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Review Article

Diagnostic approach to blastic plasmacytoid dendritic cell neoplasm: historical perspectives and current understanding

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Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematologic malignancy composed of immature cells that exhibit plasmacytoid dendritic cell (pDC) differentiation. The diagnosis of BPDCN is often challenging due to its rarity and morphologic and phenotypic overlap with other hematologic malignancies, such as acute myeloid leukemia (AML). The emergence of tagraxofusp, a CD123-directed cytotoxin, and other novel therapies has underscored the importance of accurately diagnosing BPDCN. This review initially outlined the clinical and histopathological features of BPDCN, including patients with immunoblastoid morphology. Various proposed diagnostic criteria based on flow cytometry and immunohistochemistry findings were presented, highlighting critical points of caution in the diagnostic process. Strategies for detecting minimal residual disease or microinvasion in BPDCN, a significant clinical issue, were also discussed. Additionally, we reviewed the recurrent 8q24 (*MYC*) and *MYB* rearrangements observed in BPDCN, which can aid in diagnosis. Furthermore, we explored mature plasmacytoid dendritic cell proliferation (MPDCP) associated with myeloid neoplasm, which is characterized by a clonal proliferation of pDCs in cases with a defined myeloid neoplasm and may also serve as a potential differential diagnosis for BPDCN. Lastly, we discussed pDC-AML, characterized by pDC proliferation in AML cases, which can also be part of MPDCP and is often associated with frequent *RUNX1* mutations. Overall, this review provides insights into BPDCN diagnosis and highlights the current challenges in its detection and differential diagnosis.

Keywords: blastic plasmacytoid dendritic cell neoplasm, mature plasmacytoid dendritic cell proliferation associated with myeloid neoplasm, acute myeloid leukemia with plasmacytoid dendritic cell expansion

INTRODUCTION

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematopoietic malignancy composed of immature cells that express immunomarkers similar to those of pDC. It accounts for 0.44% of all hematologic malignancies[1] and 0.7% of cutaneous lymphomas,[2] with an incidence rate of 0.04 cases per 100,000 individuals in the United States (U.S.).[3] Men are more commonly affected, with a male-to-female ratio of 2–6: 1.[4–6]

The recognition of BPDCN as a distinct disease entity began with case reports describing the unusual cases of CD4+, CD56+ histiocytosis or leukemia.[7–11] In 1994, Adachi *et al.* reported a patient with a cutaneous lymphoma that tested positive for CD4 and CD56, but negative for T-cell markers.[7,12–14] Over the following years, similar cases were sporadically reported under various terms.[7,8,11,14–16] In 1999, Petrella *et al.* proposed that these cases—characterized by primary cutaneous presentation, rapid progression to a fatal course with bone marrow involvement, and the proliferation of blastic cells with a peculiar CD3−, CD4+, CD56+, CD43+, and HLA-DR+ phenotype—should be considered a distinct disease entity. They further proposed the term "agranular CD4+ CD56+ hematodermic neoplasms" as a provisional label until the disease's exact nature could be fully elucidated.[17,18]

The association between this neoplastic disease and pDCs was initially established in 1999 when Lucio *et al.* reported that the tumor cells were positive for CD123, a marker also expressed by normal pDCs.[19] At the same time, a prevailing theory proposed that the neoplastic cells originated from natural killer (NK) cells, given the neoplastic cells' lack of major lineage markers but the expression of CD56.[11,20,21] Consequently, the disease was initially classified as blastic

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NK-cell lymphoma in the 3rd edition of the Word Health Organization (WHO) Classification (2001). However, subsequent findings revealed that the tumor cells were positive for other pDC markers, such as TCL1[22], CD303/BDCA2[23], and CD2AP,[24] and exhibited high expression of various pDC-related genes in gene expression profiling.[25] Functional analyses further supported this association by demonstrating that the tumor cells secreted interferon-α upon viral stimulation and induced naïve CD4+ T-cell proliferation through antigen presentation, similar to normal pDCs.[25–27] Eventually, in the 4th edition of the WHO Classification published in 2008, it was designated as BPDCN within the category of acute myeloid leukemia (AML)-related tumors.[28] In the revised 4th edition (2017), it became a standalone category[29]; in the latest 5th edition, it was classified within the category of histiocytic/dendritic cell neoplasms, under the subcategory of pDC neoplasms, alongside mature plasmacytoid dendritic cell proliferation associated with myeloid neoplasms (MPDCP).[30]

Approximately 60% of patients with BPDCN harbor complex chromosomal abnormalities.[30–32] Copy number losses are more common than gains, with frequent deletions or losses of tumor suppressor genes (e.g., *TP53* and *RB1*) and genes involved in the G1/S transition (e.g., *CDKN2A*, *CDKN2B*, *CDKN1B*, *RB1*, and *NR3C1*).[25,33–38] Monoallelic or biallelic deletions of 12p13/*ETV6* have been suggested to occur early in the disease process.[32] The mutational pattern of BPDCN is generally similar to that of myeloid tumors, but lymphoid-like mutations and translocations are also observed.[39] The recurrently mutated genes found in BPDCN include those involved in DNA methylation (e.g., *TET2* and *IDH2*), histone modification (e.g., *ASXL1* and *EZH2*), signal transduction (e.g., *KRAS* and *NRAS*), transcriptional regulation (e.g., *IKZF1/2/3* and *ZEB2*), cell-cycle regulators (e.g., *ATM* and *TP53*), and RNA splicing factors (e.g., *ZRSR2*, *SRSF2*, *U2AF1*, and *SF3B1*).[33,38,40–51] Additionally, gene expression profiling revealed the aberrant activation of NF-κB pathway.[52]

Diagnosing BPDCN can be challenging due to its rarity and morphological and phenotypical overlap with other hematologic malignancies, such as AML. A consensus panel of experts has identified the optimization of diagnostic pathways as a critical unmet need.[40] As our understanding of related conditions, such as MPDCP and AML with pDC expansion (pDC-AML), has evolved, the differential diagnosis has become increasingly complex. Additionally, challenges persist in detecting minimal residual disease (MRD) and addressing microinvolvement. This article aimed to discuss the diagnosis of BPDCN, incorporating recent developments in related conditions. Detailed information on disease pathogenesis, genetic mutations, and treatment, are presented in other excellent reviews.[37,39,40,53–57]

