
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.
Hematopoietic Dendritic Cells

Langerhans Cells (CD1a, CD207, E-cadherin)

Mo-DC (CD11c, CD1c, CD1a)

Classical (Myeloid) DC
- cDC1 (CD141c+)
- cDC2 (CD1c+)

Plasmacytoid DC (CD123+ CD303+)
**PDC phenotype (2017)**

*Cell Lineage Negative (lin\textsuperscript{negative})*

**B cell**
- CD19, CD20, CD79a, PAX5, sIg, cIg
- TdT
- CD34, CD117

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

**T/NK cell**
- CD3, CD5, CD8, LAT, ZAP70, TCRAB, TCRGD
- Perforin, TIA1
- CD16, CD56

**NEG**
- CD16, CD56
- Myeloperoxidase, CD11c, CD14, CD13, CD33, CD163
- Lysozyme, ASD-CAE, esterases

**POS**
- CD4, CD43, CLA
- E2-2
- BAD-LAMP
- BDCA2 (CD303)
- CD123

---

**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

Tumoral proliferations of PDC

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

**Immature PDC**
  - Agranular CD4+ natural killer cell leukemia (Brody JP; 1995)
  - Blastic natural killer leukaemia/lymphoma (DiGiuseppe JA; 1997)
  - Blastic NK-cell lymphoma (WHO; 2001)
  - Agranular CD4+CD56+ haematodermic neoplasm / tumor (Petrella; 2002) / Herling; 2007)
## NEOPLASMS derived from PDC

<table>
<thead>
<tr>
<th></th>
<th>Mature PDC</th>
<th>Blastic PDC Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basic disease</strong></td>
<td>Myeloid neoplasm (mostly CMML)</td>
<td>PDC proliferation 10%-20% associated with myeloid neoplasm (MDS, AMoL)</td>
</tr>
<tr>
<td><strong>Age/Sex</strong></td>
<td>Median: 69 (6-88) M/F = 7/1</td>
<td>Median: 65 (0-96) (5% in &lt;10 years-old) M/F = 3/1</td>
</tr>
<tr>
<td><strong>Evolution</strong></td>
<td>Evolution of the associated myeloid neoplasm (PDC may regress)</td>
<td>Systemic dissemination common Median survival: ~ 14 months (9-20)</td>
</tr>
<tr>
<td></td>
<td>Vitte’s series (2013):</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 16 cases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 52.4% alive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean from skin onset: 23 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 45.2% dead of disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(8.75 months)</td>
<td></td>
</tr>
</tbody>
</table>

## NEOPLASMS derived from PDC

<table>
<thead>
<tr>
<th></th>
<th>Mature PDC</th>
<th>Blastic PDC Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most common sites of diagnosis</strong></td>
<td>Bone marrow, Lymph node, Skin Biopsies performed during staging (BM) or for evaluation of lymphadenopathy or skin eruption</td>
<td>Skin, Bone marrow, Lymph node, Peripheral blood</td>
</tr>
<tr>
<td><strong>Histopathology</strong></td>
<td>Nodules or aggregates of cells cytologically similar to normal PDC</td>
<td>Immature blasts</td>
</tr>
<tr>
<td></td>
<td>No/few mitoses</td>
<td>Frequent mitoses</td>
</tr>
<tr>
<td></td>
<td>Apoptotic bodies frequent</td>
<td>No apoptosis</td>
</tr>
<tr>
<td></td>
<td>In skin biopsies abundant inflammatory component (macrophages, lymphocytes, indeterminate DC)</td>
<td>No/minimal inflammatory component</td>
</tr>
<tr>
<td></td>
<td>Leukemic cells may be also present in the same biopsy</td>
<td></td>
</tr>
</tbody>
</table>
### NEOPLASMS derived from PDC

<table>
<thead>
<tr>
<th>Mature PDC</th>
<th>Blastic PDC Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aberrant expression of markers usually positive in normal PDC</td>
<td>CD68 and CLA (negative or positive as paranuclear dots) Granzyme B: negative</td>
</tr>
<tr>
<td>None</td>
<td>Consistent CD56 BCL2 Frequent CD7, CD33</td>
</tr>
<tr>
<td></td>
<td>Occasional CD2, CD5, CD7, CD10, CD13, CD14, CD15, CD33, CD56weak</td>
</tr>
<tr>
<td></td>
<td>Occasional CD2, CD5, CD7, CD10, CD13, CD117, CD79A, BCL6, S100</td>
</tr>
<tr>
<td>TdT: negative</td>
<td>TdT: positive (30%)</td>
</tr>
<tr>
<td>Ki-67 &lt;10%</td>
<td>Ki-67 &gt;30%</td>
</tr>
</tbody>
</table>

### NEOPLASMS derived from mature PDC

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

- CLA
- BDCA2/CD303
### NEOPLASMS derived from mature PDC

**MPX (CMML)**

**CD68R**

#### Aberrant expression of markers usually positive in normal PDC

<table>
<thead>
<tr>
<th>Mature PDC</th>
<th>Blastic PDC Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>CD68 and CLA (negative or positive as paranuclear dots)</td>
</tr>
<tr>
<td></td>
<td>Granzyme B: negative</td>
</tr>
</tbody>
</table>

