COLLEGE of AMERICAN PATHOLOGISTS
Laboratory Quality Solutions

Surveys and Anatomic Pathology Education Programs

Bone Marrow Cell Differential BMD-B 2022

Participant Summary

1.0 Credit of Continuing Education Available

This document is available online in e-LAB Solutions Suite.

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PARTICIPANT SUMMARY

Program Update

Don't Miss Out on this Educational Opportunity!

With your participation in CAP's Surveys programs, *every member of your team* can take part in educationactivities that may earn Continuing Education (CE) credits or receive Self-Reported Training* at no additional charge.

This Survey mailing includes an online education activity to earn **1.0** CE credit. To access the activity, see page 15.

CAP Self-Reported Training activities do not offer CE credit but can be used towards fulfilling requirements for maintenance of certification (MOC) by agencies such as the American Society of Clinical Pathology (ASCP). Please verify with your certifying agency to determine your education requirements.

Evaluation Criteria

The quantitative data tables provided in this participant summary include multiple statistical values which may include the median, min, and max values reported for each peer group. The min and max values are not the limits of acceptability. The acceptable limits are located on your participant evaluation report.

To provide a timely evaluation of your results, statistics presented in this participant summary reflect participant data received by the due date.

In the event a result is not graded, a numeric code will appear next to your result. A definition of the code will appear on the first page of your evaluation. Please see "Actions Laboratories Should Take when a PT Result is Not Graded" on page 13. If your proficiency testing results are not graded, your laboratory should perform a self-evaluation. For more information, go to cap.org.

1. Hover over Laboratory Improvement and click **Proficiency Testing.**
2. Under Proficiency Testing (PT) Programs, Surveys, click **PT Resources.**
3. Under Existing Customers, click **Performing a Self-Evaluation When PT is Not Graded.**

Results for the BMD Survey are **not** formally evaluated; however, statistics will appear in the participant summary for your information.

Case History for BMD-07 – BMD-12

This bone marrow aspirate smear is from a 42-year-old man with a history of leukemia. Complete blood count includes: WBC = 185.1 x 10E9/L; RBC = 2.68 x 10E12/L; HGB = 8.7 g/dL; HCT = 25.1%; MCV = 98 fL; and PLT = 69 x 10E9/L. Identify the arrowed object(s) on each whole slide image.

(BONE MARROW, WRIGHT-GIEMSA)

Please click on the hyperlink below to view the DigitalScope images for this case:
https://www.digitalscope.org/LinkHandler.axd?LinkId=2d132697-4764-4d76-b9ac-7b7f498be22b

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.

Bone Marrow Differential – %

		N	MEAN	SD	CV%*	MEDIAN	MIN	MAX
BMD-07	Blasts	376	32.85	22.26	67.8	30.0	0.0	95.0
	Promyelocytes	359	17.53	14.99	85.5	14.0	0.0	65.4
	Myelocytes	357	8.29	6.18	74.5	6.7	0.0	29.0
	Metamyelocytes	356	3.69	3.20	86.6	2.4	0.0	14.0
	Band/Segmented neutrophils	367	6.30	3.63	57.6	5.9	0.0	17.2
	Eosinophils (all stages)	362	2.51	1.25	49.8	2.2	0.0	6.6
	Basophils	298	0.03	0.09	*	0.0	0.0	0.4
	Monocytes	367	10.26	9.90	96.5	6.0	0.0	39.8
	Lymphocytes	366	9.05	6.07	67.1	7.1	0.4	28.0
	Plasma cells (normal and abnormal)	324	0.22	0.36	*	0.0	0.0	1.4
	Erythroid precursors (all stages)	357	3.26	2.76	84.6	2.0	0.0	13.6
	Other	208	0.05	0.27	*	0.0	0.0	2.0

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

BMD- 07 Cont'd

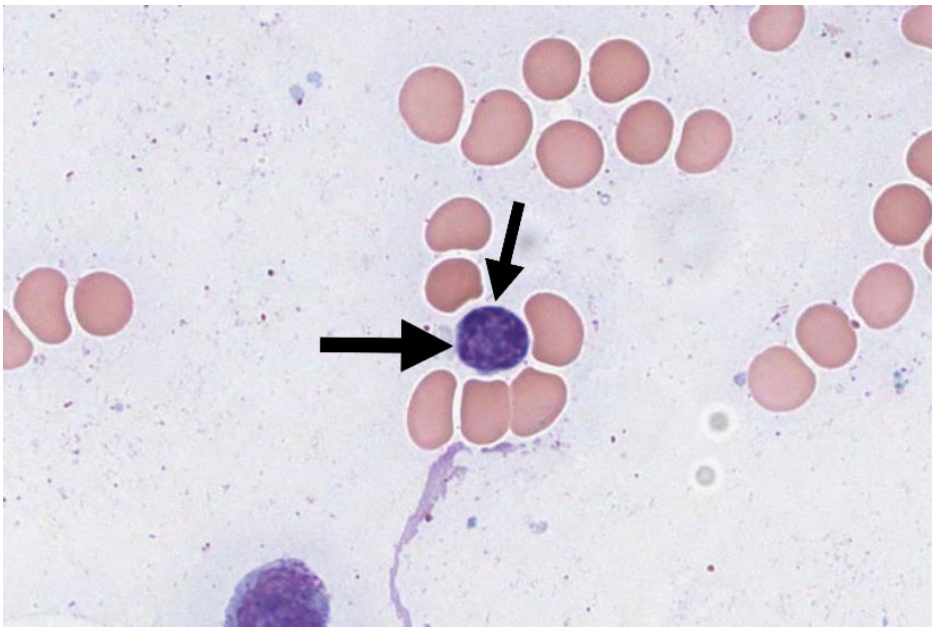
Other cells: All cells not listed/differentiated	(N = 14) Freq
Large, abnormal/atypical/immature myeloid precursor cell	5
Reticulum cell	3
Histiocyte	2
Monocyte, immature (includes promonocyte, monoblast)	2
Refer to pathologist for review	2

Committee Comments for Online Whole Slide Image

The bone marrow aspirate is hypercellular and spicular. The myeloid to erythroid ratio is markedly increased. The majority of the cellularity is composed of markedly left-shifted myeloid elements with blasts comprising greater than 20% of nucleated marrow cells, which is a diagnostic criterion for acute leukemia. Mature neutrophils are exceedingly rare. Eosinophils are present. Rare basophils are seen. Erythroid precursors are rare. Megakaryocytes are not appreciated. Morphologic dysplasia is not evident.

