Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)

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Introduction:

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, clinically aggressive hematologic malignancy that most commonly manifests as cutaneous lesions with or without bone marrow involvement and leukemic dissemination.

It often presents as leukemia or evolves into acute leukemia. The term refers to a malignant *neoplasm*, or cancer, that affects *blastic*, or immature, plasmacytoid dendritic cells.[1] The tumor was initially described in 1995 as an acute agranular CD4-positive natural killer (NK) cell leukemia.[2] Then it is described as "blastic NK cell lymphoma" based on the blastic appearance and CD56 expression. Then based on the immunophenotype and a predominant skin involvement it is described as "agranular CD4+CD56+ hematodermic neoplasm/tumor". Recently it is described as BPDCN as it is derived from plasmacytoid dendritic cells (type 2 dendritic cells).[3] BPDCN IS characterized by clonal proliferation of precursors of plasmacytoid dendritic cells, also known as professional type I interferon-producing cells or plasmacytoid monocytes.[4] The WHO recognized the term *blastic plasmacytoid dendritic cell neoplasm* in 2008, and classified it under "acute myeloid leukemia and related neoplasms."[1]

Incidence:

It seems difficult to estimate the incidence of BPDCN because it is so rare and also because it has been such a difficult disease to diagnose definitively in the past. However, Pagano and colleagues in their study stated that it likely accounts for < 1% of all hematologic malignancies.[5]

BPDCN represent 0.7 percent of primary cutaneous skin lymphomas.[6] However, cutaneous lymphoma registries likely underestimate the true incidence of BPDCN because a small but significant proportion of patients present without skin lesions.[7]

Epidemiology:

BPDCN has a male predominance; approximately 75% to 90% of cases occur in men. Dr Andrew Lane in his study presented at the 2013 American Society of Hematology (ASH) Annual Meeting described frequent, recurrent, somatic loss-of-function mutations in the splicing factor ZRSR2 in patients with BPDCN. This ZRSR2 is located on chromosome Xp22.1. All patients with BPDCN in this study who had mutations in ZRSR2 (frameshift, nonsense, or splice site mutations) were males (10 patients) [8] .BPDCN might be more common in men owing to the involvement of the X chromosome and the location of ZRSR2. BPDCN also tends to occur in older patients. The median age at onset from 60 to 70 years and older. However, this disease can occur in females and children patients but it tends to be a disease of older men[9] with a male to female ratio of approximately 2.5:1

Clinical picture and presentation:

BPDCN is characterized by an aggressive behavior with rapid systemic dissemination, however some cases presented with indolent clinical picture with apparently isolated cutaneous involvement in the form of solitary or multiple lesions [10-11]. 70% or more acquire skin lesions. The lesions can be mild and small, or they can be pronounced and extensive, covering the entire body in some cases often having a purplish discoloration. Other patients have a more traditional leukemic presentation, which means low blood cell counts and the presence of blasts in the bone marrow, such as are seen in acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL).**[12]** This cytopenia manifestations, particularly thrombocytopenia is due to bone marrow infiltration.**[10-11]**In the third type of presentation, patients have involvement of the lymph nodes, spleen, liver, or central nervous system, or they have extramedullary involvement in which the disease occurs outside the bone marrow. In other words, this disease can present in essentially any location. **[12]**

Diagnosis:

The diagnosis of BPDCN has evolved over time as clinical and pathologic technologies have improved. As with most leukemias and lymphomas, the diagnosis was once based on morphologic appearance of skin and bone marrow cells under the microscope**[13].** Typically, the malignant cell in BPDCN has abundant cytoplasm with a medium or low nucleus-to-cytoplasmic ratio and displays faint basophilia without granulation. However, microvacuoles are commonly seen, most likely made of glycogen, arranged in a way to adopt a “pearl necklace” aspect beneath the nuclear membrane and characteristic pseudopod-like cytoplasmic expansions.**[14]** Malignant cells of BPDCN generally co-express $CD4^+$ and $CD56^+$ without co-expressing common lymphoid or myeloid lineage markers (Figure 1 A, B, C).

