L’approccio del patologo
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NEOPLASIA A CELLULE DENDRITICHE PLASMACITOIDI BLASTICHE:

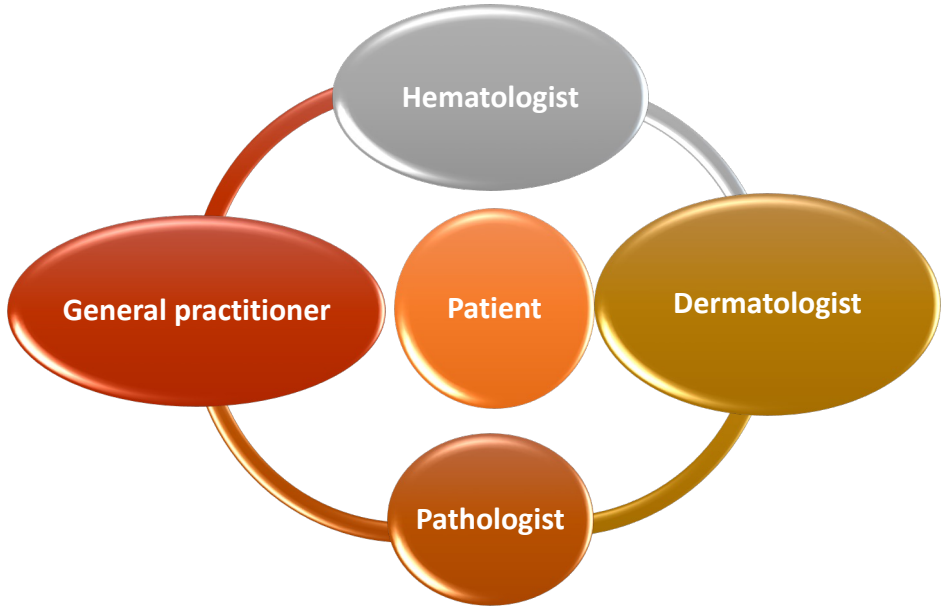
NUOVE OPZIONI DIAGNOSTICHE ED ALGORITMO TERAPEUTICO

Napoli
22 Febbraio 2024
Grand Hotel Santa Lucia

Disclosures:

- Eusa Pharma/Recordati Rare Disease
- KyowaKyrin
- Menarini Stemline

A multidisciplinary approach is required to diagnose and treat BPDCN patients



Atypical skin lesion → Dermatologist → Biopsy

Mean time between the **onset** of lesions and the pathologic **diagnosis** of BPDCN is **6.2 mos** based on a retrospective analysis

Julia F et al, Br J Dermatol 2013

Blastic plasmacytoid dendritic cell neoplasm (BPDCN):

consists of clonal proliferation of plasmacytoid dendritic cells **precursors**.

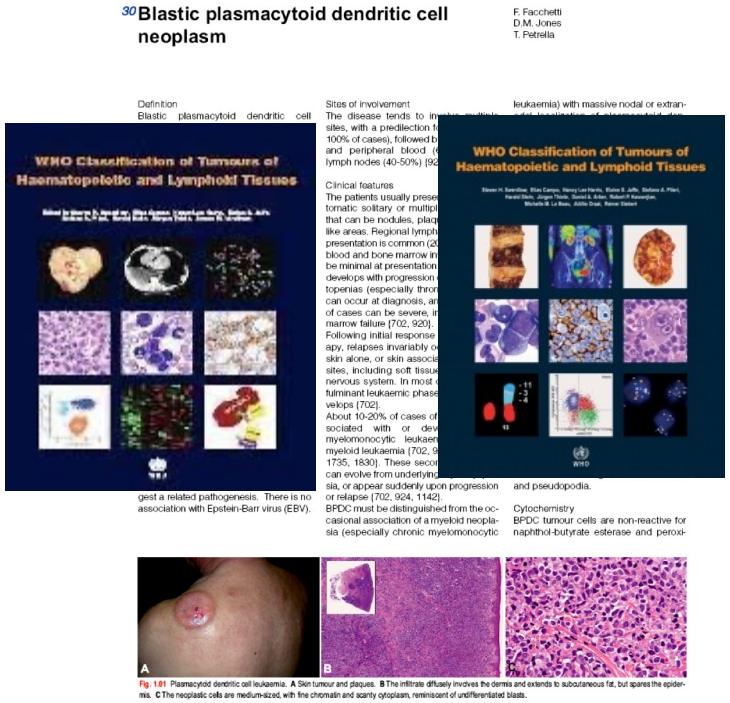
initially described by Adachi et al in 1994 : aggressive clinical course, tendency for skin involvement and quick progression to bone marrow and CNS, with a CD2–/CD4+/CD56+ immunophenotype

Origin remained unclear for long and led to different conflicting designations:
agranular CD4+ natural killer cell leukemia;
agranular CD4+/CD56+ hematodermic neoplasm;
blastic natural killer cell lymphoma/leukemia

With understanding of BPDCN: classified as a precursor neoplasm of AML (WHO 2008) and as a distinct form of AML in the 2016 revision

2022 WHO-HEAM5
included into the chapter of histyocytic / dendritic cell neoplasms
Plasmacytoid dendritic cell neoplasms
1. Mature plasmacytoid dendritic cell proliferation associated with myeloid neoplasm
2. Blastic plasmacytoid dendritic cell neoplasm

2022 ICC
stands as a separate entity in the chapter of myeloid neoplasms: blastic plasmacytoid dendritic cell neoplasm


30 Blastic plasmacytoid dendritic cell neoplasm

F. Facchetti
D.M. Jones
T. Petrella

Definition
Blastic plasmacytoid dendritic cell

Sites of involvement
The disease tends to in
sites, with a predilection f
100% of cases), followed b
and peripheral blood (
lymph nodes (40-50%) [92

Clinical features
The patients usually prese
tomatic solitary or multipl
that can be nodules, plaq
like areas. Regional lymph
presentation is common (2
blood and bone marrow in
be minimal at presentation
develops with progression
topenias (especially thror
can occur at diagnosis, ar
of cases can be severe, ir
marrow failure [702, 920].
Following initial response
apy, relapses invariably o
skin alone, or skin associa
sites, including soft tissue
nervous system. In most
fulminant leukaemic phase
velops [702].
About 10-20% of cases of
sociated with or dev
myelomonocytic leukaem
myeloid leukaemia [702, 9
1735, 1830]. These secon
can evolve from underlying
sia, or appear suddenly upon progression or relapse [702, 924, 1142].
BPDC must be distinguished from the occasional association of a myeloid neoplasia (especially chronic myelomonocytic leukaemia) with massive nodal or extranodal involvement and pseudopodia.

Cytochemistry
BPDC tumour cells are non-reactive for naphthol-butyrate esterase and peroxi-

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

Fig. 1.01 Plasmacytoid dendritic cell leukaemia. A Skin tumour and plaques. B The infiltrate diffusely involves the dermis and extends to subcutaneous fat, but spares the epidermis. C The neoplastic cells are medium-sized, with fine chromatin and scanty cytoplasm, reminiscent of undifferentiated blasts.

Adachi M et al. Am J Hematol, 1994; Brody JP et al. Cancer, 1995; Petrella T et al. Am J Surg Pathol, 1999; Aoyama Y et al. Ann Hematol, 2001; Petrella AJSP 2002, 2005; Vardiman JW et al. Blood, 2009; Arber DA et al. Blood, 2016; Arber et al. Blood 2022; Khourny et al. Leukaemia 2022

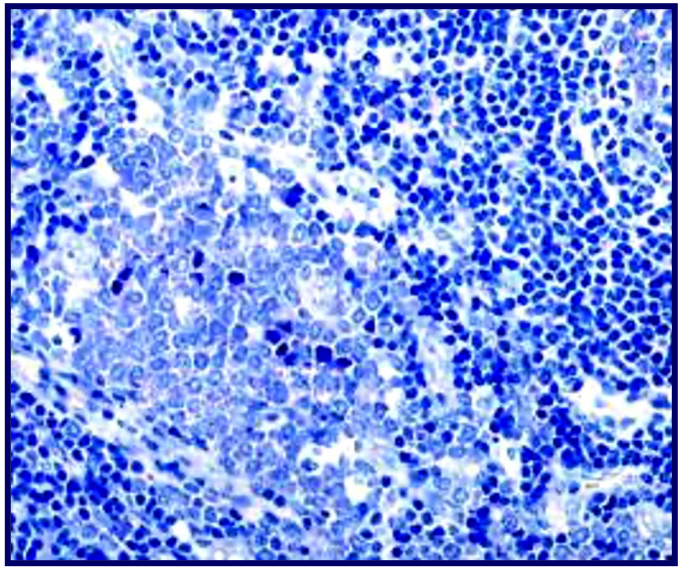
What are the pDC ?

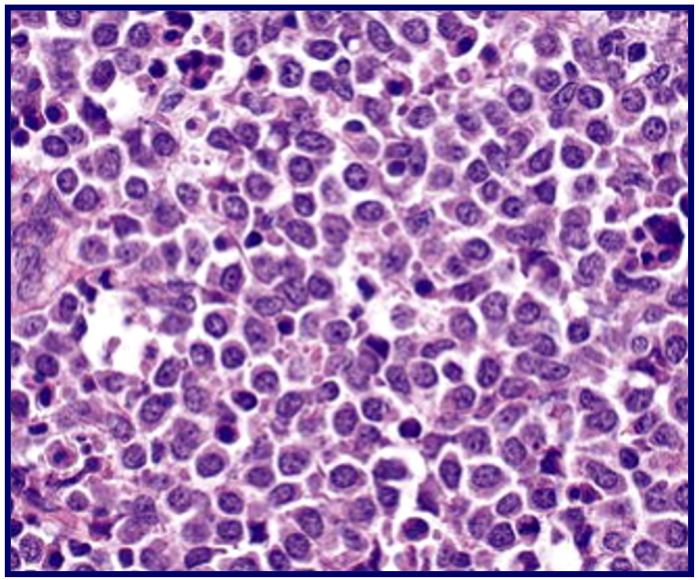
Lennert & Remmele, 1958: interfollicular cells cytologically resembling lymphoblasts

Origin was for long uncertain : variable conflicting designations proposed based on «plasma cell features» + CD4/T cell related '*T-associated plasma cell', 'plasmacytoid T cell',* and *'plasmacytoid T-zone cell'*

Demonstration of the expression of myelomonocytic markers (CD15 and CD68)+ lack of other T-lineage markers : prompted the term '*plasmacytoid monocyte*' thus questioning their lymphoid affiliation.

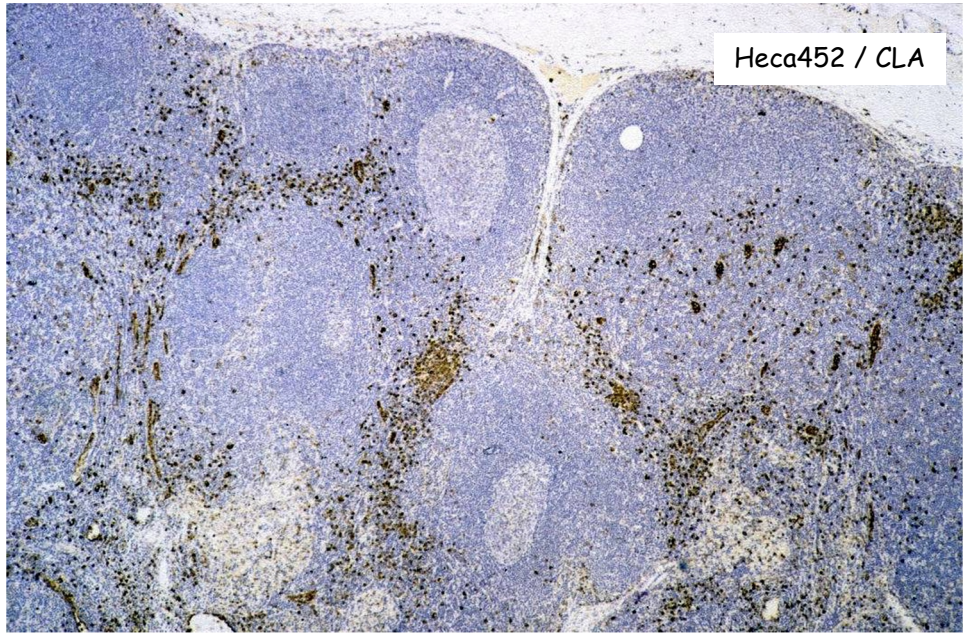
Expression of surface markers (BDCA-2/CD303, IL-3Ra/CD123), signaling molecules (BLNK, CD2AP, TCL1), and transcription factors (BCL11A, SPIB), clearly identified plasmacytoid dendritic cells (pDCs): *plasmacytoid dendritic cells; interferon producing cells*





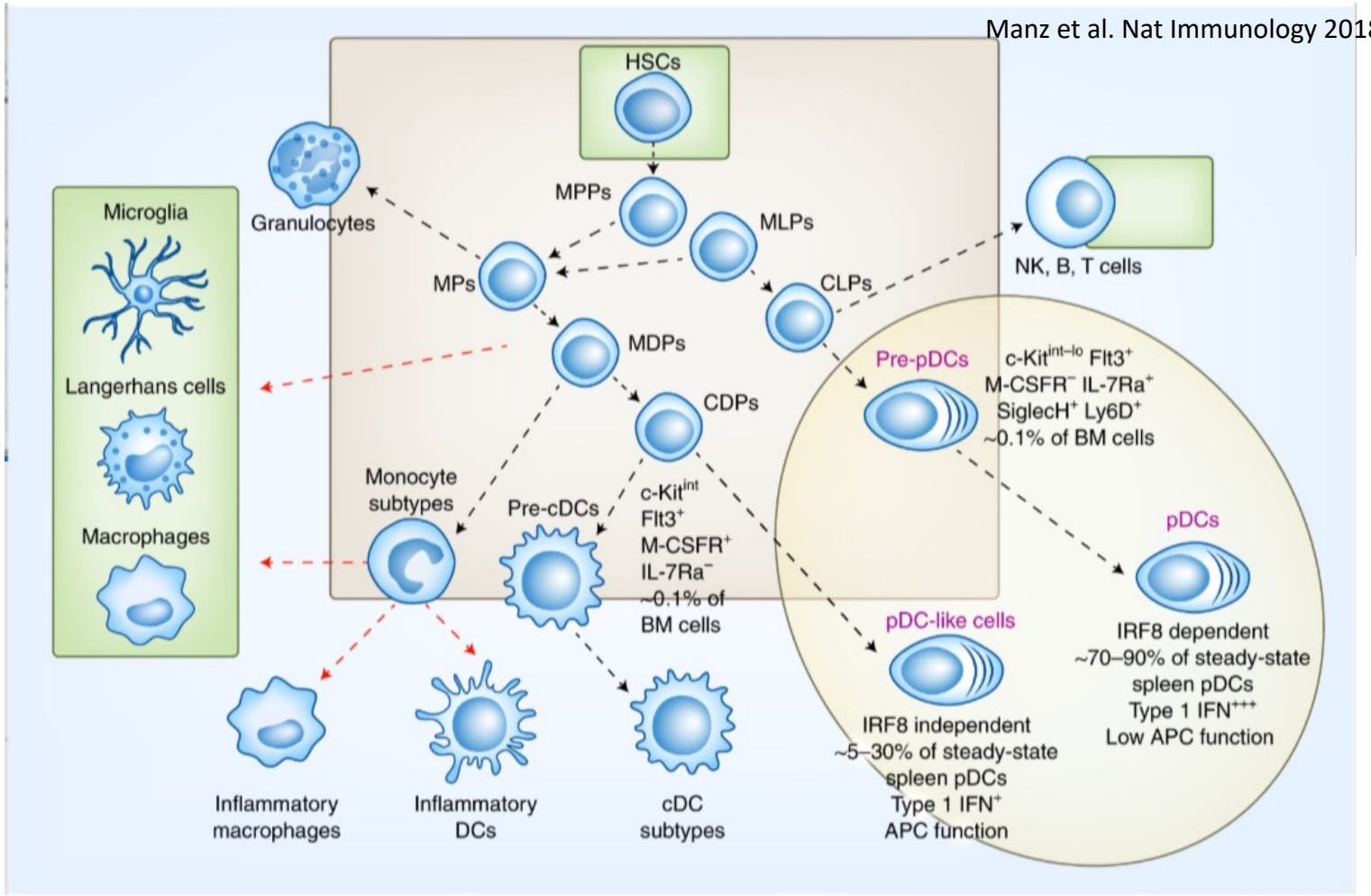
Lennert K, Remmele W. Acta Haematol. 1958; Muller-Hermelink HK et al. Am J Surg Pathol 1983 Facchetti F et al. Am J Pathol 1988; Cella M et al. Nat Med 1999; Facchetti F et al. Virchows Arch 2003; Soumelis V et al. Eur J Immunol 2006; Bjorck P et al. J Immunol 2011; Takagi H et al. Immunity 2011 Reizis B et al. Annu Rev Immunol 2011; Chaperot et al., 2001; Garnache-Ottou et al., 2009; Herling et al., 2003; Jaye et al., 2006; Marafioti et al., 2008; Montes-Moreno et al., 2013; Petrella et al., 2002)

