OTTIMIZZAZIONE DELLA STRATIFICAZIONE PROGNOSTICA

EMILIO BERTI MD

GIA' PROF ORDINARIO DI DERMATOLOGIA UNIVERSITA' DEGLI STUDI DI MILANO e FONDAZIONE Cà GRANDA IRCCS OSPEDALE MAGGIORE POLICLINICO MILANO

4.2.1.2: Blastic plasmacytoid dendritic cell neoplasm

Definition

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a haematological neoplasm consisting of immature cells with plasmacytoid dendritic cell differentiation, characterized by a high frequency of cutaneous involvement and systemic dissemination.

Related terminology

Not recommended: Blastic NK-cell lymphoma; Agranular CD4+ NK leukaemia; Blastic NK leukaemia/lymphoma; Agranular CD4+ CD56+ haematodermic neoplasm/tumour

Localization

The skin is most commonly involved (60-95% of patients) {29795241; 31869411; 31243042; 26056082; 32336414}, followed by bone marrow and lymph nodes {23940084; 31243042}. A leukaemic phase is common, with or without tissue involvement {34884997}.

Clinical features

Patients most commonly present with skin lesions, which vary in size, color (violaceous, contusiform, brown, xanthochromic), and form (solitary or multiple patches, plaques and nodules). The lesions are usually nonpruritic, with a trend to involve the upper thorax, head and neck, and upper extremities {31243042; 24441662; 32336415}. Mucosal lesions are uncommon but may be identified particularly in the oral cavity {23646868}.

Epidemiology

BPDCN is rare, with an estimated incidence of 0.04 cases per 100,000 individuals in the United States of America {30189324}. Although the disease can affect all ages and a bimodal age distribution pattern has been observed {30189324}, it most commonly occurs in elderly patients in the seventh decade (median, 62-70 years), with 4-6:1 male-to-female predominance {34884997; 31869411; 33027528; 31243042; 31261288; 29795241; 20663945

Pathogenesis

BPDCN cells derive from resting, non-activated pDCs with aberrant NF-κB pathway activation {31811114; 24504027}, and they appear to have defective type I interferon signaling postulated to be related to E-cadherin expression {34081040}. The E-box transcription factor TCF4 (previously E2-2) plays an obligatory role as a master regulator in BPDCN cells under control of the bromodomain and extra-terminal domain (BET) protein BRD4 {27846392}.

In the Japanese population, 8q24 (*MYC* locus) translocation, most frequently with 6p21 (*RUNX2* locus), is found in 38% of patients, and is associated with immunoblastoid cytomorphology and MYC overexpression {29795241}.

Histopathology

In the skin, the neoplastic infiltrate of BPDCN is usually centered in the dermis with extension to subcutaneous tissue, while sparing of the epidermis and adnexal structures {19956058}. BPDCN is characterized by a diffuse monotonous infiltrate of medium-sized immature blastic cells. These cells usually have scanty cytoplasm, eccentric nuclei with slightly irregular nuclear contours, fine chromatin, and one to several inconspicuous nucleoli. In some cases, neoplastic cells may have an immunoblastoid morphology while in others they may have lymphoid-like features. Mitotic figures are variable, and necrosis can be present {31869411; 30350260}. Intratumoural erythrocyte extravasation is a consistent finding.

Immunophenotype

CD123 (interleukin-3 receptor α-chain) expression is a characteristic feature of BPDCN, as is strong, uniform expression of TCF4 {27846392; 31261288}. Although rare, some cases of BPDCN lacking CD123 or other markers (e.g. CD5, CD56) have been reported {29795241; 34884997}. Other commonly expressed pDC antigens include TCL1, CD2AP, SPIB, CD303, CD304, E-cadherin and MX1 {24441662; 18218851; 12576313; 23165482; 34081040}. BPDCN cells are usually positive for CD4, CD56, and HLA-DR. The Ki-67 proliferation index is typically high. Absence of strong expression of lymphoid or myeloid lineage-specific markers is expected, specifically CD3, CD14, CD19, lysozyme and myeloperoxidase. CD1a, CD15, CD25, CD34, CD41, CD64, CD113, and myeloid cell nuclear differentiation antigen (MNDA) are usually negative {32241840; 29795241; 26796502; 31869411}.

Differential diagnosis

A subset of AML may show clinical, morphologic, and immunophenotypic overlap with BPDCN, including high-level coexpression of CD4, CD56, and CD123. Demonstration of TCF4, CD303 and/or TCL1 expression in this context, coupled with absence of strong expression of lineage-specific markers, usually helps establish the diagnosis of BPDCN.

Title: Immunophenotypic diagnostic criteria of blastic plasmacytoid dendritic cell neoplasm.

Expected positive expression:
CD123*
TCF4*
TCL1*
CD303 *
CD304*
CD4
CD56

Expected negative expression:
CD3
CD14
CD19
CD34
Lysozyme
Myeloperoxidase

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.

Diagnostic molecular pathology
No specific molecular or cytogenetic tests are required to make a diagnosis of BPDCN.

Essential and desirable diagnostic criteria
Essential:
•Immature cells with blastoid morphology and pDC differentiation

Desirable:
•Absence of lymphoid or myeloid lineage markers.
•Absence of CD34 expression.
•High Ki-67 proliferation index.

