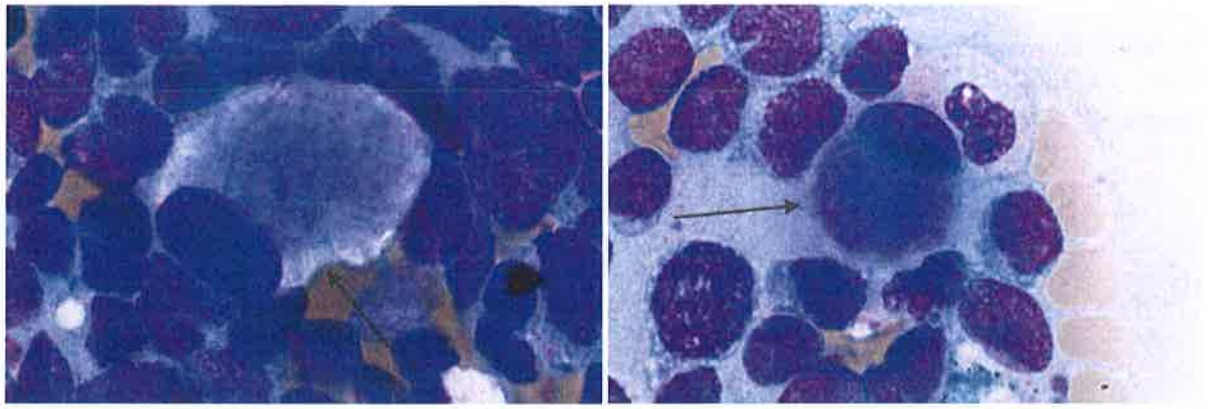
Cell Identification

BMD-02



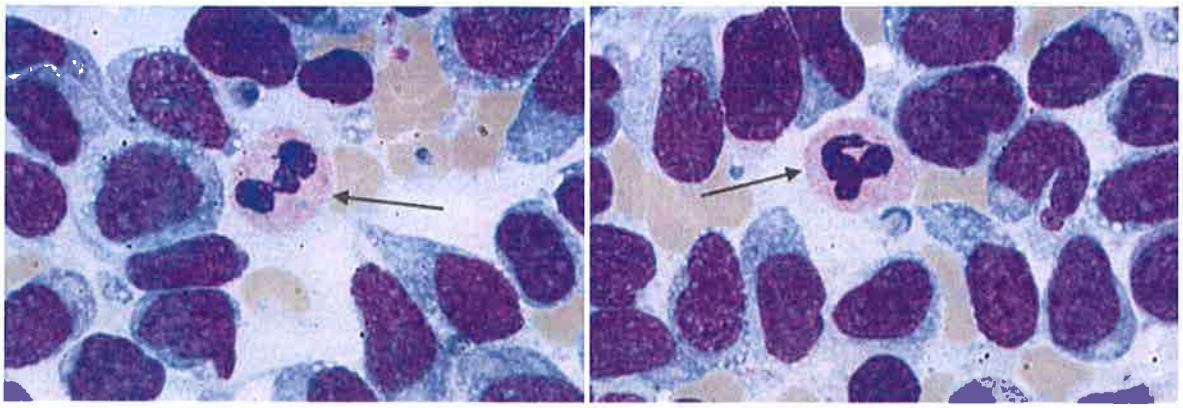
Identification	Participants No.	Participants %	Evaluation
Megakaryocyte or precursor, abnormal	196	68.8	Educational
Megakaryocyte or precursor, normal	57	20.0	Educational
Osteoblast	11	3.9	Educational
Gaucher cell, Pseudo-Gaucher cell	7	2.5	Educational
Macrophage (histocyte)	5	1.8	Educational
Plasma cell (to include morphologically mature, abnormal, and with inclusion, eg, Dutcher body, Russell body, etc)	3	1.1	Educational
Megakaryocyte nucleus	2	0.7	Educational
Histocyte, sea blue	1	0.3	Educational
Immature or abnormal cell, would refer for identification	1	0.3	Educational
Malignant lymphoid cell (other than blast)	1	0.3	Educational
Osteoclast	1	0.3	Educational

The arrowed cells are abnormal megakaryocytes, as correctly identified by 68.8% of participants. Normal megakaryocytes are 25 to 50 µm in diameter and contain nuclear lobes of various sizes, connected together by bands or threads of chromatin. In contrast, the arrowed cells are abnormally small in size, with single, eccentrically located, non-lobated nuclei. They are, however, recognizable as megakaryocytes by their size, the smudgy quality of their chromatin, and the variably basophilic, flocculent quality of the cytoplasm. Such cells are often described as micromegakaryocytes.

