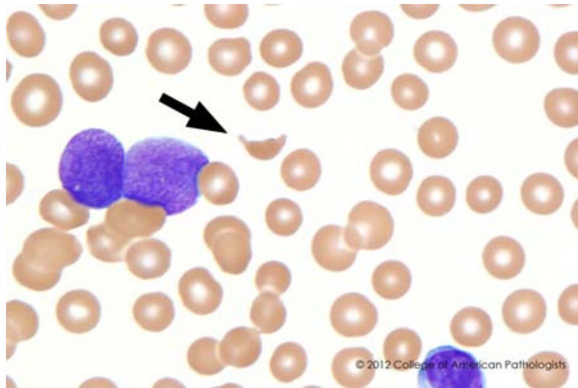
Blood Cell Identification – Graded

Case History

This peripheral blood smear is from a previously healthy 4-year-old boy who presents with 1 month of intermittent fevers, night sweats, fatigue, and weight loss. Laboratory data include: WBC = 31.4 x 10^9/L; RBC = 2.28 x 10^{12}/L; HGB = 6.6 g/dL; HCT = 19.8 %; MCV = 86.7 fL; RDW = 17.3, and PLT = 200 x 10^9/L. Identify the arrowed object(s) on each image.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

BCP-01

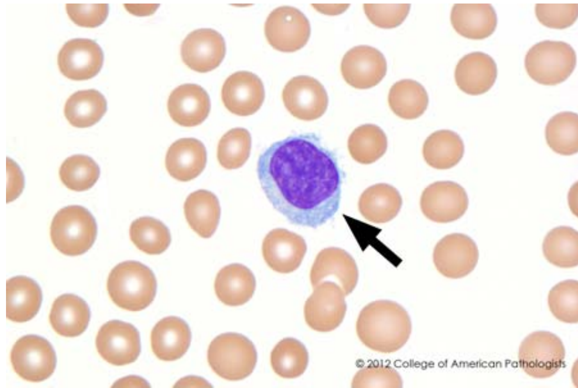


Identification	Referees No.	Referees %	Participants No.	Participants %	Evaluation
Fragmented red cell	98	99.0	4956	98.4	Good
Bite cell	1	1.0	45	0.9	Unacceptable

The red cell identified by the arrow is a fragmented red cell (schistocyte), correctly identified by 99.0% of the referees and 98.4% of participants. Other forms of fragmented red cells include helmet cells and keratocytes (horn cells). Small irregularly shaped cells which contain central pallor are best considered non-specific poikilocytes. True schistocytes should not have any central pallor. Schistocytes are only rarely seen in normal blood films. When seen together in the context of anemia and thrombocytopenia, schistocytes are reflective of a microangiopathic hemolytic anemia, such as can occur in disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP) and other causes. A minor population of microspherocytes can also be seen in the setting of a microangiopathic hemolytic anemia. In this case of acute leukemia, although the platelet count is still normal, the presence of schistocytes is concerning for the early stages of DIC.

Blood Cell Identification – Graded

BCP-02

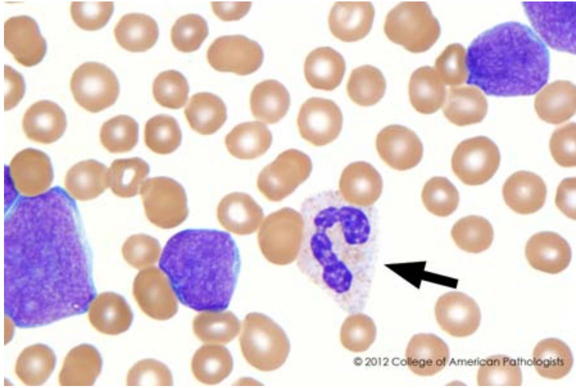


Identification	Referees No.	Referees %	Participants No.	Participants %	Evaluation
Lymphocyte, reactive	34	34.3	1547	30.7	Good
Lymphocyte	61	61.6	3018	59.9	Acceptable
Lymphocyte, large granular	2	2.0	211	4.2	Unacceptable
Lymphoma cell (malignant)	1	1.0	68	1.4	Unacceptable
Monocyte	1	1.0	66	1.3	Unacceptable

