BPDCN - diagnostic challenges

• Clinical: aggressive disseminated disease
• Specific immunophenotype (but, no consensus / guidelines!)
• Diagnosis of exclusion (no specific molecular alterations)
BPDCN - immunophenotypic criteria

CD4+CD43+CD45RA+CD56+ AND pDC-related Ag
- CD123 (IL-3RA)
- TCL1 (T-cell leukemia 1)
- CD162 (cutaneous lymphocyte-associated antigen)
- BDCA 2 / CD303, BDCA4/CD304 (blood dendritic cell antigens)
- CD2AP (adaptor protein CD2-associated protein)
- Spi-B transcription factor,
- CD31 (platelet endothelial cell adhesion molecule)

TdT+ in 1/3 of cases

Negative
CD34 and CD117
EBV (EBER)
T-cell markers (CD3, CD5)
B-cell markers (CD19, CD20, CD79a)
Lysozyme and myeloperoxidase

2008Montes-Moreno et al Blood 2013
BPDCN – Flow cytometry

CD45+CD4+CD56+CD3-CD8- population

Riaz et al. Cancer Control Oct 2014 Vol 21 No4
WHO 2008

CD4, CD43, CD45RA, CD56, CD123, BDCA2, TCL1, CLA, MxA (IF-alpha dependent molecule)

If not all Immunophenotypic features present: acute leukemia of ambiguous lineage

WHO update on diagnostic criteria is awaited!
BPDCN – DD

WHO 2008:

Because other haematologic neoplasms (acute myeloid leukemia, extranodal NK/T-cell lymphoma, nasal type and mature T-cell lymphomas) with or without skin involvement, may express CD56 with or without CD4, an extensive immunohistochemical and/or genetic analysis is mandatory before a definitive diagnosis of BPDCN is made.
Cutaneous T-cell lymphoma
- frequently present with skin lesions and blood involvement
- different morphology, disproportionate epidermotropism
- mature T-cell immunophenotype with a lack of CD56 expression

Extranodal NK/T-cell lymphoma
- can manifest with skin lesions and CD4+/CD56+ immunophenotype
- EBV positivity via in situ hybridization

Extramedullary myeloid sarcoma:
- immunophenotypic overlap
- frequently manifest with skin infiltration
- positive for lysozyme or myeloperoxidase and negative for CD56, CD123 and CD162 (myxovirus)

Sangle et al. Mol Pathol 2014; 27(8):1137-43
2016 WHO classification of mature lymphoid, histiocytic and dendritic neoplasms

Histiocytic and dendritic cell neoplasms
• Histiocytic sarcoma
• Langerhans cell histiocytosis
• Langerhans cell sarcoma
• Indeterminate dendritic cell tumour
• Interdigitating dendritic cell sarcoma
• Follicular dendritic cell sarcoma
• Fibroblastic reticular cell tumour
• Disseminated juvenile xanthogranuloma
• Erdheim-Chester disease

Swerdlow et al. Blood 19 May 2016 Vol 127 No20
Table 2. — Clinical and Pathological Findings of Dendritic Cell Sarcomas

