Blastic Plasmacytoid Dendritic Cell Neoplasm: A Review of Diagnosis, Pathology, and Therapy

Roman Shapiro1, Nikhil Sangle2, Mike Keeney3, Ian H. Chin-Yee4, Cyrus C. Hsia4 and Selay Lam5,*

1Internal Medicine resident, London Health Science Centre, London ON Canada
2Department of Pathology, London Health Science Centre, London ON Canada
3Lawson Health Research Institute, London ON Canada
4Division of Hematology, Department of Medicine, London Health Science Centre, London ON Canada
5UWO Division of Hematology, London Health Sciences Centre (LHSC), Victoria Hospital 800 Commissioners Rd. East, London, Ontario N6A 5W9, USA

Abstract

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare malignancy of dendritic cell precursors classified as a subset of acute myeloid leukemia according to WHO. It commonly presents with dermal infiltration of plasmacytoid dendritic cells that have the morphologic appearance of medium-sized blasts with irregular nuclei, faint chromatin, at least one nucleolus per cell and scant cytoplasm, expressing a CD4+CD56+CD123+lin- immunophenotype. Patients typically have discoloured cutaneous lesions that grow in size, and the diagnosis of BPDCN is confirmed on skin biopsy showing the characteristic cells. Bone marrow involvement is a common feature of this neoplasm and is found in most patients at diagnosis. There is no consensus on the most appropriate treatment for BPDCN, with the neoplasm showing initial good response to high intensity chemotherapy but inevitable relapse into a more chemotherapy-resistant disease. Hematopoietic stem cell transplant in patients who achieve their first complete remission with chemotherapy is a promising therapeutic modality requiring a prospective clinical trial to evaluate its efficacy.

Keywords: Blastic plasmacytoid dendritic cell neoplasm; Acute leukaemia

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare malignancy representing less than 1% of all acute hematological cancers [1]. Up to the year 2005, there were fewer than 200 cases of this disease reported worldwide, and only approximately 100 more have been reported since [1,2]. The median age of diagnosis is 67, but the disease can present at any age with a male: female ratio of approximately 3:1 [1,3]. There is no known ethnic or geographic predilection [3]. The difficulty with identifying the cell of origin giving rise to this disease has caused a variability of classification that through advances in disease etiology and genetics culminated in the World Health Organization (WHO) classification of BPDCN as a subset of acute myeloid leukemia (AML) in 2008 [1,3]. Although much has been learned about this disease since its discovery, there still remains much to be elucidated in the pursuit to improve the poor median survival (12 to 14 months) to cure [4].

Literature Search

A literature search strategy using PubMed (1966 to Aug 25, 2015) with the following search terms: “blastic” [All Fields] AND (“dendritic cells”[MeSH Terms] OR (“dendritic” [All Fields] AND “cells”[All Fields]) OR “dendritic cell”[All Fields] OR (“plasmacytoid” [All Fields] AND “dendritic” [All Fields] AND “cell” [All Fields]) OR “plasmacytoid dendritic cell” [All Fields]) AND (“neoplasms” [MeSH Terms] OR “neoplasms”[All Fields] OR “neoplasm” [All Fields]) yielded 228 results with 199 relevant to BPDCN and 29 not relevant to BPDCN. The review was limited to articles that had described more than two cases. Of the relevant results, 42 articles were reviewed. A search strategy for stem cell treatment was employed with the addition of the following term to the previous search: “Hematopoietic Stem Cell Transplantation” [MeSH] yielding 12 search results with 11 results being relevant to BPDCN and 1 not relevant to BPDCN. The review was limited to articles that had described adults and with more than four cases. Of the 11 relevant results, 4 articles were reviewed.

Pathophysiology

PDCN is a disorder of dendritic cells, the master regulators of the adaptive immune response that promote the development of effector T-cells in response to antigen presentation while maintaining immune tolerance to self antigens [5]. Dendritic cells are a heterogeneous group with a remarkable efficiency to present both major histocompatibility complex (MHC) I and MHC II bound antigens, depending on their gene expression profile. The latter is determined in response to a particular kind of antigen exposure, pushing the immature tissue dendritic cells to activate a signal transduction cascade that matures their functional status [5].

The cell of origin giving rise to BPDCN is believed to be a precursor of the immature dendritic cell (pDC) based on its phenotypic expression of CD123 and CD56 [1].

