CURRENT CONCEPTS IN HEMATOPATHOLOGY

BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM:
Clinicopathologic Features and Insights into Disease Ontogeny

Gabriel K. Griffin, MD
Assistant Professor of Pathology
Harvard Medical School
Dana-Farber Cancer Institute
Brigham and Women's Hospital

Acknowledgements for selected slides and clinical images to:
Dr. Andrew Lane, MD, PhD (DFCI, Medical Oncology), Dr. Nicole LeBoeuf, MD, MPH (BWH, Dermatology), Dr. Elizabeth Morgan, MD (BWH, Hematopathology), Dr. Sarah Wu, MD, PhD (BWH, Pathology), Dr. Volker Hovestadt, PhD (DFCI, Pediatric Oncology)

BPDCN OVERVIEW

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)
- Aggressive hematologic neoplasm of plasmacytoid dendritic cell (pDC)-like cells
- Rare but readily distinguished from other acute leukemias with pDC-directed IHC
- Median survival < 2 years with historical AML/ALL regimens
- Novel targeted therapies → improved outcomes

Previous names
- Agranular CD4+ NK cell leukemia
- Blastic natural killer cell lymphoma
- CD4+CD56+ hematodermic neoplasm

WHO Classification of Hematopoietic Neoplasms
- 2008 (4th ed) : Named BPDCN once pDC recognized as closest "normal" counterpart (PMID: 11342451), classified under "AML and related precursor neoplasms"
- 2016 (rev 4th ed) : Classified under its own category "Blastic Plasmacytoid Dendritic Cell Neoplasm"
- 2022 (5th ed, planned) : To be classified under "Histiocytic/Dendritic Cell Neoplasms"

BPDCN KEY TAKEAWAYS

Clinicopathologic Features

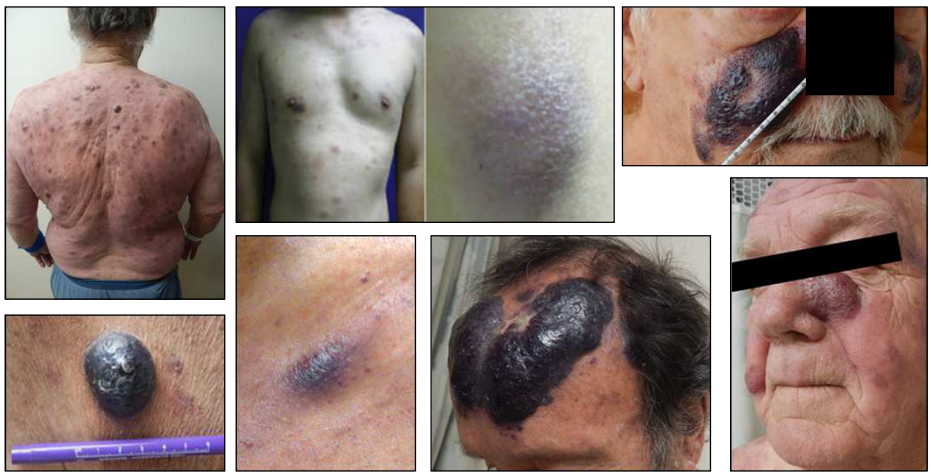
- Skin lesions: >90% of patients, often "bruise-like", ~50% with concurrent bone marrow involvement at diagnosis
- Older men: male bias (~4:1), median age ~65, also can present in kids/young adults (MYB fusions)
- CD123/TCL1/TCF4: all normal pDC markers, co-expression (double stains!) distinguishes BPDCN from ddx
- Novel therapies: standard AML/ALL regimens largely ineffective, novel tx = anti-CD123 or HMA+VEN

Disease Ontogeny

- Premalignant clones in bone marrow: detectable in most cases in older individuals
- Enriched for mutations that drive DC differentiation*: TET2, splicing factors (ZRSR2 = EXITS gene)
- Skin is likely site of malignant transformation*: pDC/pDC-like cell in skin, UV mutational signature
- Retrograde dissemination of malignant cells*: skin → uninvolved bone marrow