<table>
<thead>
<tr>
<th>Clinical Findings (usual presentation)</th>
<th>FDCS</th>
<th>IDCS</th>
<th>INDICS</th>
<th>HS</th>
<th>FRCT</th>
<th>JXG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow growing mass, usually a lymph node</td>
<td>Asymptomatic solitary lymph node mass</td>
<td>Papules, nodules, or plaques on the skin</td>
<td>Solitary mass with systemic symptoms Can have skin lesions (rash-like)</td>
<td>Asymptomatic mass</td>
<td>Small solitary papule</td>
<td></td>
</tr>
<tr>
<td>Spindle to ovoid cells with whorls</td>
<td>Spindle to ovoid cells with whorls</td>
<td>Resembles Langerhans cells with irregular nuclear grooves and clefts</td>
<td>Large and round to oval shape with focal areas of spindling</td>
<td>Spindle to ovoid cells with whorls in para cortical areas</td>
<td>Small and oval with a bland round to oval nucleus without grooves</td>
<td></td>
</tr>
<tr>
<td>CD4 (+) CD21 (+) CD34 (−) CD35 (+) CD68 (+/−) Fascin (+)</td>
<td>CD4 (+) CD45 (+/−) CD68 (+) Fascin (+) S100 (+)</td>
<td>CD1a (−) CD4 (+) Fascin (+) S100 (+) CD68 (+/−) Birbeck granules (−)</td>
<td>CD163 (+) CD68 (+) Lysozyme (+) CD1a (−) CD21 (−) CD35 (−) CD33 (−)</td>
<td>Vimentin (+) Desmin (+) Smooth muscle actin (−) Factor XIIa (+) CD21 (−) CD35 (−) S100 (−) CD1a (−)</td>
<td>Vimentin (+) sCD14 (+) CD68 (+) Stabilin-1 (+) CD163 (+) Factor XIIa (+) CD1a (−)</td>
<td></td>
</tr>
<tr>
<td>Surgical resection ± adjuvant chemotherapy or RT</td>
<td>Surgical resection or RT</td>
<td>Surgical excision</td>
<td>Surgical resection ± RT</td>
<td>Surgical resection ± RT</td>
<td>None needed for localized asymptomatic lesion</td>
<td></td>
</tr>
<tr>
<td>Lymphoma-type chemotherapy</td>
<td>Lymphoma-type chemotherapy</td>
<td>Multimodality</td>
<td>Lymphoma-type chemotherapy</td>
<td>Participation in a clinical trial</td>
<td>Langerhans histiocytosis–based treatment</td>
<td></td>
</tr>
</tbody>
</table>

FDCS = follicular dendritic cell sarcoma, FRCT = fibroblastic reticular cell tumor, HS = histiocytic sarcoma, IDCS = interdigitating dendritic cell sarcoma, INDICS = indeterminate dendritic cell sarcoma, JXG = juvenile xanthogranuloma, RT = radiation therapy.
BPDCN and related myeloid & dendritic cell neoplasms – prognosis

Julia et al Am, J Surg Pathol 2014, n=91
French Study Group on Cutaneous Lymphomas
12 IHC markers, results correlated with survival

â€¢ 46% of pts had CD4+CD56+CD123+CD303(BDCA2)+TCL1+
â€¢ 4 markers were sufficient for BPDCN diagnosis
â€¢ Expression of TdT and/or S100 correlated with various degrees of maturation
â€¢ High Ki-67 and CD303 (BDCA2) expression associated with longer survival
BPDCN – prognosis and therapy

- Poor outcomes with median survival rates 12-16 months
- Prospective data are lacking
- Paediatric pts: better survival: 72% with a median follow-up of 30 months after HSCT following induction therapy with intensive high-risk ALL-type chemotherapy
- Standard frontline therapy is not established for pts with advanced-stage disease and participation in a clinical trials is encouraged
BPDCN – Targeted therapy

No specifically targeted agents are currently available

ÂSL-401, a recombinant human interleukin 3α protein conjugated with truncated diphtheria α-toxin
  Preclinical and early clinical data of 5 month median duration of CR on 7/11 pts

ÂFMS-like TKI-3
  Clinical report/observations on 3 pts with FLT3-ITD mutations

ÂLenalidomid
  Ex vivo efficacy of in a xenograft mouse model

Â5-azacytidine
  Report of 2 pts with concurrent myelodysplasia / myeloid malignancy effective in resolution of skin lesions and stabilization of PB parameters
BPDCN and related myeloid & dendritic cell neoplasms

- Biologically diverse
- Other specific entities to be excluded
- A guidelines on diagnostic criteria are needed
- Advances in ancillary techniques are essential
- Pts participation in clinical trials and registries are encouraged
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Thank you!