The cell indicated by the arrow is a reactive lymphocyte, correctly identified by 34.3% of the referees and 30.7% of the participants. Lymphocyte is acceptable as identified by 61.6% of the referees and 59.9% of the participants. This lymphocyte is slightly larger in size than a quiescent non-reactive lymphocyte, with a modest increase in the size of its nucleus and the amount of cytoplasm. The nuclear contour is slightly rhomboid instead of round. Nuclear chromatin, although slightly less dense than that seen in non-reactive forms, is still predominantly clumped and mature in appearance. The cytoplasm in the identified cell is pale blue (and lacks granules), but reactive lymphocytes can have deeper blue cytoplasm, either diffusely or focused towards the periphery of the cell in a pattern termed "radial basophilia." The cytoplasm of reactive lymphocytes can sometimes contain scant fine granulation. Because reactive lymphocytes are usually larger, with more cytoplasm, and can have mild nuclear irregularities, they can appear somewhat similar to monocytes.

Blood Cell Identification – Graded

BCP-03

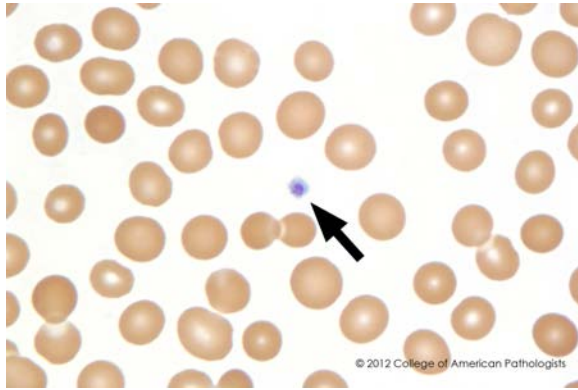


Identification	Referees No.	Referees %	Participants No.	Participants %	Evaluation
Neutrophil, segmented or band	95	96.0	4763	94.5	Good
Neutrophil, toxic	4	4.0	229	4.5	Unacceptable

The arrowed cell represents a neutrophil, accurately identified by 96.0% of the referees and 94.5% of participants. The nuclei of mature segmented neutrophils usually have three to five nuclear lobes connected by thin chromatin filaments. The identified cell appears to be a band form just beginning to segment. The cytoplasm is pale pink and contains fine secondary (or specific) granules, red-purple or lilac in color.

Blood Cell Identification – Graded

BCP-04

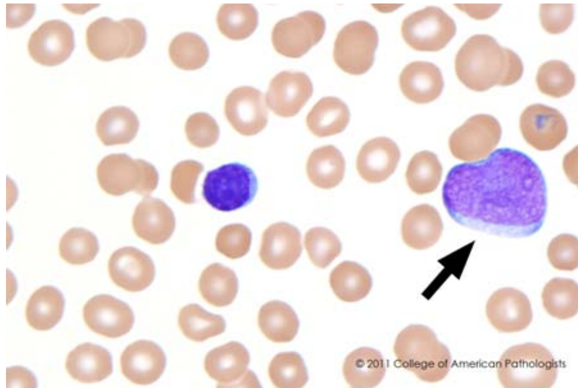


Identification	Referees No.	Referees %	Participants No.	Participants %	Evaluation
Platelet, normal	98	99.0	4996	99.2	Good
Platelet, hypogranular	1	1.0	24	0.5	Unacceptable

The arrow points to a platelet, correctly identified by 99.0% of the referees and 99.2% of participants. These are also called thrombocytes. Platelets are small blue-grey fragments of megakaryocytic cytoplasm without a nucleus. They contain fine purple granulation that is either evenly dispersed or aggregated towards the center of the cell. Their shape is usually round, but can vary. Platelets are usually less than half the diameter of a normal red cell in size, as in this photograph, but can be larger in reactive states. Significant thrombocytopenia is common in acute leukemia, but in this case the platelet count is normal.

Blood Cell Identification – Graded

BCP-05



Identification	Referees No.	Referees %	Participants No.	Participants %	Evaluation
Blast cell	82	82.8	4137	82.1	Good
Lymphocyte, reactive	7	7.1	284	5.6	Unacceptable
Monocyte, immature	4	4.0	188	3.7	Unacceptable
Monocyte	3	3.0	88	1.8	Unacceptable

