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### Identification

<table>
<thead>
<tr>
<th>Year</th>
<th>Type</th>
<th>Subtype</th>
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<tr>
<td>1958</td>
<td>Lymphoblast</td>
<td></td>
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<tr>
<td>1990</td>
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### Morphology & Immunophenotyping

<table>
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<th>T-Associated Plasma Cell</th>
<th>Plasmacytoid T-Cell</th>
<th>Plasmacytoid Monocyte</th>
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### Cell Function

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<th>Plasmacytoid Dendritic Cell</th>
<th>Type I Interferon Producing Cell</th>
<th>Biological features in vivo &amp; in vitro Role in human diseases</th>
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**2:30 PM** Plasmacytoid Dendritic Cell Neoplasms

Fabio Facciotti, MD, PhD, University of Brescia School of Medicine, Brescia, Italy
**PDC phenotype (2017)**

**Cell Lineage Negative** (linnegative)

- **B** cell
  - CD19, CD20, CD79a, PAx5, IgM, IgG

- **T** cell
  - CD3, CD5, CD8, LAT, ZAP70, TCRαβ, TCRγδ
  - Perforin, TIA1, CD56, CD96

- **My-Monocyte**
  - Myeloperoxidase, CD11c, CD14, CD13, CD33, CD163
  - Lysozyme, ASD-CAE, esterases

**NEG**

**POS**

- CD16, CD56

- Myeloperoxidase, CD11c, CD14, CD13, CD33, CD163

- Lysozyme, ASD-CAE, esterases

- TdT, CD34, CD117

- BDCA2/CD303 clone 124B3.13

**CD123**

- PDC
  - BDCA2/CD303
  - CD123
  - PDC
  - HEV
  - Epitheliod macrophages
  - Sinus lining cells

- **Other normal cells are positive**

Ma J. Biophys Rep 2015; 1:139–147
Ceribelli M. Cancer Cell 2016;30:764-778

**Antibodies recognizing the master transcription factor E2-2 (TCF-4) on PDC in paraffin sections**

E2-2/TCF4 (Rabbit monoclonal anti-human TCF-4, clone 6A by Epitomics) (Antibody courtesy by Dr. Ceribelli M., Louis Staudt Lab, NIH)
**PDC Occurrence in Normal Tissues**

- **Abundant**
  - Superficial LNs
  - Tonsils and adenoids
  - Young individuals

- **Rare**
  - Deep LNs
  - Eldery individuals
  - Thymus (medulla)
  - Spleen (MZ area)
  - Bone marrow
  - Gut

**Almost absent in non-lymphoid (human) tissues**

0.01% - 0.5% of PBL

**Marked increase of PDC in reactive processes**

- **Lymph Nodes**
  - Kikuchi’s lymphadenitis
  - Castleman (HV) disease

- **Skin**
  - Lupus erythematosus

**Cell function**

**PLASMACYTOID DENDRITIC CELL TYPE I INTERFERON PRODUCING CELL**

- **The Enigmatic Plasmacytoid T Cells Develop into Dendritic Cells with Interleukin (IL)-3 and CD40-Ligand**

- **Constitutive expression of**
  - IRF7 master regulator of INF-type I transcription
  - MxA key mediator of the INF-type I induced antiviral response

**Hematopoietic Dendritic Cells**

**MAIN CATEGORIES**

- Classical (Myeloid) DC
  - CD1c+ (CD141+) cDC
  - (CD1c+) CD141+ cDC
- Plasmacytoid DC (CD123+ CD303+)
- Langerhans Cells (Langerin/CD207+)
Agranular CD4+CD56+ haematodermic neoplasm / tumor
Blastic NK-cell lymphoma
Blastic natural killer leukaemia/lymphoma
Agranular CD4+ natural killer cell leukemia

**Histopathology**
Not recognized as a distinct entity by WHO
diagnosis

**Neoplasms derived from PDC**

### Mature PDC
- Not recognized as a distinct entity by WHO

### Immature PDC

Agranular CD4+ natural killer cell leukemia (Brody, AP; 1995)
Blastic natural killer leukemia/lymphoma (DiGiuseppe JA, 1997)
Blastic NK-cell lymphoma (WHO: 2001)

### NEOPLASMS derived from PDC

**Mature PDC**
- Myeloid neoplasm (myelo-DNK)
  - PDC proliferation
- 18%-20% associated with myeloid neoplasm
  - MDS, AML

**Age/Sex**
- Median: 69 (9-86)
- M/F: 7/3
- Median: 65 (9-86) (5/1 in <30 years-old)
- M/F: 6/1

**Evolution**
- Blastic proliferation of the associated myeloid neoplasm (PDC may regress)
  - Median survival: 12 months
  - 5-year survival: 12 months
  - Median survival: 14 months
  - 5-year survival: 14 months

**NEOPLASMS derived from PDC**

### Mature PDC
- Aberrant expression of markers usually positive in normal PDC
  - CD68 and CD163 (negative or positive as paranuclear dots)
  - Granzyme B: negative

