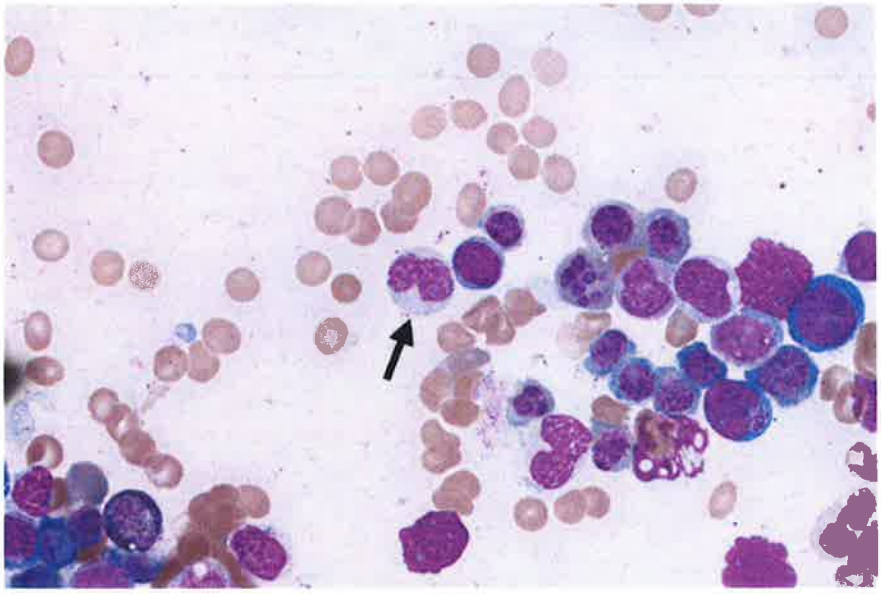
Cell Identification

BMD-08



Identification	Participants No.	Participants %	Evaluation
Neutrophil with dysplastic nucleus and/or hypogranular cytoplasm	146	42.7	Educational
Neutrophil, metamyelocyte	75	21.9	Educational
Neutrophil, segmented or band	44	12.9	Educational
Monocyte	31	9.1	Educational
Neutrophil with Pelger-Huët nucleus (acquired or congenital)	29	8.5	Educational
Neutrophil, giant band or giant metamyelocyte	16	4.7	Educational
Monocyte, immature (promonocyte, monoblast)	1	0.3	Educational

BMD-08, cont'd

The arrowed cells are dysplastic neutrophils, as correctly identified by 42.7% of participants. Dysplastic neutrophils are characteristic of myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) that evolved out of MDS or therapy-related AML. 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. For proficiency testing purposes, cells with pseudo-Pelger Huët nuclei are best defined as Pelger Huët cells. Dysplastic neutrophils often have abnormal cytochemical reactivity; levels of myeloperoxidase and leukocyte alkaline phosphatase may be low or absent. The dysplastic neutrophils may also exhibit functional defects. In addition, dysplastic cytoplasmic and nuclear changes may be seen in maturing granulocytic cells in the bone marrow, frequently appearing as dyssynchrony between the cytoplasmic and nuclear maturation and/or cytoplasmic hypogranularity.

21.9% of participants incorrectly identified the arrowed cell as a neutrophil, myelocyte stage. The myelocyte 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.