These cells are lineage-negative and may arise from either the common myeloid or common lymphoid precursor [3]. Functionally, the pDC belongs to a group of interferon alpha secreting cells responsible for the detection of viral nucleic acid fragments as well as bacterial antigens via the Toll like receptor [1,5]. Within the group of precursors of the pDC analyzed in healthy individuals, the plasmacytoid dendritic

*Corresponding author: Dr. Selay Lam, UWO Division of Hematology, London Health Sciences Centre (LHSC), Victoria Hospital 800 Commissioners Rd. East, London, Ontario N6A 5W9, USA, Tel: 519-685-8827; Fax: 519-685-8294; E-mail: Selay.Lam@lhsc.on.ca
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like cell (pDLC) has been identified with an immunophenotype that may make it the non-malignant counterpart of BPDCN [1].

Cytogenetic abnormalities in BPDCN include mutation, haploinsufficiency and loss of genes on chromosomes 5, 6, 9, 12, 13 and 15 among others based on several case series [1,3,6]. These chromosomes house numerous genes functioning as cell cycle regulators, apoptosis mediators and methyltransferases affecting epigenetic modifications of the genome. Among the affected cell cycle genes in one case series are CDKN1B and CDKN2A whose protein products are p27kip1 and p16INK4A, respectively [4]. p27kip1 is a cell cycle checkpoint regulator whose haploinsufficiency is a common feature of numerous aggressive tumors with poor prognosis [4] while p16INK4A is another cell cycle checkpoint regulator whose function as a tumor suppressor has been well-described [7].

How mutation or haploinsufficiency of these cell cycle checkpoints determines prognosis in BPDCN remains to be elucidated [3]. Gene expression profiling of skin biopsy samples from another group of patients with BPDCN revealed upregulation of the pro-survival anti-apoptotic NF-kB [1,8].

Furthermore, whole exome sequencing revealed that in a cohort of patients with BPDCN, the subset of patients with mutations in the methylation pathway genes had a much worse prognosis than those patients without these mutations [1] although still being elucidated, the pathophysiology of BPDCN may be dysregulation of the dendritic cell G1/S transition via mutation, haploinsufficiency and epigenetic silencing of tumor suppressor genes, accounting for the aberrant proliferation that gives rise to the distinguishing clinical features of cutaneous nodules and bone marrow infiltration [1,3].

Clinical Features

The most common presentation of BPDCN is characterized by asymptomatic cutaneous lesions up to 10 centimeters in diameter that may be associated with localized erythema, hyperpigmentation or purpura [1-3]. These lesions represent the invasion of the plasmacytoid dendritic cells into the dermis where they proliferate. In a large retrospective database study of 90 patients diagnosed with BPDCN, the cutaneous lesions could be categorized into three groups: nodular, bruise-like patches, and disseminated and mixed lesions (Figure 1) [9]. The former are the most common and may appear anywhere, with the face, scalp and trunk being the most common locations. Mucosal involvement is relatively uncommon, but may occur in about 6% of cases [9]. According to the retrospective study, the presence of disseminated lesions was more likely associated with extracutaneous involvement of the disease. However, there is no correlation between the type of cutaneous clinical presentation and prognosis [9].

Associated extracutaneous manifestations include involvement of the bone marrow and regional lymphadenopathy seen in 40-50% of cases, but these manifestations are rarely seen without cutaneous involvement [2]. As the bone marrow becomes infiltrated with the plasmacytoid dendritic blasts, a myelodysplastic clinical picture may ensue with peripheral cytopenias. Interestingly, about 10-20% of BPCDN are associated with a coexistent myelomonocytic leukemia with or without underlying myelodysplastic syndrome [2]. An aggressive leukemia characterizes disease progression and results in a poor prognosis. According to the Arbor staging system, most patients with BPDCN present with Stage IV disease (bone marrow involvement) at diagnosis [3].

Pathology

The morphology of BPDCN is characterized by monomorphous medium to large sized immature appearing cells with irregular nuclear contours containing fine chromatin and one or more nucleoli [1,3,6]. Bone marrow aspirate and peripheral blood film demonstrate cytoplasmic features that include glycogen-containing microvacuoles in a pearl necklace pattern localized along the cell membrane (Figure 2) [6]. Pseudopod-like cytoplasmic expansions may also occasionally be seen [6]. The bone marrow may demonstrate focal infiltrates of plasmacytoid blast cells, or in the case of disease progression an effacement of the bone marrow architecture and replacement with diffuse sheets of the blast cells [1].