### Blastic PDC Neoplasm
- Aberrant expression of markers usually negative in normal PDC
  - CD16 (negative or positive as paranuclear dots)
  - CD14 (negative or positive)
  - CD7 (negative or positive)
  - CD2 (negative or positive)

**Medullary blastic**

**Most common sites of diagnosis**
Bone marrow, lymph node, Skin
Bone marrow, lymph node, Nodules or aggregates of cells cytotologically similar to normal PDC

**Histopathology**

**Mature PDC**
- Skin, Bone marrow, lymph node, Blood
  - Nodules or aggregates of cells cytotologically similar to normal PDC

**NEOPLASMS derived from PDC**

**Mature PDC**
- Aberrant expression of markers usually positive in normal PDC
  - CD68 and CD163 (negative or positive as paranuclear dots)
  - Granzyme B: negative

**Blastic PDC Neoplasm**
- Aberrant expression of markers usually negative in normal PDC
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- Aberrant expression of markers usually negative in normal PDC
  - CD16 (negative or positive as paranuclear dots)
  - CD14 (negative or positive)
  - CD7 (negative or positive)
  - CD2 (negative or positive)

**Medullary blastic**
NEOPLASMS derived from mature PDC

CLA

24, M (CMML)
Lymphadenopathy
Skin papular eruption
>AML (DOD, 8 months)

BDCA2/CD303
CD68R
MPX (CMML)

NEOPLASMS derived from mature PDC

M: 48
AML (MO/M1)

CD68R
CD56
CD34

NEOPLASMS derived from mature PDC

CD56
Consistent
BCL2
Frequent
CD7, CD33
Occasional
CD2, CD3, CD5, CD7, CD10, CD13, CD14, CD15, CD33, CD56

TdT: negative
Ki-67 <10%

TdT: positive (30%)
Ki-67 >30%

As in normal PDC
BCL2 is negative

Cluster of PDC
Reactive LN
BCL2

BPDCN is a clinically aggressive tumour derived from the precursors of plasmacytoid dendritic cells (also known as professional type 1 interferon producing cells or plasmacytoid monocytes), with a high frequency of cutaneous and bone marrow (BM) involvement and leukaemic dissemination.

- Rare (exact incidence unknown)
- No racial or ethnic predominance
- No etiology known (EBV, HHV8, and other viruses negative)
- M/F: 3/1
- Median age at diagnosis: 65.0 years (M: 67 y; F: 58 y)
- Age peak only for males
- 5% in ≤10 years

Presentation
- Asymptomatic cutaneous lesions
- Good general health (lasting even months)
- Interval between first symptoms and diagnosis: 1-18 months (mean: 4.2-6.2)
- Not recognizable other clinical manifestation in 40%-50% of cases
- Systemic dissemination invariably (often rapidly) occurs
- Elevated WBC count, circulating blasts, massive bone marrow infiltration
- Leukemia without skin lesions in ~7% of cases
**Blastic plasmacytoid dendritic cell neoplasm**

**Skin**
- Any site, any size (few mm. → several cm.)
- Variable appearance

(Courtesy: T. Pandolfo)

**Presentation**

- **Bone marrow:** 50%-90%
  - Can be minimal and demonstrable only by immunohistochemistry
  - Increases with progression
- **Lymphadenopathy:** 40%
  - Local or disseminated
- **Splenomegaly:** 25%
- **Peripheral blood:**
  - Counts generally low (median 2%)
  - Increase with progression.
- **CNS**
  - Rare at presentation; frequent on relapse
Low density may simulate inflammation

Leukemia cutis (AML, ALL)? BPDCN ?

CD3, CD20
MPO, CD11c, CD14, CD163, Lysozyme
CD34

CD3, CD7, CD79a
CD4, CD6, CD123, TCL1, BDC24/CD303, CD1AP, BCL11a, MXA
CD4+ CD56+ coexpressed in >90% of cases

Despite their original defining role (CD4+ CD56+ Hematodermic Neoplasm), they should not be used as the "only" markers for BPDCN diagnosis

Other hematological malignancies CD4/CD56 positive (e.g., AML/AMoL)

Other hematological malignancies CD4/CD56 positive (e.g., AML/AMoL)

CD123:
AML: generally negative/deam on IHC, but frequently expressed on flow cytometry

TCL1:
AML: negative; ALL: frequently positive

BDCA2/CD303: 79%

BDCA2/CD303: 79%

Positivity for at least 3 of 5 among
CD4 CD56 CD123 TCL1 BDCA2
Negativity for
CD3 CD20 MPO Lysozyme

Immunophenotypic criteria for BPDCN diagnosis especially to differentiate from AML

Practical approach

- CD4+CD56+CD123+TCL1+
- CD4+CD56+CD123+TCL1+
- CD4+CD56+CD123+TCL1+

237 cases of BPDCN (all 4 markers applied)