[15,16,17] Garnache-Ottou et al. demonstrated, however, that some cases of BPDCN express myeloid markers (CD33), suggesting that CD33 expression on $CD4^+CD56^+$ cells should not exclude such diagnoses.[16] Differential diagnosis of $CD4^+CD56^+$ malignancy includes aggressive NK cell lymphoma/leukemia, nasal and nasal-type NK cell lymphoma, and AML (especially cases with aberrant expression of CD4 and/or CD56 and cutaneous involvement).[18] Several cases of BPDCN showed co-expression of CD2, CD7, CD33, and/or CD117.[17] Identified key markers include CD123, the interleukin-3 receptor α-chain, T cell leukemia/lymphoma 1 (TCL1), blood dendritic cell antigen-2 (CD303/BDCA-2), and CD2-associated protein (CD2AP). [15,16,19,20] CD2AP is an 80-kDa molecule identified through its binding to the terminal 20 amino acids in the cytoplasmic domain of the T cell–associated molecule CD2. CD2AP appears to be restricted to plasmacytoid dendritic cells, potentially making it a useful tool to confirm the diagnosis of BPDCN.[21,22]

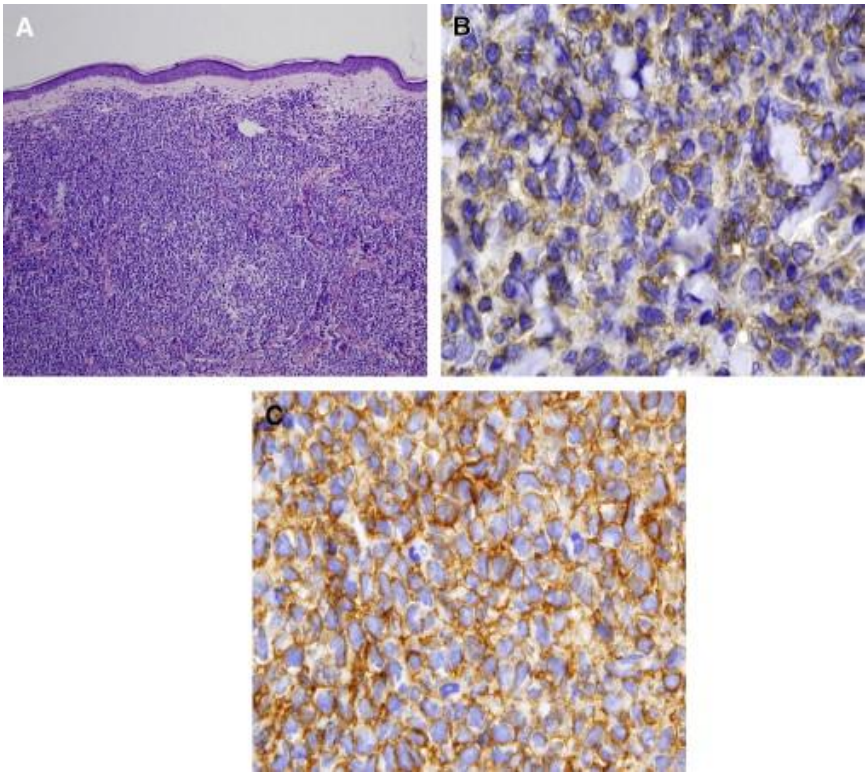

Figure 1 (A) Punch biopsy of a skin lesion in a patient with BPDCN showing a striking diffuse infiltrate of atypical mononuclear cells with round to oval nuclei and scant cytoplasm throughout the papillary and superficial reticular dermis (H&E staining). Immuno-histochemical staining showing expression of CD4 (B) and CD56 (C) on malignant cells.