The cell indicated by the arrow is a blast cell, correctly identified by 82.8% of the referees and 82.1% of participants. Specifically, it is a lymphoblast, although lineage usually cannot be determined by morphology alone. Blasts are commonly intermediate to large in size, as is the case with the arrowed lymphoblast in comparison to the mature lymphocyte seen to the left in this image. In a few cases, lymphoblasts can be small and difficult to distinguish from mature lymphocytes. The nuclei of blast cells may be round, oval or rhomboid, or may be clefted or more irregular. The blasts in this case have predominantly round or oval nuclei. Deep nuclear clefting, which is not present in this case, can be a characteristic feature of lymphoblasts. Dispersed or open nuclear chromatin is a marker of immaturity, and this immaturity can vary from subtle to more overt in lymphoblasts, and is usually quite obvious in myeloblasts. Blasts usually contain one or more nucleoli, which can vary from indistinct to large and prominent. Blasts in this case contain one to three small semi-distinct nucleoli. Although large prominent nucleoli are more characteristic of myeloblasts, these can also be seen in some lymphoblasts. Cytoplasm is small in amount, and in lymphoblasts is usually agranular and without vacuoles. Granulation may or may not be present in myeloblasts, but is only very rarely seen in lymphoblasts. Auer rods are sometimes seen in acute myeloid leukemia, but are never seen in lymphoblastic leukemia.

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Table 1: Complications of acute leukemias

Marrow failure
• Anemia → weakness, fatigue, dyspnea, tachycardia, ischemia • Neutropenia → fever, infection • Thrombocytopenia → bleeding
Tissue and organ infiltration
• Marrow expansion ± infarction → bone pain • Hepatosplenomegaly, lymphadenopathy, extramedullary tissue masses • CNS infiltration → headache, confusion, meningeal symptoms • Leukostasis → tissue ischemia or infarction

Morphologic Findings

Peripheral blood cytopenias are almost always present at diagnosis and pancytopenia (anemia, neutropenia, and thrombocytopenia) is common. The total white count can vary from very low to normal to extremely high (WBC > 100 x 10^9/L). In our case, the total white count was moderately elevated (31.4 x 10^9/L), but the differential revealed an absolute neutropenia as well as a high proportion of circulating blasts. Leukemic lymphoblasts are almost always present in the peripheral blood, often comprising a significant proportion of circulating leukocytes. In some cases with a low total WBC, it is possible that the peripheral blood may contain only rare circulating lymphoblasts, and the diagnosis may not be clear until a bone marrow biopsy is performed.

Lymphoblasts are often larger than mature lymphocytes, but their size can be quite variable from small to large. Their nuclei are predominantly round and sometimes deeply clefted, and less commonly may be more irregular. Chromatin immaturity can be subtle, but is typically smoother and less dense than a mature lymphocyte. Nucleoli are usually indistinct, but can also be prominent. The nuclear:cytoplasmic (N:C) ratio is typically higher than a mature lymphocyte, with only a very scant rim of cytoplasm, but this can also be variable. Cytoplasm is basophilic and usually without either granules or vacuoles. Auer rods, which are characteristic of acute myeloid leukemia, are never present.

Key Morphologic Points & Pitfalls

Smaller lymphoblasts with subtle immaturity can be mistaken for mature lymphocytes. T-ALL lymphoblasts and occasionally B-ALL lymphoblasts may have more coarseness to their chromatin pattern. However the lymphoblasts are typically larger, and may have indistinct nucleoli compared to the mature lymphocytes that are likely also present in the blood smear for comparison. If the peripheral blood smear staining is too dark, chromatin immaturity may be obscured. Occasionally, lymphoblasts may be fairly large with open reticular chromatin and a prominent nucleolus, resembling myeloblasts. Infrequently, there may be an associated eosinophilia, but the presence of neutrophilia, myeloid progenitors, and/or basophilia and eosinophilia should trigger consideration of blast phase transformation of CML. Lymphoid cells with round nuclei, peripherally placed nucleoli and deep blue, frequently vacuolated cytoplasm should trigger consideration of Burkitt lymphoma. These lymphoid cells typically contain coarser chromatin than lymphoblasts.

