



Blastic Plasmacytoid Dendritic Cell Neoplasm

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Abstract

Purpose of Review Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare malignancy derived from plasmacytoid dendritic cells whose biology, clinical features, and treatment options are increasingly better understood.

Recent Findings TCF4 is a master regulator that drives downstream transcriptional programs in BPDCN. In turn, TCF4 activity is dependent on the bromodomain and extra-terminal domain (BET) protein BRD4 whose inhibition provides a promising therapeutic vulnerability. Notably, TCF4 expression is a highly sensitive marker for BPDCN and augments diagnostic specificity alongside CD4, CD56, CD123, and TCL1. The gene expression profile of BPDCN is characterized by aberrant NF-kappaB pathway activation, while its genomic landscape is dominated by structural chromosomal alterations involving *ETV6*, *MYC*, and *NR3C1*, as well as mutations in epigenetic regulators particularly *TET2*.

Summary Advances in elucidating the biological characteristics of BPDCN are resulting in a more refined diagnostic approach and are opening novel therapeutic avenues for patients with this disease.

Keywords Plasmacytoid dendritic cells · Blastic plasmacytoid dendritic cell neoplasm · Acute leukemia · CD123 · TCF4 · Flow cytometry

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a hematologic malignancy arising from precursors of plasmacytoid dendritic cells (pDCs). The first description of BPDCN is attributed to Kameoka et al., who in 1998 described two cases of cutaneous agranular CD2-/CD4+/CD56+ “lymphoma” and proposed that they represented a distinct entity [1]. Characterization of this rare neoplasm remained elusive until relatively recently, resulting in a nomenclature legacy that includes agranular CD4+ natural killer (NK) cell leukemia, CD56+/TdT+ blastic NK cell tumor, blastic NK cell leukemia/lymphoma, and agranular CD4+/CD56+ hematodermic neoplasm [2–5]. A similar legacy applies to the identification and characterization of pDCs.

Known to occur in focal clusters in some cases of reactive lymphoid hyperplasia, these cells were called lymphoblasts then T-associated plasma cells, plasmacytoid T-cells, and plasmacytoid monocytes, before the current term pDCs was coined in 1997 by Grouard et al. [6]. In a case report, Lucio et al first proposed a possible relationship between pDCs and BPDCN on the basis of shared high-level CD123 expression [7]. The first systematic analysis supporting such a connection was published shortly thereafter by Chaperot et al. [8]

Plasmacytoid dendritic cells are present in blood and tissues where they play important roles in immunity as intermediaries between the innate and adaptive immune systems. [9] This is accomplished primarily through a tightly regulated toll-like receptor (TLR)7/9-MyD88-IRF7 pathway-mediated sensing of nucleic acid sequences and by functioning as antigen presenting cells in concert with other subsets of myeloid dendritic cells. Through the activation of toll-like receptor (TLR) agonists, pDCs secrete a gamut of cytokines dominated by type 1 interferons (mainly interferon alpha) and, to lesser levels, interleukin (IL)-6, IL-8, IL-12, tumor necrosis factor alpha, and other pro-inflammatory chemokines [10, 11]. In turn, pDC activation leads to the activation of T-cells, natural killer cells, and macrophages in physiologic and pathologic adaptive immunity reactions including infections and

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autoimmune diseases [12, 13]. It should be noted that the term pDC also includes other non-type 1 interferon-producing cells that represent differentiated dendritic cells in blood and tissues [14–16]. The latter subsets have been postulated to explain some of the phenotypic diversity of BPDCN [17].

Circulating pDC comprise $\leq 0.5\%$ of peripheral blood mononuclear cells [18], and in this compartment they are defined as CD11c[−]/CD123⁺/CD303⁺. In tissues, pDC are localized primarily in lymph nodes and tonsils, and to a lesser extent in the bone marrow and spleen.