Diagnosis of BPDCN requires a biopsy showing the expected morphology of the plasmacytoid dendritic blast cells, and the use of immunohistochemistry and/or flow cytometry to confirm the CD4+CD56+CD123+lin- immunophenotype (Figure 3) [1-3].

Hematological neoplasms such as myeloid sarcoma and extranodal NK/T cell lymphoma may express CD56 with or without CD4, necessitating an exhaustive immunohistochemical panel for a definitive diagnosis [10,11]. Myeloid markers such as CD7 and CD33 are commonly expressed while CD3, CD5, CD19, CD20, CD79a, lysozyme, and myeloperoxidase are regularly negative (Figure 4) [3,11].

In a retrospective database analysis of 91 patients, it was suggested that the presence of an additional dendritic cell marker such as CD303 or TCL1 is required for a diagnosis of BPDCN as the presence of CD4, CD56, and CD123 may be seen in cases of acute myeloid leukemia that is not of dendritic origin [12]. A recent study by Sangle et al. suggested that positive staining for CD56, TdT, or TCL1 and negative results for lysozyme and myeloperoxidase is the most reliable immunophenotype to diagnose BPDCN [11]. CD56 negative staining does not necessarily rule out BPDCN if CD4, CD123, and TCL1 are positive [13]. The expression of cutaneous lymphocyte-associated antigen (CD162/CLA) may account for the dermal localization of BPDCN [10,11]. Interestingly, cutaneous involvement is not necessarily a feature of BPDCN when the blast cells express a more immature CD34+ phenotype [14].

Treatment

BPDCN is an aggressive neoplasm with a variable response to therapy. Although there is no consensus on optimal therapy (Table 1), the accepted induction treatment involves aggressive chemotherapy with ALL-like regimens such as hyperCVAD irrespective of disease

Figure 1: Cutaneous manifestation of blastic plasmacytoid dendritic cell neoplasm is demonstrated: bruise-like nodular form (A) and disseminate lesions (B).
stage [1,3]. The limitation with this approach is the functional status of the patient, as the morbidity with the chemotherapy may be poorly tolerated. The response rates to initial chemotherapy range from 47-86%, but the disease often relapses and becomes resistant to previous therapy [3,6]. The mean relapse-free survival is approximately 5-9 months [1,6,15].

Hematopoietic stem cell transplant (HSCT) is a therapeutic option that has shown promise in BPDCN in preventing relapse post induction therapy, although there have been no randomized controlled trial evaluating its efficacy (Table 2). A retrospective analysis of nine patients with BPDCN reported on two groups of patients: six that received aggressive chemotherapy and three that went on to allogeneic HSCT [15]. Only one of the six patients receiving chemotherapy alone survived longer than one year, whereas all the patients receiving allo-SCT were alive with the disease in remission after 12 months [15,16]. Another retrospective analysis of 53 patients with BPDCN treated with high dose chemotherapy followed by allo-SCT showed durable long-term response rates, with 47% of patients remaining alive at 16 months and 32% of patients experiencing disease relapse at a median of eight months after allo-SCT [17]. At the 3-year mark for the above retrospective analysis, the median disease-free survival was 33% and the median overall survival was 41%. Although promising, allo-SCT is limited by the availability of donors and the tolerability of the conditioning regimen required for transplant [6]. A reduced intensity conditioning regimen in the same retrospective study resulted in only one out of nine patients remaining disease-free post transplant [17].

The data for autologous HSCT (auto-SCT) has been more mixed [1,6]. A retrospective analysis of registry data reporting on 25 patients with confirmed BPDCN treated with either autologous or allogeneic HSCT reported a 4-year overall survival of 82% for auto-SCT, comparable to a 4-year overall survival of 69% with allo-SCT [16].

Progression-free survival for auto- and allo-SCT in this analysis was 73% and 69% at 4 years, respectively. The key difference between the retrospective analysis and previous case series has been that in the former all patients received auto-SCT while in CR1 [6,16]. In the

![Figure 2](image1.png)

**Figure 2:** Morphology of blastic plasmacytoid dendritic cell neoplasm (marked with arrows) is demonstrated in a bone marrow aspirate (A) and peripheral blood sample (B). Characteristic features include irregularly shaped nuclei with fine chromatin as well as one or more nucleolus. Cytoplasmic vacuoles localized along the cell membrane in a pearl necklace pattern may be seen (A).