Figure 1: Lymphoblast morphology

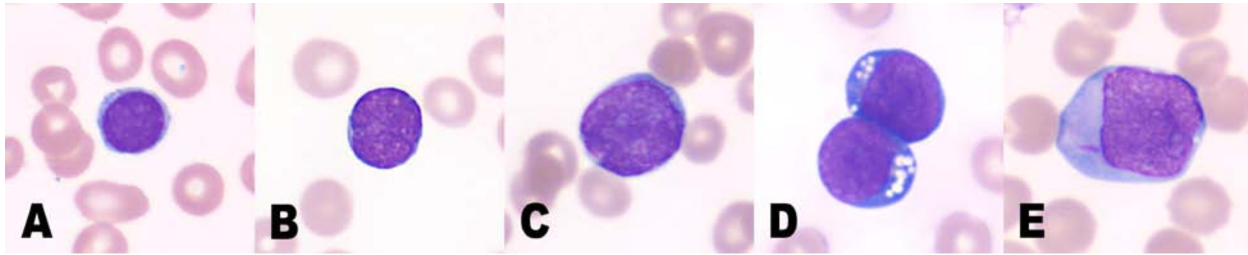

Image **A** is a small mature and benign lymphocyte with condensed chromatin and no nucleoli. **B** is an example of a smaller lymphoblast, only slightly larger than a lymphocyte, with a clefted nucleus, very subtle chromatin immaturity, and indistinct nucleoli. **C** shows a larger lymphoblast with more open immature chromatin and more prominent nucleoli. For comparison, **D** shows two Burkitt cells with round non-clefted nuclei, deeply basophilic cytoplasm, and small cytoplasmic vacuoles, and **E** shows a large myeloblast with very open reticular nuclear chromatin and its cytoplasm contains an Auer rod.

Flow Cytometric Immunophenotyping

Acute leukemias are classified as myeloid or lymphoid, and lymphoid leukemias are classified as precursor-B or precursor-T lineage. This is most readily done by analysis of cell surface markers using flow cytometric immunophenotyping on bone marrow or peripheral blood. Morphological findings may suggest either myeloid or lymphoid lineage, but morphology alone is not sufficient or definitive unless Auer rods are present, which are diagnostic of myeloid lineage.

B-ALL lymphoblasts express B-cell markers such as CD19, cytoplasmic CD79a, and cytoplasmic CD22. In most cases, there is coexpression of CD10, originally termed CALLA, the "*Common ALL Antigen*." For either B or T lymphoblasts, expression of CD34 and/or nuclear TdT, and dim to absent expression of CD45, are indicators of immaturity. For B lymphoblasts, absent to dim expression of CD20 and lack of surface immunoglobulin are additional markers of immaturity. T-ALL lymphoblasts are best identified by expression of cytoplasmic CD3. Additional markers of immaturity for T lymphoblasts include CD1a, lack of surface CD3, and either coexpression of CD4 and CD8, or absence of both CD4 and CD8. Leukemic lymphoblasts may have aberrant expression of myeloid antigens such as CD13 or CD33, but myeloperoxidase should be negative. Aberrant expression of T-cell antigens on B lymphoblasts is uncommon. The coexpression of CD15 and lack of CD10 suggests a specific genetic subtype, with a translocation of the *MLL* gene on 11q23.

Cytogenetics

The presence or absence of specific cytogenetic abnormalities confers important prognostic information, which is used to help direct chemotherapy. Some cytogenetic abnormalities, such as hyperdiploidy (the presence of multiple copies of some chromosomes without additional abnormalities) or the t(12;21) translocation indicate a favourable prognosis, whereas other abnormalities such as hypodiploidy or the t(9;22) BCR-ABL1 translocation, indicate a poor prognosis that may require more intensive chemotherapy or stem cell transplantation. The more significant cytogenetic abnormalities are reflected in the current WHO 2008 classification, outlined in table 2.

Table 2: The WHO 2008 Classification of B lymphoblastic leukemia

B lymphoblastic leukemia with recurrent genetic abnormalities
• t(9;22); *BCR-ABL1* • t(v;11q23); *MLL* rearranged • t(12;21); *TEL-AML1* (*ETV6-RUNX1*) • t(5;14); *IL3-IGH* • t(1;19) *E2A-PBX1* (*TCF3-PBX1*) • hyperdiploidy (> 50 chromosomes) • hypodiploidy (< 44 chromosomes)
B lymphoblastic leukemia not otherwise specified

Risk stratification and therapy

Treatment involves intensive multi-agent chemotherapy, which is given over several courses, and can involve low dose maintenance chemotherapy lasting up to two years to reduce the risk of relapse. Patients with ALL now receive risk-adapted therapy, in which the type and intensity of chemotherapy is determined by factors which classify patients as favorable, intermediate, or high risk. Since the 1990's, the patient's age, presenting white count, cytogenetic findings, and the presence or absence of extra-medullary disease have been successfully used for risk stratification. More recently, the early response to therapy and the assessment of minimal residual disease (MRD) by flow cytometry have proven to have strong predictive value.