Etiology and Pathogenesis

The etiology of BPDCN is unknown. Reactive pDC proliferations were first described in 1958 by Lennert and Remmele [19]. Since then, reactive pDC proliferations have been recognized in association with various inflammatory and autoimmune conditions, including Kikuchi-Fujimoto lymphadenopathy (histiocytic necrotizing lymphadenitis), psoriasis, systemic lupus erythematosus, and hyaline-vascular-type Castleman disease [20–22]. In addition, nodular pDC proliferations referred to as *mature pDC proliferations* (MPDCP) have been recognized in association with myeloid neoplasms, most notably chronic myelomonocytic leukemia, myelodysplastic syndrome, and acute myeloid leukemia. [22–24] These proliferations typically consist of cytologically bland pDC nodules comprised of cells with moderate amounts of cytoplasm, variably irregular nuclear contours, and inconspicuous nucleoli. While they have been postulated to be clonally related to the associated myeloid neoplasm [25], no data establishes MPDCP as a precursor lesion of BPDCN.

The pathogenesis of BPDCN remains poorly understood. We have identified a high rate of monoallelic and biallelic 12p13/*ETV6* deletions in BPDCN tumors as well as in the bone marrows of BPDCN patients without detectable disease, suggesting that such alterations might represent an early pathogenic event [26]. In a subset of patients, BPDCN is identified in a myelodysplastic background (see below) raising the possibility that at least a subset of cases might represent a secondary malignancy [27]. Ceribelli et al. identified a BPDCN-specific transcriptional network regulated by the E-box transcription factor TCF4 (also known as E2-2) that plays a master regulatory role in BPDCN cells and appears to be in turn regulated by the bromodomain and extra-terminal domain (BET) protein BRD4 [28]. Notably, knockdown of TCF4 results in downregulation of CD123 and CD56 expression in BPDCN cells. Indeed, TCF4 had been identified as a key regulator that controls the committed development of pDCs from common dendritic cell progenitors through a regulatory network of secondary transcription factors [29, 30]. In another study, Emadali et al. identified frequent

NR3C1 haploinsufficiency in BPDCN linked to aberrant overexpression of a novel long noncoding RNA (lncRNA) gene, *lincRNA-3q*, whose product is involved in G1/S cell cycle transition through E2F [31]. Notably, BET inhibition abrogated the impact of *lincRNA3q* overexpression. Gene expression profiling of BPDCN demonstrated a signature that is in keeping with derivation from resting (not activated) myeloid pDCc and demonstrated aberrant NF-kappaB pathway activation [32].

Clinical Characteristics

BPDCN is rare, estimated to represent < 1% of all hematologic malignancies [33]. In a recent analysis based on Surveillance Epidemiology and End Results (SEER) data, the incidence of BPDCN in the USA is estimated to be 0.04 cases per 100,000 individuals, most of whom are Caucasian [34]. Men are affected more commonly than women. Although the disease has been reported in all age groups, the median age of patients at diagnosis is 53 years. Interestingly, the disease appears to exhibit a bimodal incidence pattern in the SEER database, with peaks in individuals < 20 years and those > 60 years [34]. Cutaneous lesions are often the presenting sign for patients with BPDCN, identified in at least 64% of patients [35]. Other common sites of disease involvement include the bone marrow and lymph nodes, and some patients have an overtly leukemic presentation without discernible extramedullary disease at presentation [27, 36, 37]. Overt or occult central nervous system (CNS) involvement is common at diagnosis, and up to one third of patients have CNS involvement at relapse [37–39]. A sizeable subset of patients with BPDCN have either synchronous or metachronous myeloid neoplasms that typically include chronic myelomonocytic leukemia, myelodysplastic syndrome, or acute myeloid leukemia [2, 40, 41].