Cell Identification

BMD-08

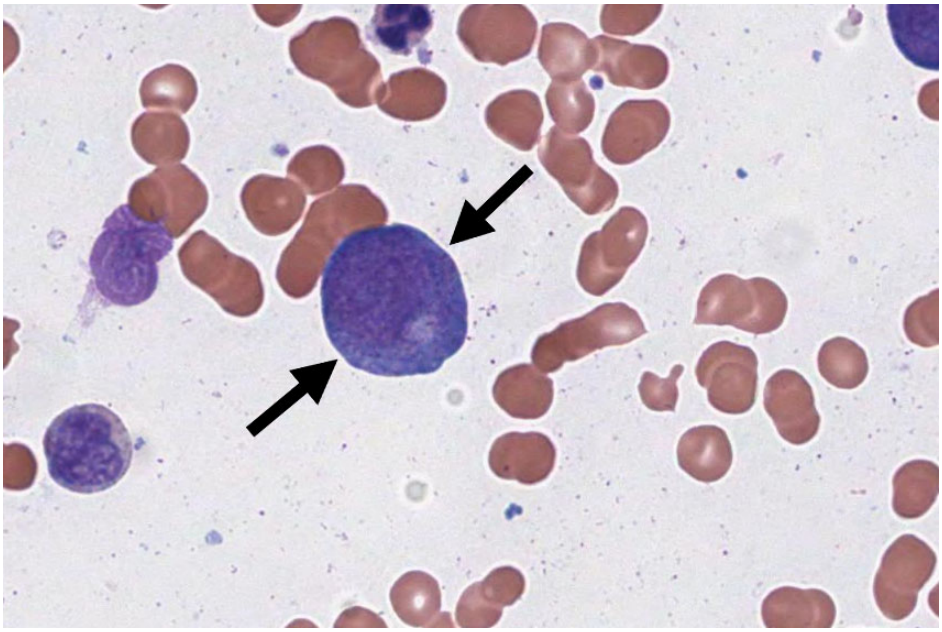


Identification	Participants Freq	%	Evaluation
Lymphocytes	375	98.4	Educational
Hematogone	4	1.1	Educational
Erythrocyte precursor, abnormal/dysplastic nuclear features (includes pronormoblast, basophilic, polychromatophilic normoblast, and orthochromic normoblasts)	1	0.3	Educational
Erythrocyte precursor, normal (includes pronormoblast, basophilic, polychromatophilic normoblast, and orthochromic normoblasts)	1	0.3	Educational

The arrowed cell is a normal lymphocyte, as correctly identified by 98.4% of participants. Lymphocytes are small, round to ovoid cells ranging in size from 7 to 15 µm with an N:C ratio ranging from 5:1 to 2:1. Most lymphocytes have round to oval nuclei that may be slightly indented or notched. 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. Occasional lymphocytes will have a small clear zone, or hof, in the cytoplasm adjacent to one side of the nucleus, indicating the location of the Golgi apparatus. While most normal lymphocytes are fairly homogeneous, they do exhibit a range of normal morphology.

1.1% of participants incorrectly identified the arrowed cell as a hematogone. Hematogones are benign B-lymphocyte precursor cells that are a normal cellular constituent of the bone marrow. The cells are typically small, but show some variability in size, ranging from 10 to 20 µm. Nuclei are round or oval, sometimes with a shallow nuclear indentation. Nucleoli are absent or indistinct. The chromatin is characteristically condensed, smooth, and homogeneous, unlike the clumped chromatin of the arrowed cells. The cytoplasm is very scant and often not discernible. Hematogones are most frequently encountered in the bone marrow of infants and young children, particularly following a viral infection, during recovery from chemotherapy, or in association with bone marrow transplant. A small number of hematogones may be seen in the bone marrow of adults.

BMD-09



Identification	Participants Freq	Participants %	Evaluation
Neutrophil, promyelocyte	284	74.5	Educational
Neutrophil, promyelocyte, abnormal with/without Auer rod(s)	46	12.1	Educational
Blast cell (includes lymphoblast)	24	6.3	Educational
Erythrocyte precursor, normal (includes pronormoblast, basophilic, polychromatophilic normoblast, and orthochromic aanormoblasts)	8	2.1	Educational
Neutrophil, myelocyte	6	1.6	Educational
Monocyte, immature (promonocyte, monoblast)	4	1.1	Educational
Erythrocyte precursor, abnormal/dysplastic nuclear features (includes pronormoblast, basophilic, polychromatophilic normoblast, and orthochromic normoblasts)	2	0.5	Educational
Erythrocyte	1	0.3	Educational
Erythrocyte precursor with megaloblastic changes/maturation	1	0.3	Educational
Malignant lymphoid cell (other than blast)	1	0.3	Educational
Megakaryocyte or precursor, abnormal	1	0.3	Educational
Myeloblast with Auer rod	1	0.3	Educational
Plasma cell, morphologically mature/abnormal/containing inclusion (eg, Dutcher body, Russell body)	1	0.3	Educational

BMD-09 Cont'd

The arrowed cell is a promyelocyte, as correctly identified by 74.5% of participants. 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 peripheral blood in pathologic states, such as chronic myeloid leukemia. The nuclear-to-cytoplasmic ratio is high (5:1 to 3:1). The nucleus has finely dispersed 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.

12.1% of participants identified the arrowed cell as a neutrophil, promyelocyte, abnormal with/without Auer rod(s). The neoplastic counterpart of the promyelocyte/leukemic cell differs from the normal promyelocyte in several respects. The nucleus is usually folded, bilobed, or reniform (often with overlapping nuclear lobes). A distinct Golgi zone is typically absent. The arrowed cell has a round nucleus and prominent Golgi zone. Cytoplasmic granules, while abundant in the classic hypergranular form of this disease, may differ in appearance, often being coarser or finer than those seen in normal promyelocytes and slightly darker or more reddish in color. The abnormal promyelocyte of acute promyelocytic leukemia frequently contains multiple overlapping Auer rods.

6.3% of participants incorrectly identified the arrowed cell as a blast cell (includes lymphoblast). Myeloblasts are the most immature cells in the myeloid series. They are normally confined to the bone marrow, where they constitute less than 3% of the nucleated cells. The myeloblast is usually a large cell, 15 to 20 µm in diameter, with a high nuclear-to-cytoplasmic (N:C) ratio, usually 7:1 to 5:1 with typically basophilic cytoplasm. The cell and nucleus are usually rounded, although irregularly shaped or folded nuclei may be present. The myeloblast nucleus has finely reticulated chromatin pattern with distinct nucleoli present. Leukemic myeloblasts may also exhibit a few delicate granules and/or Auer rods. No Auer rods are present in the arrowed cell.

Lymphoblasts are the most immature cells of the lymphoid series. They are most commonly seen in acute lymphoblastic leukemia (ALL) and lymphoid blast crisis of chronic myeloid leukemia (CML). These round to oval cells range in size from 10 to 20 µm. The N:C ratio varies from 7:1 to 4:1. Morphologically, lymphoblasts are variable in appearance, even at times within a single case. At one end of the spectrum, are small lymphoblasts with dense, but not clumped chromatin, inconspicuous or absent nucleoli, and extremely scanty cytoplasm. At the other end are large lymphoblasts with finely dispersed chromatin, variable numbers of distinct nucleoli, and moderate amounts of cytoplasm, closely resembling myeloblasts. The nuclear contours of lymphoblasts range from round to convoluted. The cytoplasm is typically slightly to moderately basophilic and is usually agranular. Auer rods are absent.