- highly specialized circulating cells normal pb/marrow they represent <1% of all cells)
- most type 1-IFN (α/β) producers (fastest responder to INF-I inducers and major cellular source of IFN-alpha)
- key players in the immune response;
  may exert effector functions by releasing cytotoxic molecules (TRAIL and granzyme B)
- home to diseased tissue (> skin and lymph nodes), in various types of inflammatory conditions (autoimmunity, cancer, virus infections)
- primarily reside in lymph nodes and tonsils (generally related to an ongoing immune reaction); rarely in thymus, bone marrow, spleen and MALT; nearly absent in peripheral non-lymphoid tissues



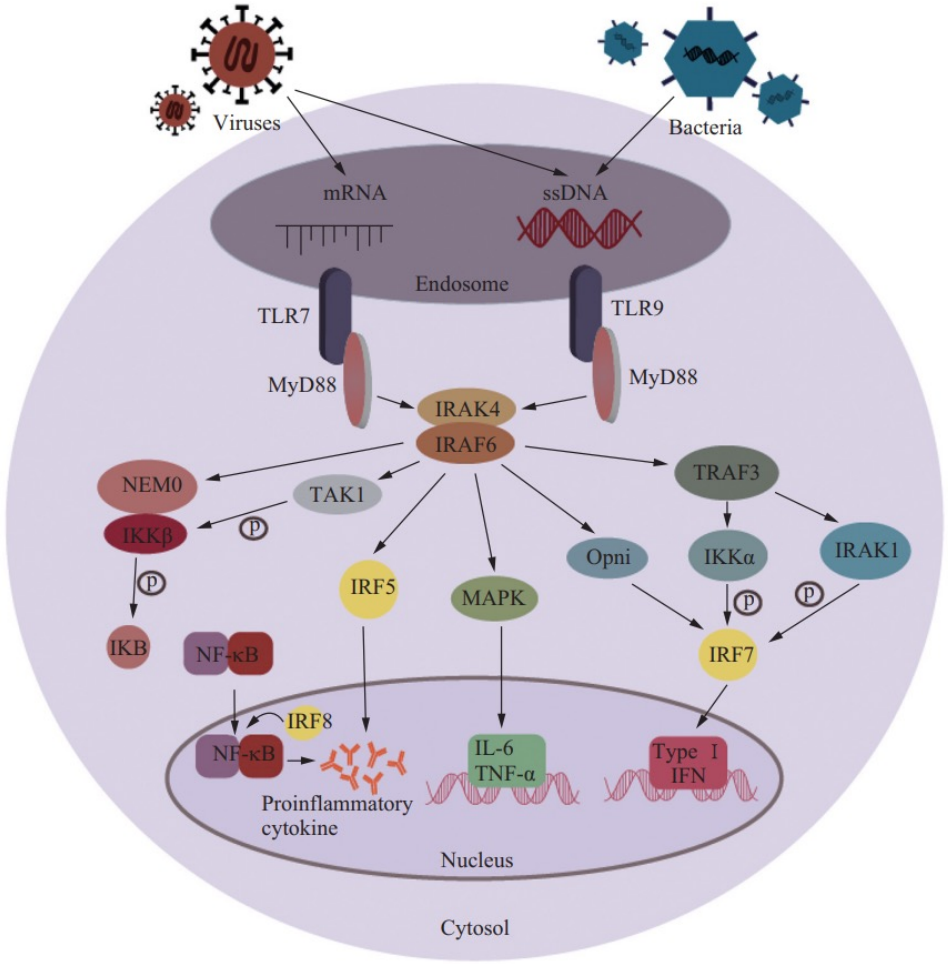
Facchetti F et al. Hum Pathol 1988; Jegalian AG et al. Adv Anat Pathol 2009; Vermi W et al. Immunobiology 2009; Vermi W et al. J Leukoc Biol 2011

Manz et al. Nat Immunology 2018



FLT3, TCF4, IRF8, BCL11A, SPIB, RUNX2, IRF7

Naik SH et al. Nat Immunol, 2007; Onai N et al. Immunity, 2013; Onai N et al. Nat Immunol, 2007; Facchetti F et al. Mod Pathol, 2016; D'Amico A et al. J Exp Med, 2003; Karsunky H et al. J Exp Med, 2003; Cisse B et al. Cell 2008; Nagasawa M et al. Eur J Immunol, 2008; Ghosh HS et al. Immunity, 2010; Reizis B Curr Opin Immunol, 2010; Belz GT et al. Nat Rev Immunol, 2012; Li HS et al. Blood, 2012; Maraskovsky E et al. Blood 2000

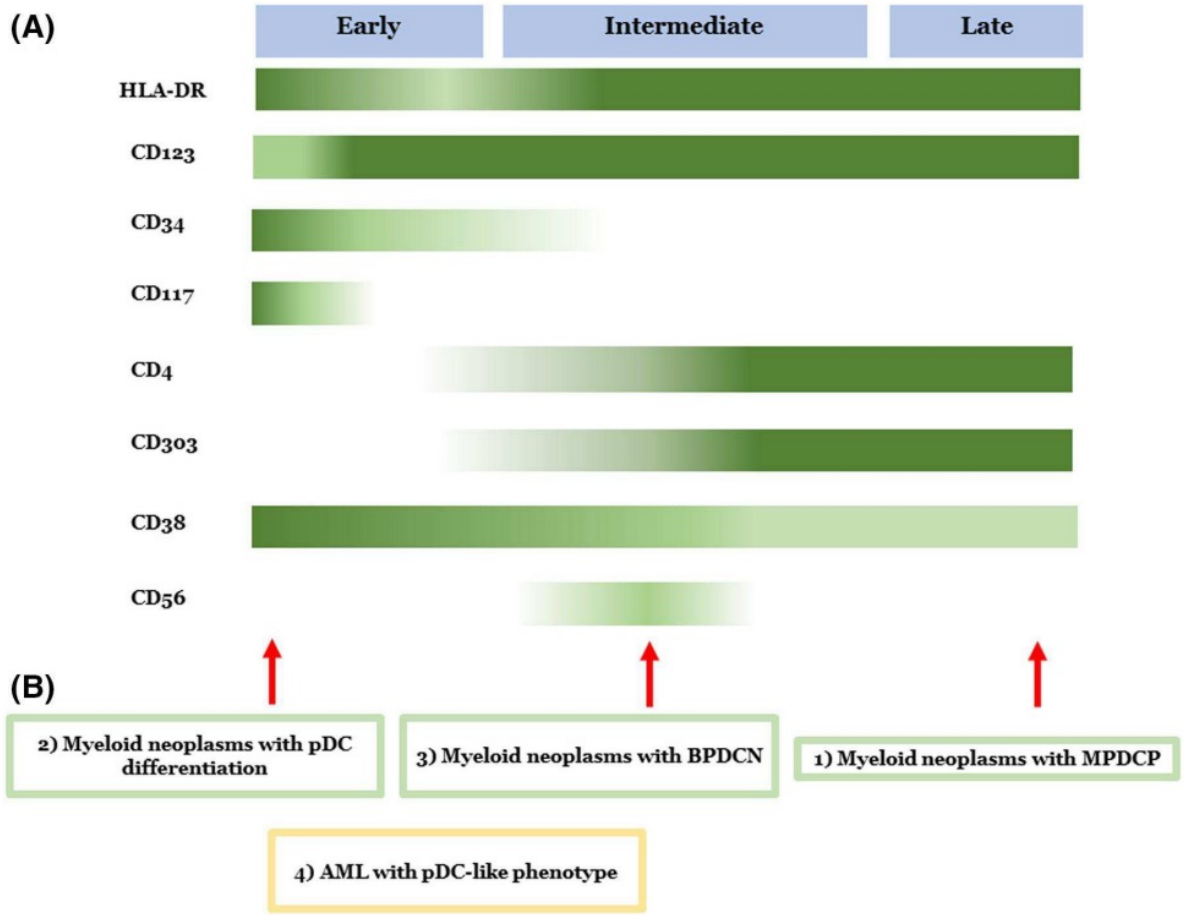


pDCs as bridge between innate and adaptive immune systems working as APC

recognizes nucleic acid sequences from virus and bacteria --- *via* the TLR 7/9-MyD88, activation of many cellular pathways (including IRF7, IRF5, MAPK, NFkB) with production of cytokines (IFN-α and IL6, IL-8, and IL-12) and activation of T cells, NK and macrophages

Colonna M et al. Nat Immunol, 2004; Honda K et al. Nature, 2005; Blasius AL et al. Immunity, 2010; Kawai T et al Nat Immunol, 2010

El Hussein&Wang, BJH 2022

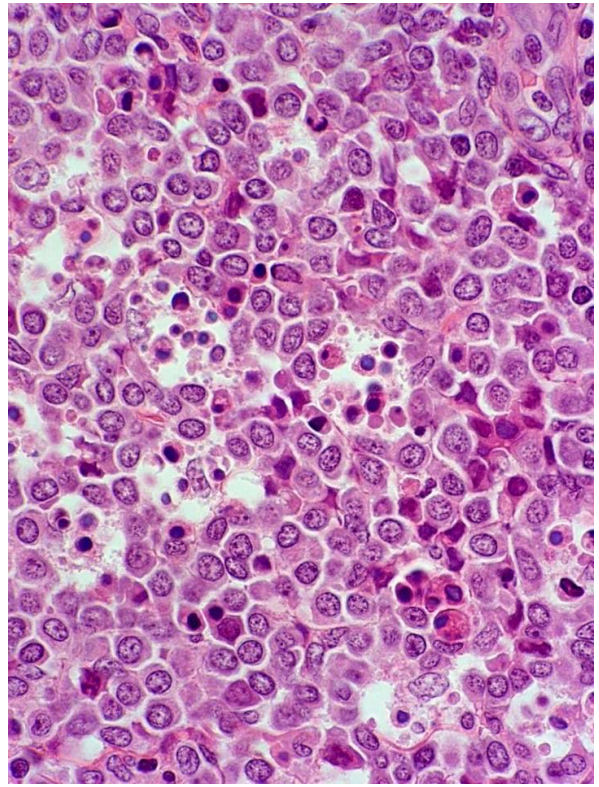


- CD45 gradually increases
- 3 step maturation from early precursors and late/mature cells based on CD34/CD117 (immature markers) and more specific pCD markers (CD303, CD4, CD123), CD56 and CD38
- subset of normal pDC expresses CD56 (mostly associated with neoplastic and blastic phenotype); this explains the heterogeneity in the phenotype of pDC proliferations
- Origin of the various disease where pDC are involved might derive from the different subsets

Table 1 Normal plasmacytoid dendritic cells immunophenotype

	Positive on plasmacytoid dendritic cells	*Negative on plasmacytoid dendritic cells*
B-cell antigens	**TCL1**[a], BCL7A[a], BCL11a[a], SPI-B[a]	CD19, CD20, CD22[b], CD79a, PAX5, sIg, cIg
T-cell antigens	CD4	CD2[c], CD3, CD5[c], CD7[c], CD8, CD103, LAT, T-bet, TCR-AB, TCR-GD, ZAP70
NK/cytotoxic cells antigens	Granzyme B	CD16, CD56[c], perforin, TIA-1
Myeloid/monocytic/ dendritic cells antigens	CD36, CD68 **BDCA2/CD303**[d], BDCA-4/CD304	CD11b, CD11c, CD13, CD14, CD15, CD33[c], CD163, DC-LAMP/CD208, elastase, esterases, langerin/CD207, lysozyme, myeloperoxidase, mannose receptor/CD206, DC-SIGN/CD209 CD1c/BDCA1, CD141/BDCA3
Miscellaneous antigens	CD11a, CD31, CD32, CD40, CD43, CD44, CD45RA, CD45RB, CD49e, CD62L, CD71, CD74, **CD123**, CD128, BAD-LAMP, CLA/CD162, **CD2AP**, E-cadherin, HLA-ABC, HLA-DP, HLA-DQ, HLA-DR, MxA, TLR1/CD281, TLR6/CD286, TLR7/287, TLR9/CD289, TLR10/290	CD1a, CD10, CD21, CD23, CD25, CD27, CD28, CD30, CD34, CD35, CD38, CD45R0, CD57, CD64, CD65, CD80, CD83, CD86, CD94, CD95, CD117, CD125, CD138, CDw150, CD161, BCL2, BCL6, FOXP3, ILT3, MUM1/IRF4, S100, TdT, TLR2/CD282, TLR3/CD283, TLR4/CD284, TLR5/CD285, TLR8/CD288

E2-2/TCF4



Neoplastic proliferation of pDC

- **Blastic Dendritic Plasmacytoid Cell Neoplasm: neoplastic proliferation of PDC precursors/blasts**
  - Coexisting myeloid and BPDC neoplasms

- **Myeloid Neoplasm associated with proliferation of mature PDC**

- Myeloid neoplasms (mostly AML) with PDC differentiation (pDC-AML)
- Myeloid neoplasms (mostly AML) with PDC-like phenotype (no PDC biology)

BPDCN

Rare
no racial or ethnic predominance
> males (M/F: 3/1)
>adults (mean/median age at diagnosis of 58/65 years; range 0–96)
5% patients younger than 10 years

from immature cells with plasmacytoid dendritic cell differentiation resting, non-activated; aberrant NF-κB pathway activation; defective type I interferon signaling postulated to be related to E-cadherin expression

Localization :
skin most commonly involved (60-95% of patients), followed by bone marrow and lymph nodes; CNS involvement may be detected at diagnosis, common at relapse