CLINICAL FEATURES

BPDCN is more common in older adults, with a median age ranging from the late 60s to the early 70s. However, it can occur in all age groups, including children.[4,6,13,48,58–63] Solitary or disseminated skin lesions are observed in 80%–97% of patients[4,6,59–61,64,65] and may present as tumors/nodules, patches, plaques, or erythema. Bone marrow involvement is reported in 46%–95% of patients,[4,6,8,59–61,64,66] while tumor cells are detected in the peripheral blood of 15%–68% of patients.[6,59,61,64–66] A few patients only exhibit leukemic presentation without cutaneous lesions at diagnosis.[30,60,67] Lymph node involvement is common (24%–63%), while splenic and hepatic infiltration occurs in approximately 20% of patients each.[5,6,30,48,59,62,64] Central nervous system (CNS) involvement has been reported in a small proportion of patients at diagnosis.[59,60,62,64,68] However, some studies suggested that when frontline lumber puncture analysis was performed, including patients without neurological symptoms, tumor cells were detected in about half of these patients.[65,69,70] CNS involvement is more commonly observed at relapse.[7,61,64,68] Antecedent or concurrent myelodysplastic or myelodysplastic/myeloproliferative neoplasm are found in 20%–30% of patients with BPDCN.[42,49,68,71]

Although an initial response to chemotherapy is often observed, the disease is characterized by early relapse and leukemic transformation, leading to a poor prognosis. The median overall survival is 8.7–28 months.[6,59,60,62,68,72] The standard treatment for BPDCN has not yet been established, but acute lymphoblastic leukemia (ALL)- or AML-type induction chemotherapy is often employed when feasible.[62,73] Several studies have indicated that allogeneic (or autologous) hematopoietic stem cell transplantation, particularly during the first remission, can lead to long-term survival in eligible patients.[66,73–79] Tagraxofusp is a CD123-directed recombinant fusion protein consisting of interleukin-3 conjugated to a truncated diphtheria toxin. It has shown promising results in improving response rates and overall survival,[65,80] and it is used as a first-line treatment in selected countries. Pivekimab sunirine (IMGN632), a novel CD123-targeting antibody-drug conjugate, received a breakthrough therapy designation (BTD) from the U.S. Food and Drug Administration in 2020 based on the results of a Phase I/II study that demonstrated a favorable safety profile and promising efficacy in patients with relapsed/refractory AML and BPDCN.[53,81] Other treatments that may be beneficial for patients with BPDCN include venetoclax,[6,82,83] hypomethylating agents,[83,84] and chimeric antigen receptor (CAR) T-cell therapy targeting CD123.[85] Clinical trials are underway to further evaluate these therapies.[53]

HISTOPATHOLOGY

Microscopically, a diffuse and monotonous proliferation of medium-sized blasts, resembling lymphoblasts or myeloblasts, is observed. In the skin, epidermal infiltration is typically absent. Infiltration can extend from the dermis to the subcutaneous adipose tissue. The tumor cells exhibit fine chromatin, slightly irregular nuclei, and scant cytoplasm, with indistinct or small nucleoli, which we define as classic BPDCN (Figure 1A). However, in approximately one-third of patients, a markedly different cell morphology is observed,

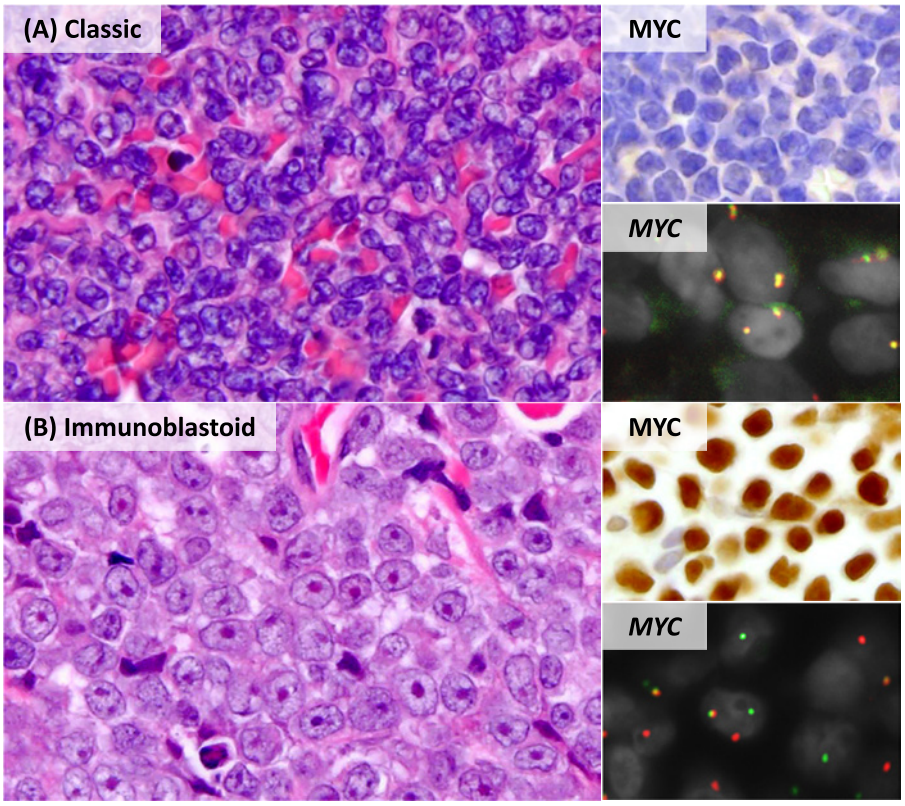

Fig. 1. Correlation between cytomorphology and MYC status in BPDCN
(***A***) A case of classic BPDCN displaying medium-sized tumor cells with irregular nuclei featuring fine chromatin, 0 to a few small nucleoli, and small to moderate amounts of cytoplasm. MYC immunostaining and *MYC* split FISH yielded negative results. (***B***) A case of immunoblastoid BPDCN characterized by tumor cells with fine chromatin, round nuclei, moderate amounts of basophilic cytoplasm, and one large prominent central nucleolus. MYC immunostaining and *MYC* split FISH yielded positive results.

characterized by a round to ovoid nucleus with a large, prominent central nucleolus and moderately abundant basophilic cytoplasm (immunoblastoid BPDCN) (Figure 1B).[6] Approximately 13% of patients exhibit an intermediate cellular morphology between classic BPDCN and immunoblastoid BPDCN, or a mixture of both.[6] Classic BPDCN has some continuous morphological variations, including pleomorphic, lymphoblastoid, or monocytoid features.[86] Due to its morphological similarities, immunoblastoid BPDCN is occasionally misdiagnosed as large B-cell lymphomas with immunoblast predominance, such as primary cutaneous diffuse large B-cell lymphoma, leg type.[6] Notably, characteristics such as a reticular pattern even in areas without intervening fibrous connective tissue, cell-to-cell adhesion, nuclei with a sigmoid or snake-like shape, eosinophilic abundant cytoplasm, or apparent cytoplasmic granules are more common in AML or myeloid sarcoma (MS) and are generally not observed in BPDCN.[86]

The findings observed in bone marrow smear specimens have been extensively documented by Garnache-Ottou and colleagues.[62] They examined 73 patients with BPDCN, noting that the tumor cells typically exhibited light-blue/gray cytoplasm with some clearer areas ("cloudy sky" appearance) and frequent small vacuoles. Although granules are not generally observed in the cytoplasm of BPDCN tumor cells, their study identified peroxidase-negative azurophilic granules in a small fraction of the tumor cells in 17% of patients. Lymphoid-like cells were predominant in 18% of the patients, while a few patients showed monoblast-like morphology in most of the tumor cells. Figure 2 shows a Giemsa-stained specimen from one patient in our study.