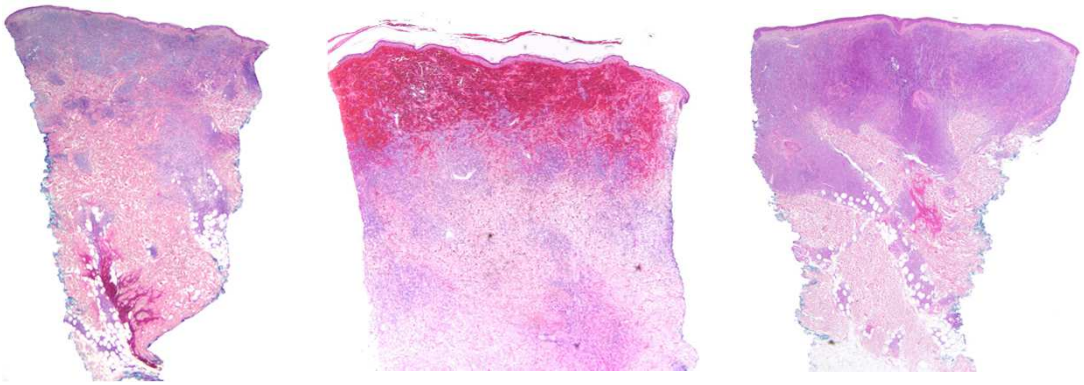
pDC : plasmacytoid dendritic cell
HMA : hypomethylating agent (azacitidine, decitabine)
VEN : venetoclax, BCL2 inhibitor
EXITS gene : chr X gene that escapes X-inactivation, often mutated in cancers with male bias
* : area of ongoing investigation

SKIN LESIONS



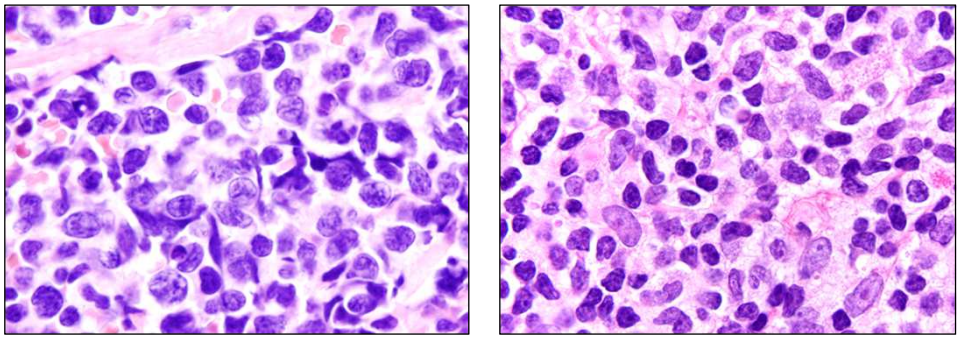
skin lesions are present in >90% of patients, usually older men, often show "bruise-like" appearance, dermatologists are often first point of clinical contact

HISTOPATHOLOGY
Skin



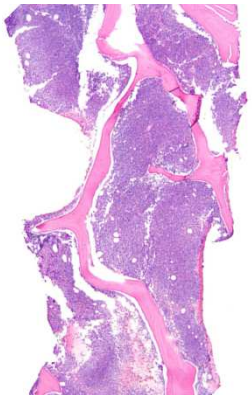
Dermal-based, Grenz zone, RBC extravasation

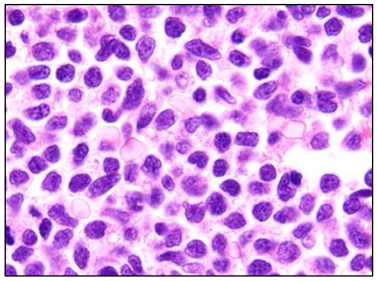
HISTOPATHOLOGY
Skin

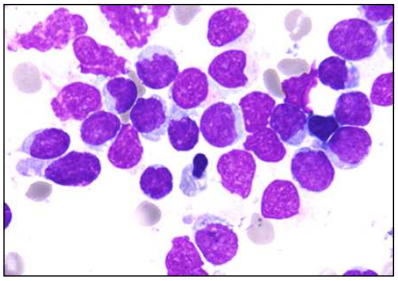


Medium to large cells, irregular nuclei, dispersed/fine chromatin, variable nucleoli