Presentation:
Dermatopathic variant
Leukemic variant

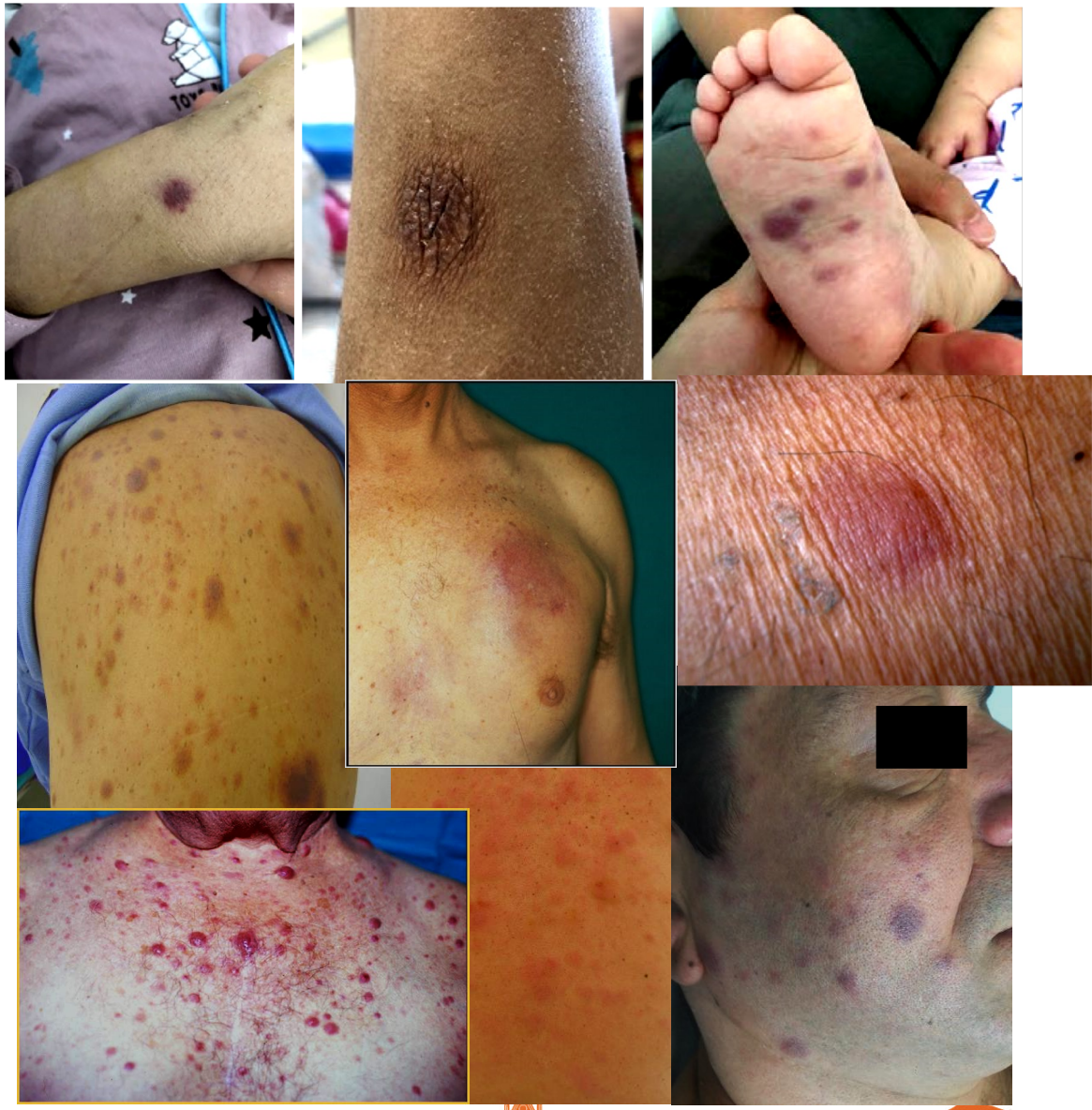
Dermatopathic variant

- >90% cases

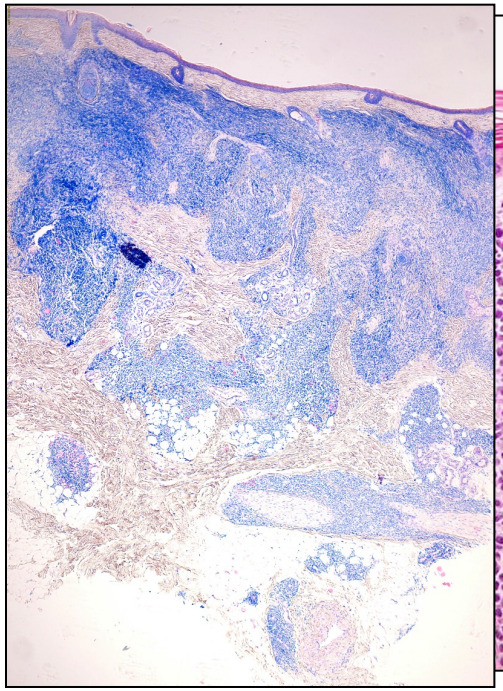
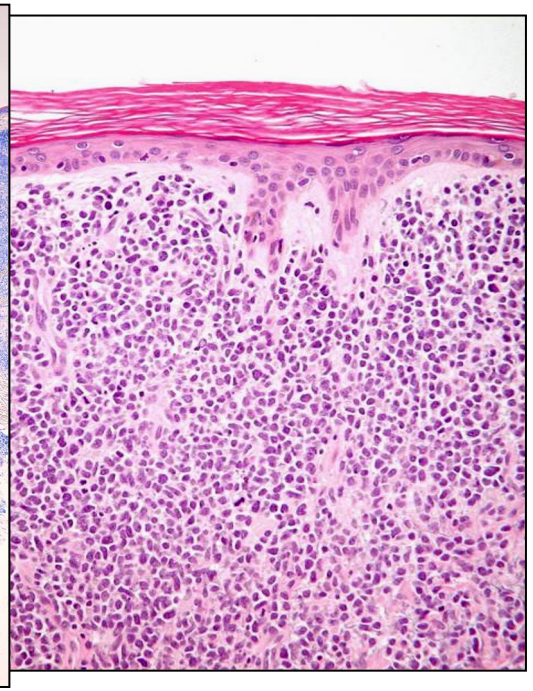
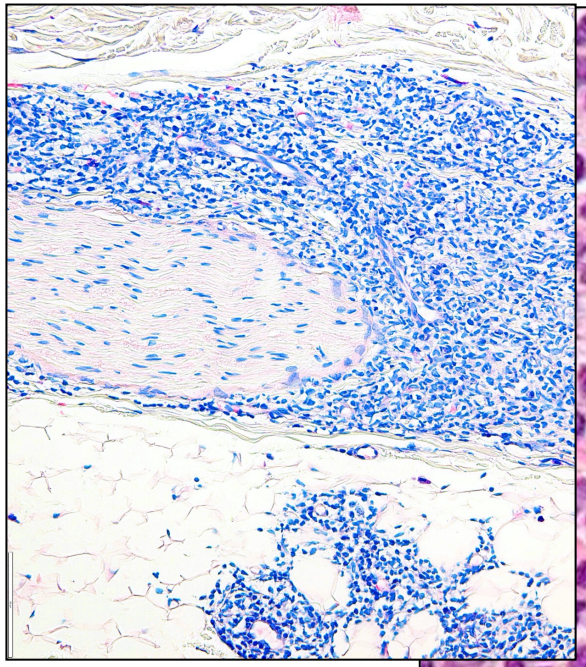
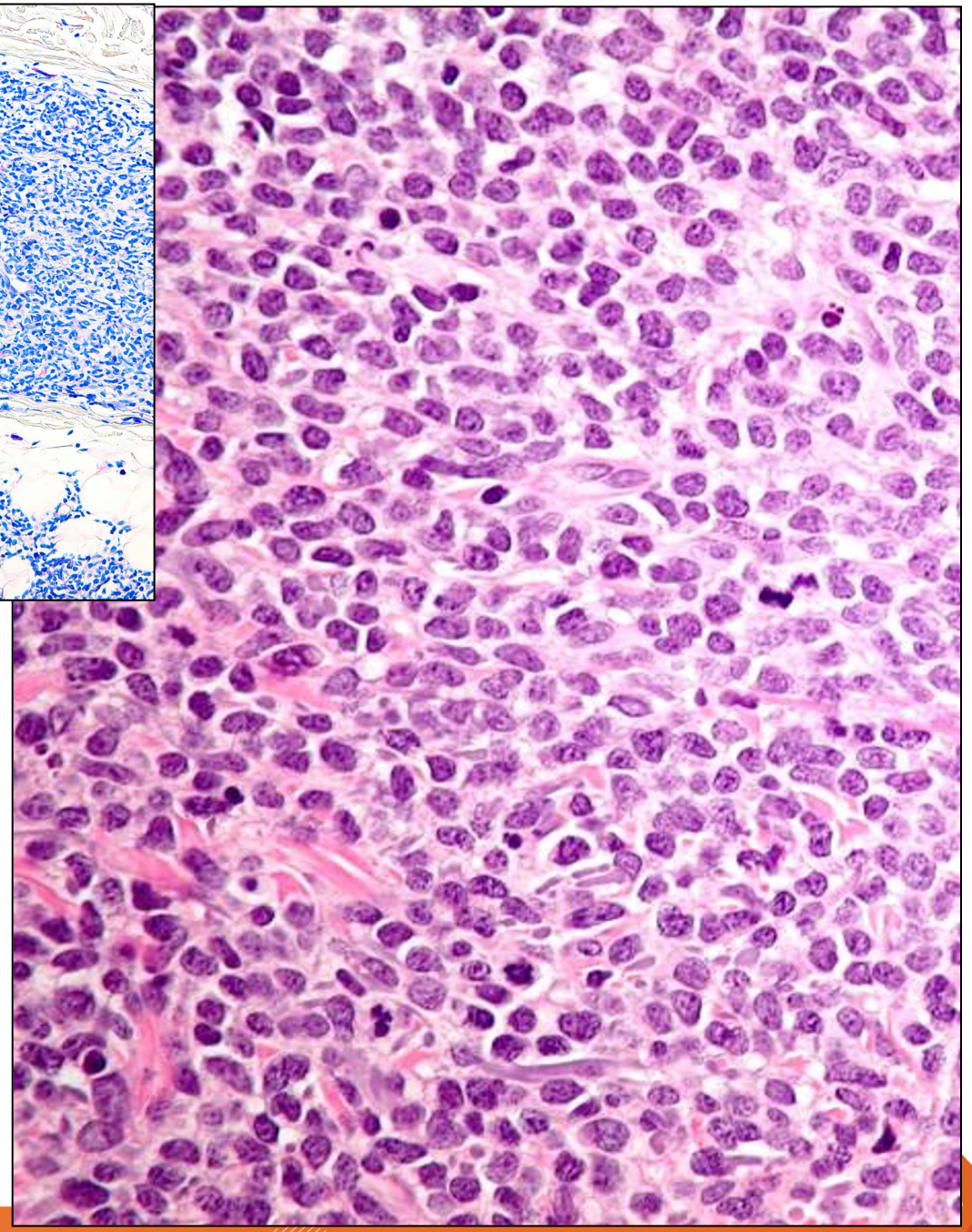
- cutaneous tropism : attributed to skin-migration antigens (CLA and CD56), and local availability of chemokines binding cognate receptor expressed by neoplastic plasmacytoid dendritic cells (CXCR3, CXCR4, CCR6, CCR7)*.

- Papules, Papulo-nodular lesions, patches, plaques, isolated nodules; violaceous or purplish-like
  Eruptive appearance; asymptomatic; rare ulceration; variable size (few mm to 10 cm)

- Skin lesions as only detectable clinical manifestation 50%
- With generalized lymphadenopathy at presentation (40%) spleen (25%), liver (16%) enlargement
- Mucosal lesions described more rarely

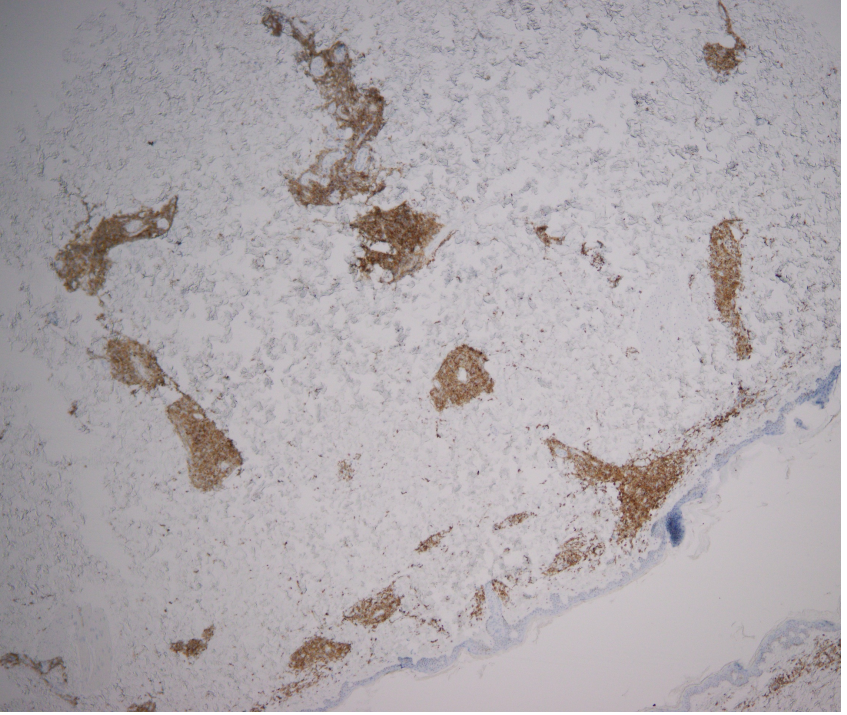


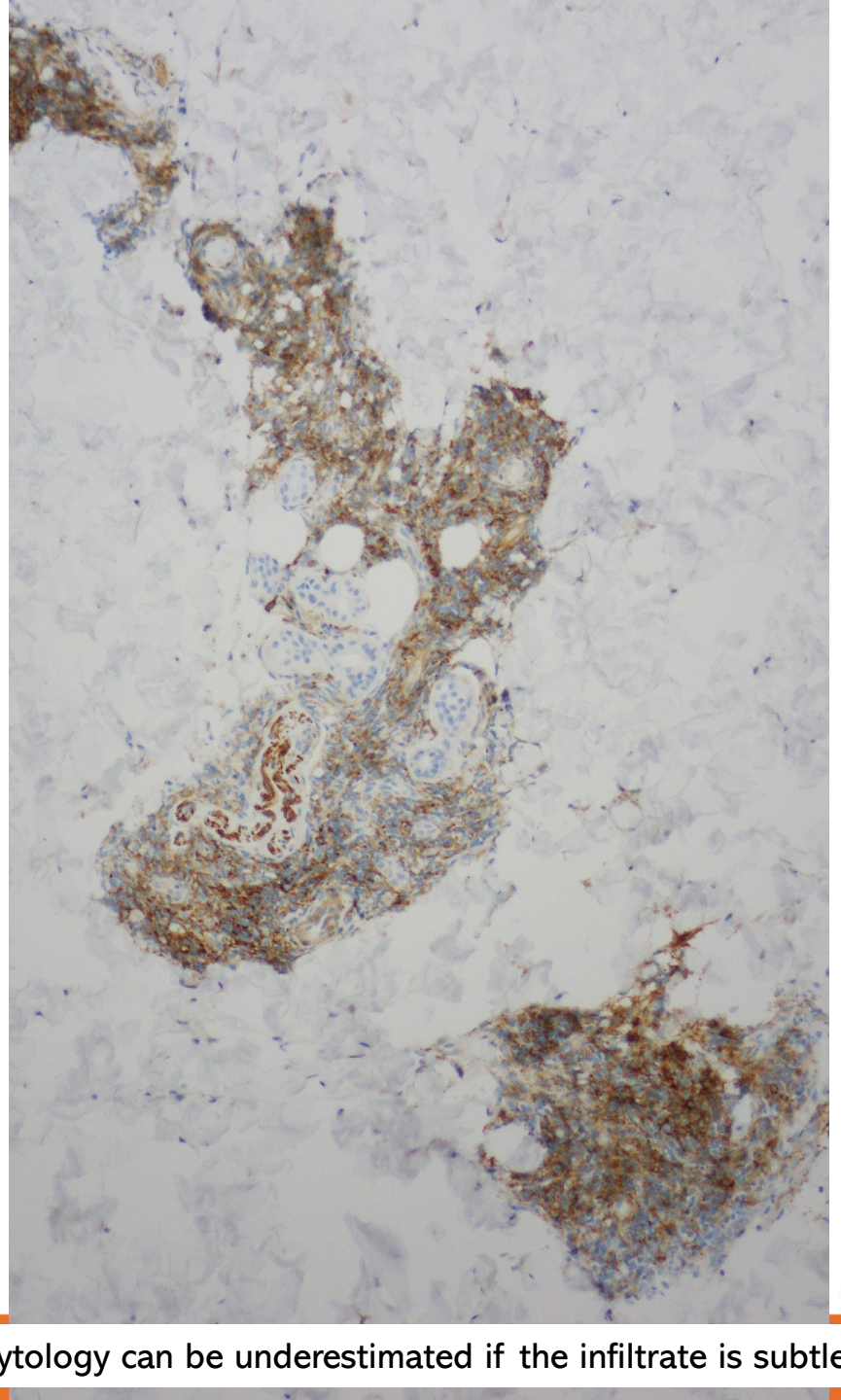
*Facchetti et al. Leukemia 2004; Khourny et al. Leukaemia 2022