CD4+CD56+CD123+TCL1+ 80%
CD4+CD56+CD123+TCL1+ 87%
CD4+CD56+CD123+TCL1+ 80%


BDCA2 represents the most specific marker for PDC leukemia using flow-cytometry

Homogeneous and strong E2-2/TCF4 expression in:
- BPDCN cases (24/28)
- BPDCN or CMML with pDC proliferation (2/2)
- Unclassified PHN (3/13)
- AML (0/10)

Cancer Cell 30, 764-778, November 14, 2016

CD220: 96%
AML: generally negative/deam on IHC, but frequently expressed on flow cytometry
TCL1: 89%
AML: negative; ALL: frequently positive

Cronin DMP, Am J Clin Pathol 2012
Sangle NA, Mod Pathol 2014
Facchetti F, Mod Pathol 2016
MOLECULAR & GENETICS

GENE EXPRESSION PROFILE STUDIES

COMPARED TO NORMAL CELLS
Closer to normal PDC than to myeloid and lymphoid precursors (Sapienza, 2014)

- BPCDN has marked overlap with PDC for TCF-4 dependent genes,
  but some relevant differences exist:
  - upregulation of BCL2, MYC, TCL1
  - downregulation of BCL11a, SpiB, IL3RA, CLEC4C

In BPDCN TCF-4 dependent transcription is attenuated for PDC-specific functions and increased for oncogenic gene expression (Ciribelli, 2016)

MOLECULAR & GENETICS

GENE EXPRESSION PROFILE STUDIES

COMPARED TO OTHER LEUKEMIAS
Distinct from CMML (cutaneous), AML, ALL (Dijkman, 2007; Sapienza 2014; Ciribelli 2016)

MOLECULAR & GENETICS

- 66% of BPDCN have an abnormal karyotype, with complex abnormalities in the same cells (average of 6 to 8)
- Most frequent chromosomal targets:
  - 4q34
  - 5q (5q21 or 5q34)(72%)
  - 9q (9p21 or 9p22)(72%)
  - 13q (13q21-32) (56%)
  - 9q (9q21-qter)(55%)
  - 15q (15q12-qter)(51%)
  - 17p (17p13)(50%)
  - 18p (18p11-p12)(48%)

MOLECULAR & GENETICS

- Good initial response to RT and/or CT (76%) generally followed by relapses (median 11 months)
  - skin (100%)
  - other sites (44%)
  - systemic with leukemia (39%)
- Median survival:
  ~ 14 months (9.0 ÷ 20.0)
- Exceptional cases (especially with single isolated skin lesion) show long survival

MOLECULAR & GENETICS

TREATMENT
- At the present time no specific, effective and durable treatment available
- Allo-BMT (Auto-BMT) remains the most efficient approach
- Best results if BMT in first remission
- ALL-type induction most efficient than AML-type induction

MOLECULAR & GENETICS

EVOLUTION
- 3/31/2017
- Sapienza, 2014
- BPDCN
- PDC
- MyP
- LyP

MOLECULAR & GENETICS

REF Gene %
Jardin Alayed Menezes
TET2 36-80
IKZF3, ZEB2 12-16
IKAROS family 20
ASXL1 20
NRAS 32
NPM1 20
12p13 64%
13q13-21 64%
6q23-qter 50%
15 partial losses
17 partial losses
Tumor suppressor
Transcription
Newly identified genes in leukemia
No common affected genes between patients
Half cases had mutations affecting either the DNA methylation or chromatin remodeling pathways
MRAS, KRAS and ATM mutually exclusive (clinical subtypes?)

MOLECULAR & GENETICS

Blood 2002; 99:4154.

Blood 2015; 126: 140-444

Blood 2013; 121: 440-446
SL-401: Immunotoxin: human recombinant anti-IL-3R alpha (CD123) joined to diphtheria toxin

BCL2 overexpressed in BPDCN
No amplification nor translocation

Cancer Discovery 2016

% priming % alive on VTCX

CAL-1 (BPDCN) high priming on BIM stimulation and high sensitive to VTCX

A Druggable TCF4- and BRD4-Dependent Transcriptional Network Sustains Malignancy in Blastic Plasmacytoid Dendritic Cell Neoplasm

- TCF4 (E2-2) master regulator of the BPDCN oncogenic program
- TCF4 downregulation causes the loss of the BPDCN-specific gene expression program and tumor cell apoptosis
- TCF4 is a lineage-survival oncogene in BPDCN
- The TCF4 transcriptional network is inhibited by Bromodomain and extra-terminal domain inhibitors (BETis)
- BETis are highly toxic to BPDCNs, both in vitro and in vivo (xeno)
- BET inhibitors promising in BPDCN treatment as single agent silencing multiple driver-genes

TCF4 (E2-2) master regulator of the BPDCN oncogenic program
TCF4 downregulation causes the loss of the BPDCN-specific gene expression program and tumor cell apoptosis
TCF4 is a lineage-survival oncogene in BPDCN
The TCF4 transcriptional network is inhibited by Bromodomain and extra-terminal domain inhibitors (BETis)
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