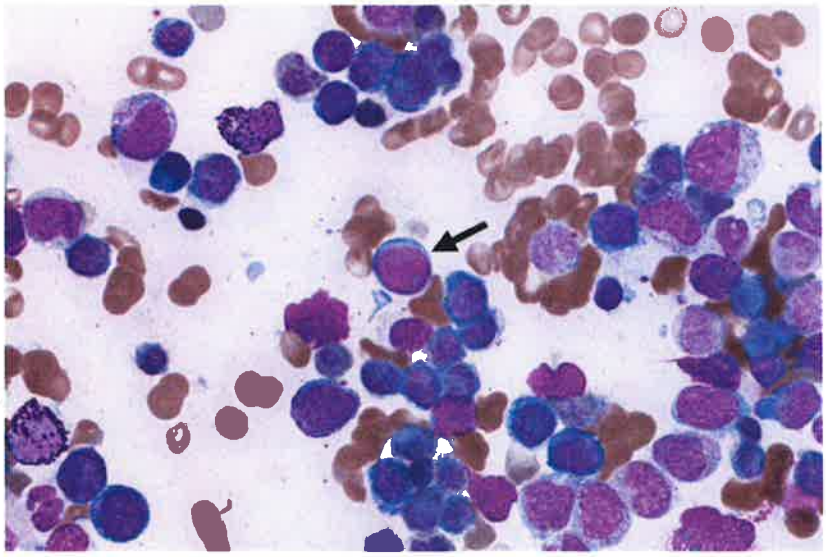
12.9% of participants incorrectly identified the arrowed cell as a neutrophil, segmented or band. Although the presence of hypolobated nucleus brings a band neutrophil into the differential, the loss of the normal synchronous maturation of nucleus and cytoplasm and the absence of specific granules in cytoplasm (hypogranular cytoplasm in the arrowed cell) does not support this cell identification. Normal nuclear segmentation of a segmented neutrophil is also not present.

9.1% of the participants incorrectly identified the arrowed cell as a monocyte. Monocytes are slightly larger than neutrophils, 12 to 20 µm in diameter. Monocytes have abundant cytoplasm with a gray or gray-blue ground-glass appearance, and may contain vacuoles or fine, evenly distributed azurophilic granules. The nuclear-to-cytoplasmic ratio is 4:1 to 2:1. The nucleus is usually indented, often resembling a three-pointed hat, but it can also be folded or band-like. The chromatin is condensed, but less dense than that of a neutrophil or lymphocyte. Nucleoli are generally absent, but occasional monocytes may contain a small, inconspicuous nucleolus.

8.5% of the participants incorrectly identified the arrowed cell as a neutrophil with Pelger-Huet nucleus. Similar to neutrophils with dysplastic nucleus and/or hypogranular cytoplasm, neutrophils with Pelger-Huet nuclei are seen in myelodysplastic syndrome or acute myeloid leukemia. However, the main distinguishing morphologic feature of the latter, is the presence of bilobed nuclei in the pince-nez conformation (ie, two round or nearly round lobes connected by a distinct thin filament), a feature not seen in the arrowed cell.

4.7% of participants incorrectly identified the arrow cell as a neutrophil, giant band. Myeloid precursors resulting from megaloblastic hematopoiesis show an increase in size, and they have nuclei that show aberrant maturation where the nuclear features appear less mature than the cytoplasmic features. These cells have diameters 1.5 times those of normal metamyelocytes or bands.

BMD-09



Identification	Participants No.	Participants %	Evaluation
Blast cell (includes lymphoblast)	328	95.9	Educational
Erythrocyte precursor, normal (includes pronormoblast, basophilic, polychromatophilic, and orthochromic normoblasts)	5	1.5	Educational
Myeloblast with Auer rod	3	0.9	Educational
Immature or abnormal cell, would refer	2	0.6	Educational
Neutrophil, promyelocyte, abnormal with/without Auer rod(s)	2	0.6	Educational
Erythrocyte precursor, abnormal/dysplastic nuclear features (Includes pronormoblast, basophilic, polychromatophilic, and orthochromic normoblasts)	1	0.3	Educational
Hematogone	1	0.3	Educational