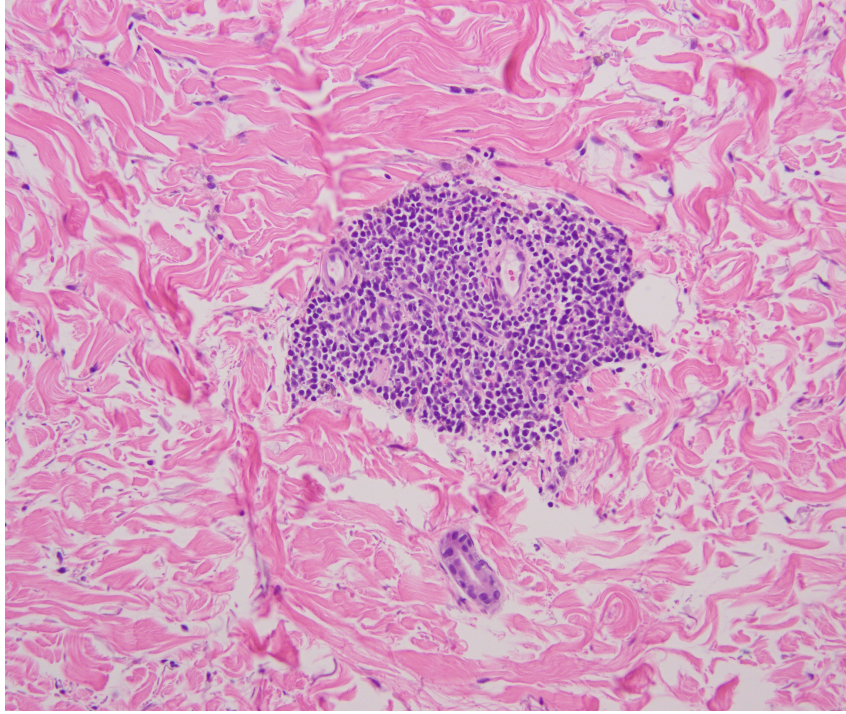





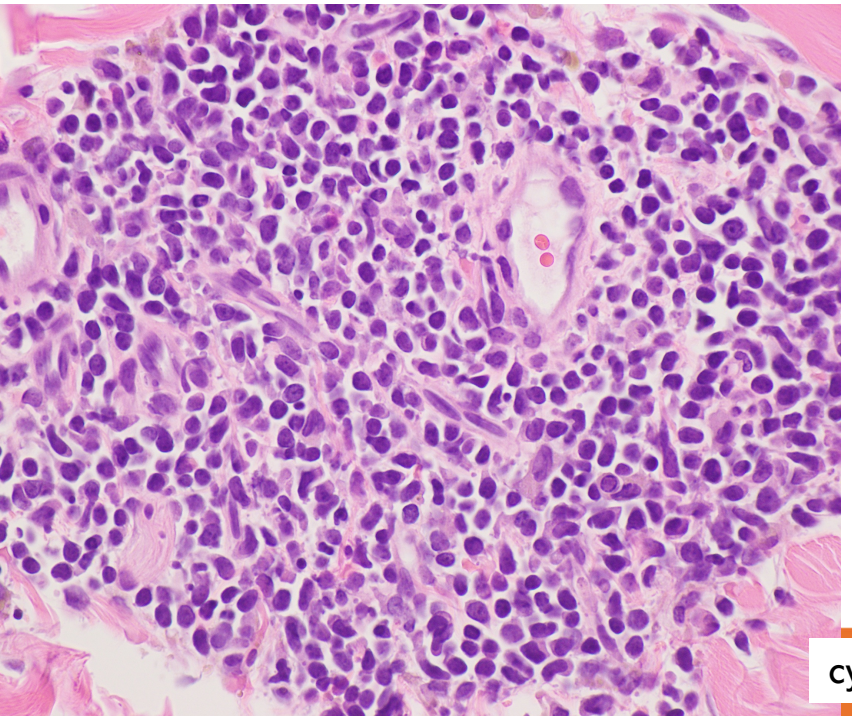
SKIN
monomorphic medium-sized blast cells (irregular, eccentrically located nuclei; finely dispersed chromatin; one/more small but distinctive nucleoli);
moderately abundant/non granular cytoplasm;
angioinvasion and coagulative necrosis rare;
dermal and adipose tissue involved; no epidermo-adxenal tropism;
Mitoses variable in number, often evident;

Khourny et al. Leukaemia 2022; Campo et al. Blood 2022

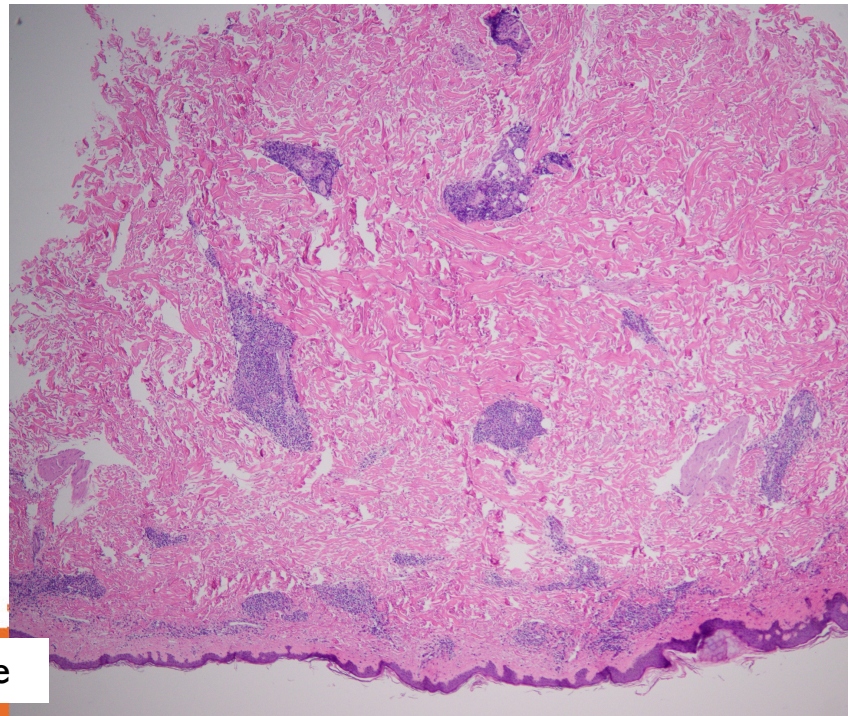








cytology can be underestimated if the infiltrate is subtle



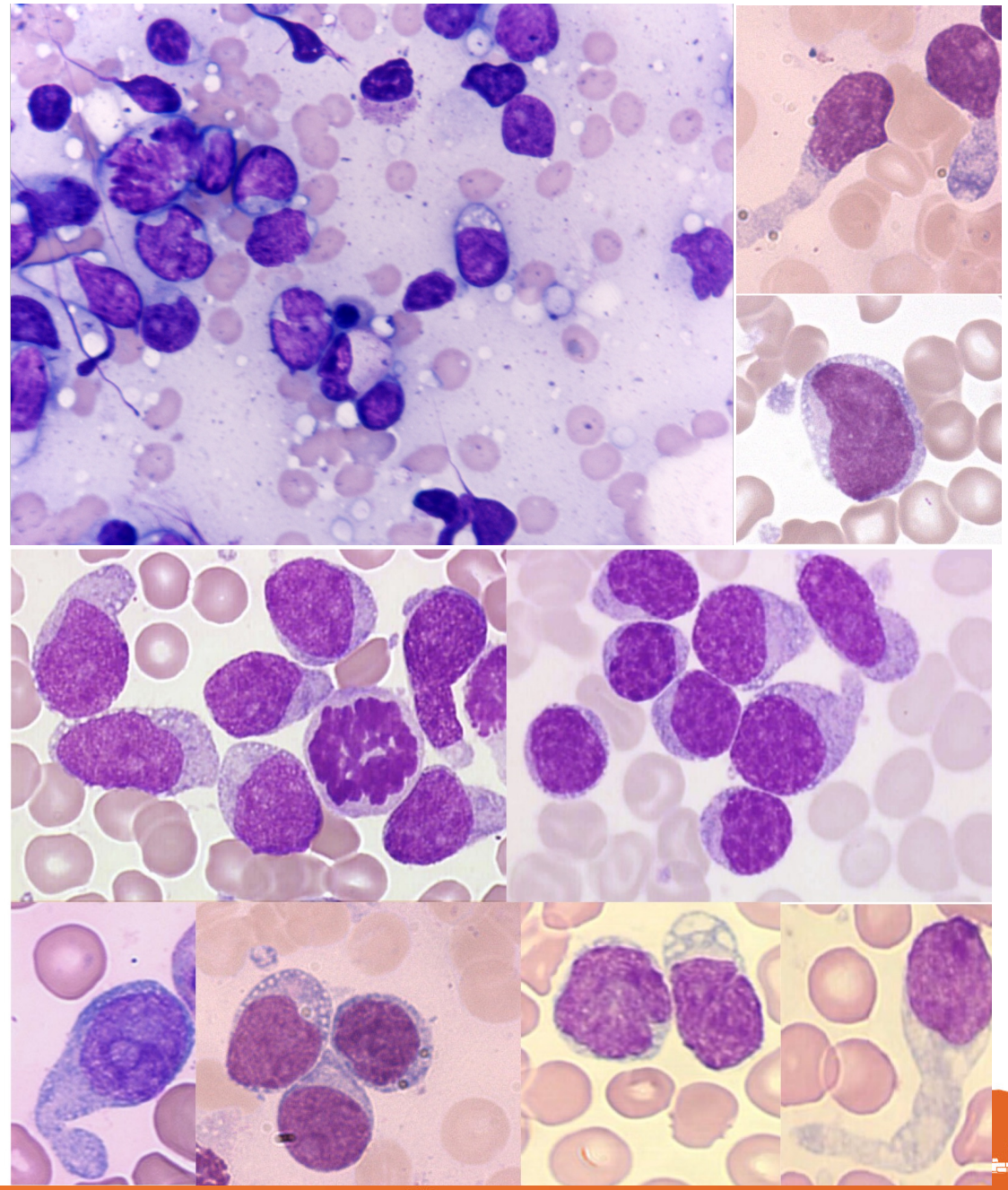
Leukaemic variant: elevated WBC, circulating blasts, and massive bone marrow infiltration; >multiple skin lesions
7% purely leukaemic

LYMPH NODE
involvement can be observed; efface the structure from the paracortical area

BONE MARROW
involvement at onset 50-90% (can be negligible); invariably becomes manifest at progression
pb 50% (>low blasts number)

Blood/marrow smears:
blastoid features, cytoplasmic *microvacuoles, pseudopodia shaped expansions*,
lack of granules or crystals

Dysplastic alteration in the remaining hematopoietic tissues, especially in megakaryocytes



Khourny et al. Leukaemia 2022; Campo et al. Blood 2022

Coexisting myeloid and BPDC neoplasms

➢Isolated or Associated with antecedent or concurrent or following MN : 20-30% of patients

➢Chronic MyeloMonocytic Leukaemia, Myeloproliferative Neoplasm, Myelodysplastic neoplasm, rarely Multiple myeloma
Some may develop BPDCN following cytotoxic therapy for other malignancies;
Possible presence of clonal haematopoiesis in elderly patients

➢Myeloid leukemic cells are phenotypically distinct from blastic plasmacytoid dendritic cell neoplasm tumor cells, but can share CD4 and CD56, as well as TCL1 and CD123, suggesting that the two diseases may have a common origin.