Microscopic Features

Cutaneous lesions consist of a diffuse dermis-based proliferation of neoplastic cells that are small or intermediate in size, often with moderate amounts of cytoplasm and an eccentrically located nucleus with a prominent nucleolus. Mitotic figures are usually present, and necrosis can be present occasionally [2, 42]. The infiltrate is typically extensive and extends deep into subcutaneous tissue, with sparing of the upper dermis, epidermis, and adnexal structures. BPDCN in lymph nodes involves the medullary and interfollicular areas. In the bone marrow, BPDCN often exhibits a diffuse growth pattern with replacement of hematopoietic elements. The cytomorphology of BPDCN on Wright-Giemsa-stained smears is variable, but in many cases the cells are elongated, with a tapered lightly basophilic agranular cytoplasm that ends with a tail-shaped

structure. The nucleus has blastoid features with open chromatin and a prominent nucleolus [27]. Less commonly, the neoplastic cells have lymphoid morphology, occasionally with cytoplasmic vacuoles, and less prominent blastoid nuclear features. Sakamoto et al. have proposed recently the term “immunoblastoid” variant to describe BPDCN cases in which the neoplastic cells resemble immunoblasts with their characteristic round nucleus with vesicular chromatin and a prominent nucleolus; 35% of BPDCN cases in their study belonged to this variant category. [43] Several groups have reported myelodysplastic morphologic and cytogenetic (see below) features in the bone marrow of BPDCN patients. [2, 27, 31]

Immunophenotype

The immunophenotype of BPDCN recapitulates that of pDC subsets. In routine practice, immunophenotypic profiling is accomplished using flow cytometry and/or immunohistochemistry. BPDCN is characterized by the expression of the pDC-associated markers CD123, CD303, and TCF4. CD123, the interleukin-3 (IL-3) receptor α -chain, is the primary low-affinity subunit of the IL-3 receptor and promotes high-affinity binding to IL-3 when co-expressed with the β -subunit. It is characteristically expressed at a high level in pDCs, MPDCP, and BPDCN. CD123 is expressed at various levels in other hematologic malignancies, including hairy cell leukemia [44], acute myeloid leukemia [45], and systemic mastocytosis [46], but in most such instances, it is expressed at a relatively lower intensity. CD303 (also known as blood dendritic cell antigen 2; BDCA2) is a pDC-specific type II C-type endocytic lectin that is able to target ligand into antigen-processing and peptide-loading compartments for presentation to T cells [47]. CD303 can also mediate inhibition of interferon α/β , providing a potential negative regulatory pathway for TLR9-induced pDC activation [47, 48]. Although CD303 is a useful specific marker for BPDCN [49], it has limited sensitivity due to its frequent aberrant loss in BPDCN. Indeed, CD303 loss is a useful marker to discern reactive from neoplastic pDC proliferations in some situations. Other pDC-specific antigens, including CD2AP, Spi-B and BCL11A, have been also proposed as useful markers for BPDCN [50]. In addition, BPDCN cells express CD4, CD56, and TCL1, and by definition they are negative for lineage-specific markers including CD3, CD19, and myeloperoxidase [27]. Notwithstanding, various lineage-associated antigens are expressed to varying extents in some BPDCN cases; these include CD2, CD5, CD7, CD33, CD38, CD68, CD117, HLA-DR, and TdT [27]. Expression of BCL2, BCL6, and S100 has also been reported [42, 43, 51, 52]. The Ki-67 proliferation rate is typically high in BPDCN. BPDCN has been shown to consistently lack myeloid cell nuclear differentiation antigen (MNDA) expression, a feature that helps in the distinction between BPDCN and

extramedullary myeloid neoplasms, which are often (65%) positive for MNDA expression [53].

Multicolor multiparameter flow cytometry plays an important role in the immunophenotyping of BPDCN, particularly in the evaluation of bone marrow samples. Besides its diagnostic utility in distinguishing BPDCN from acute myeloid leukemia, flow cytometry is useful for assessment of measurable residual disease (MRD) in patients who achieve clinical remission following induction chemotherapy. Furthermore, flow cytometry allows differential analysis of the BPDCN population as well as background hematopoietic elements (myeloblasts and maturing elements), particularly in cases where BPDCN is present in association with another hematologic malignancy. The BPDCN flow cytometry panel employed presently at MD Anderson for baseline evaluation and residual disease assessment includes the following markers: CD4, CD33, CD45, CD56, CD64, CD123, CD303, and HLA-DR. Analysis of BPDCN cells is typically achieved by gating on CD123+ events. This approach is also applicable in patients receiving CD123-targeted therapy, as most agents available to date do not cause significant alteration of CD123 expression levels.