Clonal, generally complex, chromosome aberrations have been described in 66% of cases. Leroux et al. defined 6 major recurrent chromosomal targets, 5q, 12p, 13q, 6q, 15q, and monosomy 9, implicated in 72% (5q), 64% (12p and 13q), 50% (6q), 43% (15q), and 28% (monosomy 9) of cases [23]. Lucioni et al. demonstrated that complete or partial chromosomal

losses are more frequent than gains, with common deleted regions including 9p21.3 (*CDKN2A/CDKN2B*), 13q13.1-q14.3 (*RB1*), 12p13.2-p13.1 (*CDKN1B*), 13q11-q12 (*LATS2*), and 7p12.2 (*IKZF1*). Worse outcomes were apparently described in the presence of biallelic loss of locus 9p21.3.[24]

Prognosis:

Despite an initial response to systemic chemotherapy, the disease regularly relapses and the median overall survival is (12-14 months).[10] Outcomes were poor regardless of the patient's age and regardless of a skin-only or a bone marrow presentation. Before the current era of targeted therapy, the patients with the best outcomes were those who were younger, had a complete remission, and received a stem cell transplant during first remission [9]. Some newer studies that have come out over the past 5 or 6 years suggest that the use of allogeneic[25] or, interestingly, autologous[26] transplant can improve median survival to 2 to 4 years.

Conventional Therapy:

Because of the rarity of BPDCN, no prospective data are available to define the most optimal frontline therapy. Limited cutaneous disease at presentation, without obvious nodal, bone marrow, and/or peripheral blood involvement, is not uncommon. However, even in such cases, local therapies (e.g., surgical excision or involved field radiation therapy) are ineffective, with systemic relapse anticipated in almost all cases, typically within 6 months.[27]

Frontline treatment with regimens commonly used in non-Hodgkin lymphoma (eg, cyclophosphamide, doxorubicin, vincristine, prednisone [CHOP]; CHOP-like regimens; or ifosfamide/etoposide-based regimens) yield complete remission (CR) rates of 40% to 50%, but responses are short-lived.[14,18,27] Recent literature, albeit limited by small sample size, described more intense regimens, such as hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with methotrexate and cytarabine), offered as frontline therapy for BPDCN with more encouraging responses . Pemmaraju et al. reported a CR rate of 90% in 10 patients, with a median age of 62 years (range, 20 to 86), treated with hyper-CVAD. However, responses were relatively short-lived at a median of 20 months (range, 4 to 39), and median overall survival (OS) was 29 months (range, 1 to 44)[22] .Dietrich et al. reported a CR rate of 83% in 6 patients treated with daunorubicin plus cytarabine followed by high-dose cytarabine (AML-like, n = 3) or an acute lymphoblastic leukemia–like induction regimen containing dexamethasone, methotrexate, vincristine, cyclophosphamide/ifosfamide, and idarubicin/daunorubicin (n = 3). Unfortunately, the median time-to-disease relapse was only 7 months (range, 3 to 11)[29].These

findings suggest that conventional chemotherapy does not appear to be sufficient by itself to ensure durable long-term remissions.

Autologous Hematopoietic Stem Cell Transplantation:

Several investigators used high-dose therapy and auto-HCT consolidation in BPDCN, with the goal of maximizing depth and duration of responses.[18] Suzuki et al. reported outcomes of high-dose therapy followed by auto-HCT in 6 patients; 3 died from progression, and the remaining 3 were alive and disease-free at 11, 22, and 37 months after auto-HCT, respectively.[30] On the other hand, Reimer et al. reported relapses after auto-HCT in 3 of 4 cases at a median of 13 months.[18] Several limitations are inherent to these retrospective reports, including lack of centralized review to confirm this rare histology, heterogeneity in number and types of prior chemotherapies used, varying remission status at the time of transplantation, and a possible publication bias toward reporting favorable outcomes. There are no available data to suggest an optimal conditioning regimen for auto-HCT in BPDCN (e.g., total body irradiation–based versus non–total body irradiation-containing regimens). The total body irradiation–based conditioning regimen used in the report by Reimer et al. was associated with disease relapse in 3 of 4 patients.[18] In the case series by Suzuki et al., 3 of 6 autografted cases were disease-free; however, the conditioning regimens were not specified.[30] It appears that patients with chemo-refractory disease and those with active central nervous system or bone marrow involvement at time of autografting are not likely to achieve durable remissions after auto-HCT [18]. These cases should ideally be considered for enrollment in clinical trials. However, in the absence of such trials, acknowledging the limitations and quality of available data, high-dose therapy and auto-HCT could be offered to patients with chemo-sensitive disease, preferably early in the disease course.