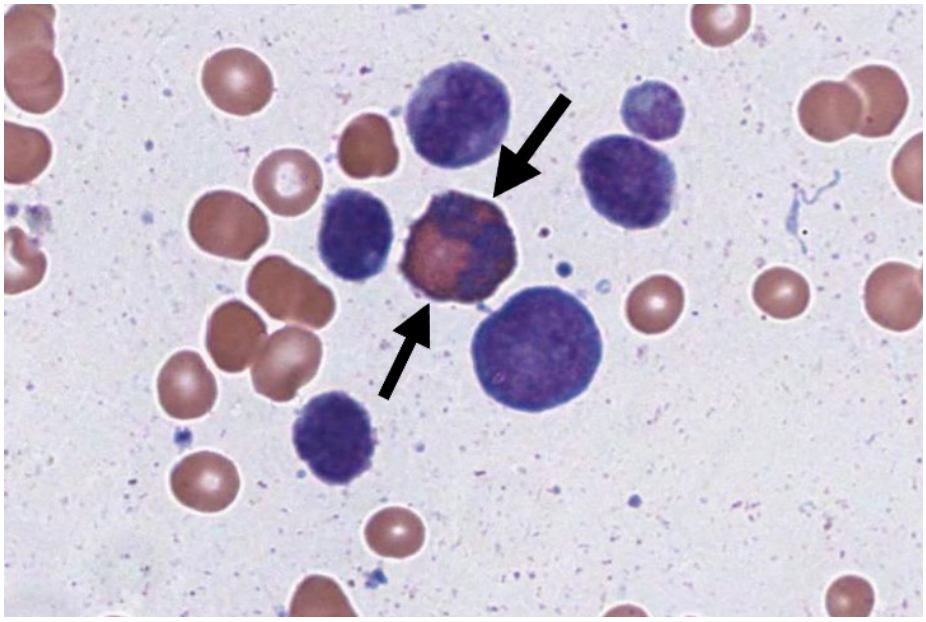
2.1% of participants incorrectly identified the arrowed cell as an erythrocyte precursor, normal (includes pronormoblast, basophilic, polychromatophilic normoblast, and orthochromic normoblasts). Pronormoblasts, morphologically the most immature cells of the erythrocytic series, are large round or ovoid cells measuring 17 to 24 µm in diameter. The nucleus is round or slightly oval and contains one or more prominent nucleoli. The chromatin is finely reticulated or lacy and blast-like without clumping. A perinuclear halo is usually evident. The cytoplasm stains darker blue (more basophilic) than that of a myeloblast and lighter blue than basophilic normoblasts. The N:C ratio is approximately 8:1. Unlike the arrowed blast cell, pronormoblast cytoplasm is agranular. The more differentiated basophilic, polychromatophilic, and orthochromic normoblasts are smaller cells (< 17 µm) and contain progressively lower N:C ratios, progressively more hemoglobin within the cytoplasm resulting in blue-gray to pinkish cytoplasm, and progressively dense chromatin pattern that should not be confused with blasts.

BMD-09 Cont'd

1.6% of participants identified the arrowed cell as a neutrophil, myelocyte. Myelocytes are usually confined to the marrow where they constitute approximately 10% of the nucleated cells. The myelocyte is smaller than the earlier precursors, usually 10 to 18 µm. The cells are round-to-oval in shape and have a nuclear-to-cytoplasmic 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.

1.1% of participants incorrectly identified the arrowed cell as a monocyte, immature (promonocyte, monoblast). The malignant monoblast is a large cell, 15 to 25 µm in diameter. It has relatively more cytoplasm than a myeloblast with the nuclear-to-cytoplasmic ratio ranging from 7:1 to 3:1. The monoblast nucleus is round or oval and has finely dispersed chromatin and distinct nucleoli. The cytoplasm is blue to gray-blue and may contain small, scattered azurophilic granules. Some monoblasts cannot be distinguished morphologically from other blast forms, hence the need for using other means (eg, cytochemistry and flow cytometry) are required to accurately assign blast lineage. Promonocytes have nuclear and cytoplasmic characteristics that are between those of monoblasts and mature monocytes. They are generally larger than mature monocytes, but they have similar appearing gray-blue cytoplasm that often contains uniformly distributed, fine azurophilic granules. Cytoplasmic vacuolization is not a typical feature. The nuclei show varying degrees of lobulation, usually characterized by delicate folding or creasing of the nuclear membrane, in contrast to the rounder nuclear profile of monoblasts. Nucleoli are present but not as distinct as in monoblasts.

BMD-10

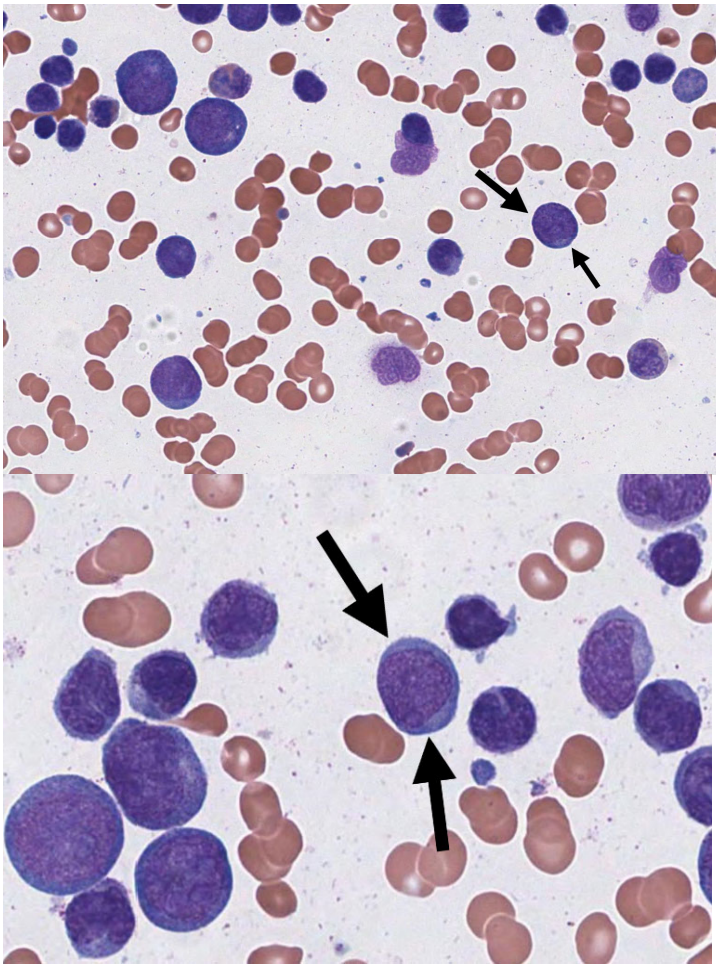


Identification	Participants Freq	%	Evaluation
Eosinophil, any stage	375	98.4	Educational
Eosinophil, any stage with atypical/basophilic granulation	5	1.3	Educational
Erythrocyte precursor, abnormal/dysplastic nuclear features (includes pronormoblast, basophilic, polychromatophilic normoblast, and orthochromic normoblasts)	1	0.3	Educational