HISTOPATHOLOGY
Bone Marrow







Bone marrow involvement in ~50% of cases at the time of diagnosis, also develops at the time of disease progression or post-transplant relapse

DIFFERENTIAL DIAGNOSIS

Myeloid Neoplasms
- Acute myeloid leukemia (with monocytic differentiation)
- Chronic myelomonocytic leukemia (CMML)

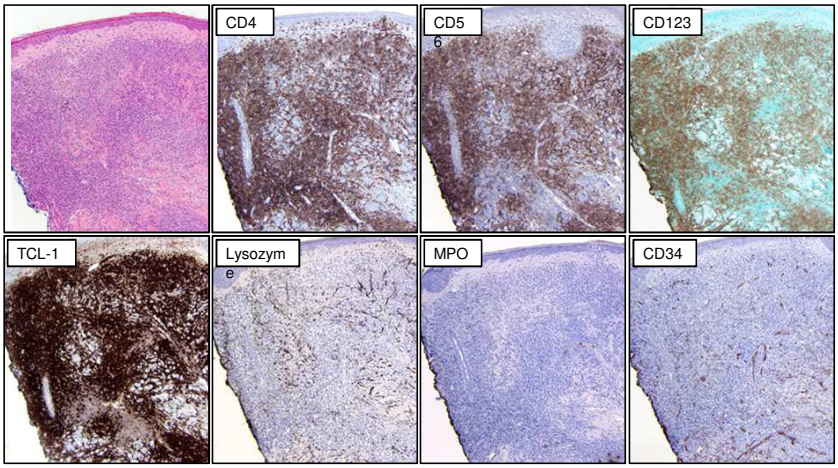
Major ddx in most cases

Extranodal NK/T-cell Lymphoma

Peripheral T-cell Lymphoma
- Adult T-cell Leukemia/Lymphoma (ATLL)
- CTCL/Mycosis Fungoides
- T-cell Prolymphocytic Leukemia (T-PLL)
- Anaplastic large-cell lymphoma

Acute Lymphoblastic Leukemia

IMMUNOPHENOTYPE

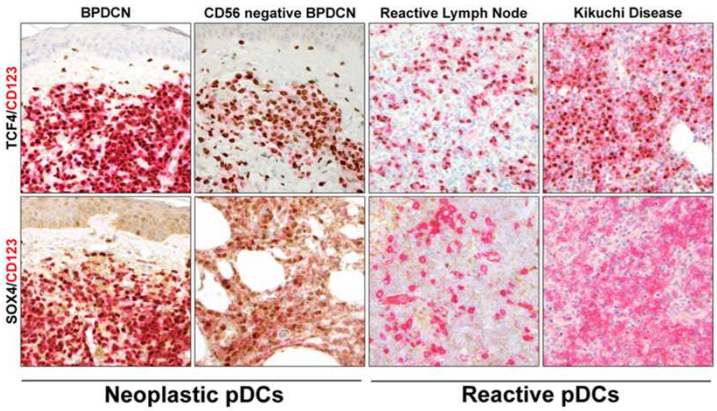


CD4+, CD56+, CD123+, TCL1+, TCF4+, Lysozyme-, MPO-, CD34-

DOUBLE STAINS ARE YOUR FRIEND!

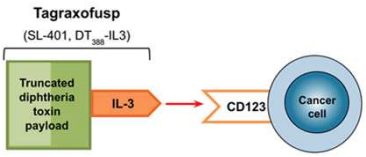
TCF4+/CD123+ high sens/spec for BPDCN vs other neoplasms, but also stains normal pDC (Sukswai et al. AJSP, 2019)

SOX4+/CD123+ stains BPDCN with high sens/spec and negative in normal pDC (Wu et al. USCAP 2022)