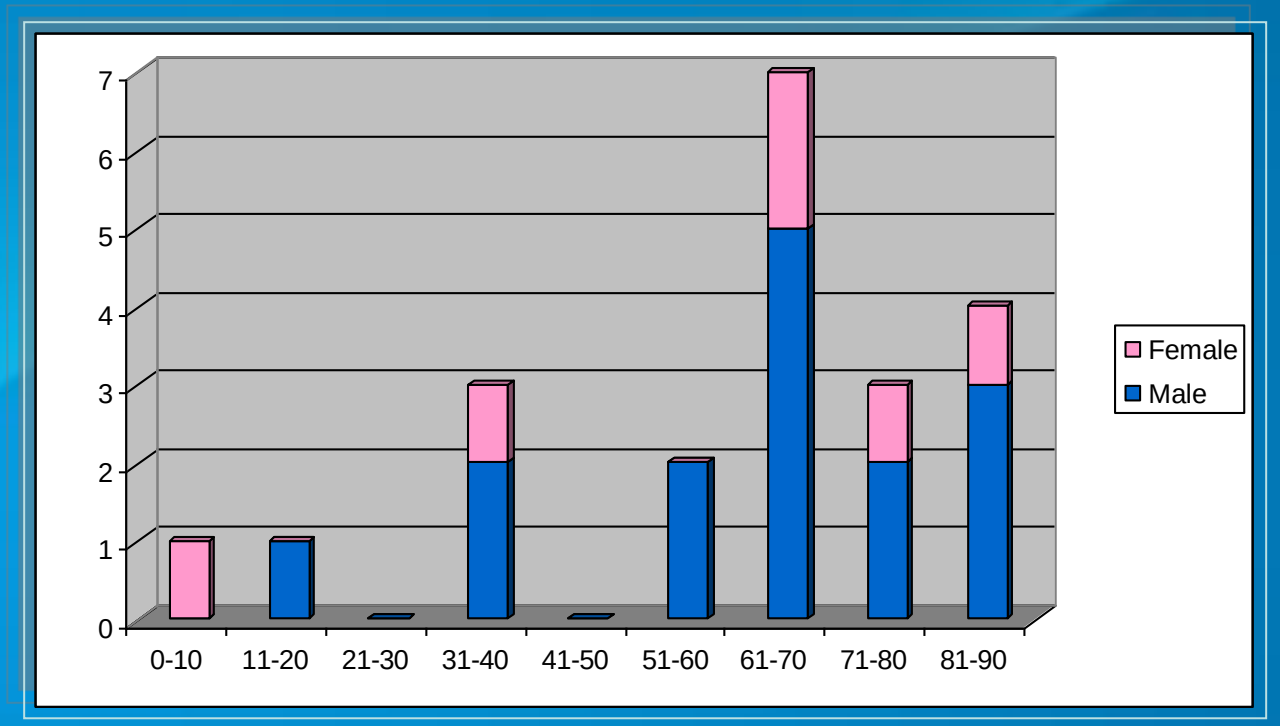
Staging
Not relevant

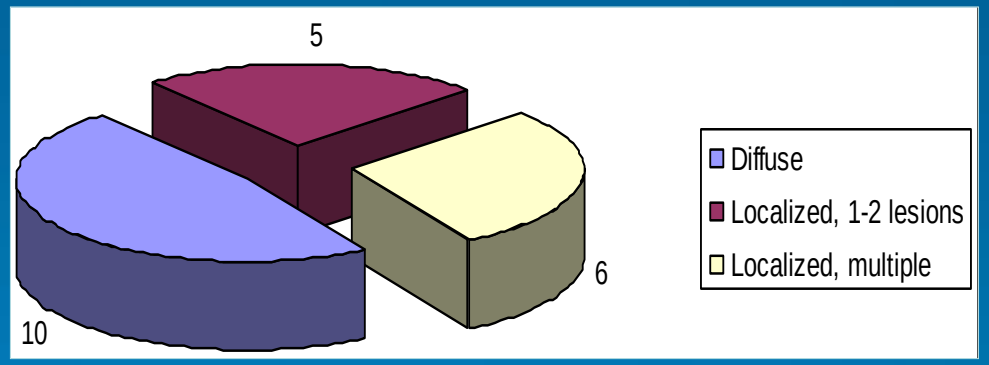
Prognosis and prediction

There is no significant difference in outcomes between patients who present with skin-only versus systemic involvement by BPDCN {31243042}. Treatment with CD123-targeted agents has improved overall response rates and overall survival {31018069; 34226167}; however, treatment with cytotoxic chemotherapy remains a mainstay in combination with targeted therapy {35061885}.

Patient Selection

- 21 BPDCN cases (15 males, 6 females)
- median age 60,6 years
- range 9-84 years



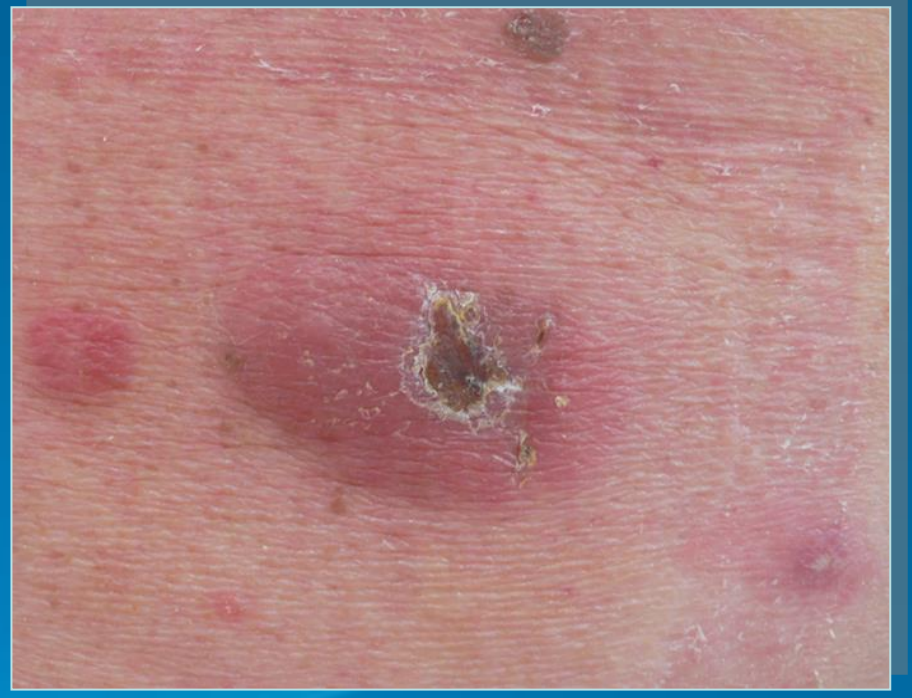


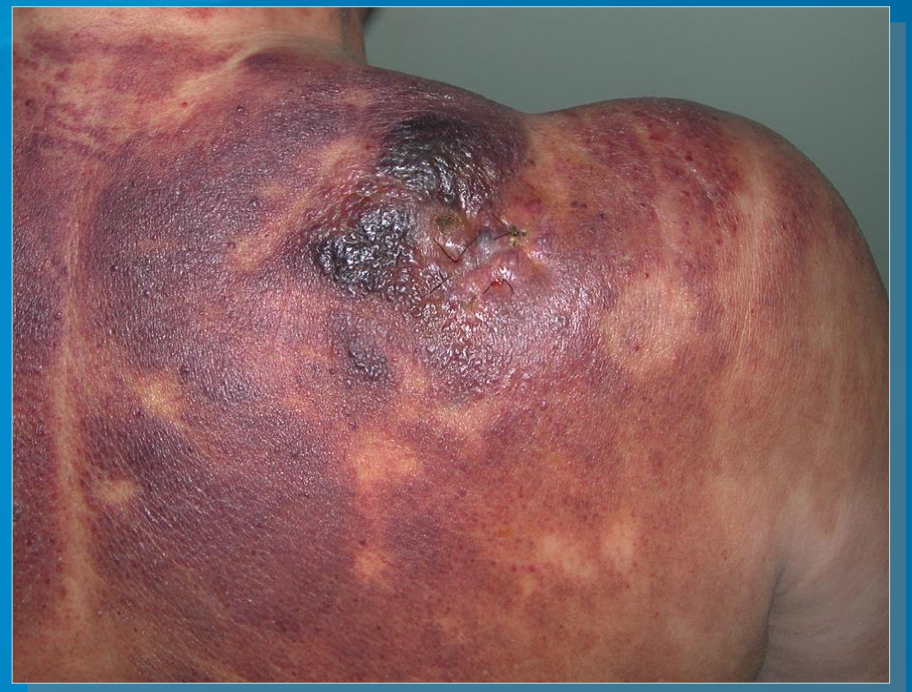
- Extra-skin: 12 cases
- Therapy: 19 pts