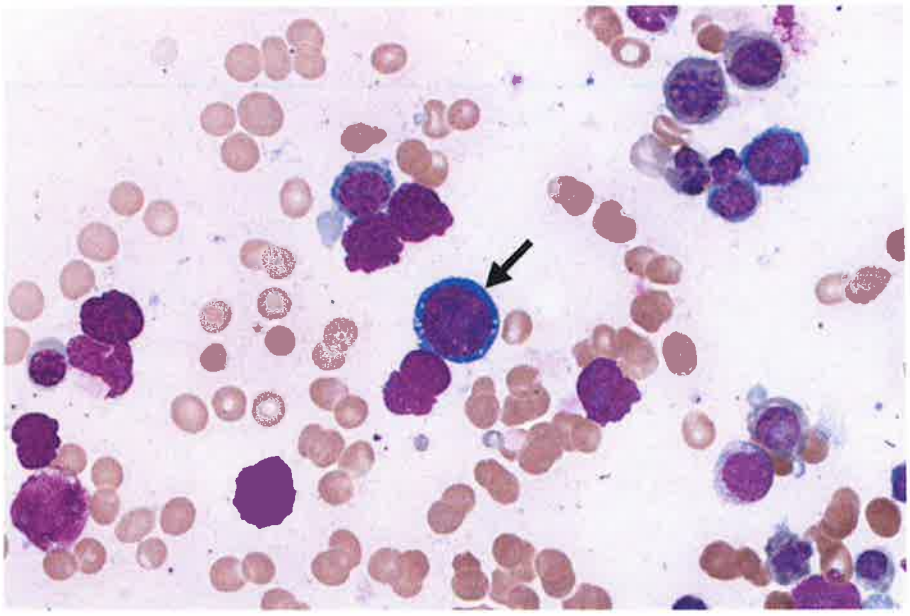
BMD-09, cont'd

The arrowed cells are blasts, as correctly identified by 95.9% of referees and 95.9% of participants. The blast could belong to the myeloid (myeloblast) or lymphoid (lymphoblast) lineage. 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. They may be present in the blood in leukemic states, myelodysplastic syndromes, myeloproliferative neoplasms, and, very rarely, leukemoid reactions. 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 (as present in this case). 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. Distinguishing one type of abnormal blast cell from another is not always possible using Wright-Giemsa stains alone. Additional testing such as cytochemical staining (eg, myeloperoxidase or Sudan black), or immunophenotyping by flow cytometry may be required to further define the lineage of a given blast population, unless morphologically obvious Auer rods are present.

Lymphoblasts are the most immature cells of the lymphoid series. They are most commonly seen in acute lymphoblastic leukemia and lymphoid blast crisis of chronic myeloid leukemia. 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. As lymphoblasts are quite variable in appearance, it is often impossible to correctly classify an individual cell based on the morphology alone. Lymphoblasts can be indistinguishable from other types of blasts and lymphoma cells. For purposes of proficiency testing, one should identify individual cells exhibiting this immature type of morphology as blast cells.

1.5% incorrectly identified the arrowed cell as an erythroid precursor, normal. The earliest recognizable erythroid precursor is the pronormoblast (proerythroblast, erythroblast). From this stage, the maturation sequence progresses through the basophilic, polychromatophilic, and orthochromic normoblast stages until the nucleus is extruded and an anucleate cell exits the bone marrow and enters the peripheral blood. The presence of an immature nucleus in the arrowed cells brings pronormoblasts, morphologically the most immature cells of the erythrocytic series, into the differential. However, unlike blasts (myeloid or lymphoid), pronormoblasts 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.

BMD-10



Identification	Participants No.	Participants %	Evaluation
Erythrocyte precursor, abnormal/dysplastic nuclear features (Includes pronormoblast, basophilic, polychromatophilic, and orthochromic normoblasts)	266	77.8	Educational
Erythrocyte precursor with vacuolated cytoplasm	34	9.9	Educational
Erythrocyte precursor, normal (includes pronormoblast, basophilic, polychromatophilic, and orthochromic normoblasts)	15	4.4	Educational
Metastatic tumor cell or tumor cell clump	11	3.2	Educational
Erythrocyte precursor with megaloblastic changes/maturation	8	2.3	Educational
Malignant lymphoid cell (other than blast)	3	0.9	Educational
Mast cell	2	0.6	Educational
Blast cell (includes lymphoblast)	1	0.3	Educational
Immature or abnormal cell, would refer	1	0.3	Educational
Neutrophil, promyelocyte	1	0.3	Educational

