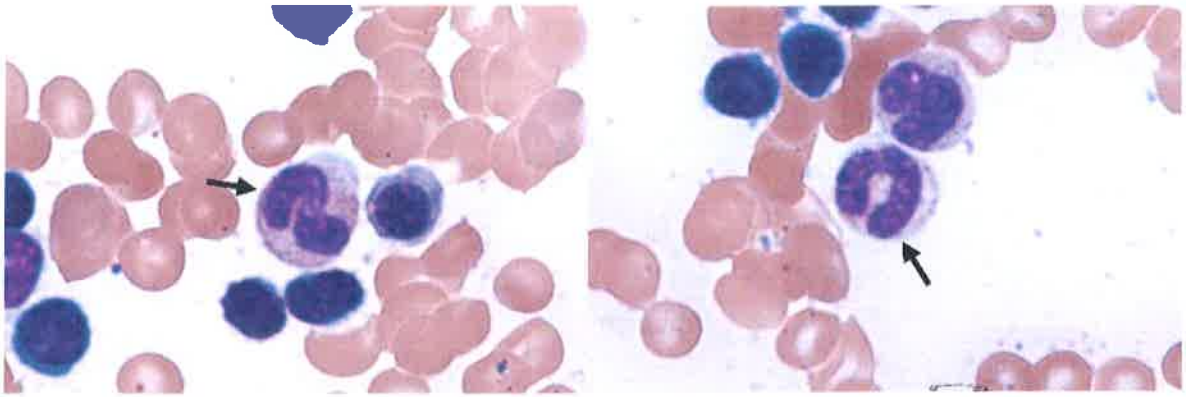
Cell Identification

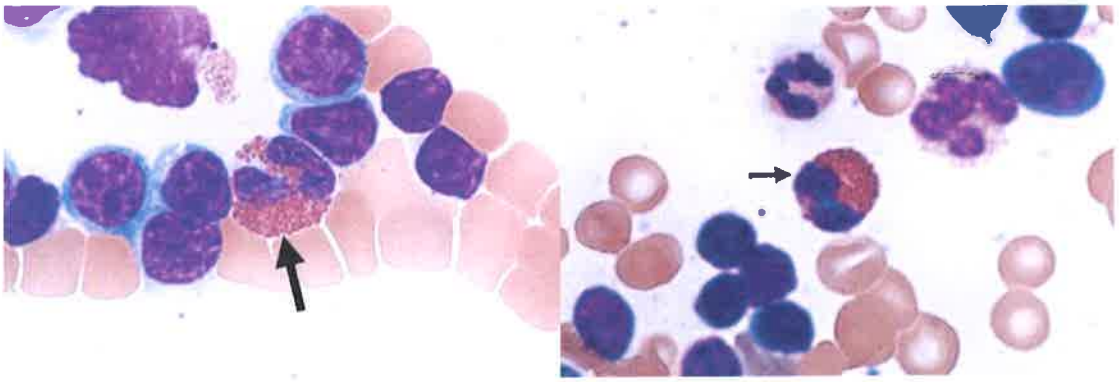
BMD-08



Identification	Participants No.	Participants %	Evaluation
Neutrophil, segmented or band	322	97.9	Educational
Neutrophil, giant band or giant metamyelocyte	5	1.5	Educational
Neutrophil, metamyelocyte	2	0.6	Educational

The arrowed cells are neutrophil band forms, as correctly identified by 97.9% of participants; in the Bone Marrow Cell Identification Master List, band and segmented forms are considered together. Band neutrophils and segmented neutrophils constitute 12% to 25% of the nucleated cells in the bone marrow. Both segmented and band neutrophils have specific granules and mature chromatin. Unlike the segmented neutrophil, however, the band neutrophil does not show nuclear condensation to thin filament. Also, unlike the next most immature neutrophil form (the metamyelocyte), the band neutrophil nucleus is indented to *more* than half the distance to the farthest nuclear margin. The nucleus can assume many shapes: it can be band-like; sausage-like; S-, C-, or U-shaped; or twisted and folded on itself. The selection "neutrophil, giant band" in this case is incorrect as such cells demonstrate decreased chromatin clumping and have diameters 1.5 times those of normal bands.