The immunophenotype of MPDCP is similar to that of pDCs, although on occasion aberrant expression patterns may be seen. The clinical and prognostic significance of the latter remains unclear. Aberrantly expressed antigens reported have included CD2, CD5, CD7, CD10, CD13, CD14, CD15, and CD33. CD56 is usually negative, but we have seen rare cases with weak focal CD56 expression. TdT is negative and, in contrast to BPDCN, the Ki-67 proliferation rate is typically low in MPDCP [23, 50, 54, 55].

Chromosomal Abnormalities and Mutations

Although BPDCN cases exhibit heterogeneous karyotypic features, salient patterns have been recognized. The majority of BPDCN cases have chromosomal abnormalities detectable by conventional karyotyping, and up to 75% have a complex karyotype (≥ 3 abnormalities, including at least one structural abnormality) [56]. Abnormalities involving the short arm of chromosome 12 and, more specifically, the 12p13 locus containing *ETV6* are the most frequent findings in BPDCN. Other frequently abnormal chromosomes include 6 and 13.

Rearrangements involving the *MYC* locus on 8q24 and resulting in *MYC* protein overexpression have been reported in 38% of BPDCN cases and correlated with so-called immunoblastoid morphology [43]. A subset of patients with *MYC* rearrangement have a recurrent balanced translocation t(6;8)(p21;q24) [57]. In a report of a single case of BPDCN with t(6;8)(p21;q24), *SUPT3H*, a TATA-binding protein-associated factors (TAF)-associated protein, was identified as a partner gene [58].

Chromosomal abnormalities associated with myelodysplastic syndrome or acute myeloid leukemia with myelodysplasia-related changes are identified often in BPDCN. These include -5 or $\text{del}(5q)$, -7 or $\text{del}(7q)$, $\text{del}(9q)$, $\text{del}(11q)$, $\text{del}(12p)$ and $\text{del}(13q)$. [27, 56, 59] Similarly, array comparative genomic hybridization has demonstrated frequent deletions involving chromosomes 4q34.1-4q34.2, 9p13.2-9p11.2, 9q12-9q34.3, and 13q12.11-13q31.1 [60].

Mutation profiling of BPDCN using next-generation sequencing techniques has demonstrated mutations involving *TET2*, *ASXL1*, *NRAS*, and *ATM* [27, 39, 61, 62]. Additional mutations identified less commonly involve *APC*, *BRAF*, *IDH2*, *KIT*, *KRAS*, *MET*, *MLH1*, *RBI*, *RET*, *TP53*, and *VHL*. *NPM1* mutations have been reported rarely in BPDCN [61, 63], but other series have reported no cases with *NPM1* mutations [62, 64]. An unpublished BPDCN series from The University of Texas MD Anderson Cancer Center had no cases with *NPM1* mutations [39].

Therapeutic Approaches and Prognosis

Although the initial presentation of cutaneous lesions may appear to be indolent, BPDCN is a highly aggressive malignancy with rapid systemic dissemination for which no consensus therapy guidelines are yet available. Accordingly, patients who are diagnosed with BPDCN should be referred for treatment under a clinical trial if feasible. At present, there is no standard therapy for BPDCN, and most published studies are based on retrospective data. Pagano et al. [37] reported that lymphoma regimens including CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and CHEOP (CHOP plus etoposide) as well as acute lymphoblastic leukemia/lymphoma (ALL) regimens such as hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, and methotrexate and cytarabine) and GIMEMA ALL trial therapy (doxorubicin, vincristine, prednisone, asparaginase), with intrathecal therapy, were associated with significantly better overall survival results compared to acute myeloid leukemia regimens such as MICE (mitoxantrone, cytarabine, etoposide) or ICE (idarubicin, cytarabine, etoposide) for patients with BPDCN. Nonetheless, without stem cell transplant therapy (SCT) the median overall survival is generally dismal [37, 38]. Stem cell transplant therapy, particularly allogeneic SCT, administered during first remission remains the only therapeutic modality that results in durable remissions [65–67]. It should be noted that Aoki et al. [66] have reported better outcomes with autologous SCT compared with allogeneic SCT, but those results have not been reproduced by other groups [67].