  8 ALL-type CHT; 1 AML-type CHT; 4 lymphoma-type CHT; 1 mono-CHT; 1 mono-CHT&RT; 2 RT; 2 BMT. At relapse, 2 of the patients treated by CHT underwent BMT

- Median survival: 21 mo

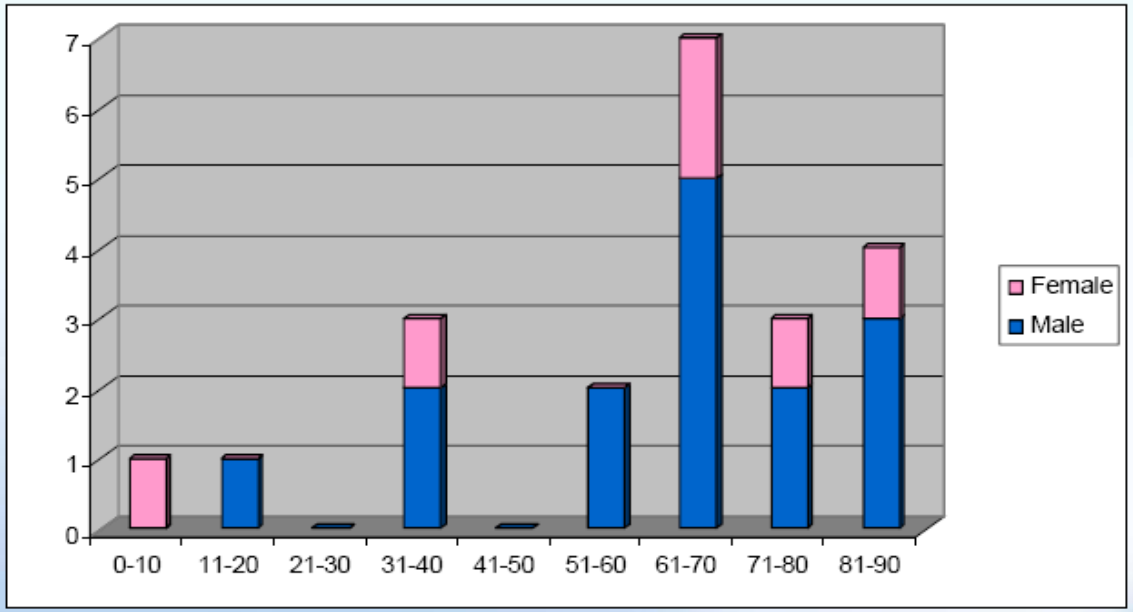
  10 DOD (1-35 mo)
  2 TRD (12, 60 mo)
  3 AWD (4, 8, 72 mo)
  6 ADF (3, 5, 12, 13, 14, 26 mo)

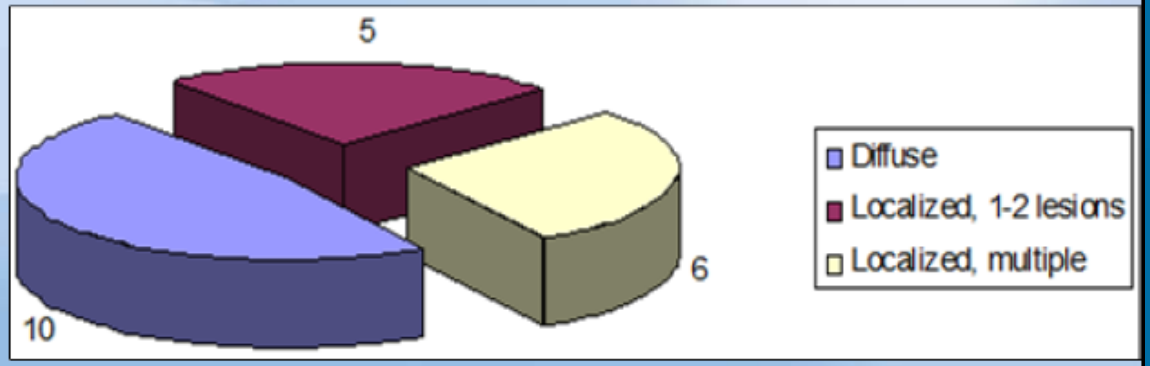




Casistica

- 21 casi
- Materiale criopreservato
- Età mediana: 60.6 (9÷84)
- Malattia extra-cutanea: 12
- Terapia
  - 8 ALL-type
  - 1 AML-type
  - 4 NHL-type
  - 1 mCHT; 1mCHT+RT; 2RT
  - 2 BMT (+2@recidiva)