Khourny et al. Leukaemia 2022; Campo et al. Blood 2022; Khanlari M et al. Leukemia 2022; Espasa A et al. Cytometry B Clin Cytometry 2021

phenotype

- Specific markers: CD123/CD303/TCL1/TCRF4/CD304; CD4/CD56

- Aberrant markers
  the frequent aberrancies define a high phenotypic heterogenity; large panel of markers is required particularly if the typical specific markers are absent

  CD20/CD79a/CD19/PAX5; CD2/CD3/CD5/CD7/CD4/CD8/CD43; MPO/CD15/CD68/CD163; CD34/TdT/CD117/CD99/CD38/CD1a; S100/MUM1/BCL2; BCL6/CD10

Expected positive expression:
CD123* (rare negative reported)
TCF4* strong uniform
TCL1*
CD303 *
CD304*
CD4
CD56 strong uniform (rare negative;§§)

Expected negative expression:
CD3
CD14
CD19
CD34
Lysozyme
Myeloperoxidase

Commonly positive: E-cadherin (**), MX1, HLA-DR
Possible : CD2, CD7, CD33, CD36, CD38, CD43, CD45RA, CD79a, *Bcl2*, TdT

Uncommon: CD5, CD13, CD22, CD117
S-100 reported in children

Ki-67 proliferation index high

PD-L1 expression in some cases

Mostly negative: *CD68* (possible granular weak staining), CD1a, CD15, CD25, CD34, CD41, CD64, CD113, MNDA

Immunophenotypic diagnostic criteria:
- Expression of CD123 and one other pDC marker (*) in addition to CD4 and/or CD56.
  Or
- Expression of any three pDC markers (*) and absent expression of all expected negative markers

§§ subset of mature reactive pDC are CD56+ (1.2-20%) mostly weaker and partial; Khourny et al. Leukaemia 2022; **Lorenzi 2021AJSP

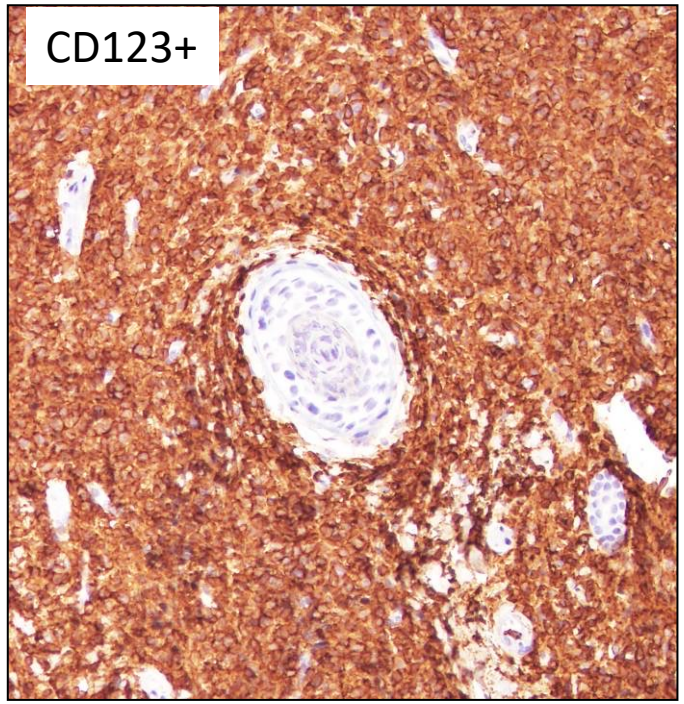
Immunohistochemistry

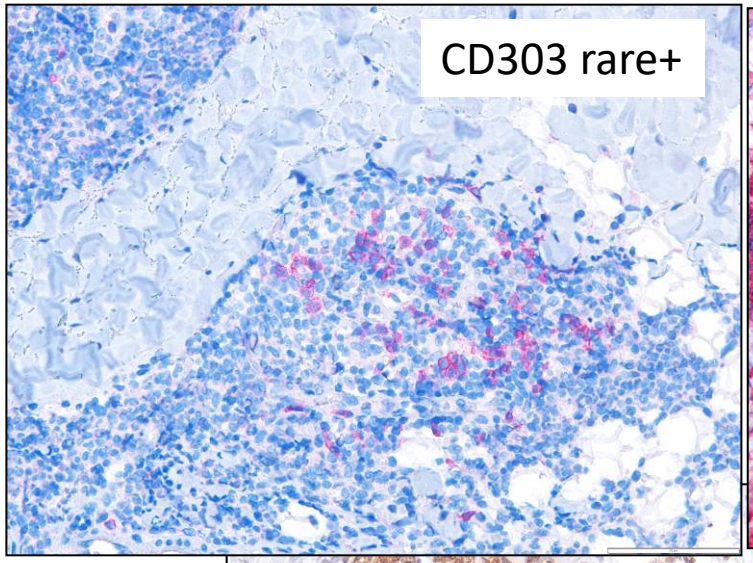
➢CD56 as only marker used to date to distinguish neoplastic from reactive PDC
But few BDPCN are negative and CD56 expression can be found in a small subset of reactive PDC (challenge in CD56negBDPCN and in assessment in post treatment BM specimens)

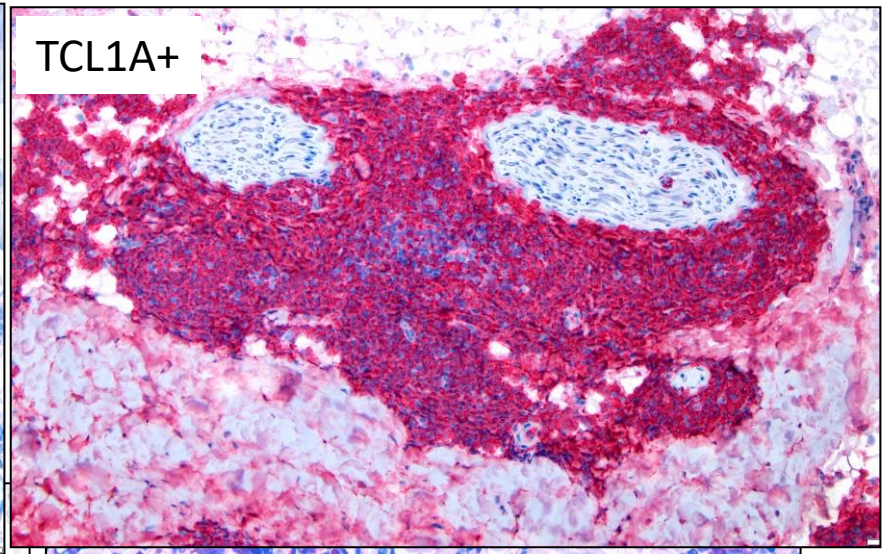
➢*AJSP 2014 Julia F et al.*
BPDCN: clinico-immunohistochemical correlations in a series of 91 patients.
co-expression of CD4, CD56, CD123, CD303, TCL1 only in 46% cases;
4/5 markers could still be reliably made without resorting to any additional stains

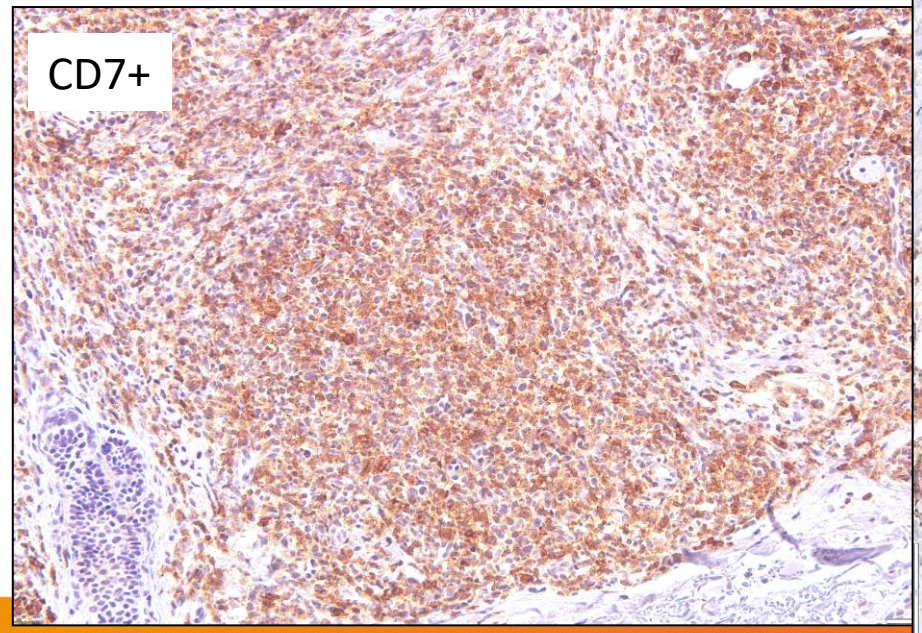
➢*AJSP 2019 Sukswai et al.*
Dual expression of TCF4 and CD123 is a highly sensitive and specific for BDPCN

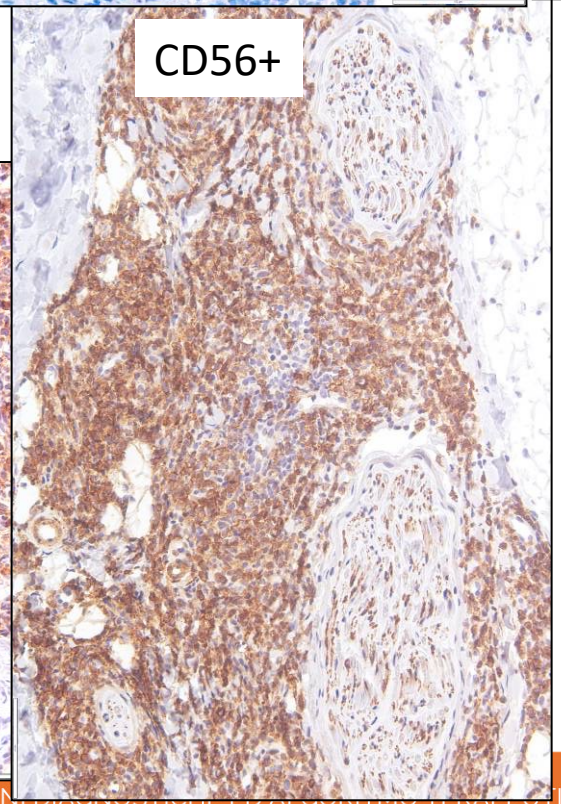
➢*AJCP 2023 Wu et al. (*neoplastic vs reactive pDC)
SOX4 positive in neoplastic pDC
SOX4/CD123 (100% sensitivity; 98% specificity) for BDPCN (against reactive pDC and other neoplasm including CD56negBDPCN
TCF4/CD123
TCF4/CD56+ 96% sensitivity; 100% specificity for BDPCN;
IRF8 non specific; positive in BDPCN, reactive p-DC and other MN