Committee Comments on Bone Marrow Differential and Aspriate

This whole slide image is from a bone marrow aspirate smear from a 61-year-old male with fatigue, bruising, lymphadenopathy, skin lesions, and pancytopenia. The slide shows that normal hematopoiesis is decreased in the face of a predominant infiltrate of immature cells with blastic morphology.

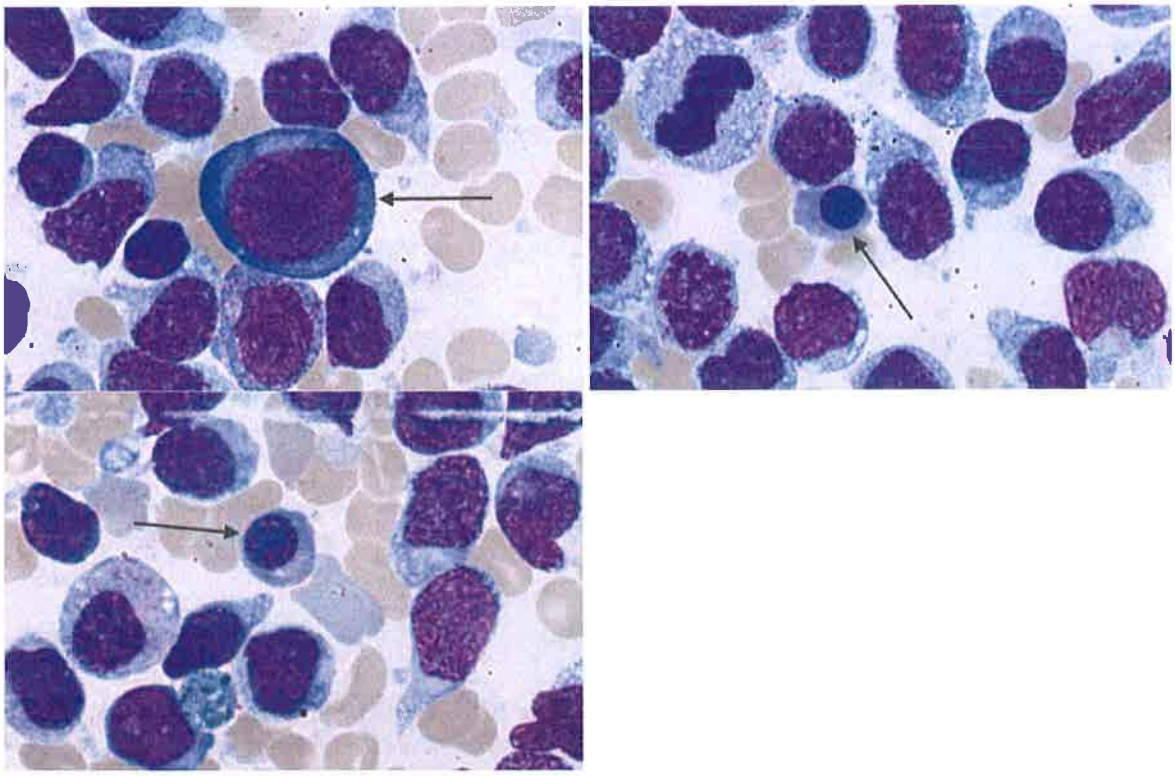
BMD-03



Identification	Participants No.	Participants %	Evaluation
Neutrophil, segmented or band	243	85.3	Educational
Neutrophil with dysplastic nucleus and/or hypogranular cytoplasm	36	12.6	Educational
Neutrophil, toxic (to include toxic granulation and/or Döhle bodies, and/or toxic vacuolization)	6	2.1	Educational