IMMUNOPHENOTYPE

Table 1 presents the immunophenotypes of BPDCN. Generally, BPDCN cells lack lineage markers, but they express CD4, CD56, and pDC markers such as CD123, TCL1, TCF4, CD303/BDCA2, CD304/BDCA4, CD2AP, BCL11A,[24,87] and SPIB[88] (Figure 3). CD4 positivity has been reported in 92%–98% of patients,[4,6,58] while CD56 in 90%–97% of patients.[6,36,58,89] Although CD123 is typically positive in BPDCN, rare cases show negative expression.[6,86,90,91] CD123 positivity prior to treatment usually persists even after tagraxofusp treatment.[92,93] CD303/BDCA2 is highly specific to pDCs, but the positivity rate in BPDCN varies among studies (44%–98%).[6,58,94,95] This variability may be attributed to differences in cutoff values, antibody variations,[23] technical limitations in immunohistochemistry (IHC), and cases with

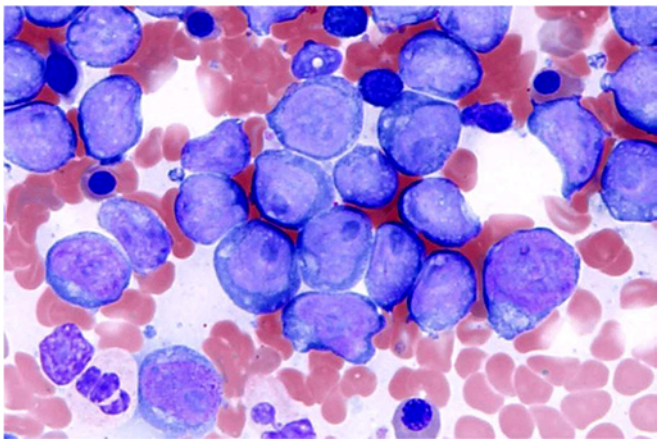

Fig. 2. A bone marrow aspirate from a patient with BPDCN
Tumor cells with round-to-irregular nuclei, basophilic cytoplasm with a "cloudy-sky" appearance, and small vacuoles in the cytoplasm (Giemsa staining).

inherently low expression. Immunostaining intensity of CD303/BDCA2 can also vary among patients, with one study reporting particularly weak expression in bone marrow specimens.[89] TCL1 positivity has been reported in 89%–99% of patients with BPDCN.[6,24,58,89,96] In 2016, TCF4 was identified as a master regulator of pDC differentiation and neoplastic maintenance in BPDCN; its immunostaining has been suggested as a pDC-specific marker useful for BPDCN diagnosis.[97] TCF4 was positive in all cases of BPDCN evaluated, demonstrating high sensitivity.[86,92,98]

B-cell markers such as CD19, CD20, and immunoglobulins are generally negative in BPDCN. CD22 is also usually negative but may show positivity in flow cytometry (FCM) particularly when using the sHCL-1 monoclonal antibody.[99] Garnache-Ottou and colleagues found surface CD22 positivity in 8 out of 40 patients, but cytoplasmic CD22 expression was not observed in any of the 35 patients analyzed.[62] CD79a is occasionally positive, with rates ranging from

Table 1. Immunophenotypes of BPDCN

Frequency of positivity	Markers
Positive (>90% of cases)	CD4, CD56[ł], CD123, TCF4, TCL1, BDCA2/CD303*, CD2AP, BCL11A, LCA, CD43, SpiB, HLA-DR, BCL2
Frequent	CD38, CD7*, CD33, TdT*, MYC, CD68*
Occasional	CD1c/BDCA1, CD2, CD5, CD10[#], CD13, CD79a, S100, CD117, MUM1/IRF4*, BCL6
Negative	CD1a, CD3, CD8, CD11c, CD14, CD16, CD19, CD20, CD25, CD30, CD34, CD57, CD138, CD141/BDCA3, lysozyme, myeloperoxidase, perforin, TIA-1, EBER, granzyme B, langerin/CD207

*The positivity rate varies among reports.
[ł] The positivity rate is lower in MYC[+]BPDCN (78%).
[#] The positivity rate is higher in MYC[+]BPDCN (41%).
The underlined markers are particularly useful for distinguishing BPDCN from other conditions.

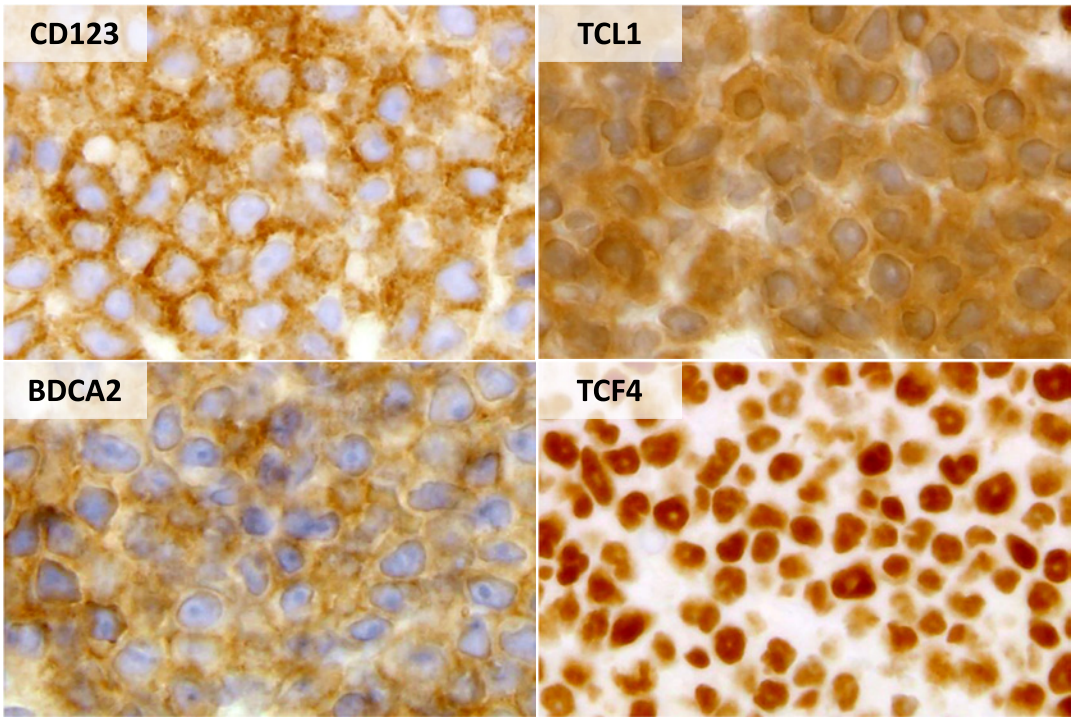

Fig. 3. pDC markers in BPDCN
A patient of BPDCN shows positivity for CD123, TCL1, BDCA2, and TCF4.