The arrowed cell is an eosinophil, any stage, as correctly identified by 98.4% of participants. Eosinophils are leukocytes most recognizable by their characteristic coarse, orange-red granulation. They are comparable in size to neutrophils: 10 to 15 µm in diameter in their mature forms and 10 to 18 µm in diameter in immature forms. The eosinophil N:C ratio ranges from 1:3 in mature forms to 2:1 in immature forms. In the most mature eosinophil form, the nucleus segments into two or more lobes connected by a thin filament. About 80% of segmented eosinophils will have the classic two-lobed appearance. Typically, these lobes are of equal size and round to ovoid or potato-shaped with dense, compact chromatin. The remainder of segmented eosinophils will have three lobes and an occasional cell will exhibit four to five lobes. The eosinophil cytoplasm is generally evenly filled with numerous coarse, orange-red granules of uniform size. The granules rarely overlie the nucleus and are refractile by light microscopy due to their crystalline structure. This refractile appearance is not apparent in photomicrographs or pictures, however. Due to inherent problems with color rendition on photomicrographs, which is sometimes imperfect, eosinophil granules may appear lighter or darker than on a freshly stained blood film. Discoloration may give the granules a blue, brown, or pink tint. Nonetheless, the uniform, coarse nature of eosinophil granules is characteristic and differs from the smaller, finer granules of neutrophils.

1.3% of participants incorrectly identified the arrowed cell as an eosinophil, any stage with atypical/basophilic granulation. Eosinophils with atypical/basophilic granules are typically the same size as their normal counterparts. Any stage of eosinophilic maturation may be affected. This finding is more commonly seen in the myelocyte stage. The abnormal granules resemble basophilic granules. The granules are purple violet in color and usually larger than normal eosinophilic granules at the immature stages. These atypical granules are usually admixed with normal eosinophilic granules in the cytoplasm.

BMD-11



Identification	Participants Freq	%	Evaluation
Blast cell (includes lymphoblast)	361	95.0	Educational
Myeloblast with Auer rod	6	1.6	Educational
Monocyte, immature (promonocyte, monoblast)	4	1.1	Educational
Erythrocyte precursor, normal (includes pronormoblast, basophilic, polychromatophilic normoblast, and orthochromic normoblasts)	3	0.8	Educational
Neutrophil, promyelocyte, abnormal with/without Auer rod(s)	2	0.5	Educational
Hematogone	1	0.3	Educational
Immature or abnormal cell, would refer for identification	1	0.3	Educational
Lymphocyte	1	0.3	Educational
Neutrophil, promyelocyte	1	0.3	Educational

BMD-11 Cont'd

The arrowed cells are blasts, as correctly identified by 95.0% of participants. Blasts are divided into myeloid (myeloblast) and lymphoid (lymphoblast) lineages. The myeloblast is usually a fairly large cell, 15 to 20 µm in diameter, with a high N:C ratio, usually 7:1 to 5:1, and typically basophilic cytoplasm. Myeloblasts may occasionally be smaller, similar to the size of a mature myeloid cell. The cell and nucleus are usually round, although irregularly shaped or folded nuclei may be present. The myeloblast nucleus has a characteristically finely reticulated chromatin pattern with distinct nucleoli present. Leukemic myeloblasts may also exhibit a few delicate granules and/or Auer rods, which are absent in the cells on the image.

Lymphoblasts are round to oval cells that range in size from 10 to 20 µm. The N:C ratio varies from 7:1 to 4:1. Morphologically, lymphoblasts are variable in appearance, at times within a single case. At one end of the spectrum are small lymphoblasts (previously termed L1 subtype) with dense but not clumped chromatin, inconspicuous or absent nucleoli, and extremely scanty cytoplasm. At the other end are large lymphoblasts (previously termed L2 subtype) with finely dispersed chromatin, variable numbers of distinct nucleoli, and moderately abundant cytoplasm, closely resembling myeloblasts. The nuclear contours of lymphoblasts range from round to convoluted. The cytoplasm is typically slightly to moderately basophilic and is usually agranular. Auer rods are absent.

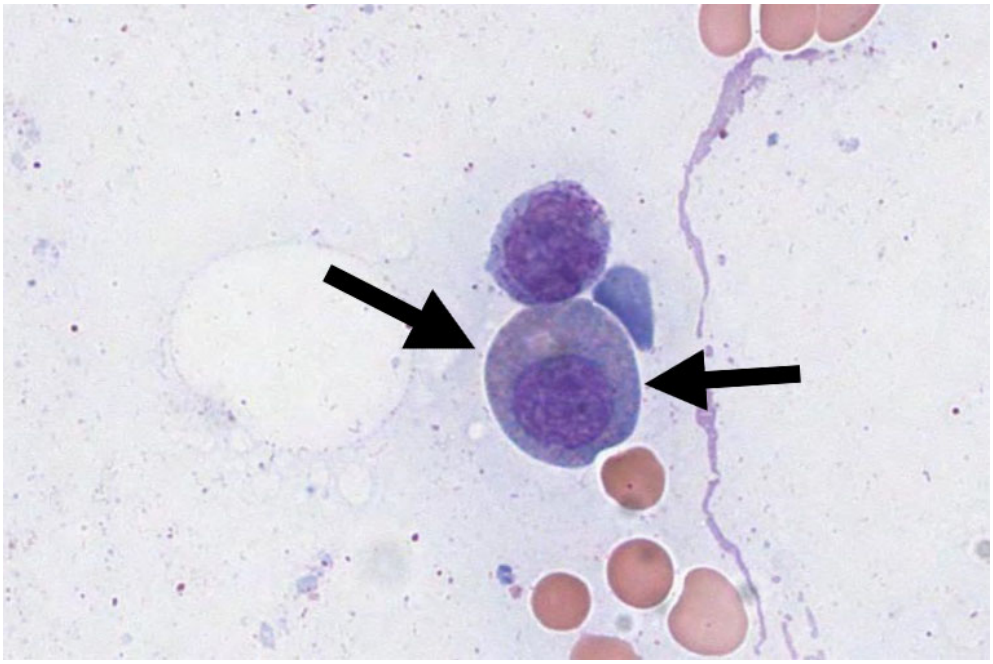
Determining blast lineage by morphology, especially in the absence of Auer rods, is not possible using Wright-Giemsa stains alone. Additional testing such as cytochemical staining (eg, using myeloperoxidase or Sudan black for myeloblasts), or immunophenotyping by flow cytometry is required to define blast lineage. (One exception to this is that myeloid lineage can be determined if clear Auer rods are present.) For purposes of proficiency testing, one should identify individual cells exhibiting any immature types of morphology as blasts.