The arrowed cells are neutrophils, as correctly identified by 85.3% of the participants. The neutrophil is 10 to 15 µm in diameter with pink granular cytoplasm. The chromatin is markedly condensed and the nucleus shows formation of distinct lobes connected by thin chromatin strands. Although the nuclear lobes in the pictured cells are not well-separated, they would not be considered in isolation as overtly dysplastic. Band forms are similar to neutrophil forms, but lack the compression of any area of the nucleus into a single filament. On proficiency testing exercises, the distinction between bands and segmented forms has proven not to be reproducible, and for proficiency testing purposes it is not required that they be distinguished.

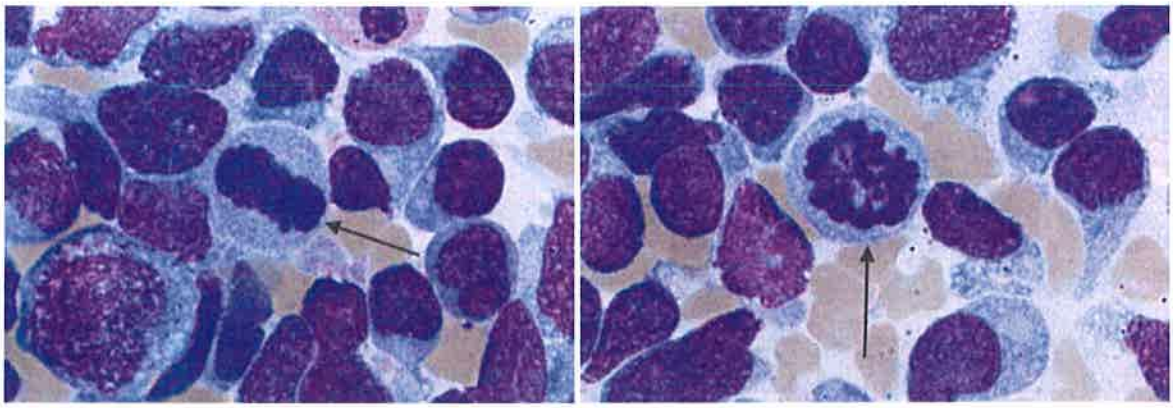
BMD-04



Identification	Participants No.	%	Evaluation
Erythrocyte precursor, normal (includes pronormoblast, basophilic, polychromatophilic, and orthochromic normoblasts)	248	87.0	Educational
Erythrocyte precursor, abnormal/dysplastic nuclear features (includes pronormoblast, basophilic, polychromatophilic, and orthochromic normoblasts)	17	6.0	Educational
Erythrocyte precursor with megaloblastic changes/maturation	8	2.8	Educational
Erythrocyte precursor with vacuolated cytoplasm	6	2.1	Educational
Plasma cell (to include morphologically mature, abnormal, and with inclusion, eg, Dutcher body, Russell body, etc)	4	1.4	Educational
Mast cell	1	0.3	Educational
Blast cell (includes lymphoblast)	1	0.3	Educational

The arrowed cells are normal erythrocyte precursors, as correctly identified by 87.0% of participants. While for proficiency testing purposes it is not required to distinguish between the various stages of erythroid maturation (ie., pronormoblast, basophilic normoblast, polychromatophilic normoblast and orthochromic normoblast), the chosen cells show progression through basophilic normoblast and polychromatophilic normoblast stages. On the earlier end of this spectrum the cells are 10 to 17 µm in diameter with moderately coarse-trabecular chromatin and intensely basophilic cytoplasm that entirely surrounds the nucleus. These cells progress to become slightly smaller with clumped, checkerboard chromatin and cytoplasm that acquires a gray color as hemoglobin accumulates. The nuclear features in the pictured cells are not overly dysplastic