0%–13%.[6,59,62,64]

T-cell markers such as cytoplasmic and surface CD3 are generally negative, although positivity is rarely observed, particularly with the use of polyclonal anti-CD3e antibodies.[4,15,89] CD7, although showing variability in positivity rates across studies, is often positive (3%–71%).[6,13,14,58,64,96] CD2 is positive in 20%–40% of patients.[4,6,14,58,59] CD5 is positive in only a small proportion of patients.[6,14,59,62] CD8, CD57, and CD16 are rarely expressed and generally negative.[6,59,62]

Myeloperoxidase (MPO) and lysozyme are not expressed, but positivity for other myeloid markers is commonly observed.[62] CD68 shows variable positivity rates among studies (23%–98%).[6,58,59,61,96] Dot-like positivity in the Golgi area can be observed via IHC,[89] although this pattern may be limited to scattered cells only.[96] CD33 is frequently positive (34%–92%),[6,59,66,100] while CD13 is less commonly positive (2%–11%).[6,59,62] CD14 is rarely positive.[6,94] The markers of classic or conventional dendritic cells (cDCs), such as CD11c and CD141/BDCA3 (cDC1 marker), are negative.[62,64] However, a low-level expression of CD1c/BDCA1 (a cDC2 marker) has been reported in 5 of 23 patients (22%).[62] As for immature markers, CD34 is regularly negative.[6,30,45,62] If the tumor cells in a patient suspected with BPDCN are diffusely or partially positive for CD34, an alternative diagnosis of AML or pDC-AML should be considered. CD117 is positive in 5%–20% of patients,[6,59,62,64] and its positivity has been associated with less frequent CD303/BDCA2 expression (25% in CD117+ patients vs. 78% in CD117− patients).[62] TdT positivity is observed in 10%–59% of patients, depending partly on the cutoff value used.[4,58,59,62,96]

The markers that are positive in normal pDCs but negative in BPDCN include granzyme B.[5] The expression levels of CD303/BDCA2, CD304/BDCA4, CD38, and CD123 are lower in BPDCN compared with normal pDCs,[94,101] while the expression level of HLA-DR is higher in BPDCN.[94] CD56 is typically negative in normal pDCs, but a small subset of normal pDCs (median 4.5%–5%[94,101]) may express CD56.[18,102] BCL2 is strongly positive in BPDCN, but not in normal pDCs.[6,52,96] Additionally, IRF4 (MUM1) can be expressed in BPDCN, which is not observed in normal pDCs.[6,52,89,96] IRF8 is positive in both normal pDCs and BPDCN.[24,90,92,96,103] The similarities and differences in the immunophenotype between normal pDCs and BPDCN are summarized in Table 2.

DIAGNOSIS OF BPDCN

Clinically, the most significant differential diagnosis of BPDCN is AML with skin infiltration (leukemia cutis) or MS. AML/MS, particularly in patients with monocytic differentiation, can exhibit similar marker profiles and clinical features to BPDCN. Consequently, diagnostic strategies for differentiating BPDCN from AML have been actively explored. Differentiation based on a single marker was not sufficient in terms of specificity or sensitivity.[86,104] Therefore, diagnostic panels that combine multiple markers have been investigated. Two primary modalities for assessing marker expression are FCM and IHC. FCM is commonly used for analyzing bone marrow and peripheral blood specimens and is particularly valuable when tumor cell quantities are low, such as during the detection of MRD. It facilitates the identification of more than one cell population, potentially revealing the differentiation of myeloblasts into pDCs in pDC-AML, which does not occur in BPDCN. However, challenges arise, including the difficulty in obtaining sufficient cellular material from small skin biopsies, which are often encountered in BPDCN, and the scarcity of facilities equipped to perform FCM with a comprehensive antibody panel for BPDCN. By contrast, IHC is more feasible in resource-limited settings compared with FCM and easier to perform on skin samples, although it may struggle to detect small cell populations. Both IHC and FCM have their respective advantages and limitations. Hence, establishing standardized criteria for effective diagnostic practices using either method is crucial. Table 3 presents the proposed diagnostic criteria for BPDCN.

The French group primarily employs FCM to diagnose BPDCN using bone marrow or peripheral blood specimens. In 2009, they devised a scoring system to differentiate BPDCN (pDC leukemia (pDCL)) from other types of leukemia, based on the findings of 16 patients with pDCL, 4 with atypical pDCL, and 113 with acute leukemia (Table 3).[95]

Table 2. Differences and similarities in immunophenotype between MPDCP and BPDCN in comparison to normal pDCs

	MPDCP (in CMML patients)	BPDCN
Positive as normal pDC	CD4, CD123, TCL1, TCF4, CD303/BDCA2, CD304/BDCA4, CD2AP, HLA-DR, CD45RA	
	granzyme B, CD68, low MIB-1 index (<10%)	
Aberrantly positive	occasional: CD2, CD5, CD7, CD10, CD13, CD14, CD15, CD33, CD56 (weak/focal)	>90%: CD56*, BCL2 frequent: CD7, CD33, MYC, TdT, relatively high MIB-1 index
Negative as normal pDC	CD1a, CD3, CD8, CD11c, CD19, CD20, CD30, lysozyme, myeloperoxidase, perforin, TIA-1, EBER, S100	
	TdT	
Aberrantly negative	occasional: TCL1, CD303/BDCA2	granzyme B, occasional: CD68†, CD303/BDCA2

The markers underlined are those with particularly different positivity rates between pDCs in MPDCP and BPDCN.
*A small subset of CD56-positive cells is present in normal pDCs.
† The positivity rate of CD68 in BPDCN varies across studies. Some reports have suggested the presence of a dot-like pattern in CD68 immunohistochemistry in BPDCN.