1.6% of participants incorrectly identified the arrowed cell as a myeloblast with Auer rod. Myeloblasts are the most immature cells in the myeloid series. The myeloblast is usually a large cell, 15 to 20 µm in diameter, with a high nuclear-to-cytoplasmic (N:C) ratio, usually 7:1 to 5:1 with typically basophilic cytoplasm. Myeloblasts may occasionally be smaller, similar to the size of a mature myeloid cell. The cell and nucleus are usually rounded, although irregularly shaped or folded nuclei may be present. The myeloblast nucleus has finely reticulated chromatin pattern with distinct nucleoli present.

Leukemic myeloblasts may also exhibit a few delicate granules and/or Auer rods. Auer rods are pink or red, rod-shaped cytoplasmic inclusions seen in neoplastic early myeloid forms and occasionally in early monocytic forms in patients with myeloid lineage leukemia. These inclusions represent a crystallization of azurophilic (primary) granules. No Auer rods are present in the arrowed cells.

1.1% of participants incorrectly identified the arrowed cell as a monocyte, immature (promonocyte, monoblast). The malignant monoblast is a large cell, 15 to 25 µm in diameter. Unlike the arrowed cells, monoblasts have relatively more cytoplasm than a myeloblast with the nuclear-to-cytoplasmic ratio ranging from 7:1 to 3:1. The monoblast nucleus is round or oval and has finely dispersed chromatin and distinct nucleoli. The cytoplasm is blue to gray-blue and may contain small, scattered azurophilic granules. Some monoblasts cannot be distinguished morphologically from other blast forms, hence the need for using other means (eg, cytochemistry and flow cytometry) are required to accurately assign blast lineage. Promonocytes have nuclear and cytoplasmic characteristics that are between those of monoblasts and mature monocytes. They are generally larger than mature monocytes, but they have similar appearing gray-blue cytoplasm that often contains uniformly distributed, fine azurophilic granules. Cytoplasmic vacuolization is not a typical feature. The nuclei show varying degrees of lobulation, usually characterized by delicate folding or creasing of the nuclear membrane, in contrast to the rounder nuclear profile of monoblasts. Nucleoli are present but not as distinct as in monoblasts.

BMD-12



Identification	Participants Freq	%	Evaluation
Neutrophil, myelocyte	342	89.8	Educational
Plasma cell, morphologically mature/abnormal/containing inclusion (eg, Dutcher body, Russell body)	10	2.6	Educational
Monocyte, immature (promonocyte, monoblast)	6	1.6	Educational
Neutrophil with dysplastic nucleus and/or hypogranular cytoplasm	6	1.6	Educational
Neutrophil, promyelocyte	4	1.1	Educational
Eosinophil, any stage with atypical/basophilic granulation	3	0.8	Educational
Eosinophil, any stage	2	0.5	Educational
Neutrophil, promyelocyte, abnormal with/without Auer rod(s)	2	0.5	Educational
Erythrocyte precursor, abnormal/dysplastic nuclear features (includes pronormoblast, basophilic, polychromatophilic normoblast, and orthochromic normoblasts)	1	0.3	Educational
Erythrocyte precursor with megaloblastic changes/maturation	1	0.3	Educational
Macrophage (histiocyte)	1	0.3	Educational
Monocyte	1	0.3	Educational
Neutrophil, metamyelocyte	1	0.3	Educational

BMD-12 Cont'd

The arrowed cell is a myelocyte, as correctly identified by 89.8% of participants. 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, or secondary) granules. Myelocytes are usually confined to the marrow where they constitute approximately 10% of the nucleated cells. In pathologic states, myelocytes may be seen in peripheral blood. The myelocyte is smaller than the earlier myeloid precursors (promyelocytes and myeloblasts), usually 10 to 18 µm. The cells are round-to-oval in shape and have a nuclear-to-cytoplasmic ratio of 2:1 to 1:1. The nucleus is slightly eccentric, lacks a nucleolus, and begins to demonstrate chromatin clumping. One side of the nucleus often shows slight flattening. Sometimes a clear space or hof is seen in the cytoplasm adjacent to the nucleus (as seen in the arrowed cell). 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.

2.6% of participants incorrectly identified the arrowed cell as a plasma cell, morphologically mature/abnormal/containing inclusion (eg, Dutcher body, Russell Body). Plasma cells represent terminally differentiated B-lymphocytes and are a normal constituent of the bone marrow where they usually comprise less than 5% of the cellularity. They range in size from 10 to 20 µm and are often oval shaped with relatively abundant cytoplasm and eccentrically located nuclei. The N:C ratio is 1:2. Their nuclei are usually round to ovoid with prominently coarse and clumped chromatin that is often arranged in a cartwheel-like or clock-face pattern. Occasional benign plasma cells are binucleated. Nucleoli are absent. The cytoplasm stains gray blue to deeply basophilic. A prominent hof or perinuclear zone of pale or lighter staining cytoplasm is typically seen adjacent to one side of the nucleus. This area corresponds to the Golgi zone, which is prominent in cells that produce large amounts of protein, such as immunoglobulin in the case of plasma cells. Cytoplasmic granules are absent, and scattered vacuoles of varying size may be seen.

1.6% of participants incorrectly identified the arrowed cell as a monocyte, immature (promonocyte, monoblast). The malignant monoblast is a large cell, 15 to 25 µm in diameter. It has relatively more cytoplasm than a myeloblast with the nuclear-to-cytoplasmic ratio ranging from 7:1 to 3:1. The monoblast nucleus is round or oval and has finely dispersed chromatin and distinct nucleoli. The cytoplasm is blue to gray-blue and may contain small, scattered azurophilic granules. Some monoblasts cannot be distinguished morphologically from other blast forms, hence the need for using other means (eg, cytochemistry and flow cytometry) are required to accurately assign blast lineage. Promonocytes have nuclear and cytoplasmic characteristics that are between those of monoblasts and mature monocytes. They are generally larger than mature monocytes, but they have similar appearing gray-blue cytoplasm that often contains uniformly distributed, fine azurophilic granules. Cytoplasmic vacuolization is not a typical feature. The nuclei show varying degrees of lobulation, usually characterized by delicate folding or creasing of the nuclear membrane, in contrast to the rounder nuclear profile of monoblasts. Nucleoli are present but not as distinct as in monoblasts.

1.6% of participants incorrectly identified the arrowed cell as a neutrophil with dysplastic nucleus and/or hypogranular cytoplasm. Dysplastic neutrophils are characteristic of myelodysplastic syndromes. Morphologically, the normal synchronous maturation of nucleus and cytoplasm is lost. As a result, in the cytoplasm, the primary and secondary granules are often decreased or absent, causing the cytoplasm to appear pale and bluish. The nucleus shows abnormal lobation accompanied by a mature chromatin pattern. In some cases, the nucleus has a "pince-nez" appearance. These cells are known as pseudo-Pelger Huët neutrophils.