The treatment of ALL, most especially in pediatrics, is truly a medical success story. In decades past, there were no effective therapies and all patients inevitably died. Whereas today, most children and up to one-third of adults successfully achieve remission and can be considered cured. Integration of newer prognostic data such as MRD into treatment plans will hopefully continue to improve outcomes further.

The significance of blasts in the peripheral blood

In most cases, blast cell lineage cannot be determined by morphology alone, and it is far more critical to recognize when blasts are present. Not all circulating blast cells represent acute leukemia, but benign reactive circulating blast cells are only rarely seen. This can occur in reactive conditions such as a significant left shift or a leukoerythroblastic blood picture reflecting a marrow stress response to severe systemic illness, or following therapy with a growth factor that stimulates myelopoiesis (such as granulocyte colony stimulating factor or G-CSF). In general, it is uncommon to find even rare blasts cells circulating in the peripheral blood. In the absence of a clear alternative explanation, the presence of a significant proportion of circulating blast cells, most especially in the setting of new cytopenias, should be considered a serious finding and worrisome for an acute leukemia.

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Kathryn Rizzo, DO, PhD

Hematology and Clinical Microscopy Resource Committee

Recommended Reading

1. Reichard K. *Precursor B- and T- Acute Lymphoblastic Leukemia/Lymphoma.* In: Foucar K, Reichard K, Czuchlewski D. Bone Marrow Pathology, 3rd Edition, volume 2. ASCP press, Chicago, 2010.
2. Borowitz MJ, Chan JKC. *B lymphoblastic leukemia/lymphoma not otherwise specified* and *B Lymphoblastic Leukemia/Lymphoma with recurrent genetic abnormalities.* In: Swerdlow SH, ed. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th Edition. IARC Press, Lyon, 2008.
3. Hoelzer D, Gökbuget N, Ottman O, et al. *Acute lymphoblastic leukemia.* Hematology Am Soc Hematol Educ Program 2002: 162-192.

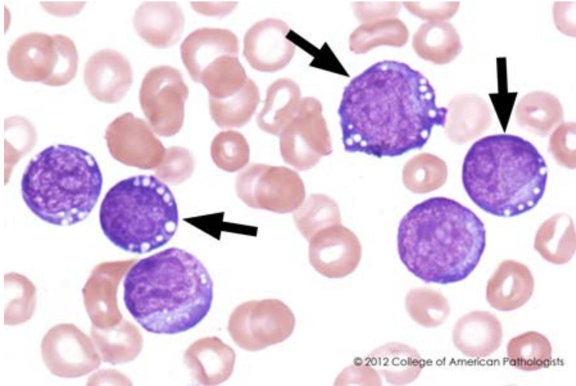
Blood Cell Identification – Ungraded

Case History

This peripheral blood smear is from a 28-year-old male with a mass in the jaw. Laboratory data include: WBC = 10.9 x 10^9/L; RBC = 3.79 x 10^{12}/L; HGB = 11.3 g/dL; HCT = 32.5 %; MCV = 85.7 fL; RDW = 14.1, and PLT = 27 x 10^9/L. Identify the arrowed object(s) on each image.

(PERIPHERAL BLOOD, WRIGHT-GIEMSA)

BCP-06

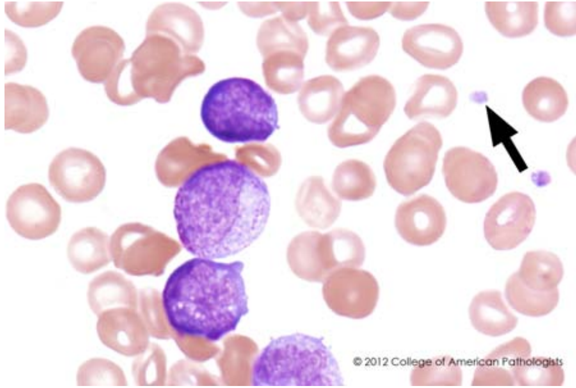


Identification	Referees No.	Referees %	Participants No.	Participants %	Evaluation
Lymphoma cell (malignant)	45	46.9	2209	44.7	Educational
Blast cell	33	34.4	1951	39.5	Educational
Monocyte, Immature	6	6.3	246	5.0	Educational
Lymphocyte, reactive	4	4.2	156	3.2	Educational
Metastic tumor cell	2	2.1	18	0.4	Educational
Neutrophil promyelocyte, abnormal	1	1.0	20	0.4	Educational
Immature or abnormal cell	5	5.2	246	5.0	Educational