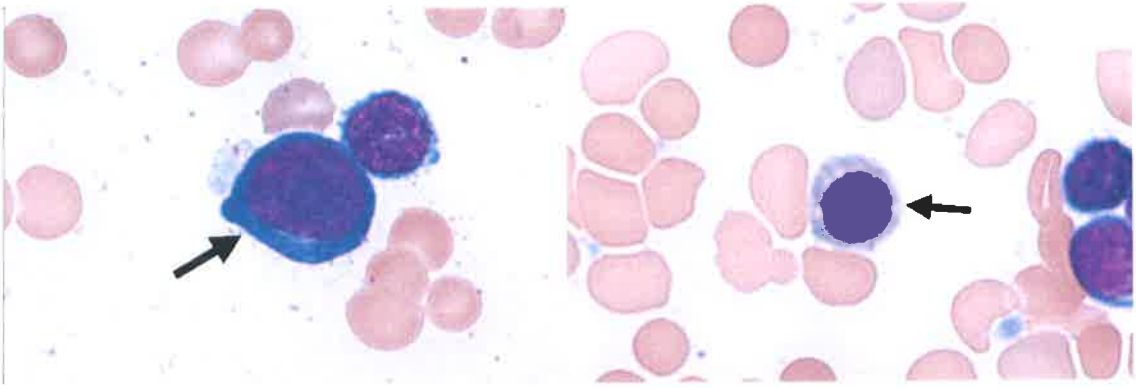
BMD-09



Identification	Participants No.	Participants %	Evaluation
Eosinophil, any stage	327	99.4	Educational
Eosinophil, any stage with atypical/basophilic granulation	1	0.3	Educational
Neutrophil, segmented or band	1	0.3	Educational

The arrowed cells are eosinophils, as correctly identified by 99.4% of participants. Eosinophils are round to oval leukocytes that are present in the blood, bone marrow, and tissues of normal individuals. They are generally easily recognized due to their characteristic coarse orange-red granulation. In the most mature eosinophilic form, the nucleus is segmented into two or more lobes connected by a thin filament. About 80% of segmented eosinophils will have the classic two-lobed appearance.