Table 3. Diagnostic criteria for BPDCN

author	year	reference no.	modality	diseases examined and number of cases	requirement for the diagnosis of BPDCN
Garnache-Ottou *et al.*	2009	95	FCM	pDCL 16, atypical pDCL 4, non-pDC acute leukemia 113	CD4+, CD56+/-, CD11c-, cCD3-, cCD79a-, MPO-; 1 point (mandatory), CD123 +/high; 1 point, BDCA4/CD303+; 1point, BDCA2/CD303+; 2 points.[#] ► Diagnose as BPDCN if total score >2 points
Julia *et al.*	2014	58	IHC	BPDCN 91	4 or all of the 5 markers (CD4, CD56, CD123, TCL1, BDCA2) are positive
Sangle *et al.**	2014	105	IHC	BPDCN 17, MS 23	(CD4 + CD56 + CD123 + TCL1 + MxA) - (lysozyme + MPO)[†] ► Diagnose as BPDCN if total score ≥2
Sakamoto *et al.**[ǂ]	2018	6	IHC	BPDCN 118	2 or all of the 3 markers (CD123, TCL1, BDCA2) are positive (If they show atypical staining patterns, confirmation of the negativity of lysozyme and MPO is required.)
Sukswai *et al.*	2019	98	IHC	BPDCN 48, non-BPDCN hematopoietic neoplasm 464	Both CD123 and TCF4 are positive with dual-color IHC (the H-score >20)
WHO classification (5th ed.)	2024 (the online beta version: 2022)	30	-	-	"Expression of CD123 and one other pDC marker (TCF4, TCL1, CD303, or CD304) in addition to CD4 and/or CD56" or "Expression of any 3 pDC markers (CD123, TCF4, TCL1, CD303, CD304) and absent expression of all expected negative markers (CD3, CD14, CD19, CD34, lysozyme, myeloperoxidase)"
Sakamoto *et al.**	2023	86	IHC	BPDCN 215, BPDCN-mimics 67, (AML/MS 21 as validation cohort)	2 or all of the 3 markers (TCF4, CD123, TCL1) are positive (>60%) (If TCF4 is weakly and/or partially positive, both CD123 and TCL1 must be positive.) (If TCF4 negative or lysozyme positive, BPDCN is excluded)

BPDCN, blastic plasmacytoid dendritic cell neoplasm; pDCL, plasmacytoid dendritic cell leukemia; AML, acute myeloid leukemia; MS, myeloid sarcoma; MPO, myeloperoxidase; FCM, flow cytometry; IHC, immunohistochemistry
[#]+ indicates that more than 20% of the blasts expressed the marker.
[†]positive (>30%), 1 point; negative, -1 point; not done/equivocal, 0 point
[ǂ]Details are described in their study published in 2023 (reference no. 86).
*These criteria were primarily aimed at differentiating BPDCN from acute myeloid leukemia and myeloid sarcoma (AML/MS) but not from acute lymphoblastic leukemia.

The scoring system requires meeting the following criteria: CD4+, CD56+/−, CD11c−, cCD3−, cCD79a−, and MPO−. A score of 1 point is assigned when each of these essential conditions is met. CD123, which was frequently positive in patients with acute leukemia, is assigned 1 point only when it shows strong expression. CD303/BDCA2, although showing sensitivity rates of 75% in the typical pDCL group and 50% in the atypical group, was negative in all patients with non-pDCL, demonstrating high specificity for pDCL and thus earning 2 points. CD304/BDCA4, despite its high sensitivity, was positive in 12% of patients with non-pDCL, and its utility in differentiation was lower, earning only 1 point. A total score of more than 2 points supports the diagnosis of BPDCN. The same research group presented a flowchart for diagnosing BPDCN in their 2019 publication.[62] The initial step involves confirming the absence of specific lineage markers (cytoplasmic/surface CD3−, CD19−, cytoplasmic CD22−, MPO−, CD14−, CD11c−/low, and CD64−/low). If high expression of CD123 and HLA-DR is observed, along with CD4 (+/low) and CD56 (+/low/−), BPDCN is suspected. The diagnosis can be confirmed by the presence of cTCL1+, CD303/BDCA2 (+/low), and CD304/BDCA4 (+/low).

With regard to the diagnostic criteria using IHC, Facchetti reviewed the IHC results of over 300 patients and concluded that the addition of CD123 and TCL1 to the classic markers CD4 and CD56 provides the most reliable and useful markers for diagnosing BPDCN.[89] Cronin and colleagues reported that at least three of the four markers (CD4, CD56, CD123, and TCL1) were positive in patients with BPDCN, while at most two markers were positive in patients with leukemia cutis.[100] Alayed *et al.* discussed that the detection of TCL1 or CD303/BDCA2 in $CD4^+$ $CD56^+$ $CD123^+$ neoplasms, in the absence of lineage-specific markers, likely represents a sufficiently specific approach for diagnosing BPDCN.[42] Sangle *et al.* reported a scoring method for differentiating BPDCN from MS (Table 3).[105] Their panel included seven markers: CD4, CD56, CD123, TCL1, MxA, lysozyme, and MPO. Additionally, they proposed that a simplified approach using just CD56 and TCL1 is generally sufficient for distinguishing between these conditions. Julia *et al.* analyzed skin biopsy specimens from 91 patients with BPDCN identified in the French cutaneous lymphoma database.[58] They found that only 46% of patients expressed all five markers considered characteristic of BPDCN (CD4, CD56, CD123, BDCA2, and TCL1). They suggested that a diagnosis of BPDCN could be made if at least four of these five markers were positive (Table 3). This criterion was probably the most reliable and widely used IHC-based diagnostic criterion for BPDCN prior

to the introduction of TCF4.

As discussed above, the traditional diagnostic criteria for BPDCN often include positivity for CD4, CD56, and CD123, but these markers can also be positive in AML/MS. Furthermore, a non-negligible number of BPDCN cases are negative for CD4[2,4,88,96] and CD56[6,36,58,89]. In a review of case reports on BPDCN published between 2010 and 2021, 67% (188/277) of patients either did not use or only used one pDC marker (predominantly CD123) for diagnosis without further confirmation.[86] Similarly, a study found that half of the Italian hematologists surveyed used an FCM panel with a sufficient number of pDC markers only in selected cases to diagnose leukemic BPDCN.[106] In our study, even when all three markers (CD4, CD56, and CD123) were positive in patients with suspected BPDCN, 12% (24/205 patients) were found to have non-BPDCN.[86] Accurate differentiation is necessary as CD123-positive AML has a significantly worse prognosis and requires different treatment approaches compared with BPDCN.[86] Therefore, confirming the expression of more specific pDC markers and the absence of myeloid markers is essential, even if CD4, CD56, and CD123 are positive.

Following the identification of TCF4 in 2016, Sukswai *et al.* reported that the double staining of TCF4 and CD123 yields high sensitivity and specificity for diagnosing BPDCN (Table 3).[98] They used the H-score, calculated as the product of the staining extent and intensity score (negative = 0, weak = 1, moderate = 2, and strong = 3), with a score of ≥20 indicating a positive result. They observed that TCF4 and CD123 were co-expressed in all 48 patients with BPDCN, while only one patient with B-ALL exhibited co-expression among the 464 with non-BPDCN hematologic malignancies. Notably, CD123 was positive in 3 of 23 patients with B-ALL, while TCF4 was positive in 7 of 23 patients with B-ALL, 6 of 8 patients with CLL/SLL, 3 of 44 patients with DLBCL, 1 of 3 patients with Merkel cell carcinoma, and 1 of 44 patients with myeloproliferative neoplasm.