The arrowed cells represent circulating Burkitt lymphoma cells, accurately identified by 46.9% of the referees and 44.7% of participants. Blast cell is also acceptable as identified by 34.4% of the referees and 39.5% of participants. Circulating Burkitt lymphoma cells were previously termed L3 lymphoblasts. However, these cells represent peripheral blood involvement by a mature B-cell lymphoma and are better characterized as circulating lymphoma cells. The cells are larger than normal lymphocytes and are relatively uniform in size with round to oval nuclei. The chromatin pattern is more condensed than is expected in a typical blast and is relatively homogeneous. As is seen in the indicated cells, one or more prominent nucleoli may be present. Circulating Burkitt lymphoma cells characteristically have a moderate amount of deeply basophilic cytoplasm containing multiple, uniformly sized, round vacuoles that surround the nucleus. The more mature appearance of the nuclear chromatin, the basophilic cytoplasm and the presence of vacuoles help to distinguish Burkitt lymphoma cells from other subtypes of circulating lymphoma cells and from true lymphoblasts.

Blood Cell Identification – Ungraded

BCP-07

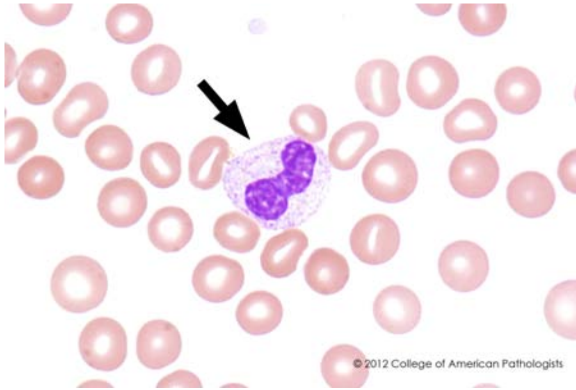


Identification	Referees No.	Referees %	Participants No.	Participants %	Evaluation
Platelet, normal	87	90.6	4555	92.0	Educational
Platelet, hypogranular	9	9.4	373	7.5	Educational

The arrow points to a platelet, correctly identified by 90.6% of the referees and 92.0% of the participants. Platelets are small anuclear fragments of megakaryocytic cytoplasm and contain fine purple-red granules.

Blood Cell Identification – Ungraded

BCP-08

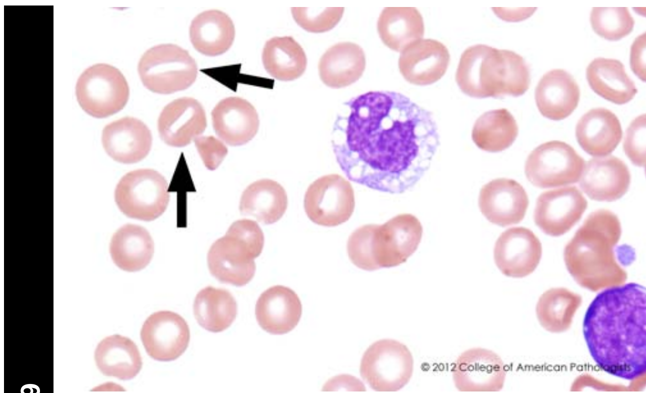


Identification	Referees No.	Referees %	Participants No.	Participants %	Evaluation
Neutrophil, segmented or band	89	92.7	4529	91.5	Educational
Neutrophil, toxic	4	4.2	215	4.4	Educational
Neutrophil, giant band	3	3.1	141	2.9	Educational

The arrowed cell represents a band neutrophil which was correctly identified by 92.7% of the referees and 91.5% of the participants. Band neutrophils may constitute five to 10 percent of the cells in the blood. Their nuclear chromatin is clumped and the nucleus is indented to more than half of the distance from the nearest nuclear margin, distinguishing them from a metamyelocyte. The chromatin never constricts to the point of a filament which helps to distinguish a band neutrophil from a segmented neutrophil (although band neutrophils and segmented neutrophils are lumped together for the purposes of proficiency testing). The cytoplasm shows plentiful specific, pink to lilac granules with rare primary or azurophilic granules. The condensed nuclear chromatin and the presence of cytoplasm with multiple granules help to distinguish the band neutrophil from other white blood cells.