1.1% of participants incorrectly identified the arrowed cell as a neutrophil, 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 peripheral blood in pathologic states, such as chronic myeloid leukemia. The nuclear-to-cytoplasmic ratio is high (5:1 to 3:1). The nucleus has finely dispersed 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.

Actions Laboratories Should Take when a PT Result is Not Graded

The CAP uses exception reason codes that signify the proficiency testing (PT) for an analyte has not been graded. The exception reason code is located on the evaluation report in brackets to the right of the result. Your laboratory must identify all analytes with an exception reason code, review, and document the acceptability of performance as outlined below and retain documentation of review for at least 2 years. The actions laboratories should take include, but are not limited to:

Code	***Exception Reason Code Description***	***Action Required***
11	Unable to analyze	Document why the specimens were not analyzed (eg, instrument not functioning or reagents not available). Perform and document alternative assessment (ie, split samples) for the period that commercial PT was not tested to the same level and extent that would have been tested.
20	Response was not formally graded due to insufficient peer group data. Please see the participant summary for additional information.	Applies to a response that is not formally evaluated when a peer group is not established due to fewer than 10 laboratories reporting. Document that the laboratory performed a self-evaluation using the data presented in the participant summary and compared its results to a similar method, all method, all participant statistics, or data tables for groups of 3-9 laboratories, if provided. Perform and document the corrective action of any unacceptable results. If self-evaluation is not possible, it is up to the laboratory director/designee to determine an alternative performance assessment.
21	Specimen problem	Document that the laboratory has reviewed the proper statistics supplied in the participant summary. Perform and document alternative assessment for the period that commercial PT was not tested to the same level and extent that would have been tested. Credit is not awarded in these cases.
22	Result is outside the method/ instrument reportable range	Document the comparison of results to the proper statistics supplied in the participant summary. Verify detection limits. Perform and document the corrective action of any unacceptable results.
24	Incorrect response due to failure to provide a valid response code	Document the laboratory's self-evaluation against the proper statistics and evaluation criteria supplied in the participant summary. Perform and document the corrective action of any unacceptable results. Document corrective action to prevent future failures.
25	Inappropriate use of antimicrobial	Document the investigation of the results as if they were unacceptable and review the proper reference documents to gain knowledge of the reason your response is not appropriate.
26	Educational challenge	Review participant summary for comparative results and document performance accordingly. Evaluation criteria are not established for educational challenges. Laboratories should determine their own evaluation criteria approved by their laboratory director for self-evaluation.
27,31	Lack of participant or referee consensus	Document that the laboratory performed a self-evaluation and compared its results to the intended response when provided in the participant summary. If comparison is not available, perform and document alternative assessment (ie, split samples) for the period that commercial PT reached non-consensus to the same level and extent that would have been tested.
28	Response qualified with a greater than or less than sign; unable to quantitate	Applies to a response that is not formally evaluated when a less than or greater than sign is reported. Document that the laboratory performed a self-evaluation and compared its results to the proper statistics supplied in the participant summary. Verify detection limits. Perform and document the corrective action of any unacceptable results.
30	Scientific committee decision	Applies to a response that is not penalized based on scientific committee decision. Document that the laboratory has reviewed the proper statistics supplied in the participant summary.

Actions Laboratories Should Take when a PT Result is Not Graded

The CAP uses exception reason codes that signify the proficiency testing (PT) for an analyte has not been graded. The exception reason code is located on the evaluation report in brackets to the right of the result. Your laboratory must identify all analytes with an exception reason code, review and document the acceptability of performance as outlined below and retain documentation of review for at least 2 years. The actions laboratories should take include but are not limited to:

Code	***Exception Reason Code Description***	***Action Required***
33	Specimen determined to be unsatisfactory after contacting the CAP	Document that the laboratory has contacted the CAP and no replacements specimens were available. Perform and document alternative assessment (ie, split samples) for the period that commercial PT was not tested to the same level and extent that would have been tested.
40 41	Results for this kit were not received. Results for this kit were received past the evaluation cut-off date.	Document why results were not received, corrective action to prevent recurrence and the laboratory's self-evaluation of the results by comparing results to the proper statistics and evaluation criteria supplied in the participant summary. If PT specimens were not analyzed, perform and document alternative assessment (ie, split samples) for the period that commercial PT was not tested to the same level and extent that would have been tested.
42	No credit assigned due to absence of response	The participant summary indicates which tests are graded (see evaluation criteria) and which tests are not evaluated/educational. Updates to grading will also be noted. If a test is educational, the laboratory is not penalized for leaving a result(s) blank. If a test is graded (regulated and non-regulated analytes) and your laboratory performs that test, results cannot be left blank. The laboratory is required to submit results for **all** challenges within that test or use an appropriate exception code or indicate test not performed/not applicable/not indicated. Exceptions may be noted in the kit instructions and/or the result form. Document corrective actions to prevent future failures.
44	This drug is not included in our test menu. Use of this code counts as a correct response.	Verify that the drug is not tested on patient samples and document to ensure proper future reporting.
45	Antimicrobial agent is likely ineffective for this organism or site of infection	Document that the laboratory performed a self-evaluation of written protocols and practices for routine reporting of antimicrobial susceptibility reports to patient medical records. Document that routine reporting of this result to clinicians for patient care is compliant with specific recommendations of relevant medical staff and committees (eg, infectious diseases, pharmacy and therapeutics, infection control).
77	Improper use of the exception code for this mailing	Document the identification of the correct code to use for future mailings.
91	There was an insufficient number of contributing challenges to establish a composite grade.	Document the investigation of the result as if it were an unacceptable result. Perform and document the corrective action if required.
35, 43, 46, 88, 92	Various codes	No action required.

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BMD-B 2022: Chronic Myeloid Leukemia, Blast Crisis

Continuing Education Information

CE (Continuing Education for non-physicians)
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Disclosure Statement

Below you will find the financial disclosure relationships for anyone who was able to affect the content of this educational activity.

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The following authors/planners have no financial relationships to disclose:
Olga Pozdnyakova, MD, PhD

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None

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None

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None

Learning Objectives

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

1. Describe the diagnostic criteria of chronic myeloid leukemia, including the classification of clinical phases.
2. Identify the clinical and morphologic features of different phases of chronic myeloid leukemia.
3. Recommend common laboratory tests for chronic myeloid leukemia patients with suspicion of disease transformation to accelerated and blast phases.
4. Recognize the essential role of tyrosine kinase inhibitors in treatment of chronic myeloid leukemia.