Allogenic Hematopoietic Stem Cell Transplantation:

Available data suggest that patients with BPDCN achieve long-term remissions, mostly if allografted in CR.[18,30] The European Group for Blood and Marrow Transplantation, recently in the largest registry study to date (n = 34), reported 3-year cumulative incidence of relapse, disease-free survival (DFS), and OS rates of 32%, 33%, and 41% respectively, after allo-HCT [25]. Patients included in this study had a careful central review of their diagnosis to confirm this rare histology. Patients allografted in first CR showed a statistically nonsignificant trend toward better 3-year DFS (36%) and OS (52%) compared with patients who underwent transplantation during more advanced disease (DFS, 26%; OS, 29%). No relapses were seen in any patients after 27 months, suggesting a possibility of cure with allo-HCT. It is, however,

important to recognize that no robust evidence of a potent and clinically relevant graft-versus-BPDCN effect is available. None of the reports has examined the rates of relapse in patients developing graft-versus-host disease compared with those without graft-versus-host disease, and no data are available to determine if post allo-HCT relapses are responsive to donor lymphocyte infusions.

Reduced-intensity conditioning (RIC) regimens could expand the applicability of allo-HCT to BPDCN patients with advanced age and at a higher risk of associated comorbidities, which would preclude them from receiving myeloablative regimens. For instance, Dietrich et al. described outcomes in 4 patients, with a median age of 66 years (range, 56 to 70), who received unmanipulated peripheral blood stem cells from unrelated donors after a combination of fludarabine, cyclophosphamide, subablative doses of busulfan with or without antithymocyte globulin, or fludarabine plus treosulfan . None of these patients died from transplantation-related toxicities, and 2 were alive in CR at 16+ and 57+ months after allografting . These findings demonstrate feasibility of RIC regimens in elderly patients.[29] It is important to point out, however, that only 1 of 9 patients undergoing an RIC allo-HCT in the European Group for Blood and Marrow Transplantation study survived disease-free posttransplantation, whereas the DFS of patients undergoing myeloablative allo-HCT reached a plateau at 40% [25].The absence of data regarding the presence (or lack thereof) of a clinically relevant graft-versus-BPDCN effect limits to recommend RIC regimens for all allo-HCT candidates. RIC regimens should probably be considered for patients who are not fit to undergo myeloablative allo-HCT due to advanced age or medical comorbidities as previously noted. Collaborative prospective clinical trials are certainly needed to better define the role of allo-HCT in BPDCN.

Targeting therapy:

Monoclonal antibodies, chimeric antigen receptor (CAR) T-cell therapies, and a class of drugs called dualtargeting agents or bispecific molecules are in development; they have the ability to target CD123, CD56, and other antigens that may be applicable to patients with BPDCN. These novel targeted agents should be studied for use in BPDCN over the next 1 to 2 years and could represent the next exciting direction in therapeutic drug development and targeting.[12]

References:

1- **Vardiman JW, Thiele J, Arber DA, et al.** The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood. 2009*; 114(5):937-951.

2- **AU Brody JP, Allen S, Schulman P, Sun T, Chan WC, Friedman HD, Teichberg S, Koduru P, Cone RW, Loughran TP.** Acute agranular CD4-positive natural killer cell leukemia (Comprehensive clinicopathologic studies including virologic and in vitro culture with inducing agent). *Cancer.* 1995; 75(10):2474.