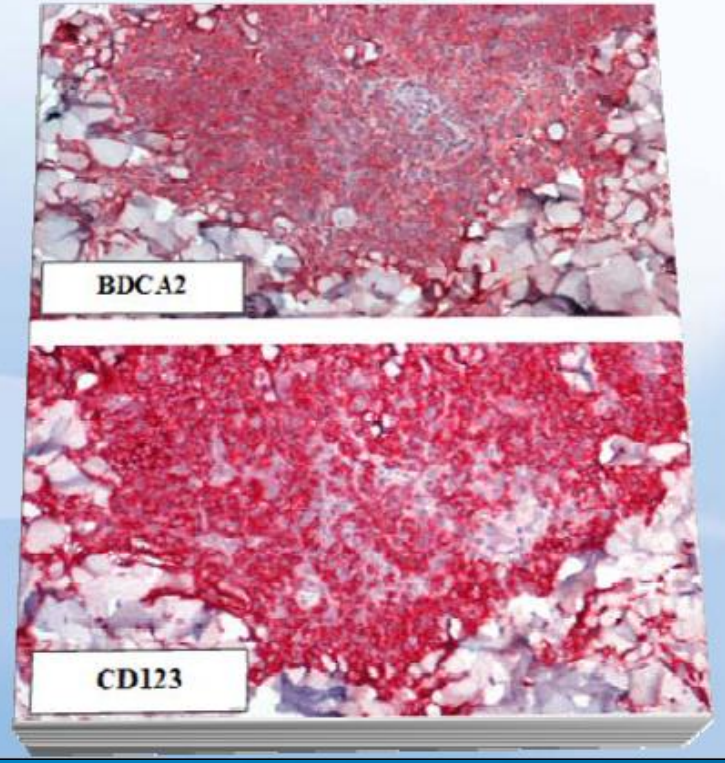


Immunofenotipo

Positive[a]
CD2, CD4, CD7, CD33, CD38, CD43, CD45RA, CD56, CD68 (a), CD117, CD123, BDCA-2/CD303, CD2AP, TCL1, BCL11a, CLA/Cutaneous lymphocyte antigen, MxA, TdT
Negative
CD1a, CD3, CD5, CD8, CD10, CD11c, CD13, CD14, CD16, CD19, CD20, CD21, CD23, CD25, CD30, CD34, CD45R0, CD57, CD138 Immunoglobulin (surface and cytoplasmic), LAT (Linker for activation of T-cells), Lysozyme, Myeloperoxidase, Neutrophil elastase, Perforin, T-cell receptor-AB and -GD, TIA-1, ZAP70

[a]In normal PDC expression is constantly diffuse, while in neoplastic PDC it is variable, punctate and limited to the Golgi region; [b]Granzyme B is rarely found in BPDCN on tissue sections; [c]Except for CD56, the expression of CD2, CD7, CD33, CD38, CD117 and TdT is inconstant; CD33 was found in normal circulating PDC in a single study.[32]

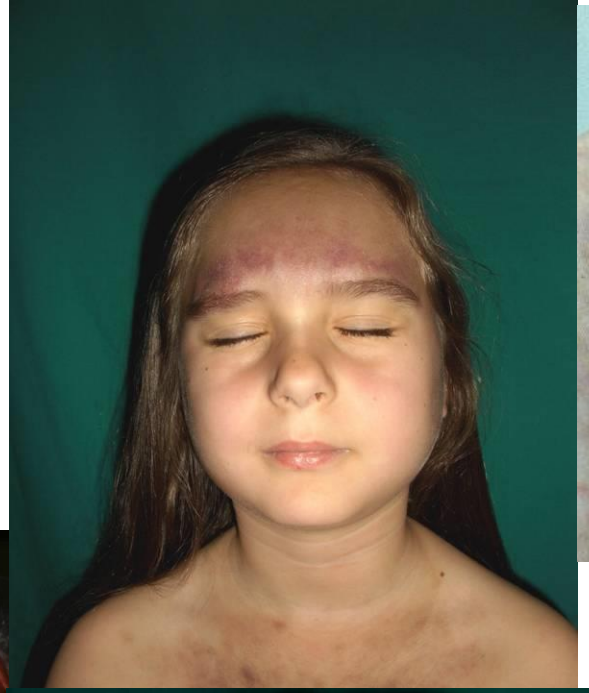
- 3 casi (14%): CD4- e/o CD56-
- 9 casi (43%): CD2+ e/o CD7+
- 3 casi (14%): TdT+

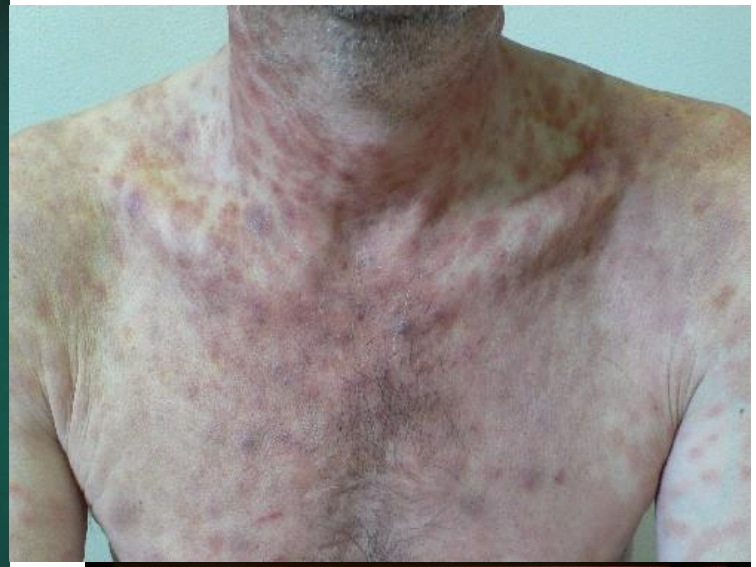


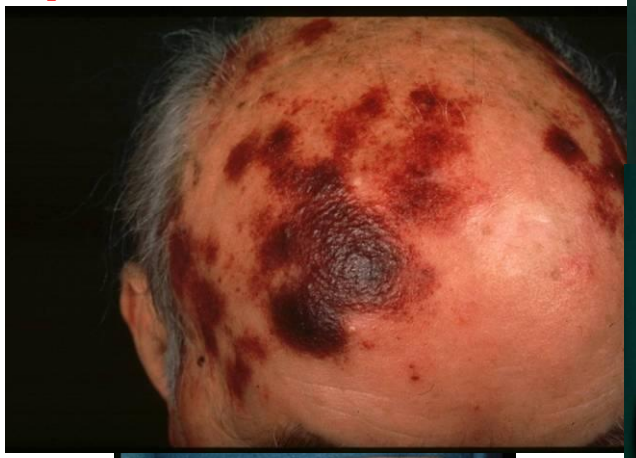
Facchetti F, et al. Hematology Meeting Reports. 2009;3(3):1-3

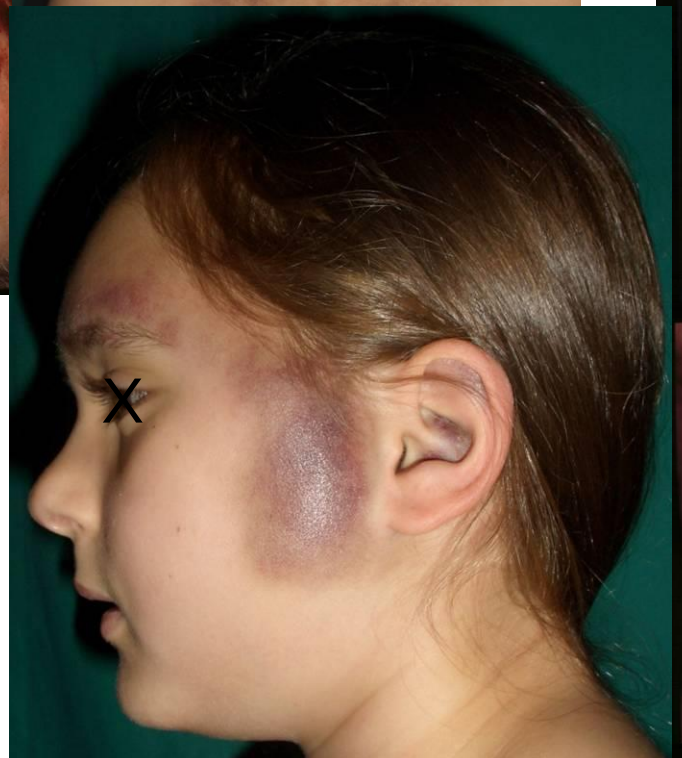
Ontogeny:

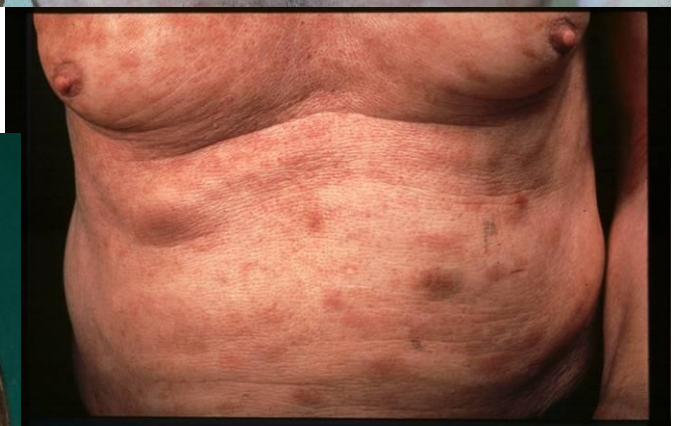
Plasmocytoid type 2 dendritic cell (DC2) precursor, possibly related to common myeloid precursor cell

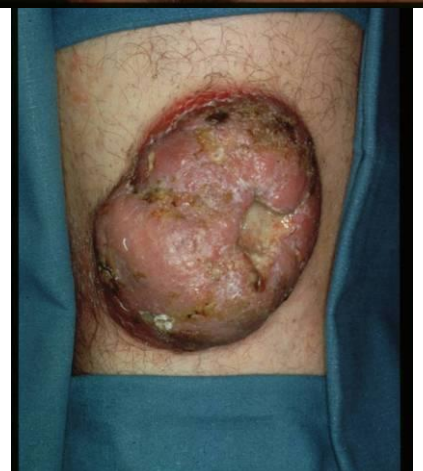


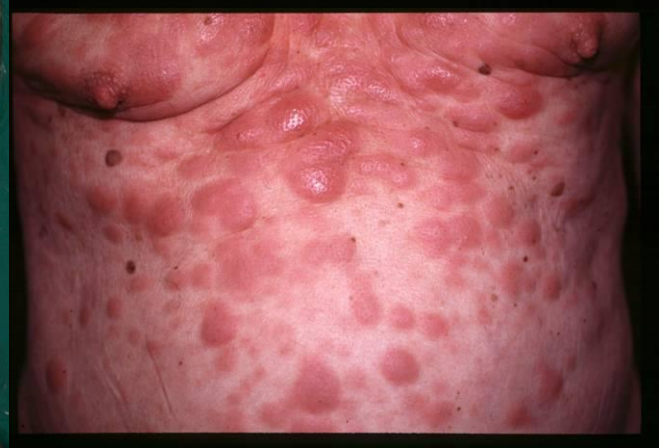


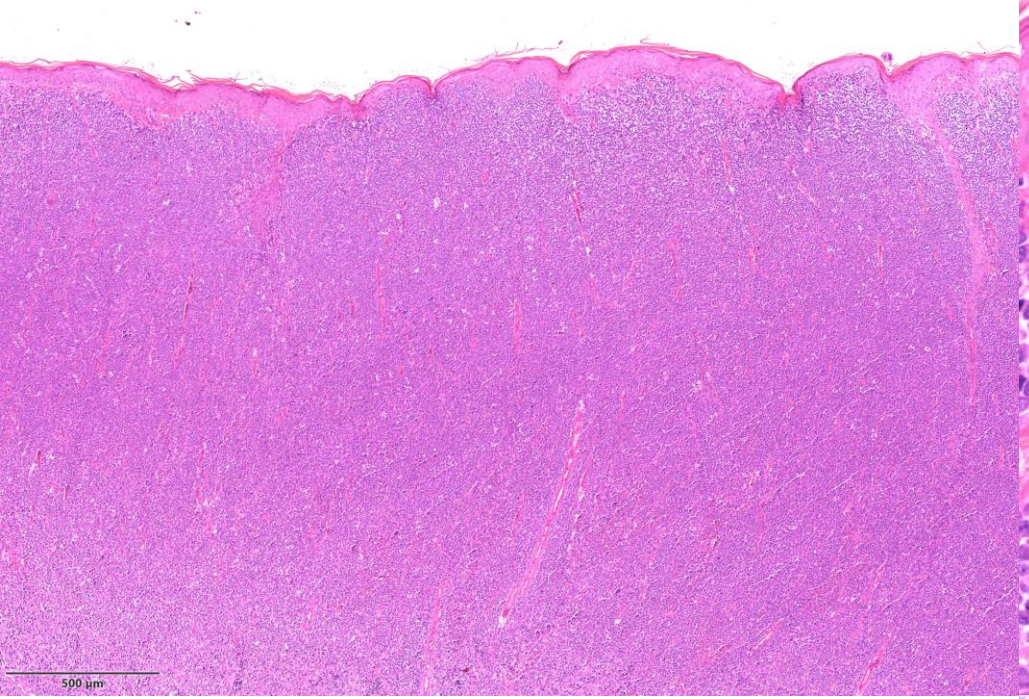


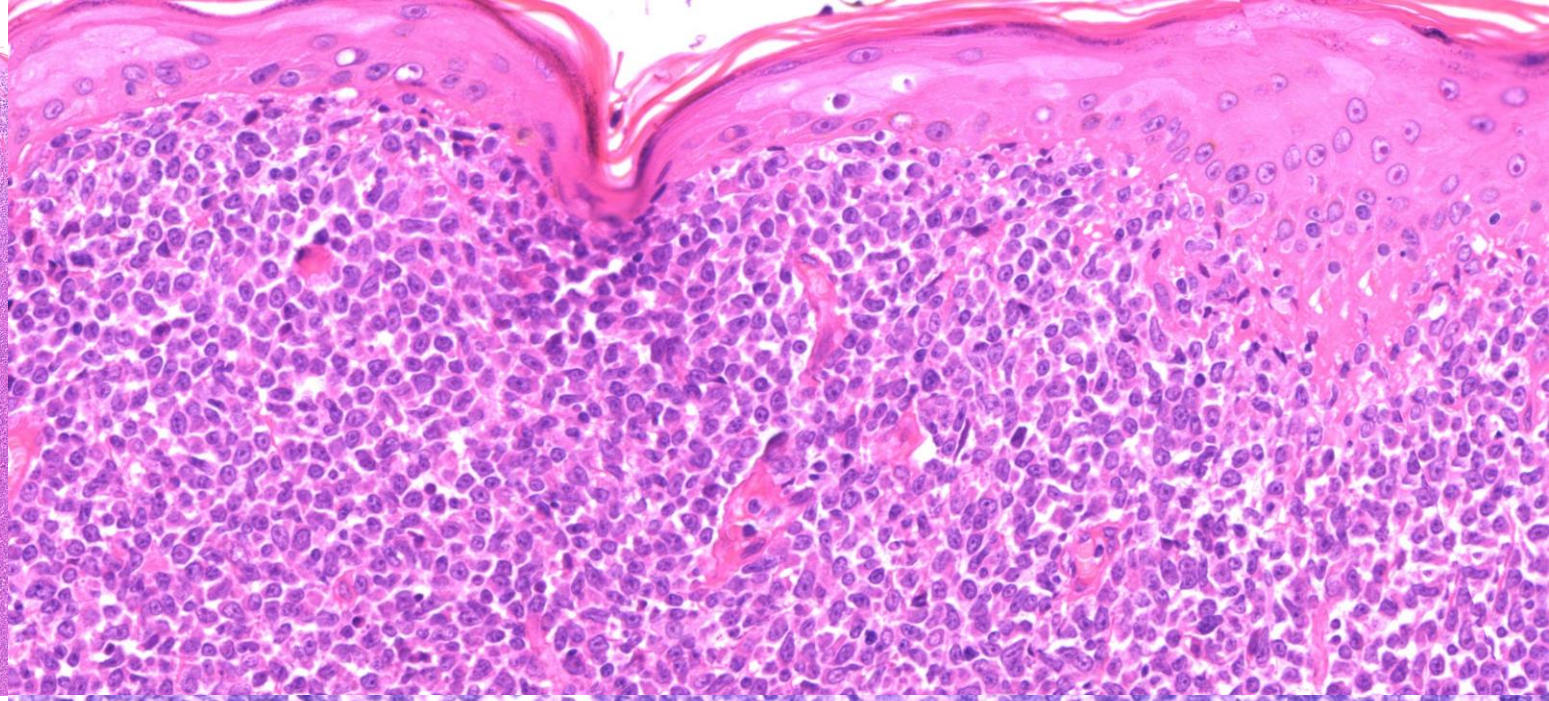


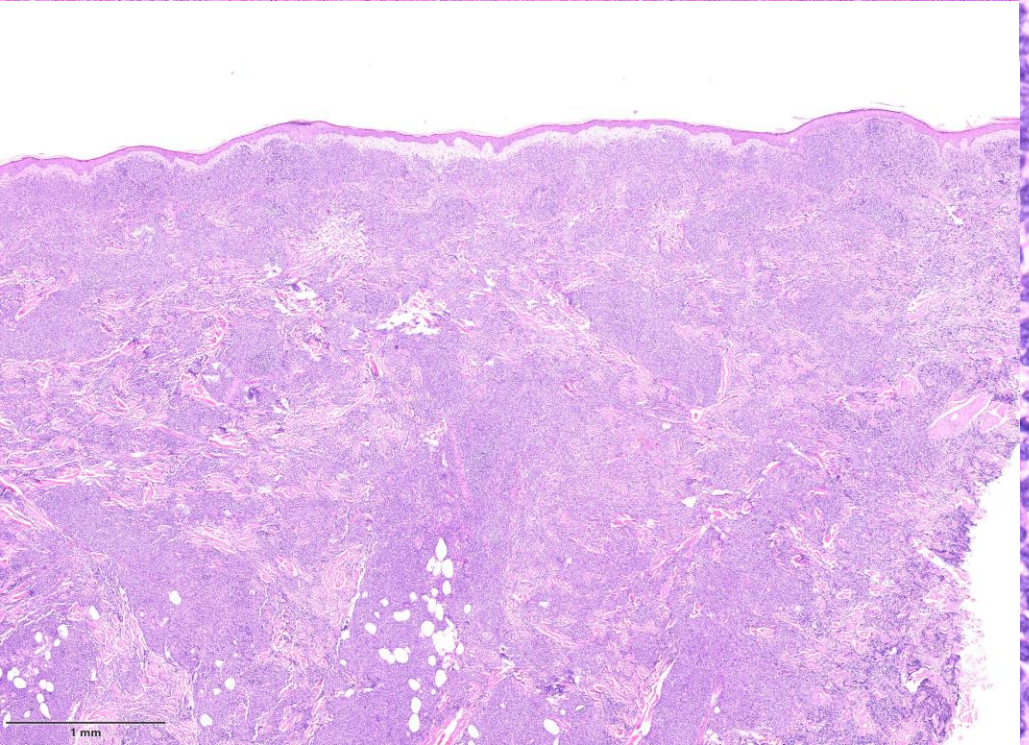


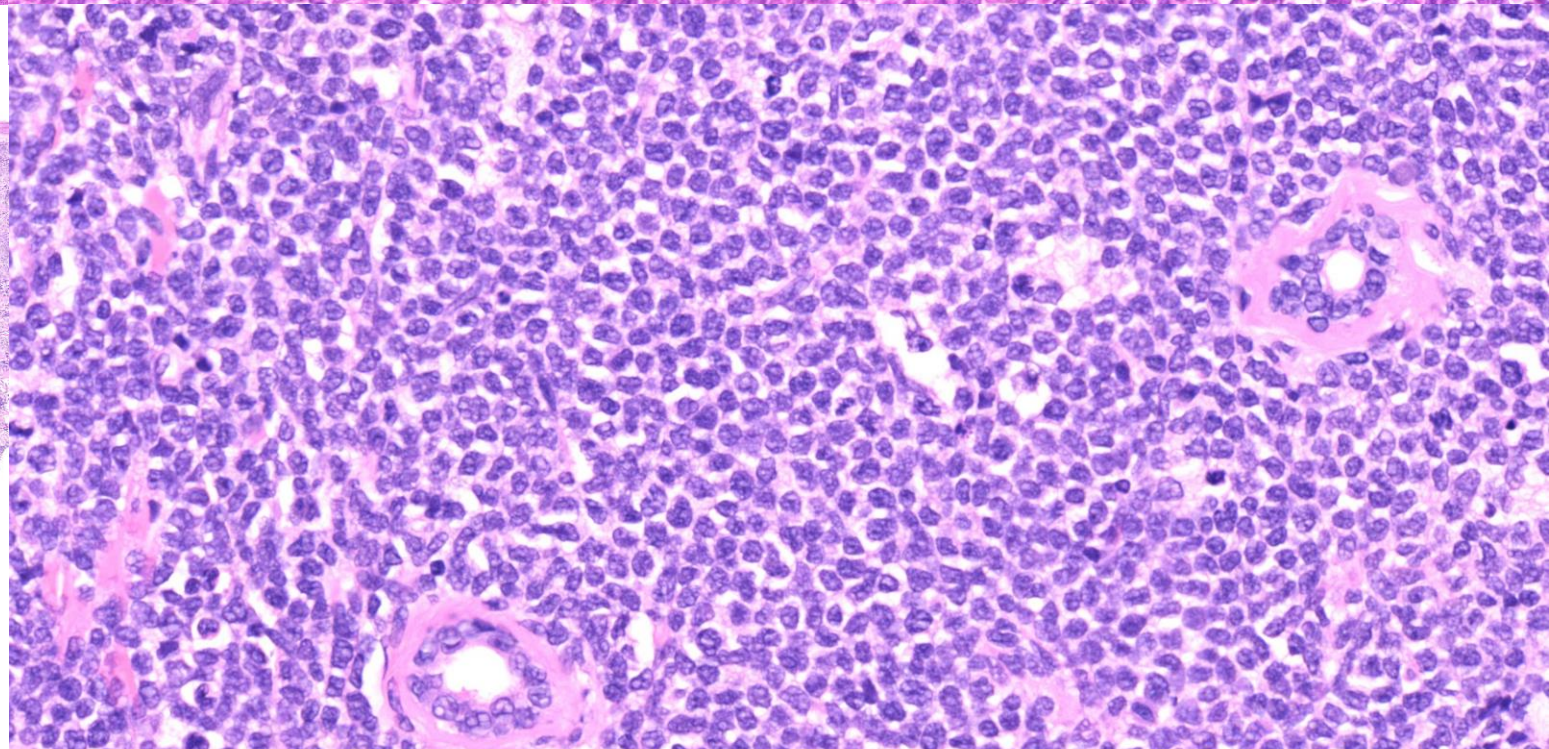


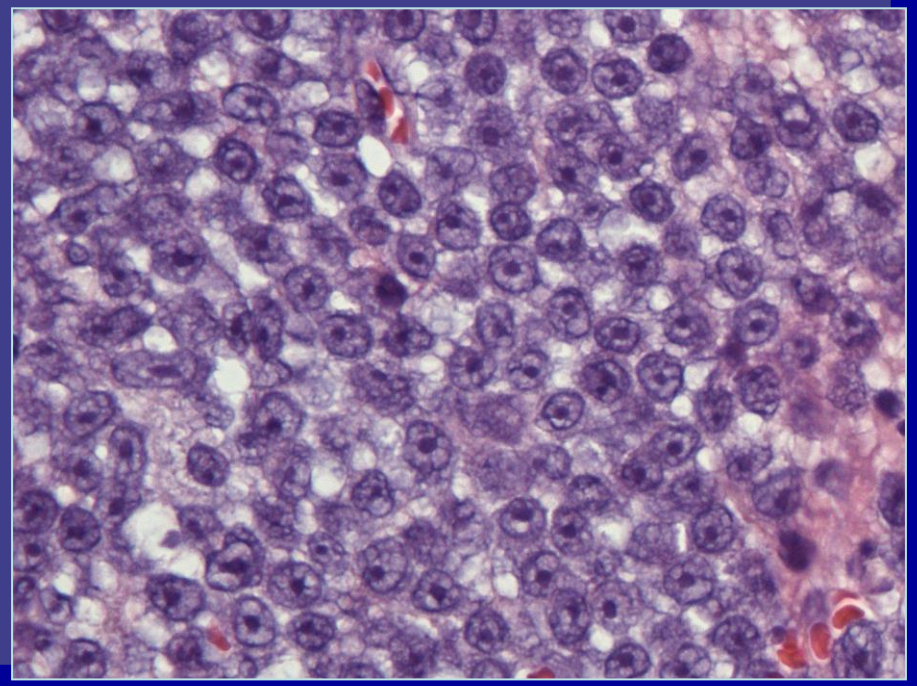


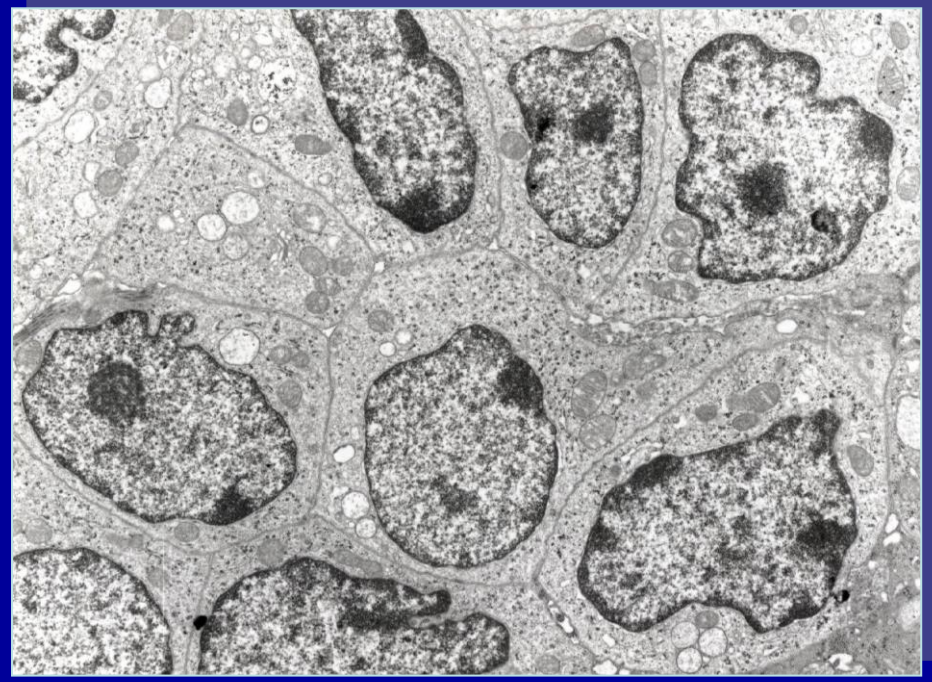

500 µm

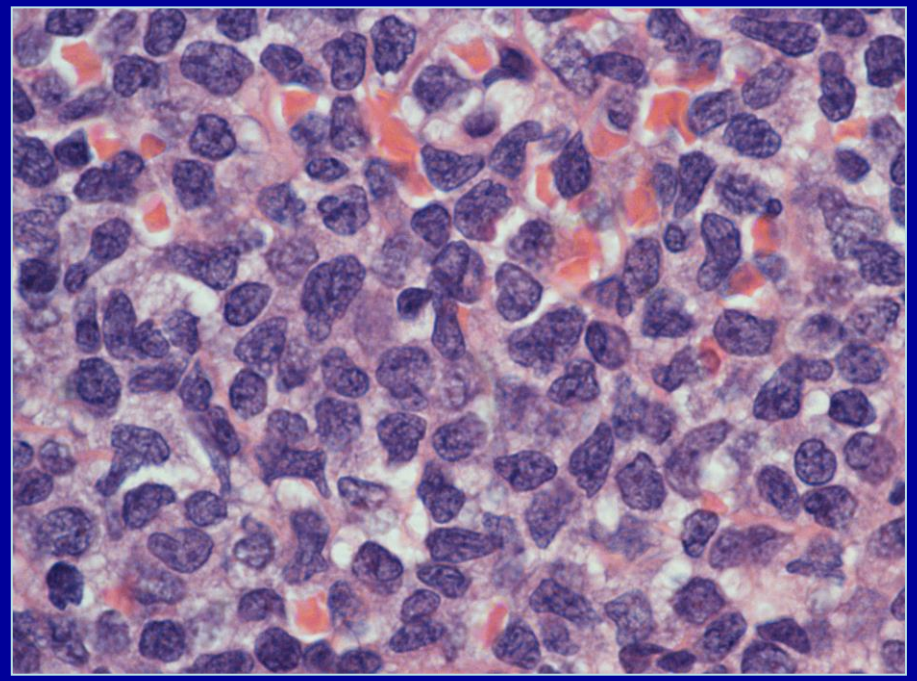


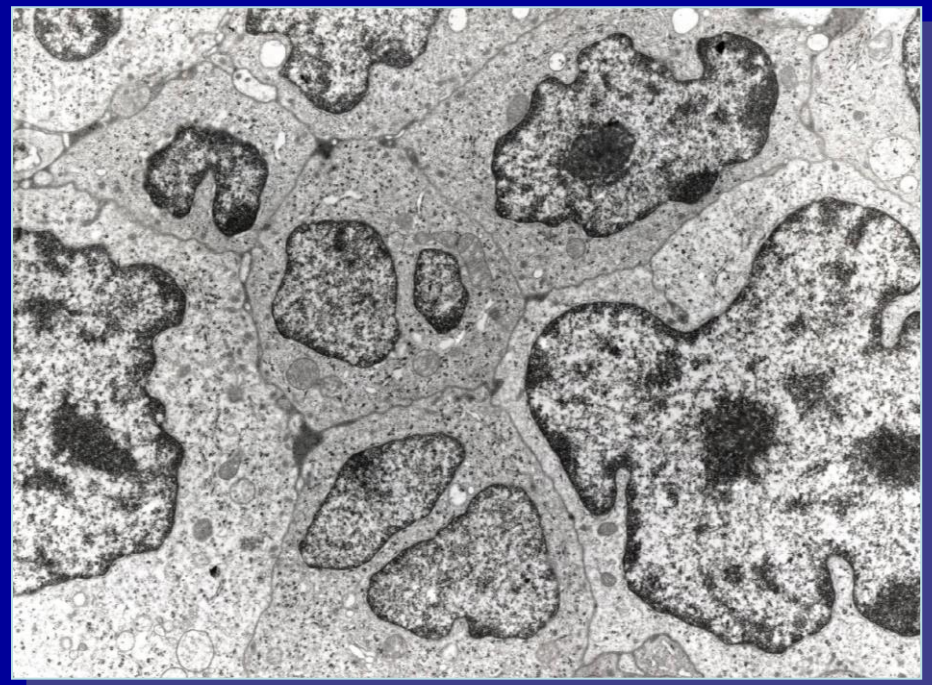

1 mm











UCN2. Optimization of the prognostic stratification

BPDCN patients show a dismal prognosis, with overall survival (OS) less than 1 year in most patients treated by conventional therapies (**20**). Due to the rarity of this condition and