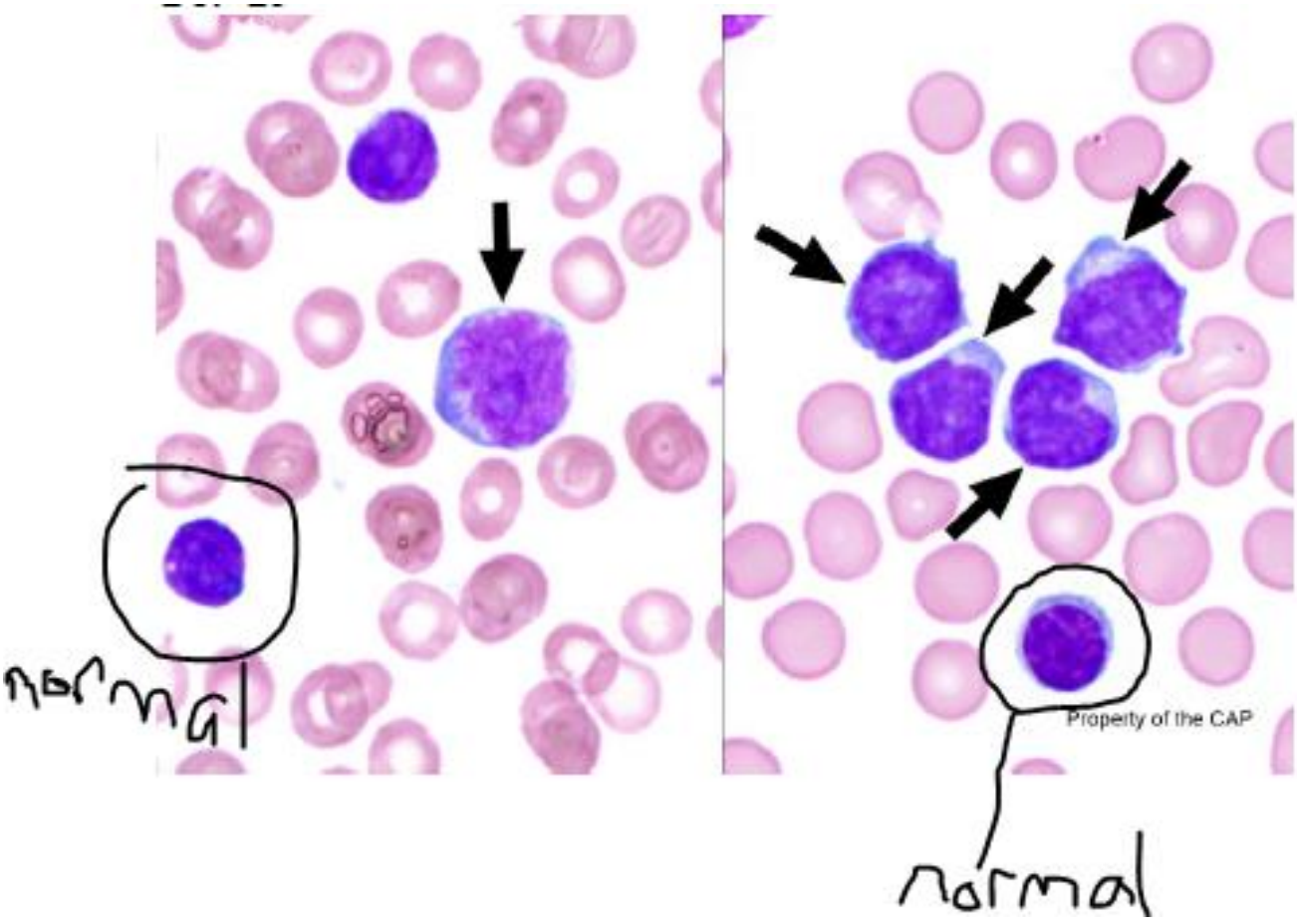
Case 2

Case History
This peripheral blood smear is from a 71-year-old woman with recent onset lymphadenopathy, poor appetite, weight loss, and progressive weakness. Laboratory data include: WBC = 102.3 x 10E9/L; RBC = 2.61 x 10E12/L; HGB = 6.7 g/dL; HCT = 18.4%; MCV = 92 fL; RDW = 24%; and PLT = 103 x 10E9/L. Identify the arrowed object(s) on each image.

First important thing to note is that WBC count (102!!!).

That likely takes us to leukemia/lymphoma territory.

What are these and why?



What characteristics can you point out? Large cells. Big nucleus with multiple nucleoli. Scant, dark cytoplasm. Vacuoles!!!! Are they uniform? Or is there lots of variance?