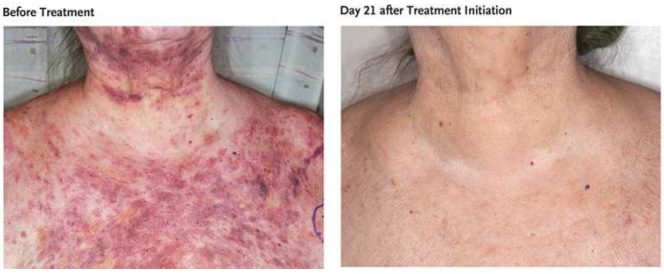


Sukswai et al. Am J Surg Pathol. 2019 Oct;43(10):1429-1437
Images from Wu et al., USCAP 2022, manuscript in preparation

NOVEL THERAPIES
anti-CD123



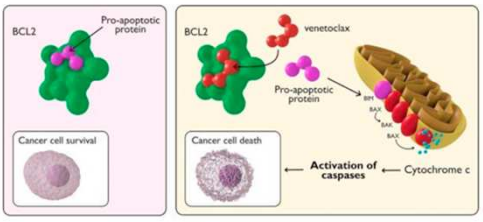
FDA approved for BPDCN in 2018



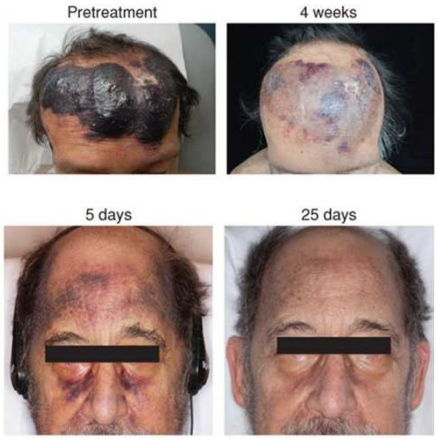
Overall response rate (ORR) ~ 90% in front line setting, including ~70% complete response (CR) rate

Pemmaraju et al. N Engl J Med. 2019 Apr 25;380(17):1628-1637

NOVEL THERAPIES
BCL2 inhibitors



Restores cancer cell apoptosis through BCL2 inhibition



Mihalyova et al. Exp Hematol. 2018 May;61:10-25.
Montero et al. Cancer Discov. 2017 Feb;7(2):156-164.

BPDCN KEY TAKEAWAYS

Clinicopathologic Features

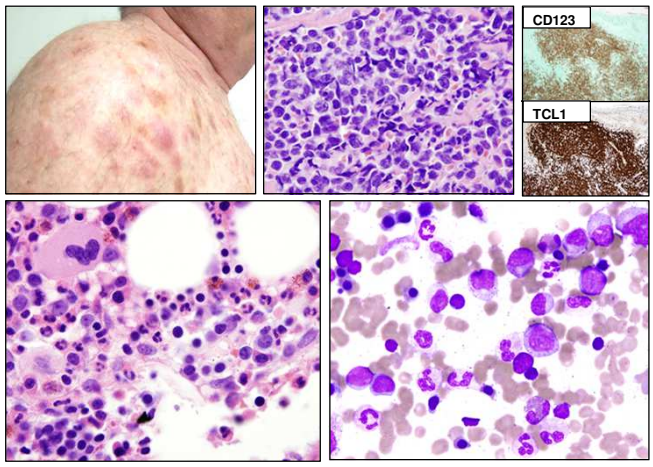
- Skin lesions: >90% of patients, often "bruise-like", ~50% with concurrent bone marrow involvement at diagnosis
- Older men: male bias (~4:1), median age ~65, also can present in kids/young adults (MYB fusions)
- CD123/TCL1/TCF4: all normal pDC markers, co-expression (double stains!) distinguishes BPDCN from ddx
- Novel therapies: standard AML/ALL regimens largely ineffective, novel tx = anti-CD123 or HMA+VEN

Disease Ontogeny

- Premalignant clones in bone marrow: detectable in most cases in older individuals
- Enriched for mutations that drive DC differentiation*: TET2, splicing factors (ZRSR2 = EXITS gene)
- Skin is likely site of malignant transformation*: pDC/pDC-like cell in skin, UV mutational signature
- Retrograde dissemination of malignant cells*: skin → uninvolved bone marrow

pDC : plasmacytoid dendritic cell
HMA : hypomethylating agent (azacitidine, decitabine)
VEN : venetoclax (BCL2 inhibitor)
EXITS gene : chr X gene that escapes X-inactivation, often mutated in cancers with male bias
* : area of ongoing investigation