Blood Cell Identification – Ungraded

BCP-09

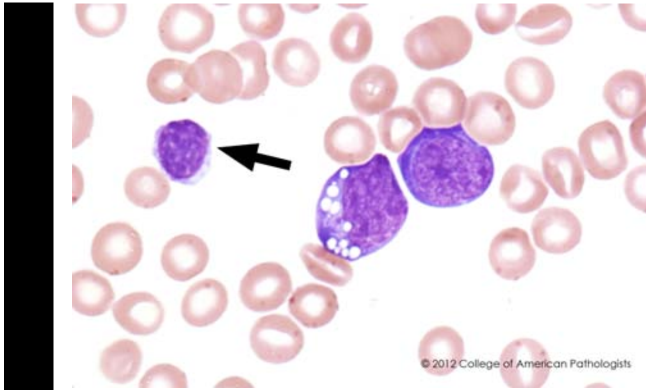


Identification	Referees No.	Referees %	Participants No.	Participants %	Evaluation
Stomatocyte	96	100.0	4938	99.8	Educational

The arrows are pointing to stomatocytes which were correctly identified by 100.0% of the referees and 99.8% of the participants. Stomatocytes are similar in appearance to normal red blood cells in size and shape; however, the central area of pallor is slit-like rather than round. Stomatocytes may be seen in a variety of different conditions that include hereditary disorders, such as hereditary stomatocytosis, which is inherited as an autosomal dominant trait. Hereditary stomatocytosis is associated with increased red cell hemolysis. In addition, stomatocytes may be seen in a variety of other disorders including cardiovascular disease, some cases of carcinoma, alcoholic cirrhosis, acute alcoholism, liver disease and in the presence of some drugs. In addition, stomatocytes may be seen as an artifact in blood smears that are slow to dry.

Blood Cell Identification – Ungraded

BCP-10



Identification	Referees No.	Referees %	Participants No.	Participants %	Evaluation
Lymphocyte	96	100.0	4847	98.0	Educational

The arrow is indicating a lymphocyte and was correctly identified by 100.0% of the referees and 98.0% of the participants. The lymphocyte is slightly larger than the surrounding red blood cells but is much smaller than the circulating lymphoma cells seen in the same picture. The lymphocyte nucleus is small and round with condensed chromatin. The cytoplasm forms a thin rim that is slightly basophilic and lacks granules. The lymphocyte is a helpful gauge of the larger size of the circulating lymphoma cells and is a useful comparison to see the degree of chromatin condensation that is characteristic of the circulating Burkitt lymphoma cell. Lymphocytes may show a variety of morphologic features and may be larger than the small lymphocyte identified here. Occasional lymphocytes may also have a few small pink granules present in the cytoplasm.

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Discussion:

Burkitt Lymphoma

This case is an example of blood involvement by Burkitt lymphoma. Burkitt lymphoma is an aggressive, rapidly growing malignancy of mature B lymphocytes that typically involves lymph nodes or extranodal sites, but occasionally involves the blood (Burkitt leukemia). Blood involvement typically occurs secondarily in patients who have bulky disease, but rarely can present as a leukemia with disease confined to the blood and bone marrow. Blood involvement is seen in up to 5% of patients and often is associated with involvement of the central nervous system (CNS). In the past, peripheral blood involvement by Burkitt lymphoma was termed L3 acute lymphoblastic lymphoma. However, it is clear based on immunophenotypic and genetic data that blood involvement by Burkitt lymphoma is not an acute lymphoblastic process, and usage of the terminology of L3 lymphoblasts to describe the Burkitt lymphoma cells is discouraged.

Clinical Features

There are three clinical variants of Burkitt lymphoma. Endemic Burkitt lymphoma affects young children (peak incidence at 4-10 years old) in equatorial Africa or Papua, New Guinea. In all patients the majority of the lymphoma cells are infected with Epstein Barr Virus (EBV). Tumors are usually extranodal and frequently involve the jaw, orbit, or other facial bones. Sporadic Burkitt lymphoma occurs throughout the world, usually in children or young adults (median age of adult patients is 30 years). It represents 30-50% of childhood lymphomas and 1-2% of adult lymphomas in Western Europe and North America. Approximately 10-20% of sporadic cases are EBV infected. Sporadic cases present as an abdominal mass, usually involving the ileocecal region, in 80-90% of cases, but may also involve the ovaries, kidneys, or breasts. Lymph node involvement is seen in only 10-15% of cases. In contrast to endemic Burkitt lymphoma, jaw tumors are rare. Immunodeficiency-associated Burkitt lymphoma is primarily seen in patients infected with human immunodeficiency virus (HIV) but may also be associated with some cases of lymphoma that arise in the setting of iatrogenic immunodeficiency associated with solid organ transplantation. EBV is identified in 25-75% of these cases, and is more commonly seen in cases associated with organ transplantation. Involvement of the CNS is a risk for all three clinical variants while extensive marrow or blood involvement is most often seen in immunodeficiency-associated or sporadic Burkitt lymphoma.