BMD-10, cont'd

The arrowed cells are dysplastic erythrocyte precursors, as correctly identified by 77.8% of referees and 77.8% of participants. Dysplastic nucleated red blood cells are similar size to their normal counterparts in the erythrocytic series but characteristically exhibit strikingly abnormal nuclear features. Compared to the round nucleus of normal erythroid precursors, dysplastic erythrocytes often have a misshapen nucleus due to nuclear "budding" (lobation or rosette formation) or fragmentation. Multinucleation is also common, and internuclear bridging by thin strands of chromatin may be present. Megaloblastic changes may also be present as manifested by dyssynchrony of nuclear and cytoplasmic maturation where the nuclear features appear less mature than those seen in the cytoplasm (see below). The cytoplasm shows normal hemoglobinization. Some dysplastic red blood cells may be vacuolated, contain multiple Howell-Jolly bodies, or exhibit coarse basophilic stippling. All of these morphologic features are present in the scanned slide. Erythroid dysplasia may be seen in a variety of benign disorders (eg, vitamin B12, folate, or copper deficiency) or malignant conditions (eg, myelodysplastic syndromes, acute myeloid leukemias).

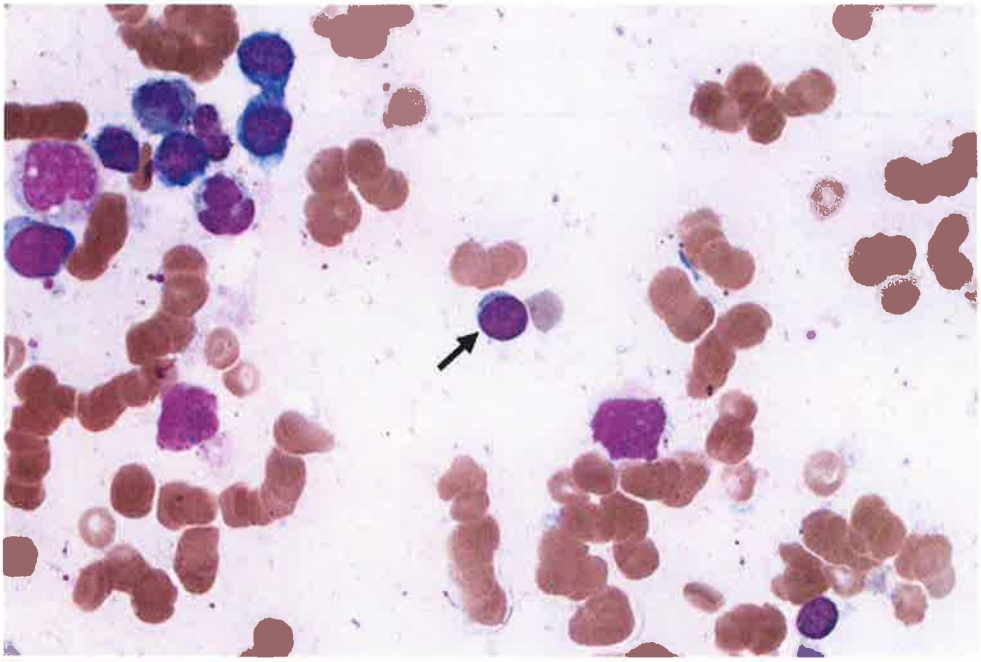
9.9% of participants incorrectly identified the arrowed cells as erythroid precursors with vacuolated cytoplasm. Cytoplasmic vacuoles may be seen in a variety of conditions not related to myelodysplastic syndrome, however, the presence of a convoluted nucleus with multinucleation, in addition to the cytoplasmic vacuoles, is characteristic of a dysplastic erythroid precursor in the setting of myelodysplasia.

4.4% of the participants incorrectly identified the arrowed cells as normal erythroid precursors. Normal erythroid precursors (pronormoblasts, basophilic, polychromatophilic and orthochromic normoblast stages) never contain cytoplasmic vacuoles or multinucleated nuclei.