"SKIN ONLY" BPDCN

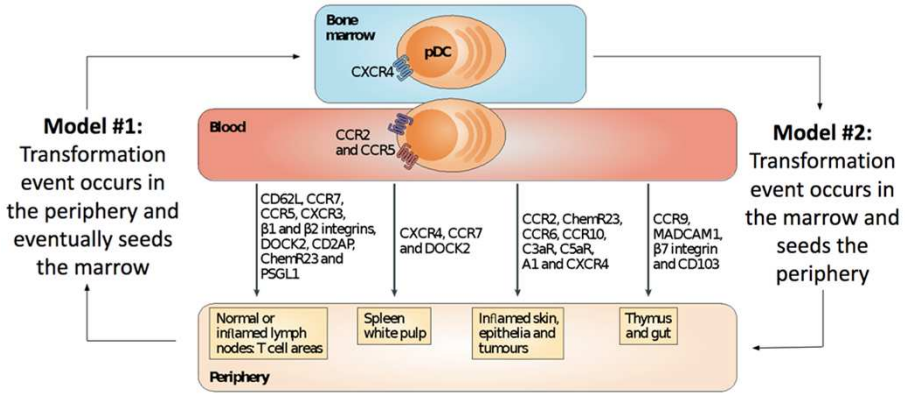


Skin lesions

Uninvolved bone marrow

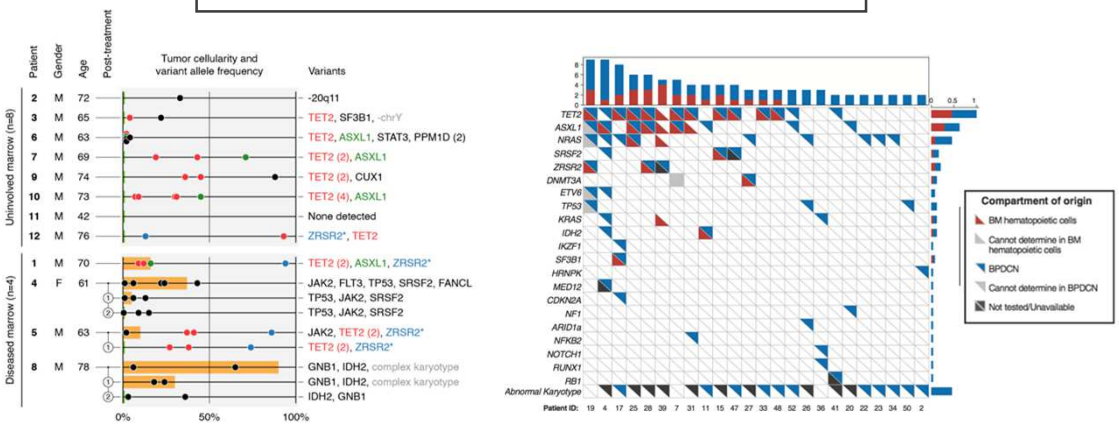
Comprises ~50% of cases at diagnosis, most will eventually develop marrow involvement at disease progression/relapse

MODELS OF BPDCN ONTOGENY



Adapted from Swiecki and Colonna, Nat Rev Immunol. 2015 Aug;15(8):471-85.

PREMALIGNANT CLONES IN BONE MARROW



Bi-allelic TET2 mutations bias towards pDC differentiation

ZRSR2 mutations contribute to male sex bias

Griffin, Hovestadt et al. manuscript in revision

Suma et al. Int J Hematol. 2018 Oct;108(4):447-451.