A number of novel therapies for BPDCN are being investigated. SL-401 (Stemline Therapeutics) is a recombinant

protein composed of the catalytic and translocation domains of diphtheria toxin (DT) fused via a Met-His linker to IL-3. The payload is delivered in a targeted fashion to CD123-positive cells via IL-3 binding, achieving cytotoxicity through DT-mediated inhibition of protein synthesis [68]. Early results showed promising response rates in BPDCN [69]. The pivotal phase 2 trial of SL-401 in BPDCN has met its primary endpoint (Pemmaraju N. et al.; presented at the Annual Meeting of the European Hematology Association, June 15, 2018).

Other agents targeting CD123 are also being evaluated in phase 1 clinical trials. These include IMGN632 (Immunogen), a conjugate of CD123-targeting antibody with a novel DNA-alkylating payload [70] and a bispecific antibody, XmAb14045 (Xencor), targeting CD123 and CD3. In addition, anti-CD123 chimeric antigen receptor T cell (CAR-T) therapy phase 1 trials for patients with BPDCN are underway.

Other therapeutic approaches have involved agents such as venetoclax, lenalidomide, and bortezomib. BPDCN cells are highly dependent on BCL2 for survival, and they demonstrate in vitro and in vivo sensitivity to BCL2 inhibition with venetoclax [71]. Anecdotal reports of venetoclax therapy for BPDCN patients seems to support its potential effectiveness [71, 72]. Similarly, preclinical data on the activity of lenalidomide [73] and bortezomib [74] in BPDCN are promising, but these agents have yet to be tested clinically. And, although BET inhibition has been shown to be a promising treatment option in preclinical studies [28, 31], this area also remains to be explored in clinical trials.

Conclusions and Future Directions

Recent advances, particularly the identification of the critical role of TCF4 in orchestrating the expression profile and much of the phenotype of BPDCN, have permitted a clearer distinction between BPDCN and other hematolymphoid malignancies, particularly acute myeloid leukemia. Indeed, TCF4 offers a novel marker that is useful for the diagnosis of BPDCN alongside other more-or-less specific markers such as CD123 and TCL1. Notwithstanding, some patients with BPDCN, particularly those who present with a mostly leukemic disease, still get mislabeled as having acute myeloid leukemia in some community-based settings. The main reason is that commercial reference labs have not all fully embraced including some of the markers of BPDCN, particularly CD123, in their acute leukemia flow cytometry panels.

Patients diagnosed with BPDCN have more treatment options today than they did just a few years ago. Chemotherapy induction with ALL-type regimens remains a mainstay for eligible patients, while allogeneic SCT offers the best chance for durable remission. The results of clinical trials evaluating targeted therapies such as SL-401 offer hope that CD123 offers a therapeutic vulnerability that

could augment other therapeutic approaches. As treatment approaches for BPDCN become clearer and more standardized, prognostic modeling to better risk-stratify patients for optimal therapy choices would be warranted. At present our best prognostic markers such as *MYC* rearrangement status remain incompletely developed and their impact on therapy selection is largely limited.

In view of its rarity and features that overlap with myeloid and lymphoid malignancies, it took until relatively recently to recognize the unique nature of BPDCN and begin to understand its enigmatic characteristics. However, the unprecedented tools for research discovery and drug development available presently have permitted an unprecedented fast-paced unraveling of the biology of BPDCN and are offering promising therapy options for patients with this disease. The collective efforts to fight this aggressive malignancy offer hope and a real-life model of the way forward in the fight against cancer.

Compliance with Ethical Standards

Conflict of Interest Joseph D. Khoury has received research funding from Stemline Therapeutics.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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