![Figure 3](image2.png)

**Figure 3:** Demonstration of the blastic plasmacytoid dendritic cell neoplasm immunophenotype on flow cytometry. The CD45/SSC blast gate (blue cells in top row, left) is further gated for CD19(-) CD3(-) cells (top row, middle). The remaining cells are gated for CD4(+) CD56(+) (top row, right). The BPDCN population is located within the CD4(+)/CD123(+) group of cells (bottom row, left) and the CD56(+)/CD123(+) group of cells (bottom row, middle). They are negative for myeloperoxidase (MPO) as shown at the bottom right of the figure.
Figure 4: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is morphologically composed of immature-appearing malignant cells with vesicular chromatin and inconspicuous nucleoli; occasional mitotic figures are present (A). The malignant cells show immunoreactivity for CD123 (B), TCL1 (C), TdT (D), MxA1 (E), CD56 (F), and are negative for CD3 (G), myeloperoxidase (H), and lysozyme (I).

Study | Type | Number of patients | Clinical Response | Survival outcomes |
--- | --- | --- | --- | --- |
Pagano et al. [19] | Retrospective registry | 43 | AML induction regimen
CR 27%, PR 19%, relapse 0%
ALL induction regimen
CR 67%, PR 7%, relapse 60% | AML regimen: Median OS 7.1 months
ALL regimen: Median OS 12.3 months |
Tsagarakis et al. [21] | Retrospective registry | 20 | AML induction regimen
CR1 50%, relapse 33%
ALL induction regimen
CR1 100%, relapse 33% | OS (2-yr) 43%, with 33% of AML regimen patients and 67% of ALL regimen patients alive |
Dalle et al. [22] | Retrospective registry | 9 | CHOP regimen
CR in 56% of patients treated | Median OS 11 months and median RFS 7 months |
Heinicke et al. [15] | Retrospective single centre | 5 | CHOP regimen
Not reported | Median OS 9 months |

Note: OS: overall survival, CR: complete remission, CR1: first complete remission, CR2: second complete remission, PR: partial remission, RFS: relapse-free survival, AML: acute myeloid leukemia, ALL: acute lymphoblastic leukemia,
1. AML induction regimen included MICE (mitoxatrone, cytarabine, etoposide), ICE (idarubicin, cytarabine, etoposide), anthracycline+cytarabine 3+7, FLAG (fludarabine, cytarabine, filgastrim), FLAG-IDA (FLAG+idarubicin).
2. ALL induction regimens included hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone), GIMEMA ALL (doxorubicin, vincristine, prednisolone, asparaginase), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), CHOEP (CHOP+etoposide).
3. ALL induction regimens included hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone), MRC UKALL XII (daunorubicin, vincristine, asparaginase, prednisolone, methotrexate, cyclophosphamide, cytarabine, 6-mercaptopurine), POMP (6-mercaptopurine, vincristine, methotrexate, prednisolone).

Table 1: Selected published data evaluating induction chemotherapy in blastic plasmacytoid dendritic cell neoplasm.
same retrospective analysis, those patients who were beyond CR1 at transplant did not respond well to allo-SCT [16]. Similar results were seen for patients treated with SCT in the European Group for Blood and Marrow Transplantation registry study [17]. This suggests that stem cell transplant in BPDCN is dependent on the state of the disease, with failure to achieve complete remission with induction chemotherapy predicting a poorer response to SCT [6,17].

Other markers of disease behaviour

There is evidence that the expression of certain cell markers in BPDCN delineates unique neoplastic subsets on a spectrum of dendritic cell maturation, with some groups reporting that markers of immature dendritic cells such as CD303-/TdT-, S100-/TdT- yield a better prognosis while markers of more mature dendritic cells such as CD303+/TdT-, S100+/TdT+ yield a worse prognosis [13,18]. Additionally K67, a marker of tumor cell proliferation has been shown in some case series to be a favourable prognostic marker [11,13]. While the prognostic strength of the dendritic spectrum of maturation has yielded mixed results in several studies [13,14,18] the concept of the spectrum has helped to shed light on disease behaviour. In a case series of 46 patients it was found that the mature CD34-/CD117- dendritic cell immunophenotype was more suggestive of secondary lymphoid organ involvement mimicking the behaviour of aggressive lymphomas whereas the more immature CD34+ immunophenotype tended to suggest bone marrow localization without dermal involvement and leukemia-like behaviour [14].