After analyzing 284 patients suspected or diagnosed with BPDCN at various institutions and 21 patients with AML/MS as a validation cohort, we proposed a criterion based on the IHC results. BPDCN can be diagnosed when at least two of the following markers are positive in >60% of the tumor cells in suspected cases: TCF4, CD123, and TCL1 (Table 3).[86] If TCF4 shows weak or partial positivity, both CD123 and TCL1 must also be positive to confirm the diagnosis of BPDCN. This condition was included because, without considering staining intensity, CD123 was positive in 34 of 65 patients (52%) and TCF4 in 6 of 49 patients (12%) of BPDCN mimics, and both CD123 and TCF4 were positive in the blasts of two patients with AML. Consequently, the specificity of TCF4 may not be high enough in diagnosing BPDCN. If the histological findings suggest AML/MS, such as the reticular pattern, confirmation of TCF4 negativity and/or lysozyme positivity can immediately exclude BPDCN. When only conventional markers (CD4, CD56, and CD123) are available, confirming the absence of lysozyme (and MPO) is useful for diagnosing BPDCN. In cases where all three markers were positive and lysozyme was negative, 79 of 80 patients (99%) were diagnosed with BPDCN.[86] Additionally, a diagnostic criterion based on the positivity of at least two out of the three markers (CD123, BDCA2, and TCL1) also demonstrated comparable accuracy (Table 3).[6,86] If atypical staining patterns are observed with these markers, the absence of both MPO and lysozyme must be confirmed.

DETECTION OF MRD

A small number of pDCs are found in the normal bone marrow, with a median of 0.11% (range: 0.01%–0.43%) of the total nucleated cells.[94] Additionally, the reactive proliferation of pDCs can occur in various conditions. Evaluating MRD or assessing for minor infiltration of BPDCN cells can be challenging due to the difficulty in distinguishing BPDCN from normal/reactive pDCs. Several methods have been proposed to address this issue. When tumor cells are known to be CD56-positive, detecting cells co-expressing CD56 and pDC markers represents one useful approach, as exemplified by double staining for TCF4 and CD56.[92] However, as mentioned earlier, subsets of CD56-positive normal pDCs also exist. Double staining with TCF4/CD123 is useful,[92,98] but reactive pDCs are also test positive for these markers.[92,94]

Wang *et al.* reported that a 10-color FCM panel including CD2, CD4, CD7, CD38, CD45, CD56, CD64, CD123, CD303/BDCA2, and HLA-DR was useful for initial workup and assessing MRD in patients with BPDCN.[94] They first gated CD123 bright cells using a CD123/SSc plot, then excluded basophils that presented as CD123+ HLA-DR− cells. Next, monocytes, which could express bright CD123 and HLA-DR, were excluded using CD64. Finally, the distribution of pDCs was visualized on a CD45/SSc plot. CD303/BDCA2 and CD4 were included as additional pDC markers, while CD2, CD7, CD38, and CD56 helped differentiate between reactive and neoplastic pDCs.[94,107] In a subsequent review by the same group, CD34 was added to highlight the earliest immature pDCs.[107] They observed that the CD56+ subset of reactive pDCs consistently tested positive for CD2 and CD303/BDCA2, was brightly positive for CD38, and tested negative for CD7.[94] By contrast, BPDCN cells often showed aberrant negativity for CD2 (81%) and CD303/BDCA2 (56%), and had decreased/negative CD38 (82%), while showing positivity for CD7 (64%), indicating a distinct difference.[94]

Wu *et al.* reported that the double staining of SOX4/CD123 is useful for distinguishing BPDCN from reactive pDCs and other hematologic tumors.[92] *SOX4* is upregulated in BPDCN compared with reactive pDCs.[46] In their study, all 18 patients with BPDCN showed positive results for SOX4/CD123 double staining, while none of the 30 samples with reactive pDCs exhibited positivity. Among 37 patients with other hematologic tumors, only one patient who had a monocytic myeloid sarcoma obtained a positive result, leading to a sensitivity of 100% and a specificity of 98%.[92] However, among five patients with MRD of BPDCN, one tested negative for SOX4/CD123.

To detect MRD or minimal infiltration of BPDCN, the

use of FCM with an extensive panel is ideal. However, the previously mentioned double-staining techniques can also be beneficial in clinical practice. In cases with *MYC* or *MYB*/*MYBL1* rearrangements, fluorescence in situ hybridization (FISH) to detect them may also be valuable.

MYC AND *MYB/MYBL1* REARRANGEMENTS

MYC is an established oncogene located at 8q24.21 and plays critical roles in cell proliferation, metabolism, and genomic stability.[108] Although 8q24 rearrangements are commonly associated with Burkitt lymphoma and diffuse large B-cell lymphoma, sporadic case reports have also documented such rearrangements in BPDCN.[109–114] Our study found that 8q24 rearrangement and MYC expression were detected in 38% (41/109) of patients with BPDCN, termed MYC$^+$BPDCN.[6] Interestingly, immunoblastoid cytomorphology was significantly associated with this MYC alteration (Figure 1). Clinically, MYC$^+$BPDCN was associated with older age at diagnosis and poorer prognosis compared with MYC-negative BPDCN (MYC$^-$BPDCN), which referred to cases lacking both 8q24 rearrangement and MYC expression. With regard to the gross appearance of the skin lesions, 92% of patients with MYC$^+$BPDCN had tumors/nodules, while relatively few patients presented with patches or plaques, which were more commonly observed in MYC$^-$BPDCN.[6] The differences in immunophenotypes were also observed: MYC$^+$BPDCN showed a significantly lower frequency of CD56 positivity (78% vs. 98%) and a higher frequency of CD10 positivity (41% vs. 6%) compared with MYC$^-$BPDCN.

In some patients with MYC$^+$BPDCN, the 8q24 rearrangement could not be detected by FISH using conventional *MYC* break-apart probe sets.[6] This suggests that the breakpoint at 8q24 lies outside the major breakpoint clusters commonly observed in other tumors. Additionally, a case series using conventional karyotyping showed a low detection rate of 8q24 rearrangements in BPDCN (12%, 5/41 patients).[115] Therefore, even if the rearrangement is not detected by standard karyotyping or split FISH assay, a diagnosis of MYC$^+$BPDCN should not be excluded when immunoblastoid cytomorphology is present and MYC immunostaining is positive.