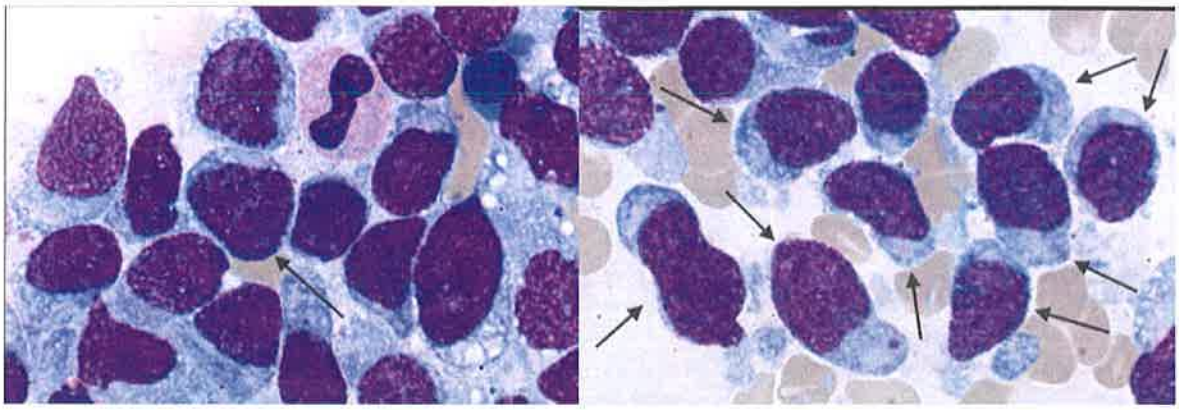
BMD-05



Identification	Participants No.	%	Evaluation
Mitotic figure	279	98.2	Educational
Neutrophil with dysplastic nucleus and/or hypogranular cytoplasm	2	0.7	Educational
Erythrocyte precursor, abnormal/dysplastic nuclear features (includes pronormoblast, basophilic, polychromatophilic, and orthochromic normoblasts)	1	0.3	Educational
Neutrophil, metamyelocyte	1	0.3	Educational
Neutrophil necrobiosis (degenerated neutrophil)	1	0.3	Educational

The arrowed cell is a mitotic figure, as correctly identified by 98.2% of participants. Mitotic figures represent cells in the process of chromosomal replication and cell division, and are recognizable by the dark, irregular mass of condensed DNA that replaces the normal nucleus. The precise arrangement of the mitotic chromosomes changes depending on the cell cycle, eventually showing an equatorial distribution in metaphase. In contrast, a pyknotic nucleus in a degenerating cell is typically broken into numerous purple, roundish inclusions.

BMD-06



Identification	Participants No.	%	Evaluation
Blast cell (includes lymphoblast)	206	72.5	Educational
Malignant lymphoid cell (other than blast)	56	19.7	Educational
Lymphocyte	7	2.5	Educational
Monocyte, immature (promonocyte, monoblast)	6	2.1	Educational
Immature or abnormal cell, would refer for identification	5	1.8	Educational
Lymphocyte, large granular	2	0.7	Educational
Neutrophil, promyelocyte	1	0.3	Educational
Plasma cell (to include morphologically mature, abnormal, and with inclusion, eg, Dutcher body, Russell body, etc)	1	0.3	Educational

The arrowed cells are blasts, as correctly identified by 72.5% of participants. Blasts are large round to oval cells, 10 to 20 µm in diameter, with high nuclear-to-cytoplasmic ratio and fine, powdery chromatin with variably prominent nucleoli. It is not possible based on morphology alone to further subclassify these blasts by lineage. However, upon immunophenotypic analysis (see case discussion) these blasts were determined to represent blastic plasmacytoid dendritic cells. Although the cells in question have some lymphoid features, the high N/C ratio and open chromatin are consistent with blasts.

Case Presentation:

This bone marrow aspirate is from a 61-year-old man presenting with fatigue, bruising, lymphadenopathy, and skin lesions on his back. CBC revealed pancytopenia. Laboratory data include: WBC = 3.6 x 10^9/L; RBC = 3.47 x 10^{12}/L; HGB = 12.5 g/dL; HCT = 36.0%; MCV = 103 fL; MCHC = 35.1 g/dL; RDW = 14; and PLT = 86 x 10^9/L. Identify the arrowed object(s) on each whole slide image.