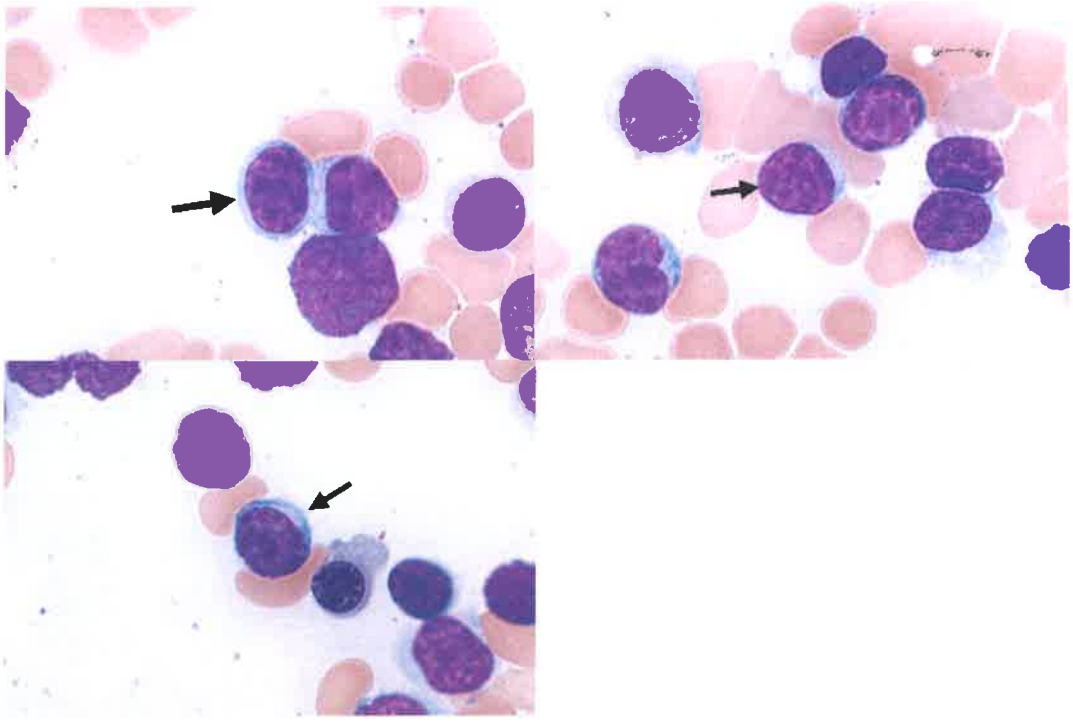
BMD-10



Identification	Participants No.	%	Evaluation
Erythrocyte precursor, normal (includes pronormoblast, basophilic, polychromatophilic, and orthochromic normoblasts)	320	97.3	Educational
Erythrocyte precursor with megaloblastic changes/maturation	5	1.5	Educational
Erythrocyte precursor, abnormal/dysplastic nuclear features (includes pronormoblast, basophilic, polychromatophilic, and orthochromic normoblasts)	2	0.6	Educational
Eosinophil, any stage	1	0.3	Educational
Erythrocyte	1	0.3	Educational

The arrowed cells are normal erythrocyte precursors, as correctly identified by 97.3% of participants, seen here at different stages of maturation. The smaller/paler erythroid precursor resembles a polychromatophilic normoblast, which is the next most mature of the nucleated erythroid precursors, characterized by well-rounded nuclei with condensed chromatin, producing a checkerboard or cartwheel appearance. In distinction to the other more immature basophilic normoblast, polychromatophilic normoblasts have a far less basophilic cytoplasm, owing to a greater degree of hemoglobinization, producing a gray colored cytoplasm.

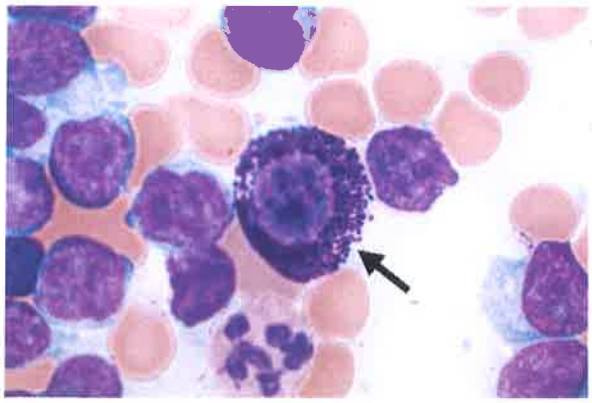
BMD-11

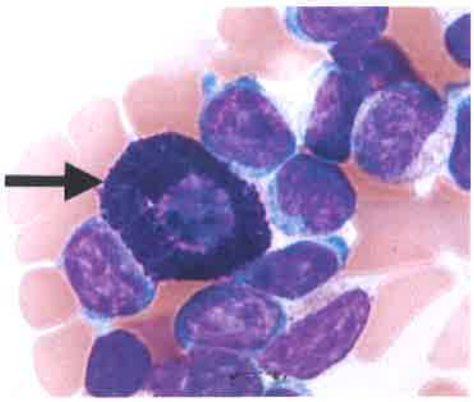


Identification	Participants No.	%	Evaluation
Lymphocyte	212	64.4	Educational
Malignant lymphoid cell	113	34.4	Educational
Blast cell	2	0.6	Educational
Eosinophil, any stage	1	0.3	Educational
Monocyte, immature	1	0.3	Educational

The arrowed cells are lymphocytes. Distinguishing between a benign lymphocyte and a malignant lymphoid cell (such as a CLL lymphocyte) is often not possible; taken in composite, this cell was correctly identified by 98.8% of participants as a lymphocyte, with 34.4% of participants opting for "Malignant Lymphoid Cell." Many of the lymphocytes in this case are likely CLL lymphocytes, which tend to have "chunky" chromatin (sometimes akin to "soccer-ball" patterns). There are, however, occasional lymphocytes in the provided images less characteristically atypical; as such, reliable classification of all the lymphocytes pictured as malignant is not possible.