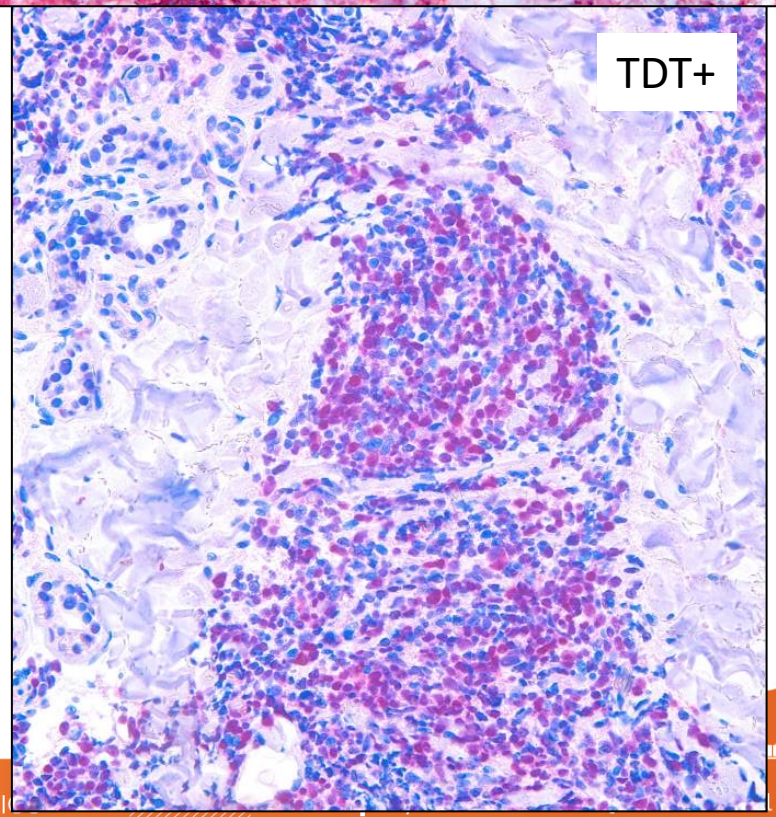

CD123+

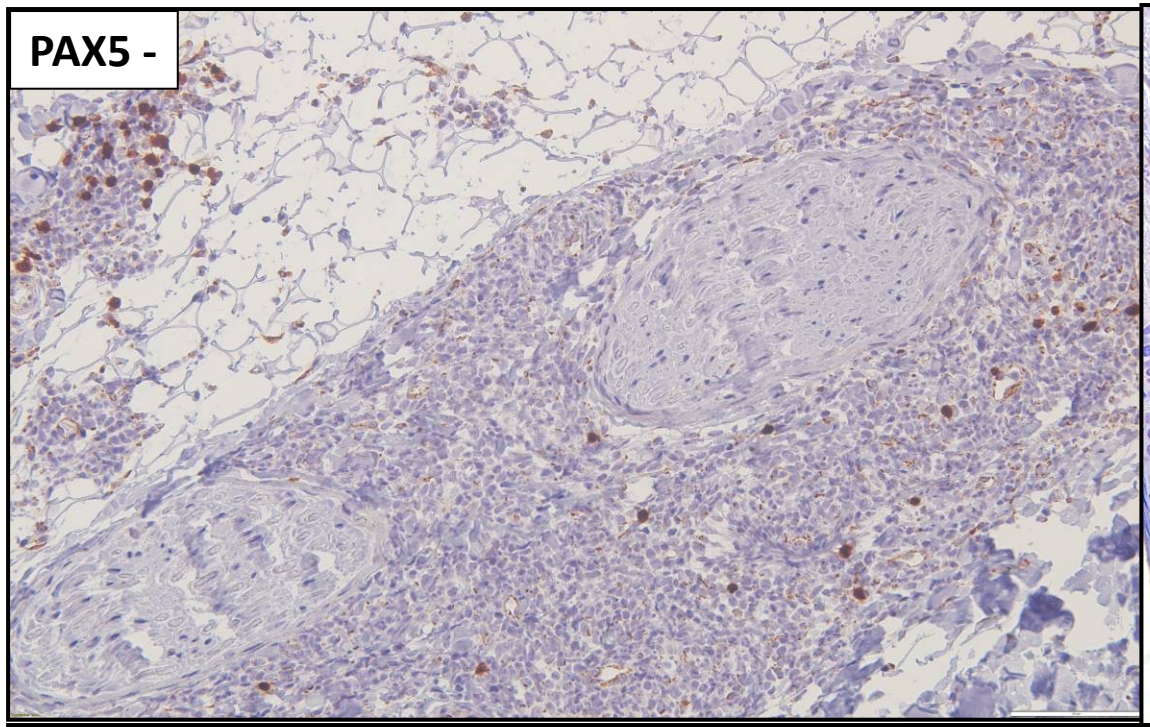

CD303 rare+

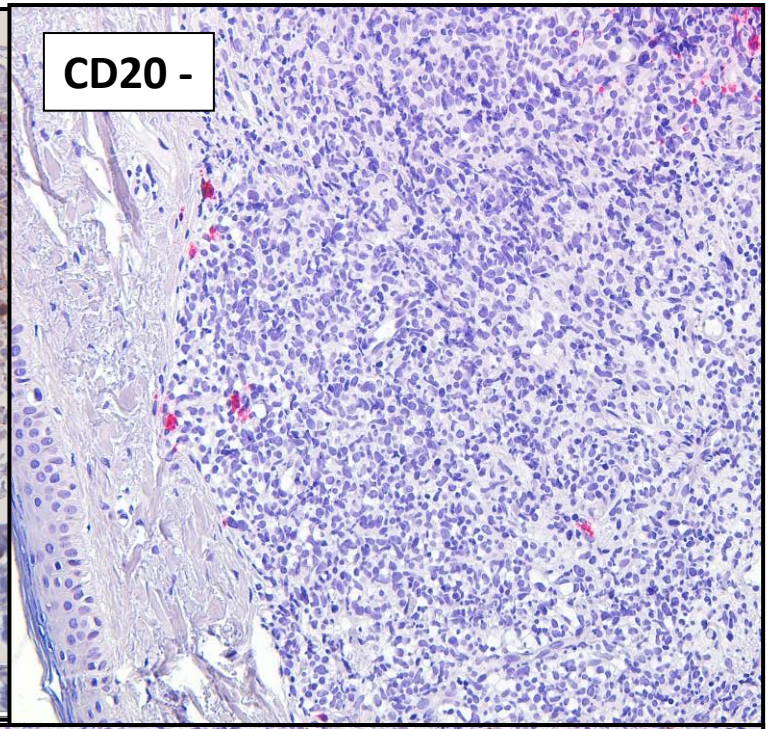

TCL1A+

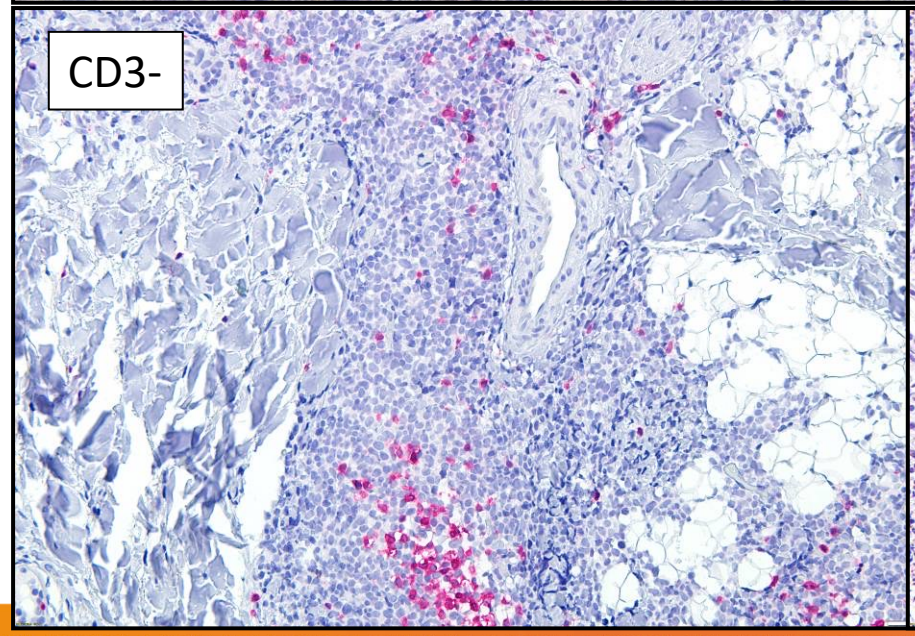

CD7+

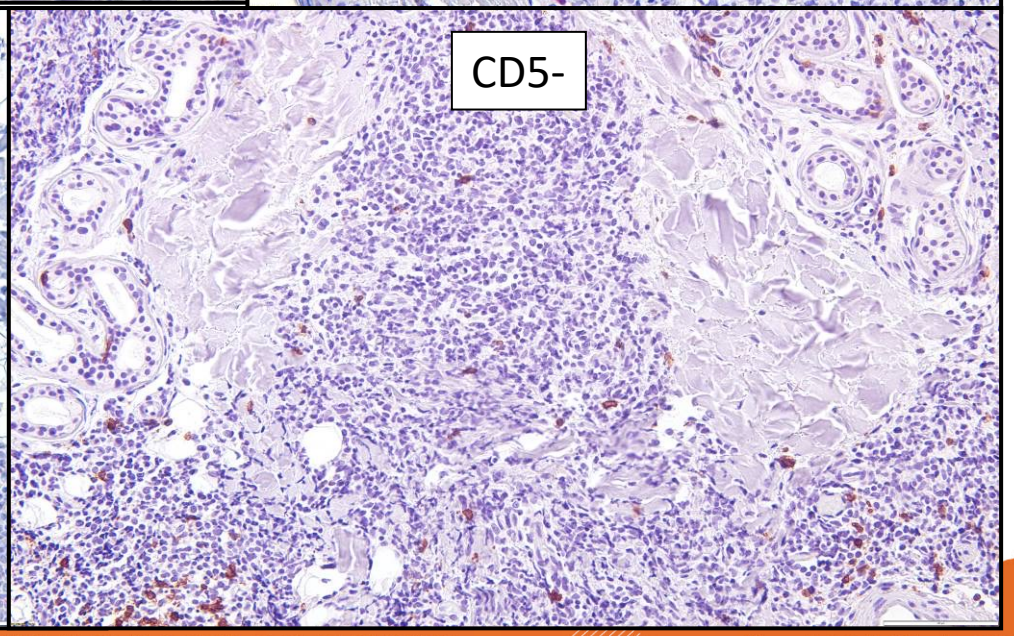

CD56+


TDT+


PAX5 -


CD20 -


CD3-


CD5-

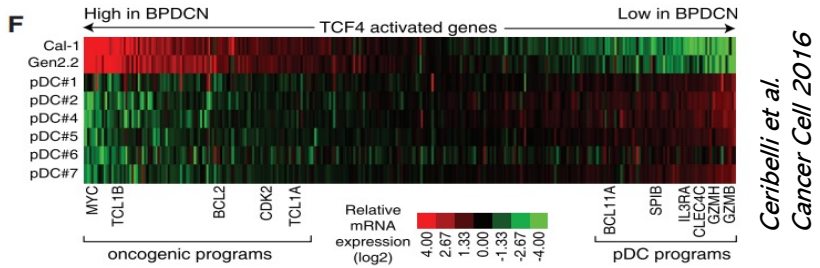
TCF4/E2-2 role in BDPCN development

- indispensable gene in the regulation of pDC development but also possible driver gene in the transformation of pDCs to BPDCNs and master regulator in BPDCNs

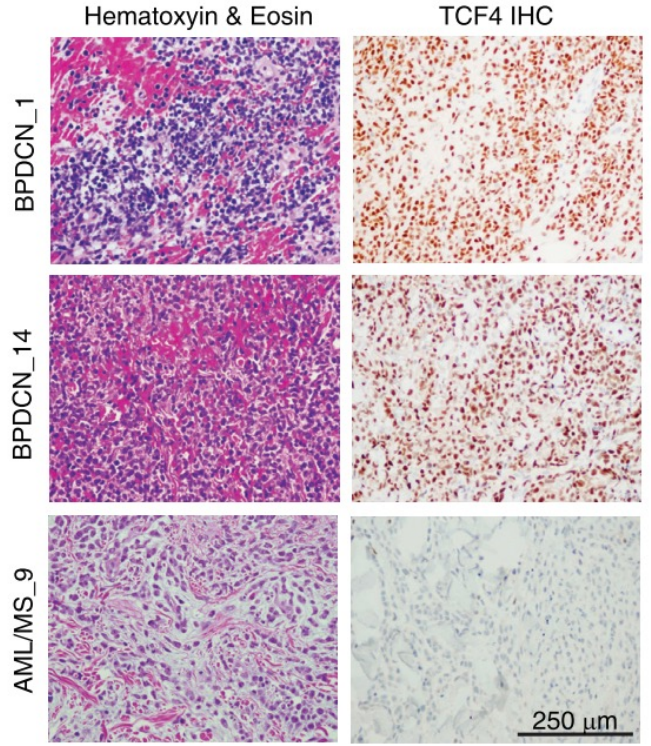
- TCF4 control several genes in the pcDC :
  some are oncogenes BCL2, TCL1A/B, MYC
  (at higher levels in BPDCNs than in pDCs)
  some are functional genes: BCL11A, SPIB, IL3RA, CLEC4C
  (at higher levels in pDCs than in BPDCNs)

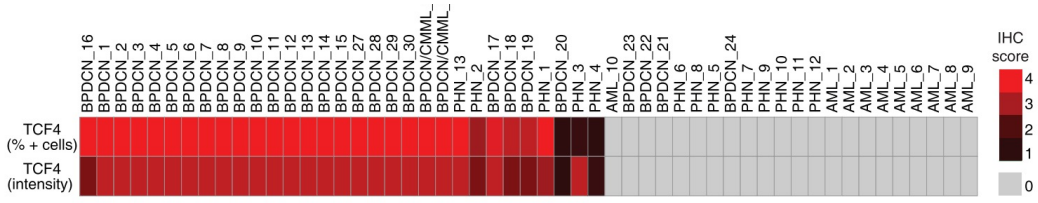
- TCF4-derived change in the gene-signature of BDPCN as opposed to normal/reactive pcDC: the pDC-specific function of TCF4 is impaired in BPDCN

- TCF4 IHC could aid in the differential diagnosis of BPDCN and AML



Ceribelli et al. Cancer Cell 2016

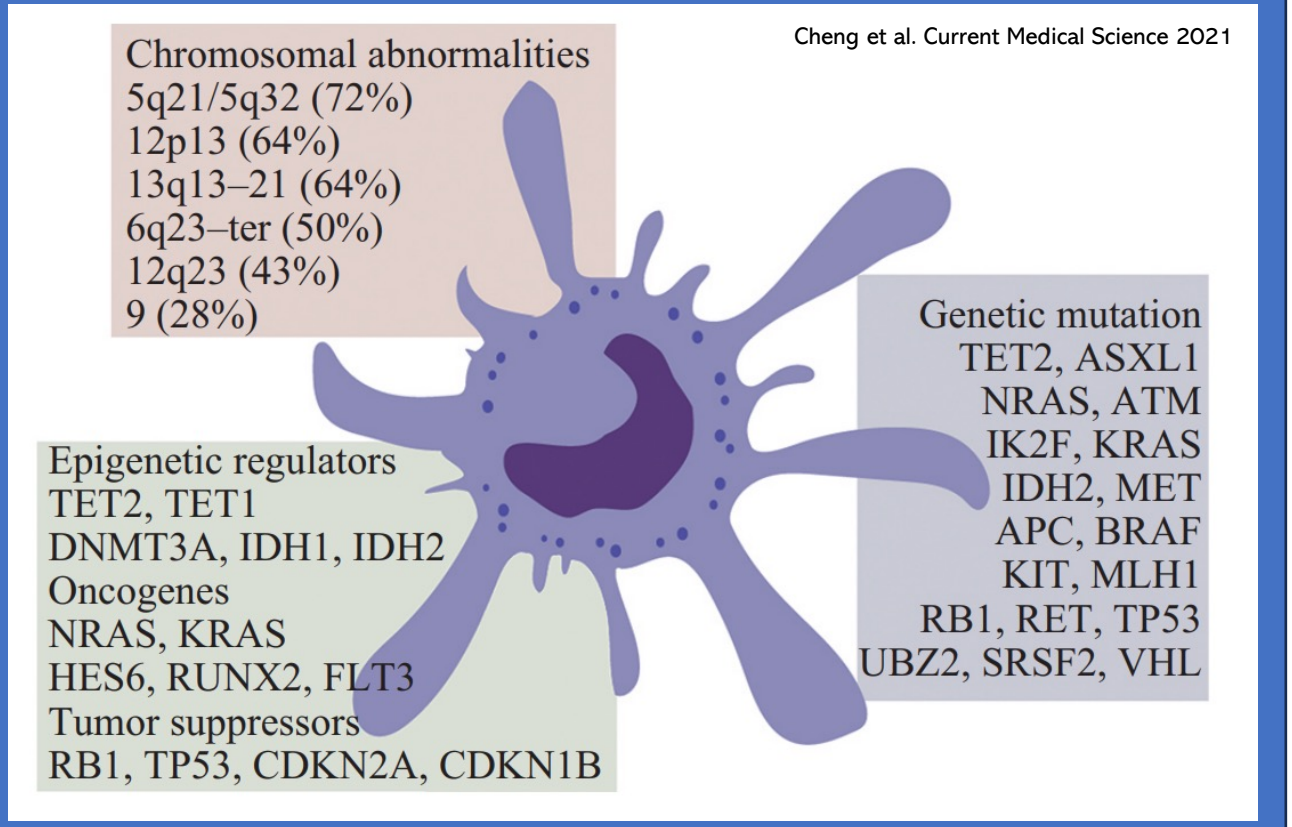




Ceribelli et al. Cancer Cell 2016

Cisse et al., Cell 2008; Nagasawa et al., 2008; Ghosh et al., 2010; Ippolito et al., 2014; Sasaki et al., 2012; Sawai et al., 2013; Schiavoni et al., 2002; Schotte et al., 2004; Tsujimura et al., 2003; Ceribelli et al. Cancer Cell 2016

>cytogenetic abnormalities; 75% complex karyotypes; “gain” >>“loss”



- rearrangement of MYC/8q24: 38% balanced translocation t(6;8)(p21;q24) (immunoblastic morphology)

Rearrangements of *MYB* (20%) and *MYBL1* (1%) >in children

- monoallelic and biallelic 12p13/ ETV6 deletions: also without detectable disease (early pathogenetic event)
- *DNMT3A, NPM1, FLT3* internal tandem duplication mutation: uncommon
- other low frequency events 4q34.1-4q34.2, 9p13.2-9p11.2, 9q12- 9q34.3, and 13q12.11-13q31.1

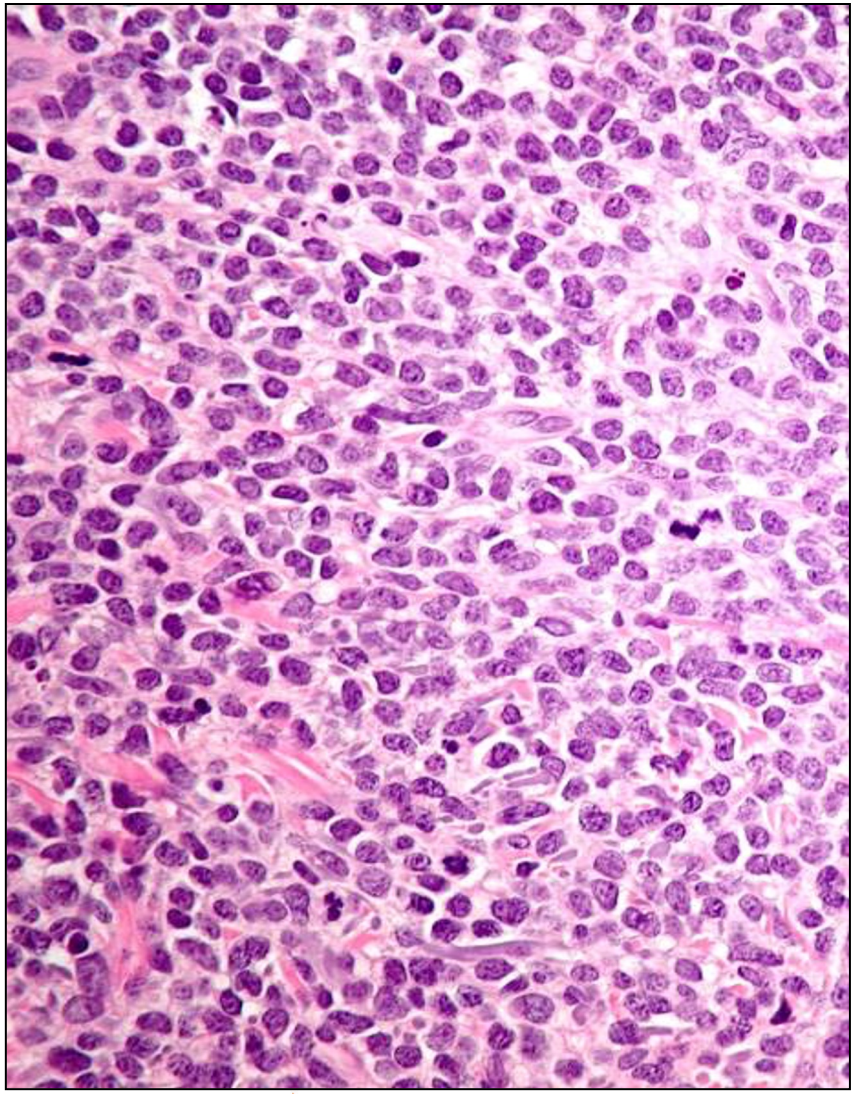
inattivazioni di geni tumore-soppressori (*RB1, TP53*, *CDKN2A*, and *CDKN1B*)
attivazioni di oncogeni (*NRAS, KRAS, HES6, RUNX2*, and *FLT3*)