Case Presentation
This bone marrow aspirate smear is from a 42-year-old man with leukemia. Complete blood count includes: WBC = 185.1 x 10E9/L; RBC = 2.68 x 10E12/L; HGB = 8.7 g/dL; HCT = 25.1%; MCV = 98 fL; and PLT = 69 x 10E9/L.
(BONE MARROW, WRIGHT-GIEMSA)

INTRODUCTION

Chronic myeloid leukemia (CML) is the most common myeloproliferative neoplasm, accounting for approximately 15% to 20% of all adult leukemias, with an annual incidence of 1 to 2 cases per 100,000. CML is slightly more common in males than females, typically presents at ages 40 to 60 years, and is discovered incidentally in 20% to 50% of patients by abnormal complete blood count (CBC) results, such as leukocytosis, anemia, thrombocytosis, and/or hepatosplenomegaly on physical examination. Other patients may present with symptoms that develop gradually and usually relate to splenomegaly (left upper quadrant discomfort or early satiety), problems from an increased white cell production (bone pain, mild fever, night sweats, weight loss), or anemia (dyspnea, fatigue, pallor).

CML is defined by the presence of the Philadelphia chromosome (Ph), a derivative chromosome 22 that harbors the *BCR::ABL1* fusion gene, the result of reciprocal translocation t(9;22)(q34;q11). CML has three stages: chronic phase (CML-CP), accelerated phase (CML-AP), and blast phase (CML-BP). CML diagnosis, including the disease phase, is made based on CBC and morphologic findings in peripheral blood (PB) and bone marrow (BM) in combination with detection of the *BCR::ABL1* translocation by cytogenetic and molecular genetic techniques [karyotype, fluorescence *in situ* hybridization (FISH) or reverse transcription polymerase chain reaction (RT-PCR)]. The presence of the *BCR::ABL1* translocation is required for the diagnosis of CML.

CML PHASES AND DISEASE PROGRESSION

Most patients with CML are diagnosed during the indolent chronic phase (CP) with leukocytosis and a markedly hypercellular marrow due to myeloid cell proliferation. Without therapy, CML-CP invariably progresses to blast phase (BP), which is transformation to acute leukemia. CML-BP is typically diagnosed when blasts represent at least 20% of leukocytes in the blood or of nucleated cells in the bone marrow. The blasts in CML-BP are usually of myeloid lineage, but in 20% to 30% of cases are of lymphoid lineage, usually B lymphoblasts. Rarely, the blasts are of mixed phenotype. The ability of CML to transform to acute leukemia of either myeloid or lymphoid lineage supports the concept that this neoplasm arises from a pluripotent bone marrow stem cell that is capable of multilineage differentiation.

In some patients, progression from CP to BP can be recognized as a discrete accelerated phase (AP) and very rarely patients can present in CML-AP. CML-AP is defined by the presence of one or more of the hematologic, cytogenetic, or clinical criteria outlined in **Table 1**.

Table 1: Defining criteria for the accelerated phase of CML

Hematologic criteria
Persistent or increasing WBC count (> 10 x 10E9/L), unresponsive to therapy
Persistent or increasing splenomegaly, unresponsive to therapy
Persistent thrombocytosis (> 1,000 x 10E9/L), unresponsive to therapy
Persistent thrombocytopenia (< 100 x 10E9/L), unrelated to therapy
≥ 20% basophils in the peripheral blood
10 - 19% blasts in the peripheral blood and/or bone marrow
Cytogenetic criteria
Additional clonal abnormalities in Ph+ cells (a second Ph chromosome, trisomy 8, isochromosome 17q, trisomy 19), complex karyotype, and abnormalities of 3q26.2
Any new clonal chromosomal abnormality in Ph+ cells during therapy
Provisional response to treatment criteria*
Hematologic resistance to the first-line treatment
Any hematologic, cytogenetic, or molecular resistance to first and second-line treatments
Occurrence of two or more mutations in the *BCR::ABL1* fusion gene during therapy

*See the **Treatment** section; Ph = Philadelphia chromosome (*BCR*::*ABL1* rearrangement)

PERIPHERAL BLOOD AND BONE MARROW MORPHOLOGY

In CML, the peripheral blood (PB) and bone marrow (BM) morphology depends on the disease phase.

Chronic phase

In the chronic phase (CP), the ability of granulocytes to mature/differentiate is retained. The hallmark of CML is marked PB neutrophilia with a prominent left shift, absolute basophilia, and often eosinophilia. The white blood cell (WBC) count typically far exceeds 25 x 10E9/L, with a median WBC at presentation of 170 x 10E9/L. There may be mild absolute monocytosis, but monocytes should comprise only a small fraction of the differential (usually 3% or less). Neutrophils do not appear dysplastic. The left shift includes a much larger proportion of

earlier precursors than is normally seen in a reactive left shift, including frequent myelocytes (so-called “myelocyte bulge,” promyelocytes, and occasional blasts (usually less than 10%). The presence of basophilia, and sometimes eosinophilia, in CML is helpful in the distinction from a reactive neutrophilia (leukemoid reaction). Additional findings in CML may include occasional circulating nucleated red blood cells, rare megakaryocyte nuclear fragments, and frequent thrombocytosis, which may be marked (> 1,000 x 10E9/L). Thrombocytopenia can occur but is uncommon in CP. While granulocytes in the peripheral blood are morphologically normal, platelets can be abnormally large, and sometimes not well granulated.

The BM morphologic findings mimic PB and show hypercellularity due to marked granulocytic hyperplasia and eosinophilia; blasts constitute less than 5% in CP by definition. The majority of cases show increased megakaryocytes with abnormal morphology, such as small hypolobate forms (micromegakaryocytes). Due to the excessive hematopoiesis, the number of cells that eventually die increases, and macrophages containing the lipids from dead cell membranes may be visible in the bone marrow as sea-blue histiocytes or pseudo-Gaucher cells.

Accelerated phase

Peripheral blood CBC findings associated with the accelerate phase (AP) are outlined in **Table 1.** BM findings suggestive of CML-AP are the presence of large clusters or sheets of abnormal small megakaryocytes associated with marked reticulin or collagen fibrosis, along with increased blasts up to 19% either in the PB or BM.

Blast phase

The criteria for chronic myeloid leukemia in blast phase (CML-BP) include ≥ 20% blasts in the PB or BM or the presence of an extramedullary proliferation of blasts. In most cases, the blast lineage is myeloid, and may include neutrophilic, monocytic, megakaryocytic, basophilic, eosinophilic, or erythroid differentiation. In approximately 20% to 30% of cases, the blasts are of lymphoid lineage, usually B-cell origin (B lymphoblasts). In addition to or instead of BM, the blast proliferation may present in skin, lymph nodes, bone, and brain, but can occur anywhere. In the absence of Auer rods, a morphologic hallmark of a myeloblast, additional immunophenotypic testing is needed to confirm the blast lineage (**Table 2**). Multicolor multiparametric flow cytometric analysis of cell suspensions (ie, peripheral blood, bone marrow aspirate, or disaggregated bone marrow core biopsy or extramedullary tissue mass) is the preferred and most common testing modality. However, if flow cytometry is not available, immunohistochemical staining on tissue sections may be performed. Examples when flow cytometric analysis cannot be performed include inaspirable marrow (“dry tap”) due to BM fibrosis, insufficient sample, and inability to homogenize cells into a suspension.