BMD-12





Identification	Participants No.	%	Evaluation
Mast cell	278	84.5	Educational
Basophil, any stage	47	14.3	Educational
Eosinophil, any stage with atypical/basophilic granulation	2	0.6	Educational
Mast cell, atypical, spindled	2	0.6	Educational

The arrowed cells are mast cells, as correctly identified by 84.5% of participants. The mast cell is a large, round or elliptical cell with a small, round nucleus and abundant cytoplasm packed with black, bluish-black, or reddish-purple metachromatic granules. Normal mast cells are differentiated from basophils by the fact that they are larger (often twice the size of basophils), have more abundant cytoplasm, and have round rather than segmented nuclei. Atypical mast cell features (not seen in this case) may be seen with clonal mast cell disorders (mastocytosis) and may include spindling, clustering, uneven/hypo-granularity or immature/atypical nuclei.

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BMD-B 2019: Chronic Lymphocytic Leukemia

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Disclosure Statement

The following authors/planners have no financial relationships to disclose:
Etienne Mahe, MD, MSc; Stephanie A. Salansky, MEd, MS, MT(ASCP)

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Learning Objectives

Upon completing the reading and answering the learning assessment questions, you should be able to:

1. Understand the definitions and diagnostic criteria applicable to chronic lymphocytic leukemia (CLL) and related conditions.
2. Understand the epidemiology and common clinical features of CLL.
3. Understand the pathobiology and behavior of CLL as well as clinical interventions in CLL

CHRONIC LYMPHOCYTIC LEUKEMIA

Case Presentation:
This bone marrow aspirate smear is from an 87-year-old woman presenting with weakness and headaches. Laboratory peripheral blood data includes: WBC = 183.9 x 10E9/L; RBC = 2.52 x 10E12/L; HGB = 8.8 g/dL; HCT = 26.1%; MCV = 99 fL; and PLT = 202 x 10E9/L. (BONE MARROW, WRIGHT-GIEMSA)

Note: Slide image can be found in the BMD-B 2019 Participant Summary

DEFINITION & RELATED CONDITIONS

Chronic lymphocytic leukemia (CLL) is a mature B-cell neoplasm characterized by lymphocytosis of at least 5.0 x 10E9/L clonal CD5 positive lymphocytes.[1] CLL is closely related to small lymphocytic lymphoma (SLL), a diagnosis that is rendered when the disease is effectively limited to tissues only, without sufficient circulating lymphocytes meeting the diagnostic criteria for CLL.[1,2] As such, CLL and SLL are often described together as CLL/SLL. Clonal lymphocytosis not meeting the 5.0 x 10E9/L threshold, and not meeting criteria for a diagnosis of SLL, is classified as monoclonal B-cell lymphocytosis (MBL).[1,2] MBL is most frequently detected in the peripheral blood, and is categorized into CLL-type, atypical CLL-type, and non-CLL type. CLL-type MBL is further subcategorized into low-count (< 0.5 x 10E9/L CLL-type lymphocytes) and high-count (≥ 0.5 x 10E9/L CLL-type lymphocytes); the latter are believed to represent CLL precursor lesions, with an annual rate of progression to CLL of 1%-2%.[1,2] It is important to recognize atypical/non-CLL type MBLs in order that low-level peripheralization of lymphocytes from another lymphoid malignancies be adequately excluded.[1] A nodal form of MBL has been proposed: CLL-type clonal B-cells without proliferation centers in patients with minimal adenopathy (ie, lymph node size <1.5 cm).[1]

EPIDEMIOLOGY

In Western countries, CLL is the most common lymphoid malignancy of adults, with an estimated annual incidence of 5 cases per 100,000. Notably, this incidence increases substantially with age, but with over 20 cases per 100,000 in people over 70 years of age.[1] CLL is most frequently diagnosed in men, with a mean age at diagnosis of 70 years.[1] Interestingly, CLL is far less common in Asian countries and in peoples of Asian descent, with the bulk of incident cases identified in patients with Western heritage.[1]

The most significant risk factor for CLL/SLL to date is age.[2] Indeed, given the progressive increase in frequency of CLL/SLL with age, it has been suggested that persistent or progressive antigenic stimulation might contribute to CLL/SLL pathogenesis.[2] There are also data suggesting that some cases of CLL/SLL might result from an underlying genetic predisposition (so-called "familial CLL").[3]

