CORRESPONDENCE

Blastic Plasmacytoid Dendritic Cell Neoplasm: Still an Enigma

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Dear Sir,

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare aggressive malignancy representing less than 1% of all acute hematologic cancers with no ethnic predilection [1]. It arises from precursor of the plasmacytoid dendritic cells and functionally 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 receptors [2, 3]. Here we report a case series of three BPDCN patients which show marked heterogeneity in terms of their clinical presentation, skin or bone marrow involvement, immunophenotypic expression and treatment strategies applied as shown in Table 1 and Figs. 1, 2.

BPDCN is known to be frequently seen in elderly (median age at presentation: 67 years). However, it can occur in any age group with slight male predominance [1, 4]. In this case series, all the three patients were ≤ 25 years of age with an M:F ratio of 2:1. BPDCN is associated with high frequency of primary cutaneous involvement (64–100% of cases) attributable to expression of antigens such as CLA and CD56 that favor skin migration and chemokine receptors expressed by neoplastic plasmacytoid dendritic cells (pDC) [5]. Cutaneous lesions may occur in the form of non-pruritic asymptomatic single or multiple skin lesions like plaques, nodules or brown to violaceous bruise-like skin lesions. Patients with skin involvement at diagnosis are considered to have better

prognosis [6]. BPDCN without skin lesions is typically seen in young patients with peripheral involvement [7] as seen in Case I.

In Case II, trucut biopsy from the left arm mass exhibited a cellular tumor with focal areas of necrosis and comprised of sheets of small to intermediate sized atypical cells with hyperchromatic nuclei, irregular nuclear membrane and scant to absent cytoplasm. On IHC, tumor cells expressed LCA (diffuse and strong), CD99, Tdt (focal) and were negative for CD3, CD5, CD7, CD10, CD22, SOX11, EMA, ALK, CD30, MPO, MIC-2, CD34 and PAX-5. In the absence of any lineage specific markers and after ruling out the commoner lymphomas with cutaneous presentation such as anaplastic large cell lymphomas, peripheral T cell lymphoma etc., it was decided to rule out a distant possibility of BPDCN. An extended panel of markers comprising of CD4, CD43, CD56 and CD123 was applied which came out to be strongly positive. Diagnosis of BPDCN is based on expression of CD4, CD56, CD123 and HLA-DR by flowcytometry or immunohistochemistry along with other pDC associated antigens such as TC1, BDCA-2 and CLA and negative expression of B, T or myeloid lineage-specific markers. In about 8% cases of BPDCN, CD4 or CD56 is negative. Differential diagnosis includes other hematologic neoplasms such as extranodal NK/T cell leukemia/lymphoma, cutaneous T cell lymphoma, leukemia cutis etc. which may express CD56 with or without CD4, necessitating an exhaustive IHC panel for a definitive diagnosis. In such overlapping cases, presence of additional dendritic cell markers such as CD303/BDCA-2 or TCL-1 may be useful. Here, it should be made clear that CD56 negative staining does not rule out BPDCN if CD4, CD123 and TCL-1 are positive [8–13]. All the three patients in this case series had positive expression of CD4/CD56/CD123, with or without bone marrow involvement. Myeloid

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Table 1 The demographic, clinical and treatment details of the three BPDCN patients

Parameters	Case I	Case II	Case III
Age (years)	25	19	13
Sex (male/female)	M	F	M
Presenting complaints	Acute-onset weakness, breathlessness	Progressively increased swelling over left arm for 8 months	Fever, gum bleeding, petechial spots all over the body for 1 month
Examination findings	Pallor, mild hepatomegaly, no cutaneous lesions	Hard lump in left mid-arm, bilateral inguinal lymphadenopathy, multiple skin nodes, no hepatosplenomegaly	Gum hyperplasia, papular red lesions on scrotal skin, hepatosplenomegaly
Provisional diagnosis	Acute Leukemia	Primary cutaneous lymphoma	Acute Leukemia
Hemogram [Hb (g/L), TLC ($\times 10^9/L$), Platelet count ($\times 10^9/L$)]	86/18.5/32	115/5.4/244	85/12.5/50
Blast percentage in Peripheral blood	78	Nil	60
Bone marrow findings	Cellular smears showing 40% agranular blasts, MPO negative on cytochemistry	Normal bone marrow with no increase in blasts	Hemodiluted smears showing 40% undifferentiated blasts with high N/C ratio, inconspicuous nucleoli and scant cytoplasm, MPO negative on cytochemistry
CNS involvement	Nil	Nil	Nil
Ancillary testing	BM Flowcytometry: CD45 dim+/CD4 dim+/- CD56+/CD123+/HLA-DR+/CD34-/ CD38+; negative for rest of the B, T, immaturity and myeloid markers	Immunohistochemistry done on trucut biopsy from left mid-arm: the tumor cells express LCA, PAX-5 (dim), TDT (dim), CD4, CD43, CD123, CD56; immunonegative for CD20, CD3, CD10, CD34, CD1a, MPO, MIC-2, CD7, CD30, EMA, ALK, CD22 etc.	BM Flowcytometry: CD45 dim+/CD4 dim+/- CD56+/CD123+/HLA-DR+/CD33+/CD7+/ CD34-/CD38+; negative for rest of the B, T, immaturity and myeloid markers
Cytogenetics	Normal karyotype	Normal karyotype	46XY, del12p11.2
PET Scan at presentation	NAD	Metabolically active supra and infra diaphragmatic nodal disease with cutaneous involvement	NAD
Treatment given	AML type induction followed by Allo-HSCT in CR	ALL type Induction (COG0232 regimen)	ALL type Induction followed by Allo-HSCT in CR