Table 2. Blast lineage-associated immunophenotype (most common antigens)

Immature cell markers (could be present in any lineage)
CD34, TdT
Myeloid lineage
Myeloperoxidase, CD13, CD33
Monocytic lineage
CD11b, CD11c, CD14, CD15, CD64
Megakaryocytic lineage
CD41, CD61
Erythroid lineage
E-cadherin, Glycophorin A
B-cell lineage
CD19, CD20, PAX5, CD10, CD22, CD79a

GENETIC AND MOLECULAR FEATURES

CML arises due to a specific acquired translocation in a pluripotent BM stem cell that involves exchange of genetic material between chromosomes 9 and 22, written as "t(9;22)" where "t" refers to translocation. This translocation results in the creation of an abnormal fusion gene, *BCR::ABL1* (due to juxtaposition of the *BCR* gene from chromosome 22 to the *ABL1* gene on chromosome 9), which is present by definition in CML. The resultant derivative (abnormal) chromosome 22 is referred to as the Philadelphia chromosome (Ph), named after the city in which this important discovery was made.

The abnormal *BCR*::*ABL1* fusion gene produces a novel BCR::ABL1 protein, a constitutively active tyrosine kinase, that drives the proliferation of myeloid cells, particularly granulocytes and megakaryocytes. Unlike normal proteins whose activities are regulated by cellular signaling pathways, the abnormal BCR::ABL1 protein is always active, resulting in the characteristic marked leukocytosis and frequent thrombocytosis seen in CML.

Although 100% of CML cases have the *BCR*::*ABL1* fusion gene, the classic Philadelphia chromosome is found in only 90% to 95% of cases. Most of the remaining cases have variant genetic abnormalities that involve other chromosomes in addition to 9 and 22. These structural translocations can also be identified by conventional karyotyping. A small number of cases have cryptic *BCR*::*ABL1* translocations, meaning that they cannot be identified by routine cytogenetic analysis. When this is suspected, molecular genetic studies such as RT-PCR or FISH analysis, are indicated. The sensitivity of RT-PCR for detecting the BCR::ABL1 fusion transcript is approximately 99% and for FISH analysis is greater than 99%. In addition to establishing the diagnosis, real-time

quantitative RT-PCR (RT-qPCR) of BCR::ABL1 RNA is a necessary laboratory technique for monitoring the efficacy of TKI therapy (see the **Treatment** section) and quantitatively assessing minimal residual disease (MRD). The molecular response measured by BCR::ABL1 RT-qPCR assists in identifying suboptimal responses and can help inform the decision to switch to different therapies that may be more efficacious (or to pursue more stringent monitoring). Furthermore, the TKI-mediated molecular response provides valuable risk stratification and prognostic information on long-term outcomes.

Evaluation of Patients With Suspected CML

CML-CP and AP must be differentiated from other benign and neoplastic conditions associated with leukocytosis. Leukemoid reaction, a reactive condition, usually presents with WBC counts lower than 50 x 10E9/L, toxic granulation and Döhle bodies in neutrophils, and absence of basophilia. Other myeloproliferative neoplasms must also be excluded based on the absence of their clinical, pathologic, and molecular genetic features. Since leukocytosis is a common CBC finding and the detection of *BCR*::*ABL1* translocation has significant diagnostic, prognostic, and therapeutic implications, many patients presenting with unexplained increased WBC counts undergo genetic testing to evaluate for the *BCR*::*ABL1* fusion.

Evaluation of Patients With Suspected Transformation to CML-BP

CML-BP must be differentiated from other acute myeloid or lymphoblastic leukemias, which in most cases could be done by interrogating the patient's history and by demonstrating the presence of the *BCR*::*ABL1* gene fusion (see the **Genetic and Molecular Features** section). Most cases of CML-BP will have a known diagnosis of CML at the time of transformation. However, a minority of patients with CML will be in blast crisis at the time of diagnosis.

Transformation to CML-BP may be suggested clinically by the development of signs and symptoms more typical of acute leukemia, such as night sweats, weight loss, fever, bone pain, symptoms of anemia, and bleeding. Evaluation of the patient with suspected CML-BP should include the following:

1. Laboratory studies including CBC with differential, chemistries with liver and renal function and electrolytes, and glucose.
2. BM aspiration and biopsy for morphologic examination, flow cytometry immunophenotyping (myeloid vs. lymphoid), and cytogenetics (clonal evolution with additional cytogenetic abnormalities).
3. *ABL1* mutation analysis to aid in selection of TKI.
4. Human leukocyte antigen (HLA) typing for patients who are candidates for potential allogeneic hematopoietic stem cell transplantation (bone marrow transplant).

Treatment

Historically, CML was treated with low-dose chemotherapy such as hydroxyurea or cytarabine to control cell counts, as well as interferon, which could induce remission in some patients but at the cost of poorly tolerated side effects. The only proven long-term cure for CML is allogeneic hematopoietic stem cell transplantation, a therapy with significant associated risks.

The therapy of CML was revolutionized by the development of imatinib in the late 1990s, a TKI that specifically targets the abnormal BCR::ABL1 protein and blocks its oncogenic activity. Imatinib has been proven to induce remission in the vast majority of patients with CML-CP, including hematologic remission (ie, resolution of blood and marrow abnormalities with normalization of blood counts), cytogenetic remission [ie, absence of detectable t(9;22)], and molecular remission (ie, absence of detectable BCR::ABL1 transcript by RT-qPCR).

In most patients, imatinib is well tolerated without significant side effects, and has permitted sustained disease remission for many years without disease progression or transformation to CML-AP or CML-BP.

As mentioned earlier, patients should continuously undergo molecular and/or cytogenetic monitoring. Rising levels of *BCR*::*ABL1* transcripts may be associated with development of drug resistance and/or disease progression. An alternative TKI is used in patients who become intolerant to a first-line TKI; show excessive toxicity, treatment failure, or suboptimal response; or develop a resistance mutation in the *ABL1* gene. The prognoses of CML-AP and CML-BP are poor, particularly for patients with prior TKI therapy, as many of them develop resistance mutations in the *ABL1* gene (**Table 3**). There is a significant relapse rate even after successful initial TKI treatment with or without chemotherapy, and these patients should be considered for transplantation.

Table 3. Selective tyrosine kinase inhibitors and their sensitivity to *ABL1* gene resistance mutations

First generation
Imatinib: • First-line treatment in the absence of mutations • 2nd choice for *F317L/V/I/C*, *V299L* mutations
Second generation
Nilotinib; • 1st choice for *F317L/V/I/C*, *V299L* mutations
Dasatinib: • 1st choice for *Y253H*, *E255K/V*, *F359V/C/I* mutations • 3rd choice for *F317L/V/I/C*, *V299L* mutations
Third generation
Ponatinib: • Only choice for *T315I* mutation

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NOTES

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This concludes the report.

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