CLINICAL PRESENTATION

Most patients with early CLL/SLL are asymptomatic; diagnosis is frequently incidental, most often identified by peripheral blood lymphocytosis.[1,2,4] CLL/SLL frequently involves the bone marrow, and often to an extensive degree; as such, patients may also present (or develop) anemia or thrombocytopenia.[1,2,4] Patients may present

with (or more frequently progress to having) adenopathy or hepatosplenomegaly.[1,2,4] While presenting symptoms related to involvement of extra-medullary sites are rare,[2] anecdotal experience suggests that low-level secondary involvement of a wide variety of tissues is possible. A minority of CLL/SLL patients may present with B-type symptoms of weight loss, fevers, and night sweats.[1,2,4] Perhaps of greater interest, however, CLL/SLL patients have a peculiar predisposition to the development of "autoimmune" complications, attributable to secondary dysregulation of the immune system.[2] CLL/SLL patients may develop angioedema, glomerulonephritides, immune hemolysis/thrombocytopenia, and other paraneoplastic phenomena.[2] Immune dysregulation also may predispose CLL/SLL patients to infections and secondary malignancies.[1,2,4]

DIFFERENTIAL DIAGNOSIS

CLL/SLL does present a differential diagnosis that must be resolved, and this is typically performed by immunophenotypic methods.[2] The primary differential diagnoses include mantle cell lymphoma (MCL), marginal zone lymphoma, and B-cell prolymphocytic leukemia,[2] however these are typically excluded by a combination of appropriate morphology and typical immunophenotypes. CLL/SLL is characterized by dim expression of CD20 and cell surface immunoglobulin light chains (indicating B-cell origin) with co-expression of CD5, without cyclin D1. Challenging cases of CLL/SLL resembling MCL may require the use of molecular techniques to demonstrate a lack of the t(11;14) translocation characteristic of MCL.

CLINICAL STAGING & PROGNOSTICATION

The current methods of prognostication and treatment decision-making employ a combination of clinical, laboratory, and molecular parameters.[1,2] The two most frequently used clinical prognostic systems are the Rai and Binet systems; these use combinations of anatomical extent of disease and other laboratory data such as hemoglobin and/or platelet count to stage patients.[1,2] More recent work has underscored the utility of molecular genetic data as helpful for prognostication, as well as for treatment planning purposes.[1,2] The identification of *TP53* structural or sequence-level variation or lack of *IGHV* somatic hypermutation, for example, are adverse prognostic factors and may indicate that standard treatment approaches may be ineffective.[2,5,6]

TREATMENT STRATEGIES

CLL/SLL patients with early stage asymptomatic disease are not generally treated immediately.[2,5] Instead, treatment is generally reserved for patients demonstrating progressive disease (eg, progressive adenopathy or organomegaly), worsening cytopenias, constitutional symptoms, increasing lymphocytosis, or non-responsive immunologic phenomena.[2,5] Prior to the start of first-line treatment, *TP53* and *IGHV* assessments are suggested. For patients who are deemed clinically fit, without adverse *TP53* or *IGHV* features, a combination of fludarabine, chlorambucil, and rituximab is recommended.[2,5] For patients deemed unfit, or with adverse *TP53* or *IGHV* features, the use of alternative regimens such as the *Bruton's tyrosine kinase* (*BTK*) inhibitor ibrutinib, is recommended.[2,5] Agents such as ibrutinib, idelalisib (a phosphoinositide 3-kinase inhibitor), or venetoclax (an inhibitor of the anti-apoptotic B-cell lymphoma-2 [BCL2] protein) may also be considered as salvage therapies.[2,5] Allogeneic stem cell transplant is also a potential therapeutic strategy in appropriate patients with relapsed/refractory disease.[2]

TRANSFORMATION

Richter's transformation is a generic clinicopathologic term referring to the development of histologically proven high-grade lymphoma in the context of an established case of CLL.[7] Diffuse large B-cell lymphoma is the most common entity of transformation in Richter's syndrome. [7] The 5- and 10-year incidence of Richter's transformation has been estimated at 5% and 10%, respectively.[7] The median time to transformation in cases of Richter's syndrome is 23 months.[7]

CONCLUSION

CLL is a relatively common diagnostic entity with a broad range of clinical features, including indolent forms, as well as forms that progress to high-grade disease. Tailoring of therapies in CLL patients relies on a number of features including; clinical, pathologic, and molecular-genetic parameters.

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