CASE N 138

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Clinical features:

45 years old female with a single nodular, firm, reddish skin lesion (6cm diameter) in the left extremity. The lesion has appeared in the last 6-8 months (spring 2006).
Clinical features:

BM biopsy at diagnosis: NED.
PBM: NED.

TREATMENT: Hyper C-VAD/MTX-Ara C (3 cycles).
FOLLOW UP: NED 5 years after the initial diagnosis (last clinical evaluation, 4/19/2011).
Proposed Diagnosis:

Blastic plasmacytoid dendritic cell neoplasm (WHO)

Interesting Feature(s) of Submitted Case:

Here we show a particular case of blastic plasmacytoid dendritic cell neoplasm (WHO), formerly named as agranular CD4+CD56+ haematodermic neoplasm, with a defective phenotype (CD56 negative).

We show an extended panel of markers including a novel monoclonal antibody against SPI-B, a plasmacytoid dendritic cell associated antigen, that may be useful in the differential diagnosis of these lesions.

1 WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.; 2008
**Blastic plasmacytoid dendritic cell neoplasm (BPDC).**

**Definition:**

Blastic plasmacytoid dendritic cell neoplasm (WHO)\(^1\) is a clinically aggressive tumour derived from the precursors of plasmacytoid dendritic cells (plasmacytoid monocytes and professional type 1 interferon producing cells). This type of neoplasm has a high frequency of cutaneous and bone marrow (BM) involvement and leukemic dissemination.

**Synonyms:** Blastic NK-cell lymphoma, agranular CD4+ natural killer cell leukemia, blastic natural killer leukemia/lymphoma, agranular CD4+CD56+ haematodermic neoplasm/tumour.

**Epidemiology:** BPDC is a rare haematologic neoplasm without any known racial or ethnic predilection. It has a male/female ratio of 3.3:1 to 7.25:1 according to the series\(^1,2\). Most patients are elderly (mean age 61 y) but it can occur at any age, including childhood\(^3\).

\(^1\) F. Facchetti, DM Jones, T Petrella. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.; 2008


Clinical features:
Clinical onset with generalized, localized (multiple) or solitary macules, plaques and or tumors\(^1,2\).
Regional lymphadenopathy at presentation is common (20%)\(^1\). Cytopenias and splenomegaly can occur at diagnosis\(^4\). PB and BM involvement can be minimal or absent at presentation (13-60% in larger series\(^2,4\)) but invariably develops with progression of disease.

\(^1\) F. Facchetti, DM Jones, T Petrella. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.; 2008
Clinical features:

The prognosis is rapidly fatal in the absence of treatment. Albeit a good initial response (78% CR\(^4\)) to polychemotherapy, elderly patients invariably relapse in less than 2 years\(^4,5\), mainly in the bone marrow, skin and central nervous system\(^4\). Overall the outcome is very poor with an average survival of 14 months (range 1-40 m, variable according to age)\(^3,5\).

Association with other myelodysplastic/myeloproliferative disorders at diagnosis or during progression (MML, AML)\(^4,5,6\). Differential diagnosis with massive mature CD56- plasmacytoid dendritic cell expansion CMML related.

6. Herling et al. TCL1 expression in plasmacytoid dendritic cells (DC2s) and the related CD4+CD56+ blastic tumors of skin. Blood 2003; 101: 5007-5009.
Histopathological and phenotypical features:

Histopathological patterns: diffuse dermal, perivascular/periadnexal, interstitial. Grenz zone, rare cases may show papillary dermal involvement and epidermotropism. Angiotropism can be found without angiodestruction or coagulative necrosis.

Minimal immunophenotypic criteria: coexpression of CD4, CD56, CD123 and TCL1 in the absence of B, T and myeloid/myelomonocytic cell lineage markers. However, phenotypic variability exists and some cases lack 1 or 2 of 4 markers (34% of cases; CD4- (20%), CD56- (8.9%), CD123 (4.4%), TCL1- (10.2%)).

Other markers: CD68 (dot like staining in a minority of cases), BCL2, CD7, BDCA2, CD101, BDCA-4, IRF-8, BCL11A, CD2AP

1 F. Facchetti, DM Jones, T Petrella. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.; 2008
6. Herling et al. TCL1 expression in plasmacytoid dendritic cells (DC2s) and the related CD4+CD56+ blastic tumors of skin. Blood 2003; 101: 5007-5009.
Genetics /Molecular features

Complex karyotypes with chromosomal abnormalities in 70% of the cases (5q, 6q, 9, 12p, 13q and 15q)\(^1\). Recurrent deletions in 4q34 and 13q12-q31 (with downregulation of RB1 and LATS2 and overexpression of HES6, RUNX2, FLT3)\(^8\).

Deletions of chromosome 9, 13, partial loss affecting 17p or 12p lead to combinations of deletions of tumor suppressor genes RB1, CDKN1B, CDKN2A and TP53\(^9\). Loss of CDKN1B locus and p27 protein expression (64%), loss of CDKN2A-ARF-CDKN2B locus (9p21.3) in 50%\(^10\), and 66%\(^11\) with loss of p16 function. Disruption of G1/S transition and biallelic loss of 9p21.3 as a marker of poor outcome\(^11\).

**Primary acquired somatic mutations in TET2 (53%) and “secondary” TP53 mutations (38%)**\(^12\).

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9. Jardin et al. Recurrent genomic aberrations combined with deletions of various tumour suppressor genes may deregulate the G1/S transition in CD4+CD56+ haematodermic neoplasms and contribute to the aggressiveness of the disease. Leukemia. 2009 Apr;23(4):698-707.


SPI-B is an Ets family transcription factor that is expressed exclusively in mature B cells, T cell progenitors and plasmacytoid dendritic cells\textsuperscript{13,14}. Together with its role during B cell differentiation SPIB has been shown to be a key regulator of human pDC development\textsuperscript{13} and a component of the signature of pDC neoplasms\textsuperscript{9}. It is also upregulated at the gene-expression level when pDC neoplasms are compared to myelomonocytic leukaemia\textsuperscript{9}.

SPI-B immunohistochemical expression in reactive lymph node hyperplasia
SPI-B protein is expressed with variable intensity among B cell lymphoma types.
Phenotypic Variability in BPDCN

29/45 (64%) express all 4 markers (TCL1, CD123, CD56, CD4).
11/45 (24%) lack 1 marker (8 cases CD4, 2 cases CD56, 1 case TCL1).
3/45 (6%) lack 2 markers.
2/45 (4%) lack 3 markers.

CD4- (12/45: 26%), CD56- (5/45: 11%), CD123- (4/45: 8%), TCL1- (2/45: 4%).

SPI-B protein expression in BPDCN and its cutaneous mimickers

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SPI-B protein is overexpressed in Blastic Plasmacytoid Dendritic Cell Neoplasms
Summary/ Conclusions:

Blastic plasmacytoid dendritic cell neoplasm (WHO)\textsuperscript{1} shows relatively uniform clinical and morphological characteristics but significant phenotypic diversity (with a 34-36\% of cases with a defective phenotype).

Additional (and specific) markers are required to better identify this rare type of aggressive neoplasm.

SPI-B expression, used in the adequate clinicopathological context, can be used as a tool for diagnosis of BPDCN.