the challenges in the nosologic definition and diagnosis, no standardised prognostic factor has been identified to be used in clinical practice. Some studies however, reported significant differences in terms of disease outcome according to specific clinical, as well as phenotypical and molecular parameters.

In the largest series reporting a total of 398 patients from 75 centers, a significant negative impact on OS was found for age, ECOG score, peripheral involvement, disseminated disease with or without skin involvement. (**21**) Also a CD4+CD56+CD123+TCL1+BDCA2+ phenotype revealed a negative impact on prognosis, while high expression of terminal deoxynucleotidyl transferase (TdT) was associated with better prognosis (**21**). Other studies confirmed the favorable prognostic role of high levels of TdT expression (more than 50%) (**8**). Survival analyses showed also that CD303 expression and high Ki67 index are associated with better OS, while 9p21.3 deletion was associated with a shorter one (**8,22**).

On clinical background, reports document that patients with isolated cutaneous lesions display a better clinical outcome with respect to those with widespread lesions (progression free survival: 23 vs.9 months, respectively) (**23**). However, not all studies agree that limited cutaneous involvement correlates with better OS. In a French retrospective study of 86 patients, the variables with a significant impact on OS were: treatment with acute leukemia-like versus CHOP-like, ECOG and age (**24**). In a retrospective group of 49 patients treated at 3 US centers, a worse outcome was associated with age (> 60 years old), abnormal karyotype and TdT negativity (**25**). Similarly, in a series of 50 BPDCN cases, patients < 65 years showed a better OS, whilst the presence of ≥3 mutations or mutations in DNA methylation pathway genes was associated with shorter OS (**17**). In a series of 49 consecutive patients treated with either conventional chemotherapy or the new anti-CD123 tagraxofusp target therapy, there were no difference according to the extent of the disease (skin vs BM vs both) or younger age (<60 years old) (**26**).

Recommendations and proposals

Based on the currently available data, young age, high TdT expression and absence of karyotype abnormalities are associated with a better OS.

Multicentre studies are needed to define prognostic/predictive factors associated with disease outcome and therapy response, which at the time of writing are unavailable.