The most frequent partner of the 8q24 rearrangement in MYC$^+$BPDCN is 6p21 (22/39 patients, 56%).[6] The translocation t(6;8)(p21;q24) has been sporadically reported in BPDCN[26,37,109–113,115–117]; in one such case, a chimeric transcript involving *SUPT3H* (6p21) and *PVT1* (located 50 kb downstream of *MYC*) was detected.[113] Apart from BPDCN, this rearrangement has only been reported in three patients: one with follicular lymphoma[118] and two with multiple myeloma.[119,120] In myeloid tumors, 8q24 rearrangements have been rarely documented,[121] except for t(3;8)(q26;q24), which involves *MECOM* (*MDS1* and *EVI1* complex locus) at 3q26.2.[122] Thus, t(6;8)(p21;q24) is nearly specific to BPDCN and could be a valuable diagnostic marker. The genomic sequence of *SUPT3H* overlaps with *RUNX2*, which is highly expressed[25] and identified as a super-enhancer gene in BPDCN.[97] The t(6;8)(p21;q24) is believed to bring the *RUNX2* superenhancer into close proximity with *MYC*, resulting in the overexpression of MYC.[6,109,123]

The rearrangements of *MYB*, a gene encoding a transcription factor located at 6q23.3, are also recurrently observed in patients with BPDCN, especially in children and young adults. Suzuki *et al.* detected *MYB* rearrangements in all five pediatric patients and 4/9 adult patients with BPDCN using RNA sequencing.[124] The identified fusion genes included *MYB*::*PLEKHO1*, *MYB*::*ZFAT*, *MYB*::*DCPS*, and *MYB*::*MIR3134*, which were thought to result in the truncation of the negative regulator domain of MYB, leading to its activation. *MYB*::*PAIP1* fusion was also reported in a pediatric patient.[125] In our cohort, *MYB* rearrangements were identified by FISH assay in 19 of 96 (20%) patients with BPDCN.[6] Additionally, a rearrangement of *MYBL1*, located at 8q13.1 and encoding a protein with a similar structure to MYB, was identified in 1 of 95 (1%) patients. The median age of patients with *MYB*/*MYBL1* rearrangements was 50 years (range: 3–87 years). Notably, no *MYB*/*MYBL1* rearrangements were observed in patients with MYC$^+$BPDCN, suggesting mutual exclusivity, while they were found in 18 of 51 (35%) patients with MYC$^-$BPDCN. *MYB*/*MYBL1* rearrangements are common in adenoid cystic carcinoma.[126] *MYB* rearrangements are also observed in hematopoietic neoplasms, such as *TRB*::*MYB* and tandem duplication in T-ALL,[127,128] *MYB*::*TYK2* in B-ALL,[129] *MYB*::*GATA1* in acute basophilic leukemia,[130] acute erythroid leukemia,[131] and AML FAB-M5.[132] Although *MYB* rearrangements are not specific to BPDCN, they may still aid in its diagnosis when the differential diagnosis has been sufficiently narrowed.

MATURE PLASMACYTOID DENDRITIC CELL PROLIFERATION ASSOCIATED WITH MYELOID NEOPLASM

MPDCP is characterized by the proliferation of mature pDCs in the skin, lymph nodes, bone marrow, and other tissues in association with myeloid neoplasms.[5] It serves as a potential differential diagnosis for BPDCN. Studies investigating MPDCP involving lymph nodes began in the 1980s.[133] In 2004, Vermi *et al.* reported a series of nine patients, including those with extranodal involvement, refining and expanding the concept of MPDCP.[134] MPDCP is most frequently observed in patients with chronic myelomonocytic leukemia (CMML),[134,135] where it occurs in >20% of cases.[136–138] Other underlying myeloid neoplasms described include AML, myelodysplastic syndrome, and various myeloproliferative neoplasms. Sporadic studies have also documented MPDCP-like pDC proliferation in lymphoid neoplasms.[139,140] Traditionally, the proliferation of pDCs associated with CMML and AML has been categorized under the term MPDCP and classified as such in the 5th edition of the WHO classification.[30] Emerging evidence, however, suggests there could be potential differences in their pathogenic mechanisms and phenotypes. Those observed in CMML are occasionally

designated as "pDC-CMML"[39,101] or "pDC-rich CMML," in alignment with the term "pDC-AML."[138]

Histopathologically, the pDCs in MPDCP typically form nodules and show cytomorphology that closely resembles that of mature normal pDCs. They are medium-sized cells with eccentrically located round or oval nuclei containing clumped chromatin and typically lack mitotic figures.[30] Some patients demonstrated perivascular or diffuse infiltration of pDCs, always intermingled with T-cells, in the dermis, a condition referred to as "pDC dermatosis."[141,142] The concurrent proliferation of indeterminate dendritic cells and pDCs has also been reported in skin samples from patients with CMML and other conditions.[135,142] A comparison of the immunophenotype of MPDCP and BPDCN is presented in Table 2. Overall, it is similar to normal mature pDCs.[5,30,39,92,107,133,135,138] However, the aberrant loss of CD303/BDCA2[135] and TCL1[24] and the expression of CD2, CD5, CD7, CD10, CD13, CD14, CD15, and CD33, may be observed.[5,135] Meanwhile, CD56 is usually negative but weak/focal expression can be observed.[5,24]

To differentiate MPDCP from BPDCN, determining the presence of underlying myeloid neoplasms is crucial. Hence, engaging in thorough discussions with clinicians is essential. Histopathological features that may indicate MPDCP include mature cell morphology,[133] nodular distribution, CD56 negativity, and granzyme B positivity. Although TdT can be positive in BPDCN, it is typically negative in MPDCP associated with CMML.[24] In addition, a lower MIB-1 index[134,143] and intense CD68 staining[89] in MPDCP may aid in differentiation. However, due to the limited number of patients studied, definitive diagnostic criteria have not yet been established.

Previous studies have suggested that pDCs in MPDCP are clonally related to the underlying myeloid neoplasm.[114,134,141,143,144] Lucas *et al.* classified CMML cases based on the presence of pDC proliferation, with cutoff values of 1.2% in the bone marrow and 0.6% in the peripheral blood of mononucleated cells. Their findings revealed that patients with CMML exhibiting pDC proliferation had a higher frequency of RAS pathway mutations compared with those without pDC proliferation (59% vs. 26% in the U.S. cohort and 69% vs. 40% in the French cohort, respectively).[138] In several patients, mutations in RAS pathway genes and genes like *TET2* and *ASXL1* were found to be shared between CMML clones (monocytes) and pDCs, supporting the idea that pDCs are an integral part of the leukemia clone.[138] Additionally, CD34+ cells in patients with CMML exhibiting pDC proliferation were shown to generate a substantial number of pDCs even in the absence of FMS-like tyrosine kinase 3-ligand in vitro. Bone marrow infiltration by pDCs (defined as >5% of bone marrow cells in pathological specimens) was associated with leukemic transformation, with a hazard ratio of 2.59. Although MPDCP is generally associated with a poor prognosis,[133,134] its impact on prognosis when involving the skin remains unclear.[141,145]