Fig. 1 **a** Undifferentiated blast morphology in Case I and III. **b** Trucut biopsy in Case II showing sheets of small to intermediate sized atypical cells with hyperchromatic nuclei, irregular nuclear

membrane and scant to absent cytoplasm. **c–e** The tumor cells expressed CD123, TdT (dim) and CD56 respectively on IHC in Case II

antigens such as CD7 and CD33 can be commonly expressed as seen in Case III while CD3, CD5, CD19, CD20, CD79a, myeloperoxidase and lysozyme are regularly negative. TdT is positive in one-third of cases, with expression in 10–80% of cells. Tdt negative/BDCA-2 positive phenotype is associated with worse prognosis [14] while more immature CD34 positive immunophenotype is associated with leukemia-like behavior without dermal localization [13]. In the present study, TdT positivity was observed in Case II with no bone marrow localization while CD34 was negative in all three cases suggestive of more mature phenotype.

Cytogenetic abnormalities in BPDCN are non-specific and include mutation, haploinsufficiency and loss of genes on multiple chromosomes [8]. Recently, recurrent somatic loss of function mutations have been described in the splicing factor ZRSR2, located on chromosome Xp22.1 [15]. Two out of three patients in this study showed normal karyotype while Case III had del12p11.2.

Few previously published studies have shown improved CR rates and overall survival outcomes with ALL induction regimens over AML-like treatment such as Pagano and Tsagarakis et al. but there is still no consensus on the best therapeutic approach [16, 17]. Results of the first line treatments of 86 patients recruited in the French BPDCN network published recently showed that there was no statistically significant difference in response rates as well as relapse rates in groups treated with ALL-like, AML-like and NK/T-like regimens although their outcomes were significantly poorer for the CHOP-like group [18]. Median OS for patients who received HSCT, auto or allo versus other patients was 49 and 8 months respectively ($p < 0.0001$), which elucidates the beneficial effects of HSCT independent of age. Relapses are almost inevitable with median overall survival in different studies ranging from 8 to 20 months [19, 20] except those who benefit from allogeneic hematopoietic stem cell transplantation (HSCT) in CR1. In the present study also, patients

Fig. 2 Flowcytometry showing positivity for LCA (dim), CD56, HLA-DR, CD33, CD4 (dim) and CD123 as in Case I and III

received variable therapies. Case I received AML-like induction followed by Allo-HSCT in CR1. He later relapsed and died due to primary graft failure (OS ~ 13 months). Case II was started on ALL type Induction (COG0232 regimen) but she defaulted and came back with progressive disease few months later. She was lost to follow up thereafter, with a follow up duration of 6 months. Case III received ALL-like therapy followed by Allo-HSCT in CR1 and is currently in remission at last follow up (6 months). Advances in the understanding of the pathogenetic and clinical aspects of BPDCN have prompted use of newer drugs with different mechanisms of action, more importantly IL3R- α inhibitor i.e. SL-401, which has shown promising results in few prospective trials [21]. Other targeted therapeutic agents include hypomethylating agents, PI3K-AKT/NF-KB pathway inhibitors and monoclonal antibodies to CD56/CD303 but more clinical trials are required to validate their efficacy in BPDCN patients [5].

Thus, it can be concluded that BPDCN should be kept as an important differential diagnosis for patients of all age groups with undifferentiated blast morphology with or without cutaneous and bone marrow involvement. Also, it

needs to be treated promptly with ALL-like or AML-like regimens followed by allo/auto HSCT in first clinical remission as soon as possible for sustained response and better overall survival.

Compliance with Ethical Standards

Conflict of interest The authors state that there is no conflict of interest present.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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