(BONE MARROW, WRIGHT-GIEMSA)

Discussion

Blastic plasmacytoid dendritic cell neoplasm

The diagnosis in this case is blastic plasmacytoid dendritic cell neoplasm (BPDCN), an aggressive hematologic malignancy categorized under "acute myeloid leukemia and related precursor neoplasms" in the WHO 2008 classification.

The neoplastic cells in BPDCN are derived from precursors of plasmacytoid dendritic cells, specialized antigen presenting cells of the innate immune system that produce large amounts of interferon-α when stimulated. They are especially important in the recognition of and response to viruses. After developing in the bone marrow, normal plasmacytoid dendritic cells circulate at a very low level in the blood to reach lymph nodes as well as peripheral tissues.

Clinically, BPDCN occurs mostly in older patients, with a male predominance. Skin involvement is present in most cases, manifesting variably as nodules, patches, plaques, bruises, or ulcers. Blood and bone marrow are also commonly involved (as reflected in an obsolete name for this entity, the "CD4+CD56+ hematodermic neoplasm"). As seen in the current case, the cells are immature and blastic in appearance, with fine chromatin, absent or inconspicuous nucleoli, and scant cytoplasm. They are commonly intermediate in size, but a range of cytologic appearances have been described. Some cells may show the formation of "hand mirror" shapes, in which the cytoplasm becomes eccentrically localized like the handle of a mirror, though this is a non-specific and inconsistent finding. Final identification depends on immunophenotypic findings. Bone marrow involvement follows a diffuse and/or interstitial pattern, and may be massive (as in the current case) or subtle.

Immunophenotyping, whether by flow cytometric analysis and/or immunohisotochemistry, is essential in the diagnosis of BPDCN. Characteristic positive markers include CD4, CD56, CD123, and TCL1 (though of these CD56 may be absent in rare cases). The cells are negative for myeloperoxidase and lysozyme. However, they commonly and variably express myeloid-associated antigens such as CD13 and CD33, and lymphoid-associated antigens including CD7 and CD2. While CD34 is reliably negative, TdT is expressed in at least a subset of the cells in up to 33% of cases.

Karyotyping of BPDCN shows recurrent but non-specific cytogenetic abnormalities, chiefly deletions and losses of genetic material including at 5q, 12p, 13q, 6q, 15q, and monosomy 9. Recurrent mutations are seen in genes often mutated in myeloid neoplasms, including *TET2*, *ASXL1*, *NPM1* and *ZRSR2*.

BPDCN can be difficult to distinguish, both morphologically and immunophenotypically, from other immature hematologic neoplasms such as acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), myeloid sarcoma, and acute leukemia of ambiguous lineage. The difficulty is exacerbated by the fact that most of the markers characteristically positive in BPDCN (eg., CD56, CD4, CD123, and TCL1) may be seen in other blastic

neoplasms, while BPDCN itself has a strong propensity to express antigens associated with, but not specific for, myeloid and lymphoid lineages. Interestingly, this may reflect the underlying cell biology, as normal plasmacytoid dendritic cell development seems to incorporate elements of both myeloid and lymphoid developmental programs. For the diagnostician, extensive immunophenotyping and a high index of suspicion are crucial elements in the diagnosis of BPDCN.

Patients with BPDCN follow an aggressive clinical course, with overall survival of less than one year. Given the rarity of the diagnosis, treatments have not been standardized. Regimens appropriate for AML and ALL both yield suboptimal results. Several patients who have undergone stem cell transplantation, however, have achieved longer term remission.

David Czuchlewski, MD
Hematology and Clinical Microscopy Committee

References

1. Riaz W, Zhang L, Horna P, et al. Blastic plasmacytoid dendritic cell neoplasm: update on molecular biology, diagnosis, and therapy. *Cancer Control.* 2014;21:270-89.
2. Swerdlow SH, Campo E, Harris NL, et al., eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon: International Angency for Research on Cancer (IARC) Press;2008.
3. Swiecki M, Colonna M. The multifaceted biology of plasmacytoid dendritic cells. *Nat Rev Immunol.* 2015;15: 471-485.
4. Wilson CS, Medeiros LJ. Extramedullary manifestations of myeloid neoplasms. *Am J. Pathol.* 2015;144: 219-239.