Pathogenesis

The cause of Burkitt lymphoma is unknown. A consistent factor implicated in the disease pathogenesis is rearrangement of the MYC gene on chromosome 8. The MYC oncogene is translocated or mutated in virtually all cases of Burkitt lymphoma in all three clinical variants. Deregulation of this gene is thought to promote cellular proliferation and to facilitate evasion of the host immune response thereby promoting tumor growth. However, MYC gene rearrangement is not specific for Burkitt lymphoma as it is also found in up to 10% of diffuse large B-cell lymphoma and rarely in other lymphomas. Thus, other factors are involved in the pathogenesis of Burkitt lymphoma and are the subject of ongoing research. The precise role of EBV in the pathogenesis of Burkitt lymphoma has remained elusive.

Morphology

The tumor cells of Burkitt lymphoma are medium-sized and relatively monotonous. In smear preparations, they are characterized by round to oval nuclei and a moderate amount of deeply basophilic cytoplasm that usually contains clear lipid vacuoles. The nuclear features are non-specific and include moderately condensed chromatin and one or more nucleoli. In contrast, myeloblasts and lymphoblasts have more dispersed nuclear chromatin and usually lack the deep blue cytoplasm and cytoplasmic vacuoles typical of Burkitt lymphoma. In addition, circulating Burkitt lymphoma can usually be distinguished from blood involvement by other lymphoma subtypes. Depending on the subtype, other lymphomas involving the peripheral blood will demonstrate morphologic features similar to the mature neoplastic lymphoid cells seen in tissues, with mature chromatin, variable cytoplasm and lack of cytoplasmic vacuoles and cytoplasmic basophilia that characterize Burkitt lymphoma cells.

Phenotype

The diagnosis of Burkitt lymphoma may be suspected based on clinical presentation and morphologic features, but requires ancillary studies including immunophenotyping and cytogenetic studies for definitive diagnosis. Immunophenotyping on a blood sample is performed using flow cytometry. The cells express mature B-cell associated antigens such as CD19, CD20, and CD22 with kappa- or lambda-light chain restriction. They typically express CD10, BCL6, IgM, and CD38. In tissue sections, nearly 100% of the cells are positive for the Ki-67 nuclear antigen. This antigen is expressed during all active phases of the cell cycle and thus is indicative of an actively proliferating cell. The fact that essentially all Burkitt lymphoma cells are Ki-67-positive corresponds to the rapid tumor growth that is characteristic of this tumor.

Cytogenetics

As mentioned previously, all cases of Burkitt lymphoma have a rearrangement of the *MYC* gene on chromosome 8q24. In most cases, *MYC* is translocated with the immunoglobulin heavy chain gene (*IGH@* locus) on chromosome 14q32. Less commonly, *MYC* is translocated with either the kappa light chain gene (*IGK@* locus) on chromosome 2 or the lambda light chain gene (*IGL@* locus) on chromosome 22. As a result of these translocations, control of normal *MYC* expression is lost, leading to constitutive expression of the protein throughout the cell cycle. These translocations are typically detected using fluorescence in situ hybridization (FISH) or conventional cytogenetic studies (karyotyping). Up to 10% of Burkitt lymphoma cases may lack a *MYC* translocation using FISH, the explanation for which is unclear. The *MYC* translocation in these cases may be demonstrated using other techniques.

Prognosis

In endemic and sporadic Burkitt lymphoma, the tumor is highly aggressive but potentially curable. Intensive combination chemotherapy results in cure rates of 60-90% depending on the extent of disease. Poor prognostic factors include bone marrow or CNS involvement, an unresectable tumor greater than 10 cm in diameter, and a high serum LDH level. However, even patients with advanced disease, including bone marrow or CNS involvement, may be cured. Likewise, with high intensity treatment, most patients presenting with Burkitt leukemia have a very good prognosis with 80-90% survival. For HIV-infected patients, standard anti-HIV therapy (highly active antiretroviral therapy, HAART) has been very effective at preventing development of Burkitt lymphoma and other lymphomas.

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