Studies are ongoing as to the use of targeted therapy for BPDCN using known cytogenetic data. Data from an Italian centre study of BPDCN, for example, identified a subset of patients with FLT3-ITD mutations without an underlying myeloproliferative neoplasm, suggesting that this abnormality may be localized to the aberrant dendritic cells and that therapy with FLT3 inhibitors may be used in these patients [19]. On the other hand, a case series of two patients with BPDCN and concurrent myelodysplastic syndrome (MDS) was reported whereby the patients exhibited regression of their skin lesions in response to 5-azacitidine, an inhibitor of DNA methylation that is used in the treatment of high risk MDS [20]. As more patients with BPDCN are diagnosed and stratified according to their immunophenotype and cytogenetics, more definitive targeted therapy may be developed that improves the prognosis of this very aggressive neoplasm.

### Conclusion

BPDCN is a rare neoplasm of dendritic cell origin that often presents at an advanced stage with cutaneous infiltration and bone marrow involvement. While responding well to aggressive chemotherapy, it tends to relapse and become resistant to further medical management, heralding a poor prognosis. HSCT holds promise as a therapeutic option for patients who can tolerate it, providing the most benefit in those who attain CR1 after initial induction chemotherapy. A prospective trial evaluating HSCT in BPDCN patients who achieve CR1 is required to more rigorously evaluate this therapy. Tolerance to stem cell transplant is limited by the morbidity of the conditioning regimen, however, and alternative therapy would be required for those whose functional status precludes HSCT. A better understanding of disease pathophysiology will help to identify markers for targeted therapy in those patients for whom HSCT is not an option, while also improving existing prognostic tools.

### References


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**Table 2:** Selected published data evaluating hematopoietic stem cell transplant in blastic plasmacytoid dendritic cell neoplasm.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Number of Patients</th>
<th>Therapy</th>
<th>Stem cell source</th>
<th>Donor Type</th>
<th>Conditioning regimen</th>
<th>Survival Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roos-Weil et al. [17]</td>
<td>Retrospective registry</td>
<td>34</td>
<td>Allo-SCT</td>
<td>BM (56%) PBSC (26%) Cord blood (18%)</td>
<td>Related (32%) Unrelated (68%)</td>
<td>MAC (73%) RIC (27%)</td>
<td>OS (3-yr) 41% DFS (3-yr) 33%</td>
</tr>
<tr>
<td>Tsagarakis et al. [21]</td>
<td>Retrospective registry</td>
<td>5</td>
<td>Allo-SCT</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>OS (2-yr) 60%</td>
</tr>
<tr>
<td>Aoki et al. [16]</td>
<td>Retrospective registry</td>
<td>25</td>
<td>Auto-SCT Allo-SCT</td>
<td>BM (57%) PBSC (36%) Cord blood (7%)</td>
<td>Related (50%) Unrelated (50%)</td>
<td>Auto-SCT High-dose allo-SCT MAC (57%) RIC (43%)</td>
<td>Auto-SCT OS (4-yr) 82% DFS (4-yr) 73% Allo-SCT OS (4-yr) 69% DFS (4-yr) 60%</td>
</tr>
<tr>
<td>Heinicke et al. [15]</td>
<td>Retrospective single centre</td>
<td>3</td>
<td>Allo-SCT</td>
<td>NR</td>
<td>Related (0%) Unrelated (100%)</td>
<td>MAC* (33%) RIC (67%)</td>
<td>OS 18, 35, and 41 months, respectively</td>
</tr>
<tr>
<td>Dalle et al. [22]</td>
<td>Retrospective registry</td>
<td>9</td>
<td>Allo-SCT</td>
<td>NR</td>
<td>NR</td>
<td>median SO 21 months</td>
<td></td>
</tr>
</tbody>
</table>

Note: OS: overall survival, DFS: disease-free survival, PFS: progression free survival, allo-SCT: allogeneic stem cell transplant, auto-SCT: autologous stem cell transplant, NR: not reported

*MAC (myeloablative conditioning) regimen defined as ≥8 Gy of total-body irradiation, ≥10 mg/kg of busulfan, or ≥150 mg/m² of melphalan. All other regimens defined as RIC (reduced-intensity conditioning).

**High-dose regimen included MEC (ranimustine, carboplatin, etoposide, cyclophosphamide), MEAM (ranimustine, etoposide, cytarabine, melphalan), or total-body irradiation

***MAC regimen included total-body irradiation, cyclophosphamide, cytarabine, or busulphan. RIC regimen included fludarabine, busulphan, melphalan, total-body irradiation.

**MAC regimen included total-body irradiation and etoposide. RIC regimen included fludarabine and thiopeta.


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