pDC-AML

An increase in cDCs or pDCs in peripheral blood has been observed in patients with AML.[146,147] In 2020, two notable studies by Xiao *et al.* and Zalmai *et al.* examined patients with pDC-AML.[148,149] pDC-AML is observed in approximately 3%–5% of patients with AML,[148,150] with a median age of 68–70 years, and a higher prevalence in men than women (M:F = 2.1–4:1).[148–150] Patients with pDC-AML may have a higher incidence of skin lesions (14%–27%) compared with those with standard AML,[148,149] although this occurrence is less frequent compared with that in BPDCN.[148] pDC expansion is commonly defined as comprising ≥2% of nucleated cells in the bone marrow.[148,150] The proportion of pDCs observed in patients with pDC-AML varies widely, with a median of 6.6%–15% and a range of 2%–36%.[148–150] In terms of the subtypes of AML, AML with an immature myeloid (FAB M0) and myelomonocytic immunophenotype are the most common, often fulfilling the criteria for mixed-phenotype acute leukemia.[148,149,151,152] Secondary AML, including AML with myelodysplasia-related changes and therapy-related AML, is frequently observed.[148,149] Histopathologically, pDC-AML frequently shows an interstitial distribution, although loose clusters may occasionally be observed, while MPDCP in CMML typically presents with nodular formation. No specific chromosomal abnormalities were identified, but the most commonly observed karyotypic abnormality was the deletion of chromosome 7.[148,152] Adverse cytogenetics were found in 23% of patients, a frequency similar to that in AML without pDC proliferation.[148] *RUNX1* mutations were detected in 64%–71% of patients with pDC-AML[148,150] and in 100% of patients with M0-pDC-AML.[149] When including translocations, Xiao *et al.* reported *RUNX1* abnormalities in 32 of 41 (78%) patients with pDC-AML, but in only 14 of 100 (14%) patients with AML without pDC proliferation.[148] *RUNX1* mutations rarely occur in BPDCN (2% of patients).[44,148,150]

Table 4 summarizes the results from five studies that investigated the immunophenotype of pDC-AML with a relatively large number of patients.[148–152] In pDC-AML, pDCs exhibited positivity for CD4, CD123, and CD304/BDCA4, but negativity for MPO, similar to BPDCN. However, the positivity rates for CD56 (0%–13%) and TCL1 (37%) differed from those observed in BPDCN. Even in patients who tested positive for TCL1, the expression intensity was lower compared with BPDCN and normal pDCs.[149] The positivity rate for CD303/BDCA2 was higher than that in BPDCN, with stronger expression intensity.[149] Notably, a majority of cases were CD34 positive (101 of 130 cases (78%)), although the positivity rates varied across studies (33%, 61%, and 96%, respectively).[148–150] CD34 positivity represents a significant point of differentiation from BPDCN. Additionally, markers such as CD13, CD22, CD25, CD36, CD38, and CD117 were more frequently positive in pDC-AML than in BPDCN.

Myeloblasts in pDC-AML frequently expressed CD123 at low levels (63 of 77 patients, 82%) on FCM analysis. These myeloblasts were typically immature, showing positivity for

Table 4. Immunophenotype of pDCs and myeloblasts in pDC-AML

	pDC in pDC-AML			myeloblasts in pDC-AML		
	+	tested	%	+	tested	%
CD1c	1	20	5	0	20	0
CD2	27	94	29	7	53	13
cCD3	1	57	2	0	4	0
CD4	105	111	95	6	70	9
CD5	15	97	15	5	56	9
CD7	46	108	43	25	70	36
CD10	0	14	0	0	14	0
CD11b	1	21	5	4	21	19
CD11c	3	29	10	0	29	0
CD13	48	128	38	66	76	87
CD14	0	130	0	0	77	0
CD15	4	88	5	8	35	23
CD19	0	53	0			
CD22	40	74	54	6	21	29
CD25	27	53	51			
CD33	50	120	42	55	77	71
CD34	101	130	78	55	77	71
CD36	51	53	96	5	14	36
CD38	107	108	99	36	55	65
CD45	82	82	100	29	29	100
CD56	8	112	7	8	70	11
CD64	6	107	6	7	55	13
CD117	32	89	36	32	36	89
CD123	130	130	100	63	77	82
CD141	4	18	22	0	18	0
CD303/BDCA2	44	51	86	0	36	0
CD304/BDCA4	31	35	89	0	36	0
CXCR4	14	14	100			
HLA-DR	126	126	100	64	73	88
MPO	0	72	0	1	20	5
TCL1	14	38	37	0	12	0
TdT	24	71	34	5	9	56

The markers in bold are those with particularly different positivity rates between pDCs in pDC-AML and BPDCN.

CD34 (55 of 77 patients, 71%) and CD117 (32 of 36 patients, 89%), while other pDC markers (CD303/BDCA2, CD304/BDCA4, and TCL1) were not expressed. Only a few patients demonstrated positivity for CD4 (6 of 70 patients, 9%) and CD56 (8 of 70 patients, 11%). Furthermore, in some patients with pDC-AML, maturation of CD34+ blasts toward the pDC lineage was demonstrated by FCM analysis, characterized by the downregulation of CD34 expression and the upregulation of CD123, CD303/BDCA2, and CD304/BDCA4 expression.[149,151,152] This maturation process could mimic the normal maturation process of pDCs.[153] These findings suggest that pDCs may originate from immature CD34+ blasts in pDC-AML.[149] Xiao *et al.* demonstrated that leukemic blasts from patients with pDC-AML exhibit high pDC output in vitro, indicating the potential for these blasts to differentiate into pDCs.[148] Moreover, monocytes, pDCs, and blasts in pDC-AML share common mutations, indicating clonal relatedness.[148,149]

The pDCs observed in pDC-AML differ from those in CMML, with many cases showing CD34 positivity, which may challenge the characterization of these cells as "mature" pDC proliferation.[149] It remains unclear whether pDC-AML, characterized by frequent *RUNX1* mutations, should be classified as a distinct entity or included within the traditional scope of MPDCP. Cases of AML have been reported that showed the classic MPDCP features of CD34-negative pDCs with nodular proliferation, suggesting that not all AML cases with pDC expansions should be labeled as "pDC-AML." Furthermore, the concept of "immature BPDCN," characterized by the co-existence of CD34+ myeloblasts and pDCs that are partially positive for CD34 and exhibit CD56 negativity or dim expression with minimal extramedullary involvement, was previously proposed. However, current understanding indicates that these cases were likely to represent pDC-AML.[149,151] Conversely, it is reasonable to consider BPDCN as CD34 negative.

CONCLUSIONS AND PERSPECTIVES

Since the emergence of the BPDCN disease concept, the diagnostic criteria for BPDCN have been progressively refined. Concurrently, researchers have continuously uncovered new insights into clonal pDCs, adding complexity to the classification of pDC neoplasms. Accurate diagnosis and classification are essential for understanding the pathogenesis of pDC neoplasms and ensuring appropriate treatment for patients. As new findings emerge, they may further refine the classification and diagnostic process, necessitating ongoing updates to maintain diagnostic accuracy.

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest directly relevant to this article.

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