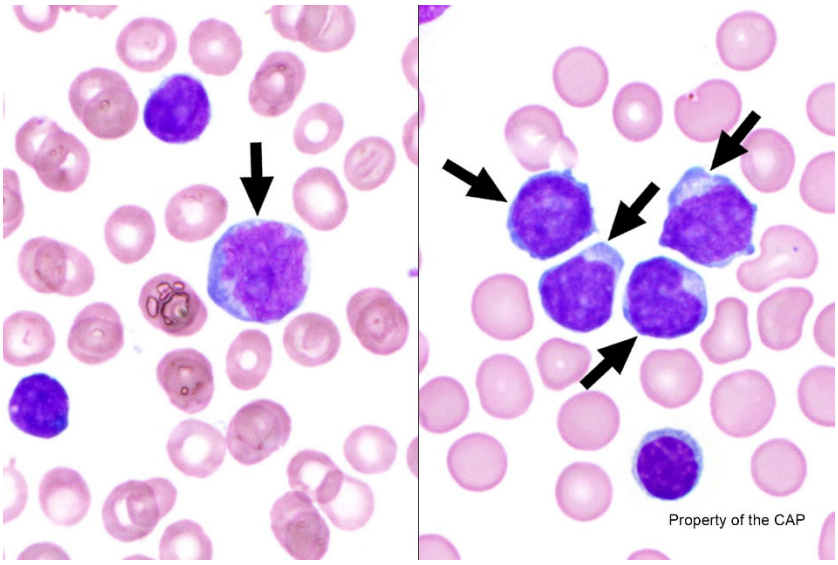
Those were the two clues that CAP wanted us to use to call these Lymphoma cells (malignant lymphoid cell other than blast). The **non-uniformity** and the **vacuoles**. Blast cells should not have vacuoles. Lymphoma cells can. 36% of participants knew this and got this correct.

We called them blasts because they were clearly abnormal and immature, but there was no previous lymphoma diagnosis.

Again, we would have been acceptable here using the response “Abnormal/Immature – would refer.” And it is true for our laboratory that we would send cells like this to SMJH or the pathologist STAT, especially with no history. Therefore, we will start to use this response in CAP surveys where appropriate.

Blood Cell Identification – Ungraded

BCP-28



Identification	Referees Freq	Referees %	Participants Freq	Participants %	Evaluation
Malignant lymphoid cell (other than blast)	71	35.1	1850	36.9	Educational
Lymphocyte, reactive (includes plasmacytoid and immunoblastic forms)	48	23.8	1372	27.4	Educational
Lymphocyte	43	21.3	927	18.5	Educational
Blast cell	28	13.9	591	11.8	Educational
Immature or abnormal cell, would refer for identification	10	5.0	212	4.2	Educational
Lymphocyte, large granular	1	0.5	39	0.8	Educational
Neutrophil necrobiosis (degenerated neutrophil)	1	0.5	1	0.0	Educational

The arrowed cells are malignant lymphoid cells (other than blasts), as correctly identified by 35.1% of referees and 36.9% of participants. Lymphoma cells can exhibit a variety of appearances depending on the lymphoma subtype, and definitive diagnosis can be difficult. 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. Large lymphoma cells may exhibit some highly abnormal morphologic appearances. They are large (20 to 30 µm) and have scant to moderate amounts of basophilic cytoplasm. The nuclei are generally round to oval, but they may be angulated, folded, indented, or convoluted. Nucleoli are prominent, and they may be single or multiple. Vacuoles can occasionally be seen in the cytoplasm. These cells can be easily confused with blasts, and additional studies such as immunophenotyping (flow cytometry) are often necessary to make the correct diagnosis.

5.0% of referees and 4.2% of participants selected the response of immature/abnormal cell, would refer for identification. This is considered an acceptable answer if your laboratory routinely sends the cells in question to an outside laboratory with another CLIA number.

BCP-28, cont'd

23.8% of referees and 27.4% of participants incorrectly identified the arrowed cells as reactive lymphocytes. Reactive lymphocytes show a range of cellular shapes, sizes and chromatin patterns. The most common type of reactive lymphocyte (Downey type II) are larger lymphocytes with round to oval nuclei, moderately condensed chromatin, and abundant blue-gray cytoplasm. Immunoblasts and immunoblastic-like reactive lymphocytes (Downey type III cells) are large cells with deeply basophilic cytoplasm and round to oval nuclei with moderately to finely dispersed chromatin and abundant parachromatin. The arrowed cells have a higher N:C ratio than is typical of reactive lymphocytes.

21.3% of referees and 18.5% of participants incorrectly identified the arrowed cells as lymphocytes. Normal lymphocytes are small, round to ovoid cells. 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.

13.9% of referees and 11.8% of participants incorrectly identified the arrowed cells as blast cells. A blast is a large, round-to-oval cell, 10 to 20 µm in diameter. In the blood film, the cell may appear flattened or compressed by adjacent red blood cells. The nuclear-to-cytoplasmic ratio is high, varying from 7:1 to 5:1. The blast often has a round to oval nucleus, but sometimes it is indented or folded. The blast cell has fine, lacy or reticular chromatin. One or more prominent nucleoli may be seen. The cytoplasm is variably basophilic and typically agranular.