3- **Facchetti F, Jones DM, Petrella T.** Blastic plasmacytoid dendritic cell neoplasm. In: WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues, Swerdlow SH, Campo E, Harris NL, et al. (Eds), IARC, Lyon. 2008. p.145.

4- **Pilichowska ME, Fleming MD, Pinkus JL, Pinkus GS.** CD4+/CD56+ hematodermic neoplasm ("blastic natural killer cell lymphoma"): neoplastic cells express the immature dendritic cell marker BDCA-2 and produce interferon. *Am J Clin Pathol*. 2007; 128(3):445-53.

5- **Pagano L, Valentini CG, Pulsoni A, et al.** GIMEMA-ALWP (Gruppo Italiano Malattie EMatologiche dell'Adulto, Acute Leukemia Working Party). Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study. *Haematologica.* 2013;98(2):239-246.

6- **Petrella T, Bagot M, Willemze R, Beylot-Barry M, Vergier B, Delaunay M, Meijer CJ, Courville P, Joly P, Grange F, De Muret A, Machet L, Dompmartin A, Bosq J, Durlach A, Bernard P, Dalac S, Dechelotte P, D'Incan M, Wechsler J, Teitell MA.** Blastic NK-cell lymphomas (agranular CD4+CD56+ hematodermic neoplasms): a review. *Am J Clin Pathol.* 2005;123(5):662-75.

7- **Pagano L, Valentini CG, Pulsoni A, Fisogni S, Carluccio P, Mannelli F, Lunghi M, Pica G, Onida F, Cattaneo C, Piccaluga PP, Di Bona E, Todisco E, Musto P, Spadea A, D'Arco A, Pileri S, Leone G, Amadori S, Facchetti F.** GIMEMA-ALWP (Gruppo Italiano Malattie E Matologiche dell'Adulto, Acute Leukemia Working Party. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study. *Haematologica.* 2013;98(2):239-46.

8- **Taylor J, Kim SS, Stevenson KE, et al.** Loss-of-function mutations in the splicing factor ZRSR2 are common in blastic plasmacytoid dendritic cell neoplasm and have male predominance [ASH abstract 741]. *Blood.* 2013;122(21)(suppl).

9- **Pemmaraju N, Kantarjian HM, Cortes JE, et al.** Blastic plasmacytoid dendritic cell neoplasm (BPDCN): a large single-center experience: analysis of clinical and molecular characteristics and patient outcomes [ASH abstract 3746]. *Blood.* 2015; 126(23)(suppl).

10- **Feuillard J, Jacob MC, Valensi F, Maynadié M, Gressin R, Chaperot L, et al.** Clinical and biologic features of CD4(+)CD56(+) malignancies. *Blood.* 2002;99(5):1556-63.

11- **Cota C, Vale E, Viana I, Requena L, Ferrara G, Anemona L, et al.** Cutaneous manifestations of blastic plasmacytoid dendritic cell neoplasm-morphologic and phenotypic variability in a series of 33 patients. *Am J Surg Pathol.* 2010;34(1):75-87.

12- **Naveen P.** Blastic Plasmacytoid Dendritic Cell Neoplasm. *Clinical Advances in Hematology & Oncology.*2016;14(4):220-222.

13- **Alayed K, Patel KP, Konoplev S, et al.** TET2 mutations, myelodysplastic features, and a distinct immunoprofile characterize blastic plasmacytoid dendritic cell neoplasm in the bone marrow. *Am J Hematol.* 2013;88(12):1055-1061.

14- **Feuillard J, Jacob MC, Valensi F, et al.** Clinical and biologic features of CD4(+)CD56(+) malignancies. *Blood*. 2002; 99: 1556–1563.

15- **Chaperot L, Bendriss N, Manches O, et al.** Identification of a leukemic counterpart of the plasmacytoid dendritic cells. *Blood*. 2001; 97: 3210–3217.