Sapienza MR et al. HaematolOncol Clin North Am 2020; Sapienza MR et al. Hematol Oncol 2020;; Sapienza MR et al. Cancers (Basel) 2021; Renosi F et al. Cancers (Basel) 2022; Cheng et al. Current medical science 2021; Khoury et al. Leukaemia 2022; Alayed et al., 2013; Dijkman et al., 2007; Jardin et al., 2009, 2011; Lucioni et al., 2011; Menezes et al., 2014; Sapienza et al., 2014; Stenzinger et al., 2014); Sakamoto K et al. Leukemia, 2018; Sumarriva Lezama L et al. Histopathology, 2018; Yu YT, Blood 2022; Tang Z et al. Leuk Res, 2018

Differential diagnoses

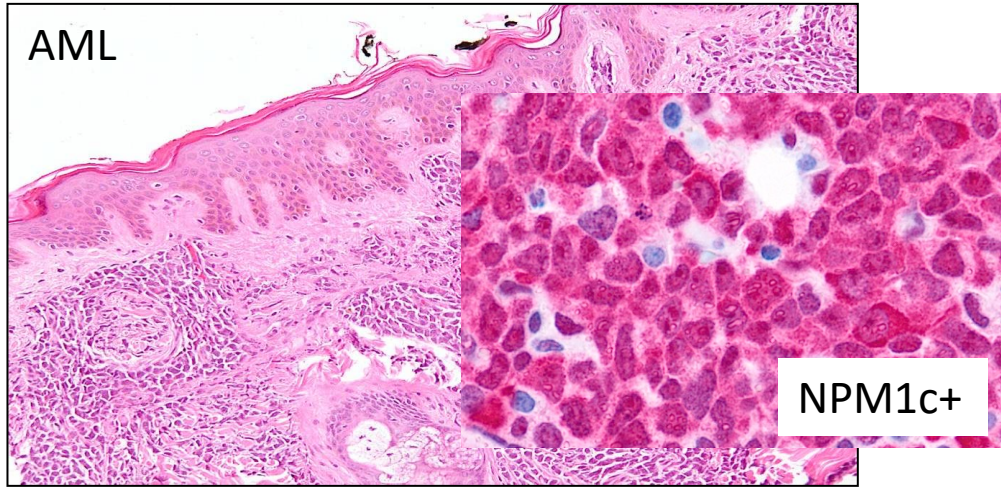
Blastoid cytology, mitoses, high Ki67: malignant disease
(cytology can be misleading in mild infiltrate, but Ki67 should help)

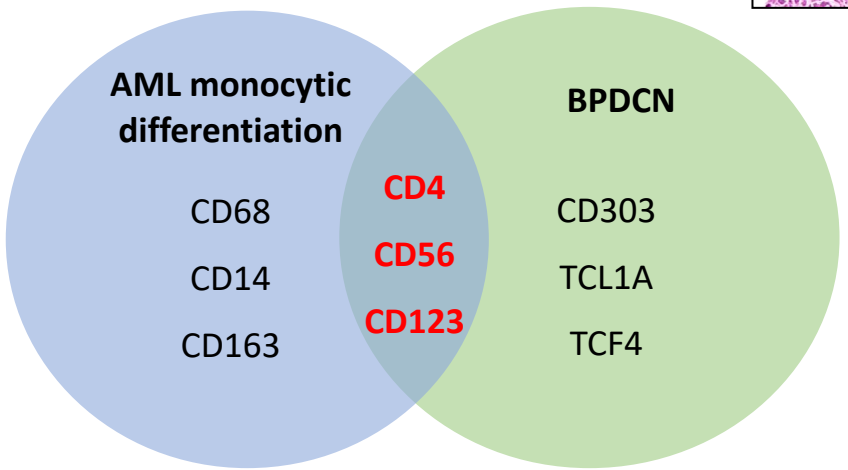
expression of «haematologic» molecules (CD45)
differential diagnosis with haematologic neoplasms
(myeloid or lymphoid/precursor or peripheral



(1) AML with pDC-like phenotype

- CD123+/CD4+/CD56+ (pDC-like) phenotype can be observed in AML negative for specific pDC markers (TCF4, CD303, TCL1)
- >AML with myelomonocytic/monocytic differentiation w/wo NPM1 mutation; NPM1mutatedAML with pDC-like phenotype bear worse prognosis AML-Mo/NMP1mut
- can present with skin lesions and is mostly CD34 negative





(2) AML with mixed/ambiguous phenotype

- Need to express lineage specific marker (CD3/CD19) and MPO, whihc must be negative in BPDCN

(3) B- ot T- precursor leukaemia/lymphoma

- For the possibile expression of TdT and T/B associated markers and lack of specific myeloid antigens/CD34

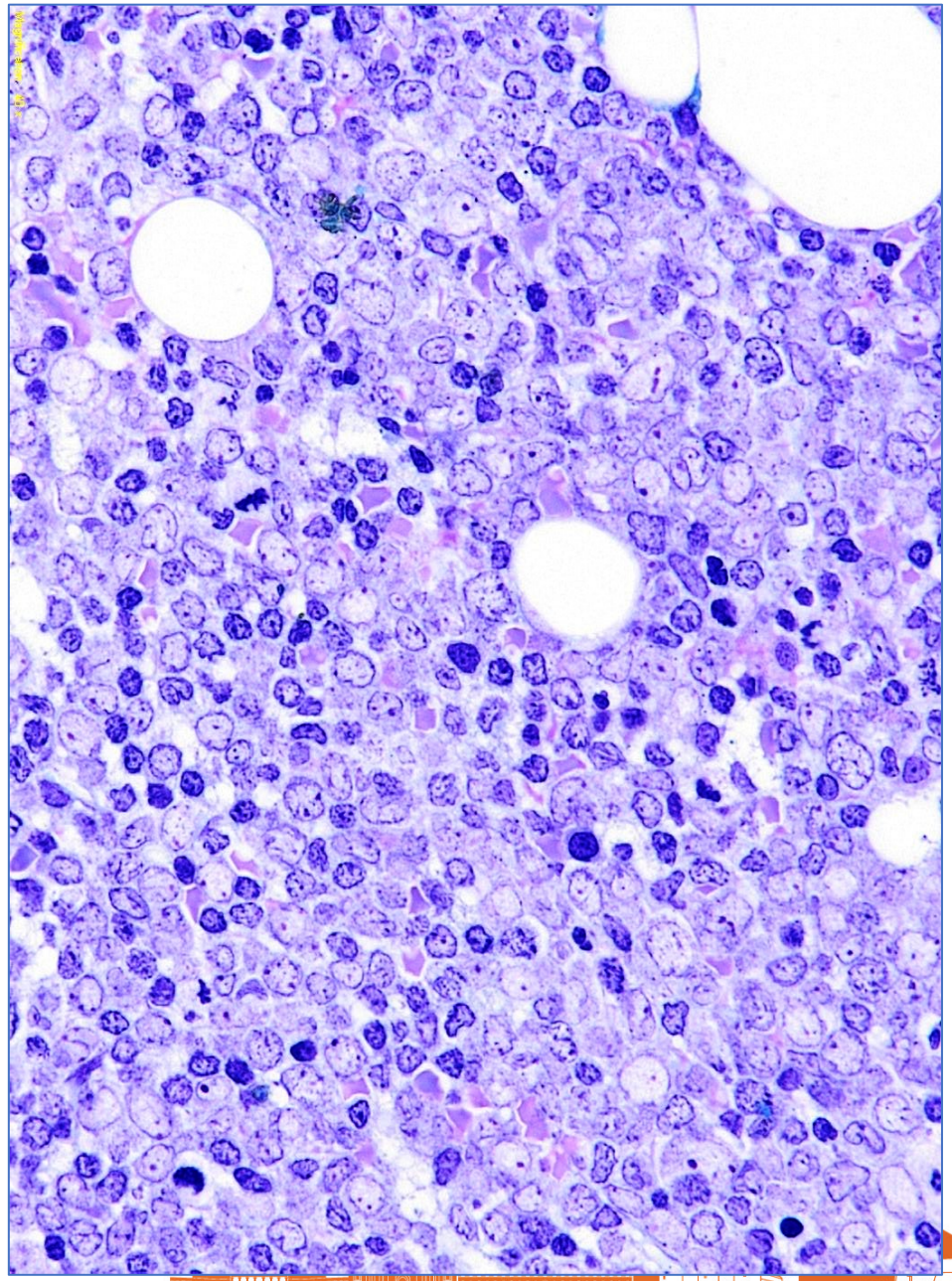
(4) MN with pDC differentiation (pDC-AML)

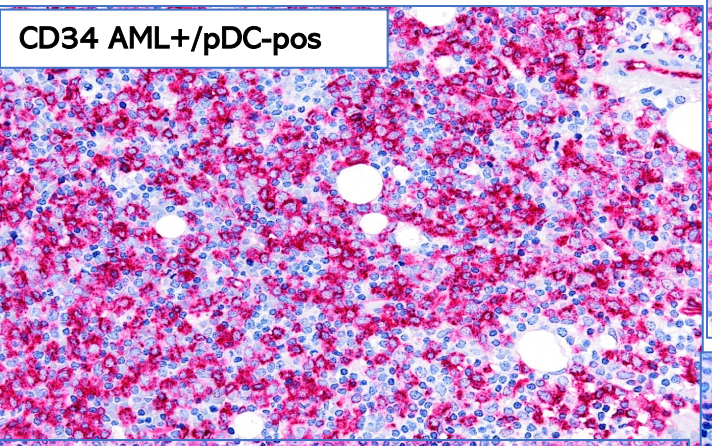
3-5% AML; pDC confers worse prognosis; *no skin lesions*
clonally expanded pDCs (pDC-AML) and related with the AML blasts

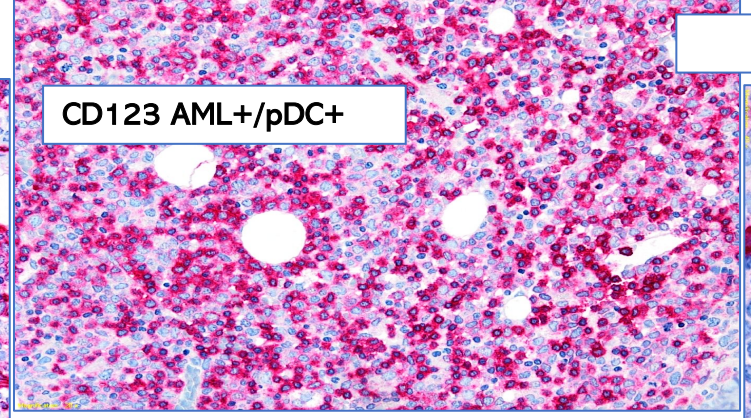
70% in association with AML with RUNX1 mutations (remaining: RUNX1-wild type, TP53mut; CD2pos); DNMT3A, BCOR,FLT3 mutations; TET2 rare

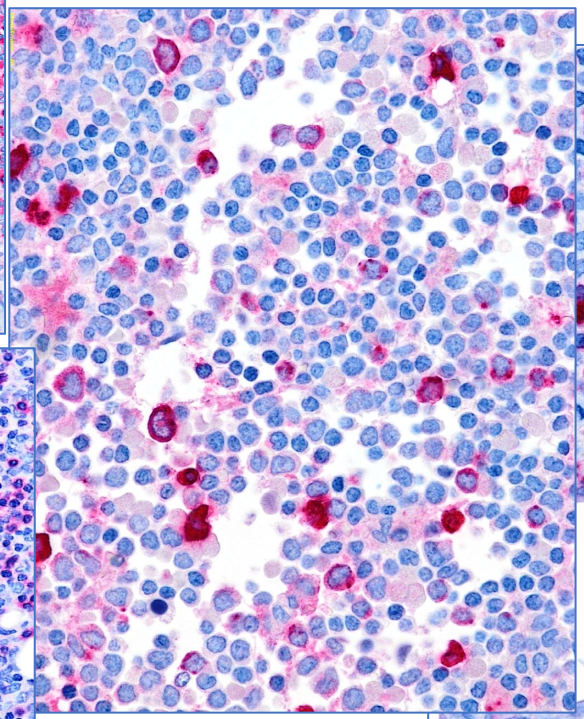
Predominant AML (blasts) usually with immature phenotype (CD34/TdT/HLA-DR, CD117pos); more rarely with myelomonocytic differentiation; negative pDC markers (*possible CD123*)
+
Minority (6.6% of all leukaemic cells) of pDC morphologically "mature/mildly blastoid"; interstitial, *no nodular aggregation*; clonally related to leukaemic blasts [spectrum from early immature pDCs (CD34+, CD303 dim/-) to mature pDCs (CD34-, CD303+)]; CD123+, T markers +/- >negative CD56/TCL1

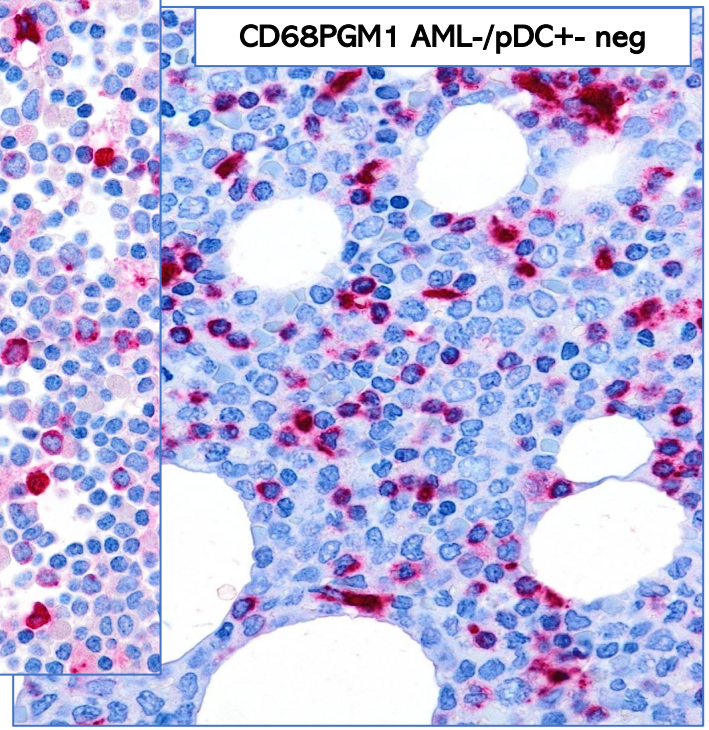
DD BDPCN
CD34-/TCL1+/CD56+;
skin lesions;
RUNX1 mutations very rare; > TET2 mutations

