F. Facchetti
M. Ungari
D. Marocolo
S. Lonardi
W. Vermi

Department of Pathology 1
Spedali Civili,
University of Brescia,
Piazzale Spedali Civili
Brescia, Italy

Blastic plasmacytoid dendritic cell neoplasm

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare haematological malignancy characterized by the clonal proliferation of immature or precursors of plasmacytoid dendritic cells (PDC), also known as professional type I interferon producing cells.[1] This neoplasm was originally recognized in 1994[2] and the uncertainty regarding its histogenesis was reflected by the several changes of name, that included agranular $CD4^+$ natural killer cell leukemia,[3] blastic natural killer leukemia/lymphoma,[4] agranular $CD4^+CD56^+$ hematodermic neoplasm[5] or tumor.[6] In 2001 the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissue coined the term blastic NK-cell lymphoma on the basis of the blastic cytology, and the expression of CD56 in the absence of other lineage specific markers. A relationship to plasmacytoid dendritic cells was hypothesized first by Lucio *et al.* in 1999[7] and subsequently confirmed by several studies.[5,8-13] The term blastic plasmacytoid dendritic cell neoplasm was introduced in 2008 by the updated WHO classification (4^{th} edition).[14] The clinical hallmarks of BPDCN are predominant cutaneous involvement, with subsequent or simultaneous extension to bone marrow and peripheral blood. Systemic dissemination and short survival are characteristic. Morphologically tumor cells show an immature "blastic" appearance; the diagnosis rests upon the demonstration of CD4 and CD56, together with markers more restricted to PDC (such as BDCA-2, CD123, TCL1, CD2AP and BCL11a) and negativity for lymphoid, NK and myeloid lineage-associated antigens.

The male/female ratio is 3.5/1. Most patients are older adults, with a mean/median age at diagnosis of 57.5/66.0 years, that is lower for females (51.6/55.5 versus 59.2/67.0). The clinical features and evolution of BPDCN are rather homogeneous from series to series[3,4,6,8,915-19] and consist of two main patterns, one (90% of cases) characterized by an indolent onset dominated by cutaneous lesions followed by tumor dissemination; the other (10%) showing features of an acute leukemia with systemic involvement from the beginning. Also in these cases multiple skin nodules are frequently present.[17]

In about 15-20% of cases BPDCN is associated with or develops into a myelomonocytic leukemia or acute myeloid leukemia.[6,9,15,18,20-23] BPDCN with associated myeloid leukemia should be distinguished from the tumoral proliferation of mature PDC that regularly manifests in association with other myeloid

neoplasms, although the pathogenesis may be analogous, with a common clonal origin in both settings.[24-26] BPDCN is characterized by a diffuse and monomorphous infiltrate of medium-sized cells, with an obvious blastic morphology, suggesting either lymphoblasts or myeloblasts. At present, the diagnosis of BPDCN is primarily based on immunohistochemistry and relies on the expression of CD4 and CD56, together with other antigens more specific for PDC (Table 1). EBV antigens or EBV-encoded small nuclear RNA (EBER) are not found. On flow cytometry the lack of lineage-associated antigens, together with the expression of CD4, CD45RA, CD56 and CD123 is considered to represent a unique and virtually pathognomonic phenotype.[27] Other immuno-phenotypic characteristics useful in flow analysis include both negative (CD45RO, CD57, CD117, CD116/GM-CSF receptor) and positive (CD36, CD38, BDCA-2, HLADR) markers.[12,21,28] BPDCN tumor cells are non-reactive for alpha-naphthyl butyrate esterase, ASD chloroacetate esterase and peroxidase cytochemical reactions.[9,20,21,29] T-cell and B-cell receptor gene are usually germline.[9,15,18] No specific chromosomal aberrations have been identified, but complex abnormalities in the same cells are a distinctive feature. BPDCN do not show cytoplasmic expression of nucleophosmin, the immunohistochemical surrogate for NPM1 mutations, indicating that the gene is wild type.[30]

Despite the apparently indolent clinical presentation, the course is aggressive and the median survival is approximately 12-14 months based on several series.[6,8, 15,19,21]

At present, there is no consensus for optimal treatment of BPDCN. With intensive therapy for acute leukemia the rate of sustained complete remission increases, but only myeloablative treatment with allogenic bone marrow during the first remission resulted in chance of long term survival.[21,31]

Table 1. Immunohistochemical markers expressed by BPDCN tumor cells.

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]

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