16- **Jegalian AG, Buxbaum NP, Facchetti F, et al.** Blastic plasmacytoid dendritic cell neoplasm in children: diagnostic features and clinical implications. *Haematologica*. 2010; 95: 1873–1879.

17- **Garnache-Ottou F, Chaperot L, Biichle S, et al.** Expression of the myeloid-associated marker CD33 is not an exclusive factor for leukemic plasmacytoid dendritic cells. *Blood*. 2005; 105: 1256–1264.

18- **Reimer P, Rüdiger T, Kraemer D, et al.** What is CD4+CD56+ malignancy and how should it be treated?. *Bone Marrow Transplant.* 2003; 32: 637–646.

19- **Facchetti F, Jones D, Petrella T.** Blastic plasmacytoid dendritic cell neoplasm. in: S.H. Swerdlow, E. Campo, N.L. Harris, (Eds.) WHO classification of tumours of haematopoietic and lymphoid tissues. International Agency for Research on Cancer, Lyon, France; 2008

20- **Petrella T, Bagot M, Willemze R, et al.** Blastic NK-cell lymphomas (agranular CD4+CD56+ hematodermic neoplasms): a review. *Am J Clin Pathol*. 2005; 123: 662–675.

21- **Dustin ML, Olszowy MW, Holdorf AD, et al.** A novel adaptor protein orchestrates receptor patterning and cytoskeletal polarity in T-cell contacts. *Cell*. 1998; 94: 667–677.

22- **Marafioti T, Paterson JC, Ballabio E, et al.** Novel markers of normal and neoplastic human plasmacytoid dendritic cells. *Blood*. 2008; 111: 3778–3792.

23- **Leroux D, Mugneret F, Callanan M, et al.** CD4(+), CD56(+) DC2 acute leukemia is characterized by recurrent clonal chromosomal changes affecting 6 major targets: a study of 21 cases by the Groupe Français de Cytogénétique Hématologique. *Blood*. 2002; 99: 4154–4159.

24- **Lucioni M, Novara F, Fiandrino G, et al**. Twenty-one cases of blastic plasmacytoid dendritic cell neoplasm: focus on biallelic locus 9p21.3 deletion. *Blood*. 2011; 118: 4591–4594.

25- **Roos-Weil D, Dietrich S, Boumendil A, et al.** European Group for Blood and Marrow Transplantation Lymphoma, Pediatric Diseases, and Acute Leukemia Working Parties. Stem cell transplantation can provide durable disease control in blastic plasmacytoid dendritic cell neoplasm: a retrospective study from the European Group for Blood and Marrow Transplantation. *Blood.* 2013;121(3):440-446.

26- **Aoki T, Suzuki R, Kuwatsuka Y, et al.** Long-term survival following autologous and allogeneic stem cell transplantation for blastic plasmacytoid dendritic cell neoplasm. *Blood*. 2015;125(23):3559-3562.

27- **Dalle S, Beylot-Barry M, Bagot M, et al.** Blastic plasmacytoid dendritic cell neoplasm: is transplantation the treatment of choice?. *Br J Dermatol*. 2010; 162: 74–79.

28- **Pemmaraju N, Thomas DA, Kantarjian H, et al.** Analysis of outcomes of patients (pts) with blastic plasmacytoid dendritic cell neoplasm (BPDCN). (Abstract 6578)*J Clin Oncol*. 2012; 30.

29- **Dietrich S, Andrulis M, Hegenbart U, et al.** Blastic plasmacytoid dendritic cell neoplasia (BPDC) in elderly patients: results of a treatment algorithm employing allogeneic stem cell transplantation with moderately reduced conditioning intensity. *Biol Blood Marrow Transplant*. 2011; 17: 1250–1254.

Suzuki R, Suzumiya J, Nakamura S, et al. Hematopoietic stem cell transplantation for natural killer-cell lineage neoplasms. *Bone Marrow Transplant*. 2006; 37: 425–4