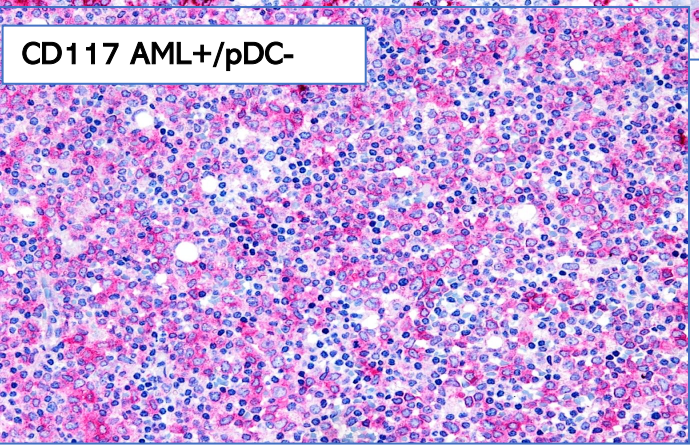


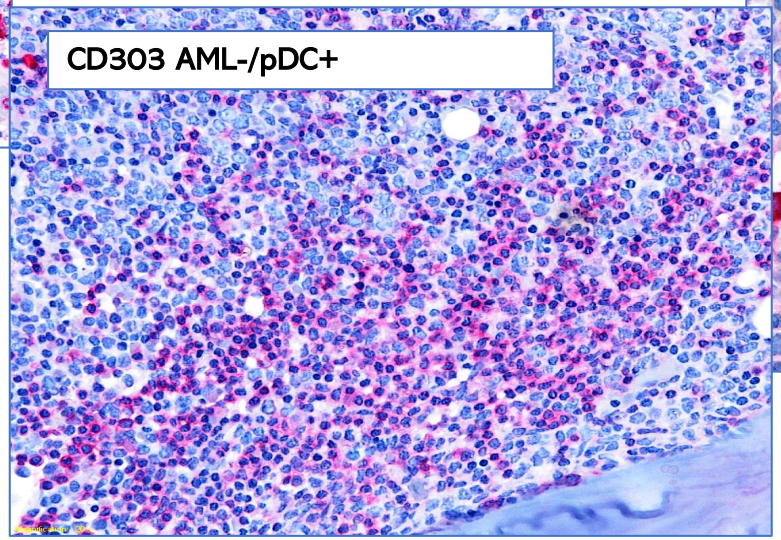

CD34 AML+/pDC-pos

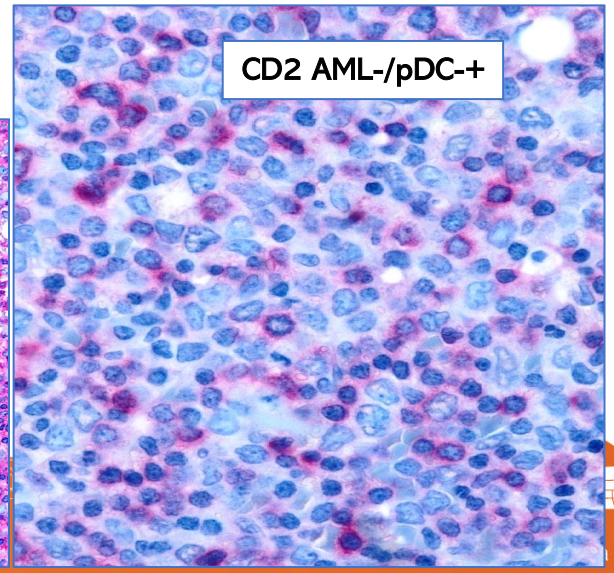

CD123 AML+/pDC+

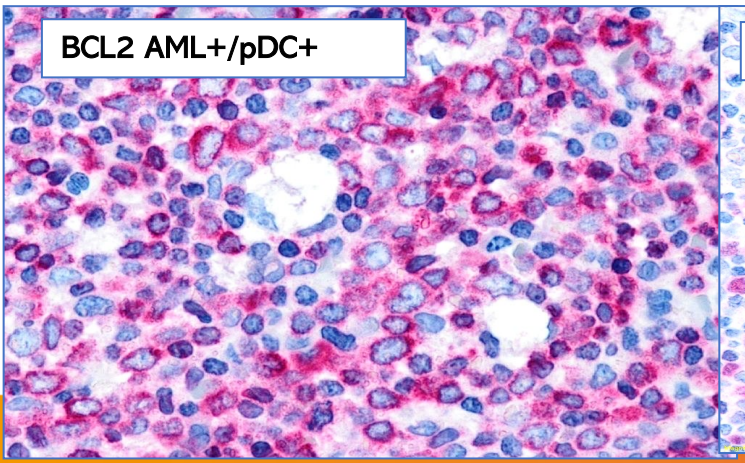

MPO AML-/pDC-

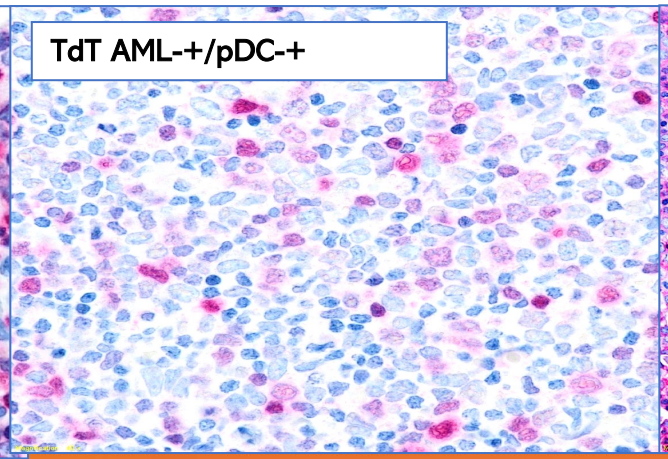

CD68PGM1 AML-/pDC+- neg

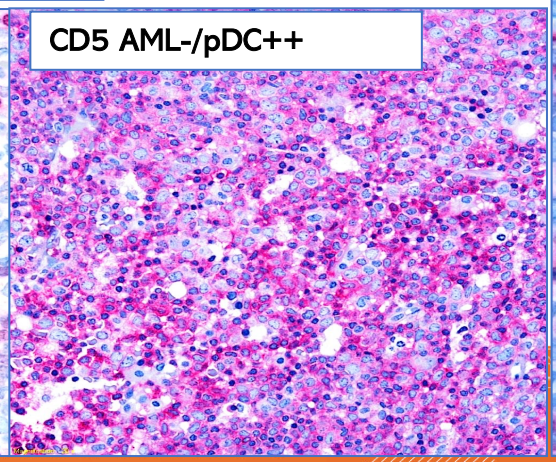

CD117 AML+/pDC-


CD303 AML-/pDC+


CD2 AML-/pDC-+


BCL2 AML+/pDC+

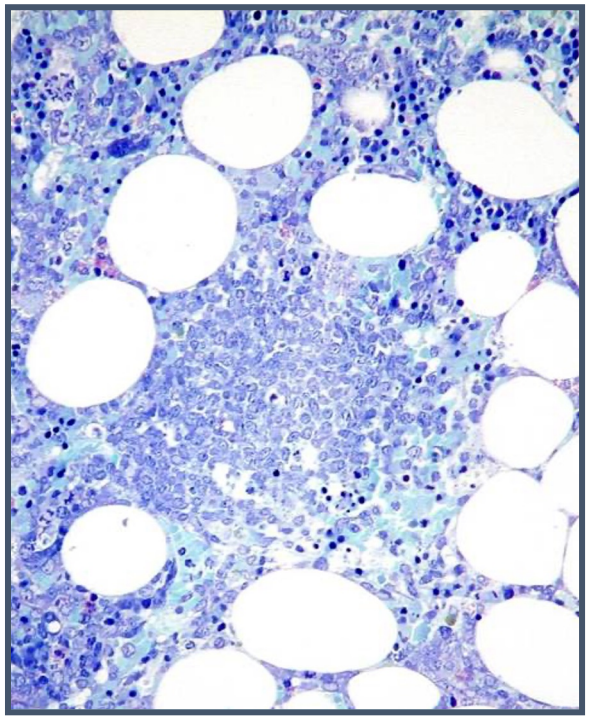

TdT AML-+/pDC-+


CD5 AML-/pDC++

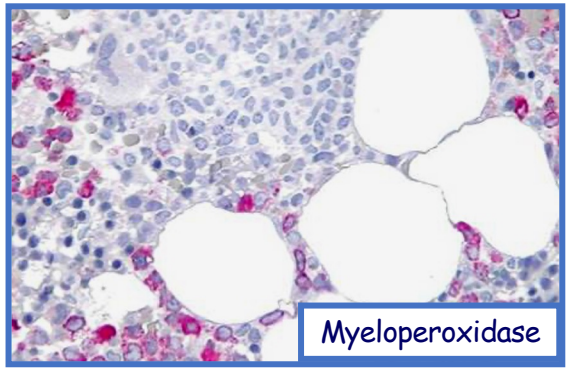
(5) Myeloid Neoplasm associated with proliferation of mature PDC

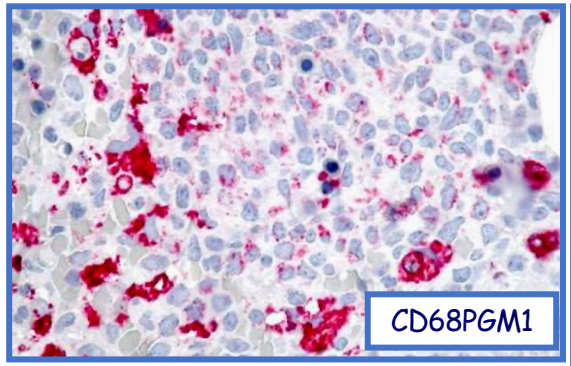
- predominantly male, the median age is 69-72 year
- Associated with MN: chronic myelomonocytic leukaemia (CMML) most frequently (>in RAS mutCMML; increased number of pDC correlate with higher risk of leukaemictransformation also AML (4.9%), MDS, MPN
- Reported to be clonally related to the underlying MN
- Cytologically bland looking/not blastic; in aggregates in bone marrow, skin (clusters surrounding vessels or adnexa, in the upper dermis with abundant T cells) or more rarely in lymph nodes
- Mature phenotype: CD123, TCF4, CD2AP, SPIB, CD303, CD304 and MX1.
  - Aberrant loss of markers expressed on normal pDCs (e.g., CD303 and TCL1): desirable
  - Absence/low partial expression of CD56 (mostly weak; usually neg)
  - Possible rare TdT

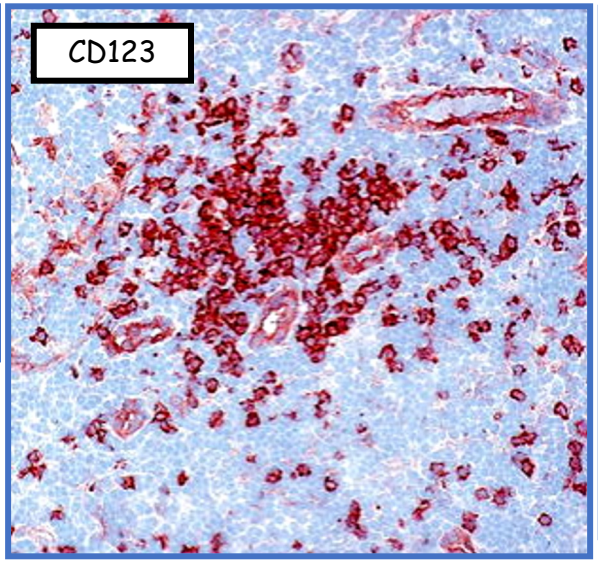
  Ki-67 low
- Presence of mature pDC can add additional therapeutic targets (immunomodulatory drugs, lenalidomide, anti –CD123)

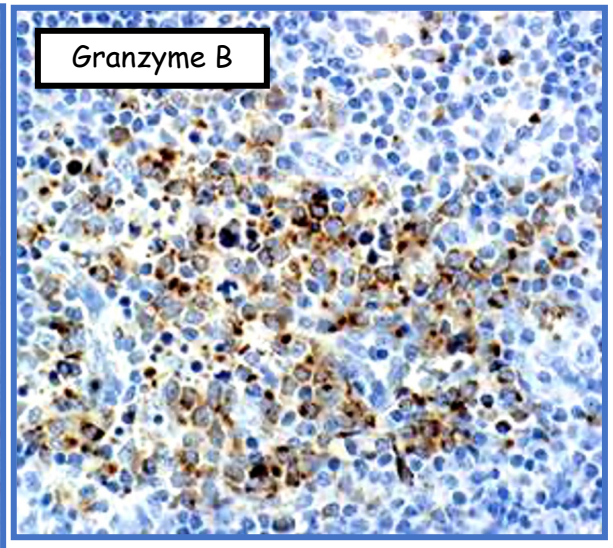


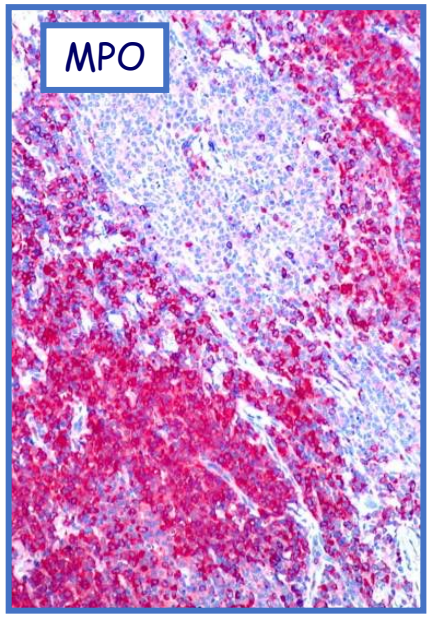
WHO 2022
Desirable:
Aberrant pDC immunophenotype
Absence or low/partial expression of CD56

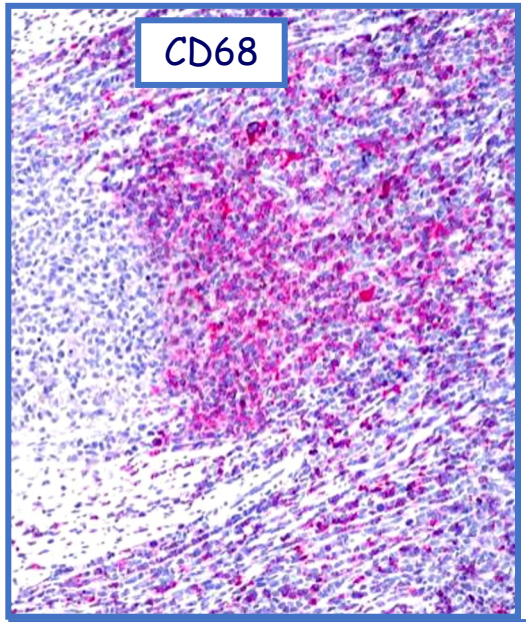


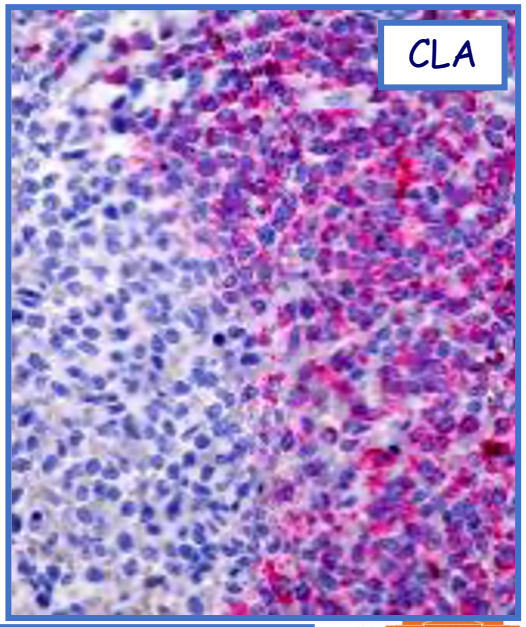












intestinal MS (inv16) Pileri 2007

BPDCN is rare and awareness needs to be raised

- In skin

consider BPDCN in
cytologically blastic/blastoid neoplasm, with mitoses/high Ki67
expression of «haematologic» molecules (CD45)
(when considering any type of HN)
In bone marrow

- Apply wide panel of markers

including at least specific markers + expected negative markers
(CD68PGM1 and Bcl2 are also suggested)

- remember that CD123+/CD4+/CD56+ is not sufficient for a BPDCN
and few BPDCN can be CD56 negative

- In case no full panel of markers is available do not sign out for «any-type AML» but highlight the possibility of a BPDCN and ask/suggest for second opinion