Clinical Presentation:

This peripheral blood smear is from a 71-year-old woman with recent onset lymphadenopathy, poor appetite, weight loss, and progressive weakness. Laboratory data includes: WBC = 102.3 x 10E9/L; RBC = 2.61 x 10E12/L; HGB = 6.7 g/dL; HCT = 18.4%; MCV = 92 fL; RDW = 24%; and PLT = 103 x 10E9/L.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

Case Discussion: Diffuse Large B Cell Lymphoma

The diagnosis in the presented case is diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS).

DLBCL usually involves the lymph nodes or extranodal tissues and typically exhibits a diffuse growth pattern of large neoplastic cells, hence its name.[1] On occasion, though, neoplastic lymphoid cells infiltrate the blood and bone marrow, leading to peripheral blood involvement termed ‘leukemic phase’.

On peripheral blood smears, DLBCL lymphoma cells are larger in size (20 - 30 µm) than typical normal mature lymphocytes (7 - 15 µm), and have scant to moderate cytoplasm. The nuclear features may include irregular nuclear membranes with variably condensed chromatin and one or more prominent nucleoli. Vacuoles may also be seen in the cytoplasm. On examination of a peripheral blood smear, it may be difficult to distinguish DLBCL cells from reactive lymphocytes or blasts. Blasts are usually fairly large cells (15 - 20 µm) with a high N:C ratio and typically basophilic cytoplasm. The cell and nucleus are usually round, although irregular or folded nuclei may be present, and the chromatin is fine/lacy and nucleoli can be prominent. Myeloblasts may exhibit cytoplasmic granules and/or Auer rods aiding in their distinction from lymphoblasts. Reactive lymphocytes (15 - 25 µm) are larger than normal lymphocytes and show moderately abundant cytoplasm. The N:C ratio tends to be low in reactive lymphocytes compared to DLBCL lymphoma cells where the N:C is usually high. Reactive lymphocytes are characterized by their wide range of morphologic appearances within the same blood smear. In contrast, while DLBCL cells can exhibit a range of morphologic appearances, any individual case tends to show a more monotonous population of cells on the blood smear. The clinical history can also be important since a prior history of DLBCL aids in an increased suspicion for identification of these cells.

Peripheral blood involvement by DLBCL can mimic leukemic presentation of other non-Hodgkin lymphomas such as follicular lymphoma (FL), Burkitt lymphoma, and chronic lymphocytic leukemia (CLL). Small cell size is the main distinguishing feature between DLBCL and FL or CLL, the latter of which may be the same size as normal lymphocytes. Prolymphocytes are larger lymphoid cells that are seen in some cases of CLL or prolymphocytic leukemia and are characterized by a centrally placed, oval-to round nucleus, prominent nucleolus, condensed chromatin and a moderate amount of blue cytoplasm. Follicular lymphoma cells are slightly larger than normal lymphocytes and demonstrate characateristic clefted, indented, folded, convoluted or even lobulated nuclei. Burkitt lymphoma cells are intermediate-sized and tend to exhibit one or more prominent nucleoli, moderately abundant basophilic cytoplasm and numerous small and uniform round cytoplasmic vacuoles. Although the morphologic characteristics of the lymphoma cells may be helpful in generating a differential diagnosis, definitive diagnosis of DLBCL generally requires additional testing such as flow cytometry and genetic testing.

Flow cytometric immunophenotyping for assessment of: (1) the presence of B-cell markers and (2) B-cell clonality with the latter being essential in differentiating from reactive B-cell proliferations. It is important to mention that flow cytometic analysis may be falsely negative due to the large size of the neoplastic cells that may not be amenable to cell passage through the capillary of the flow cytometer. Most cases of DLBCL will undergo fluorescence in situ hybridization (FISH) studies to evaluate for rearrangements of the *MYC* and *BCL2* (and potentially for the *BCL6*) loci. This is highly recommended to exclude the diagnosis of more aggressive forms of DLBCL which have a worse prognosis.[4-5] A conventional karyotype can also be performed.

The standard therapeutic approach for the treatment of DLBCL, NOS is a combination of chemotherapy and immunotherapy using rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP). Although R-CHOP therapy remains the main treatment of choice for DLBCL, about 40% of patients do not achieve remission.[7] Recent clinical trials have investigated whether there is a benefit to more dose-intensive immunochemotherapy regimens or regimens that include targeted therapeutics. A molecularly driven approach to classification may lay the foundation for precision medicine in treatment of DLBCL.

Ifeyinwa Obiorah, MD, PhD, FCAP
Aadil Ahmed, MD, FCAP
Hematology and Clinical Microscopy Committee

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