#### Aberrant expression of markers usually negative in normal PDC

**As in normal PDC**

**BCL2 is negative**

<table>
<thead>
<tr>
<th>Mature PDC</th>
<th>Blastic PDC Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occasional</td>
<td>Consistent</td>
</tr>
<tr>
<td>CD2, CD5,</td>
<td>CD56</td>
</tr>
<tr>
<td>CD7, CD10,</td>
<td>BCL2</td>
</tr>
<tr>
<td>CD13, CD14,</td>
<td>Frequent</td>
</tr>
<tr>
<td>CD15, CD33</td>
<td>CD7, CD33</td>
</tr>
<tr>
<td></td>
<td>Occasional</td>
</tr>
<tr>
<td>CD2, CD5,</td>
<td>CD2, CD5, CD7, CD10,</td>
</tr>
<tr>
<td>CD7, CD13,</td>
<td>CD117, CD79A, BCL6,</td>
</tr>
<tr>
<td>CD117, CD79A, BCL6, S100</td>
<td></td>
</tr>
<tr>
<td>TdT: negative</td>
<td>TdT: positive (30%)</td>
</tr>
<tr>
<td>Ki-67 &lt;10%</td>
<td>Ki-67 &gt;30%</td>
</tr>
</tbody>
</table>
30 Blastic plasmacytoid dendritic cell neoplasm

- 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
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

**SKIN**

**LEUKEMA**

---

**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
30 Blastic plasmacytoid dendritic cell neoplasm

**DIAGNOSIS**

Leukemia cutis (AML, ALL)?
BPDCN?

<table>
<thead>
<tr>
<th>EXCLUSION</th>
<th>IRRELEVANT</th>
<th>INCLUSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3, CD20</td>
<td>CD2, CD7, CD79a</td>
<td>CD4, CD56, CD123</td>
</tr>
<tr>
<td>MPO, CD11c, CD14, CD163</td>
<td>CD33</td>
<td>TCL1, BDCA2/CD303</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>TdT, CD117</td>
<td>CD2AP, BCL11a</td>
</tr>
<tr>
<td>CD34</td>
<td>S100</td>
<td>MXA</td>
</tr>
</tbody>
</table>
**CD123**: 95%
AML: generally negative/deam on IHC, but frequently expressed on flow cytometry

**TCL1**: 89%
AML: negative; ALL: frequently positive

**BDCA2/CD303**: 79%

<table>
<thead>
<tr>
<th>CDCA2/CD303</th>
<th>Neg</th>
<th>Pos</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPDCN (n=21)</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>AML (all FAB subtypes) (n=55)</td>
<td>55</td>
<td>0</td>
</tr>
<tr>
<td>ALL (15 B-ALL; 5 T-ALL)</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>DLBCL (n=35)</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>PTCL (n=20)</td>
<td>25</td>
<td>0</td>
</tr>
</tbody>
</table>

Garnache-Ottou F, et al.
*Br J Haematol* 2009;145:624

**BDCA2 represents the most specific marker for PDC leukemia using flow-cytometry**
Immunophenotypic criteria for BPDCN diagnosis and differentiation from AML
A practical approach

**Positivity** for at least 3 of 5 among
CD4  CD56  CD123  TCL1  BDCA2

+ 

**Negativity** for
CD3  CD20  MPO  Lysozyme

Sangle NA, Mod Pathol 2014
Facchetti F, Mod Pathol 2016

---

**MOLECULAR & GENETICS**

**GENE EXPRESSION PROFILE STUDIES**

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

Compared to normal PDC
- Upregulation of BCL2, CCND1, IRF4
- NFKB pathway activation (Sapienza 2014)

- BPDCN overlaps with PDC for TCF-4 dependent genes, but:
  - 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 (Ceribelli, 2016)
MOLECULAR & GENETICS

GENE EXPRESSION PROFILE STUDIES

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

Unsup Hier Clust of top 2500 genes

(Stenzinger 2014)

Ceribelli 2016)

MOLECULAR & GENETICS

<table>
<thead>
<tr>
<th>REF</th>
<th>Gene</th>
<th>%</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jardin</td>
<td>TET2</td>
<td>36-80</td>
<td>Tumor suppressor From onset of disease Common in many myeloid neoplasms</td>
</tr>
<tr>
<td>Alayed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menezes</td>
<td>IKZF3, ZEB2</td>
<td>12-16</td>
<td>Transcription Newly identified genes in leukemia</td>
</tr>
<tr>
<td></td>
<td>IKAROs family</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ASXL1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NRAS</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NPM1</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Menezes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenzinger</td>
<td>NRAS, KRAS, ATM</td>
<td>27</td>
<td>NRAS, KRAS and ATM mutually exclusive (clinical subtypes?)</td>
</tr>
<tr>
<td></td>
<td>MET, IDH2, KIT</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 (each)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Jardin, Br J Haematol 2011 (15 cases - PCR+Sequencing)
Alayed, Am J Hematol 2013 (5 cases -Targeted NGS (28 genes)
Menezes, Leukemia 2014 (25 cases -Targeted NGS (32 genes)
Stenzinger, Oncotarget 2014 (33 cases - Targeted NGS (30 genes)
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

• Dalle S, Br J Dermatol 2009
• Pagano L, Haematologica 2013
• Ross-Weil D, Blood 2013 (*)
• Aoki T, Blood 2015

BCL2 overexpressed in BPDCN
No amplification nor translocation

(*) Patients allografted in CR1
Patients allografted in more advanced status
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 = *lineage-survival oncogene* in BPDCN

BETis (Bromodomain and extra-terminal domain inhibitors)

→ inhibition of TCF4 transcriptional network
→ loss of the BPDCN-specific gene expression program
→ tumor cell apoptosis (*in vitro* and BPDCN xenografts)

? BET inhibitors promising epigenetic treatment of BPDCN as single agent capable to silence multiple driver-genes?