3.2% of the participants incorrectly identified the arrowed cells as metastatic tumor cells. Metastatic tumor cells are larger than most bone marrow cells, except megakaryocytes, varying from approximately 15 µm to 100 µm in diameter, with a highly variable nuclear-to-cytoplasmic ratio (7:1 to 1:5). They frequently adhere in tight clusters, forming syncytial sheets or mulberry-like aggregates (morulae), best detected at the periphery of the aspirate smear. Nonhematopoietic malignant cells are frequently not aspirable ("dry tap") due to associated marrow fibrosis; thus, tumor cells may not be detected in marrow smears.

2.3% of the participants incorrectly identified the arrowed cells as an erythroid precursor with megaloblastic changes/maturation. Megaloblastic erythroid precursors are larger than the corresponding normal cells of the erythrocytic series and are characterized by nuclear and cytoplasmic maturation dyssynchrony. This is manifested by delayed nuclear maturation relative to the degree of cytoplasmic maturation (ie, cells have an immature chromatin pattern compared to the degree of cytoplasmic hemoglobinization). Coexisting features of dyserythropoiesis, such as multinucleation, abnormal nuclear shapes, and cytoplasmic Howell-Jolly bodies, may also be seen, however, cytoplasmic vacuolization is not characteristic.

BMD-11

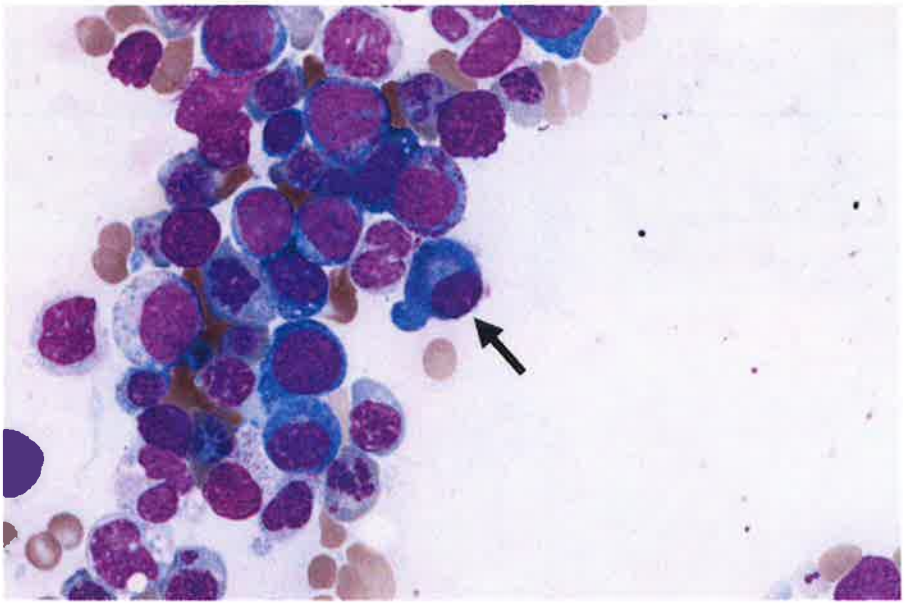


Identification	Participants No.	%	Evaluation
Lymphocyte	335	98.0	Educational
Hematogone	4	1.2	Educational
Blast cell (includes lymphoblast)	2	0.6	Educational
Lymphocyte, large granular	1	0.3	Educational

The arrowed cell is a normal lymphocyte, as correctly identified by 98.0% of referees and 98.0% 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, adjacent to one side of the nucleus.

1.2% of the participants incorrectly identified the arrowed cells 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 and homogeneous. The cytoplasm is very scant and often not discernible.

BMD-12



Identification	Participants No.	%	Evaluation
Plasma cell, morphologically mature/abnormal/containing inclusion (eg, Dutcher body, Russell body)	341	99.7	Educational
Erythrocyte precursor, normal (includes pronormoblast, basophilic, polychromatophilic, and orthochromic normoblasts)	1	0.3	Educational

The arrowed cells are the normal plasma cells, as correctly identified by 99.7% of referees and 99.7% of participants. 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. Plasma cells 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.