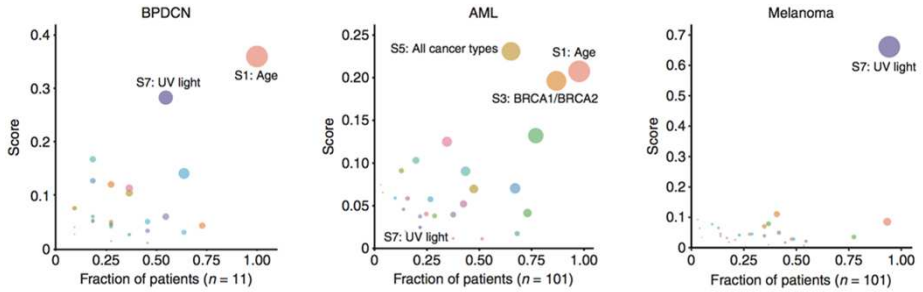
Ruhangaza et al. J Glob Oncol. 2019 Jun;5:1-6.

Batta et al. Leukemia. 2021 Nov;35(11):3299-3303.

Togami et al. Cancer Discov. 2022 Feb;12(2):522-541.

Khanlari et al. Leukemia. 2022 Mar 12. Online ahead of print.

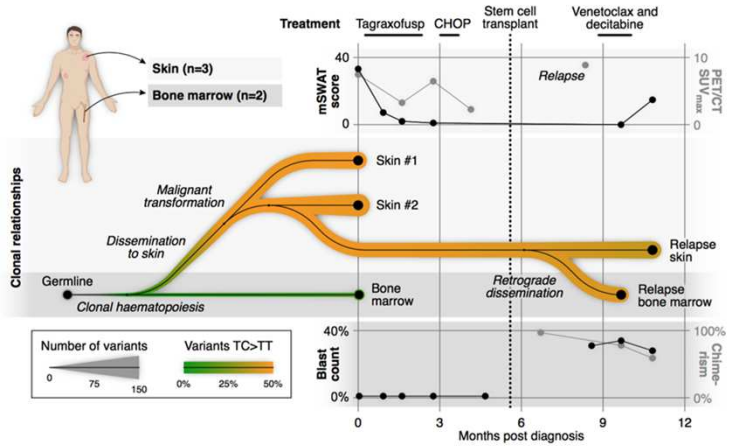
UV-INDUCED DNA DAMAGE



Clonally expanded UV signature mutations in BPDCN tumors reveal skin as likely site of malignant transformation

Griffin, Hovestadt et al. manuscript in revision
Togami et al. Cancer Discov. 2022 Feb;12(2):522-541.

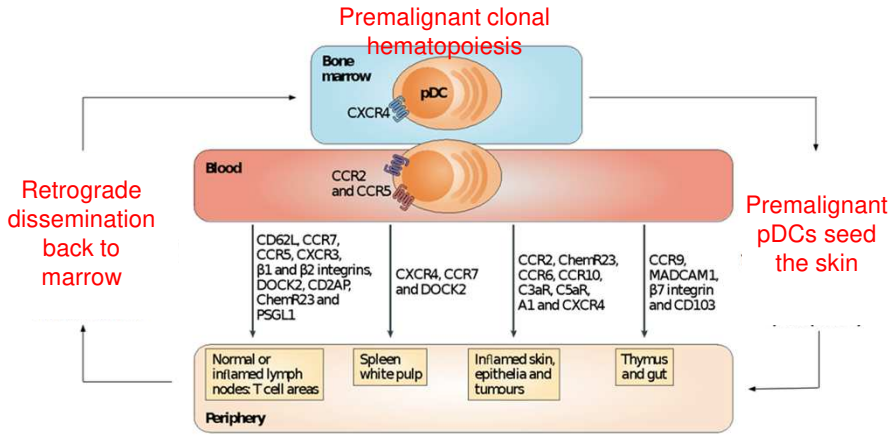
RETROGRADE DISSEMINATION



Malignant BPDCN cells spread from skin back to bone marrow at relapse

Griffin, Hovestadt et al. manuscript in revision

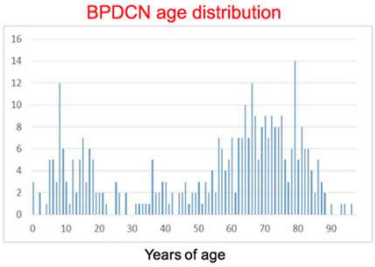
A WORKING MODEL FOR BPDCN PATHOGENESIS

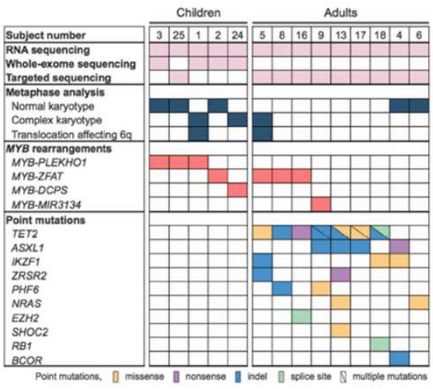


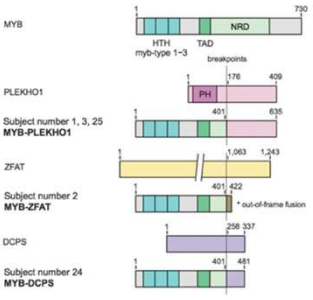
Malignant transformation in skin (UV)

Adapted from Swiecki and Colonna, Nat Rev Immunol. 2015 Aug;15(8):471-85.

BPDCN A Tale of Two Diseases?







Recurrent MYB fusions and absence of other typical mutations (e.g., TET2) in Pediatric BPDCN

Kim et al. J Pediatr Hematol Oncol. 2017 Oct;39(7):528-537.
Suzuki et al. Leukemia. 2017 Jul;31(7):1629-1633.

BPDCN KEY TAKEAWAYS

Clinicopathologic Features

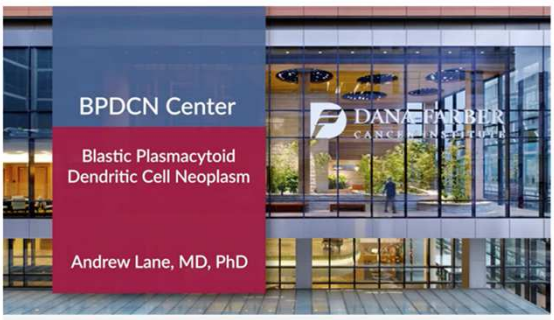
- Skin lesions: >90% of patients, often "bruise-like", ~50% with concurrent bone marrow involvement at diagnosis
- Older men: male bias (~4:1), median age ~65, also can present in kids/young adults (MYB fusions)
- CD123/TCL1/TCF4: all normal pDC markers, co-expression (double stains!) distinguishes BPDCN from ddx
- Novel therapies: standard AML/ALL regimens largely ineffective, novel tx = anti-CD123 or HMA+VEN

Disease Ontogeny

- Premalignant clones in bone marrow: detectable in most cases in older individuals
- Enriched for mutations that drive DC differentiation*: TET2, splicing factors (ZRSR2 = EXITS gene)
- Skin is likely site of malignant transformation*: pDC/pDC-like cell in skin, UV mutational signature
- Retrograde dissemination of malignant cells*: skin → uninvolved bone marrow

pDC : plasmacytoid dendritic cell
HMA : hypomethylating agent (azacitidine, decitabine)
VEN : venetoclax (BCL2 inhibitor)
EXITS gene : chr X gene that escapes X-inactivation, often mutated in cancers with male bias
* : area of ongoing investigation

BPDCN Center @ Dana-Farber



Andrew Lane, MD, PhD, director of the BPDCN Center, explains the symptoms and diagnosis of BPDCN. The BPDCN Center offers a multidisciplinary approach to care for patients, and focuses on basic and clinical research to better understand BPDCN and improve outcomes.

CURRENT CONCEPTS IN HEMATOPATHOLOGY

BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM:
Clinicopathologic Features and Insights into Disease Ontogeny

Gabriel K. Griffin, MD
Assistant Professor of Pathology
Harvard Medical School
Dana-Farber Cancer Institute
Brigham and Women's Hospital

Acknowledgements for selected slides and clinical images to:
Dr. Andrew Lane, MD, PhD (DFCI, Medical Oncology), Dr. Nicole LeBoeuf, MD, MPH (BWH, Dermatology), Dr. Elizabeth Morgan, MD (BWH, Hematopathology), Dr. Sarah Wu, MD, PhD (BWH, Pathology), Dr. Volker Hovestadt, PhD (DFCI, Pediatric Oncology)