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ORIGINAL ARTICLE

Blastic Plasmacytoid Dendritic Cell Neoplasm: Single Center Experience on a Rare Hematological Malignancy

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Abstract
Purpose Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and poor prognostic hematological malignancy. There is still no standard treatment established for BPDCN patients. We aim to summarize the main clinical, biological features and treatment of 9 BPDCN patients.
Methods Nine patients with BPDCN who had been diagnosed between July 2008 and December 2018 in Ankara University School of Medicine, were retrospectively evaluated.
Results All patients (n = 9) were male, median age was 64 (21–80). Five patients (55.6%) had bone marrow infiltration, 5 patients (55.6%) cutaneous lesions, 6 patients (66.7%) lymph node involvement, 2 patients (22.2%) central nervous system involvement and 2 patients (22.2%) spleen involvement at time of diagnosis. Complex karyotype was observed in 2 patients. CHOP was given to 5 patients (55.6%), hyper-CVAD to 2 patients (22.2%), fludarabine, cyclophosphamide and mitoxantrone to 1 patient (11.1%) and cyclophosphamide, etoposide, methylprednisolone to 1 patient (11.1%) as first line chemotherapy. Four patients (44.4%) underwent allogeneic hematopoietic stem cell transplantation (AHSCT) in complete remission (CR) 1. Venetoclax was given to a transplant ineligible patient who had skin and lymph node involvement, with the off-label use. The median follow-up time was 15.9 months (3–48.6 months). Estimated median overall survival was 15.9 + 1.6 (95% CI 12.7–19.1) months.
Conclusion Intensive induction therapies followed by AHSCT in CR seems to be best approaches for patients with BPDCN. Thus, more effective treatment strategies particularly targeted therapies should be warranted to improve the survival of patients with this rare disease.

Keywords Blastic plasmacytoid dendritic cell neoplasm · Clinical and biological features · Intensive chemotherapy regimens · Allogeneic hematopoietic stem cell transplantation

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, clinically aggressive hematological malignancy derived from the precursor of plasmacytoid dendritic cells involved in innate immunity. Although it was named previously as agranular CD4 + NK cell leukemia, blastic NK cell leukemia/lymphoma, agranular CD4 + CD56 + hematodermic neoplasm or tumor due to uncertainty of histogenesis, it has been defined as 'blastic plasmacytoid dendritic cell neoplasm' in 2008 World Health Organization (WHO) classification of acute myeloid leukemia and related neoplasms [[1], [32]].

However clonal evolution in the development of BPDCN is not clear yet, current data suggest that BPDCN

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arises from clonal hematopoiesis with SRSF2, TET2 and NPM1 mutations like other myeloid neoplasms [2].

The neoplastic blastic cells in BPDCN are expected to express CD4, HLA-DR, CD56, TCL1, CD123, BDCA2, BDCA4, CD2AP. The other immunophenotypic characteristics are $CD34^{-}$, $CD3^{-}$, MPO^{-}, $CD45RA^{+}/RO^{-}$, $CD11c^{-}$, $CD116^{low}$, $CD36^{+}$ [3]. In addition to presence of CD4 and CD56 expression, demonstration of CD123 and TCL1 expressions are important for making the diagnosis of the disease [4].

Previous reports indicate that overall incidence of BPDCN is extremely low, accounting for less than 1% of all hematologic malignancies [5] and 0.7% of cutaneous lymphomas [6]. The exact incidence of BPDCN is unknown however, the overall incidence is thought to be 0.04 cases per 100,000 population [7]. BPDCN generally occurs in the elderly, with the median age ranging from 60 to 70 years. There is a male predominance with a male to female ratio of approximately 3:1 [8–10].

The disease common manifestation is cutaneous involvement with or without bone marrow leukemic infiltration. Unfortunately there is no consensus on treatment for patients with this highly aggressive neoplasia [11].

Here, we report the clinicopathological features and the treatment outcomes of 9 BPDCN cases at a single institution in Turkey.

Materials and Methods

We retrospectively evaluated 9 BPDCN patients who had been diagnosed between July 2008 and December 2018 in Ankara University School of Medicine. The diagnosis of BPDCN was based on clinical, morphological, and immunophenotypically features identified by the 2008 revision of the WHO classification of acute myeloid leukemia and related neoplasms [12]. The medical records of Ankara University School of Medicine were reviewed in terms of age, sex, clinical presentation, complete blood count, peripheral blood smear, bone marrow aspiration and biopsy, cytogenetic data, radiological imaging including CT and PET, as well as pathologic findings of the skin lesions. $SPSS_{22}$ was used for statistical analysis and overall survival was assessed by of Kaplan–Meier method.

Results

Clinical and Laboratory Characteristics

All our patients (n = 9) were male, median age was 64 (21–80). At the time of diagnosis, 5 (55.6%) patients had bone marrow infiltration, 5 (55.6%) patients had cutaneous lesions, 6 (66.7%) patients had lymph node (LN) involvement, 2 (22.2%) patients had central nervous system (CNS) involvement and 2 (22.2%) patients had spleen involvement. No liver involvement was observed. The cytogenetics revealed complex karyotype in 2 patients and del 13q in 1 patient (Table 1).

Two patients had hypercellular diffuse bone marrow infiltration with atypical round shaped cells (Fig. 1) and others had hypercellular bone marrow with various amount of atypical blastic cell infiltration on bone marrow aspiration and biopsies. Five of 9 patients were presented with cutaneous involvement including purple nodular lesions, bruise-like brown to violaceous infiltrated multiple patches and mixed lesions (Fig. 2; Table 1). Skin biopsies revealed BPDCN (Fig. 3). Immunohistochemistry (IHC) of skin biopsies were summarized in Table 1.

Treatment Protocols and Outcomes

Two patients were treated with Hyper-CVAD chemotherapy regimen including cyclophosphamide, doxorubicin, vincristine, dexamethasone, methotrexate, cytosine arabinoside and folinic acid. AHSCT with full match sibling donor was performed to patient no.1 in first complete remission (CR1). Patient no.2 underwent AHSCT with 9/10 mismatch unrelated donor (MUD) in CR1.

Both was conditioned with cyclophosphamide and total body irradiation regimen (Cy-TBI). Anti-thymocyte globin (ATG) was added to conditioning regimen of patient no.2 due to MUD. Third patient was ineligible for AHSCT. Six cycles of CHOP chemotherapy including cyclophosphamide, doxorubicin, vincristine and methylprednisolone was administered to him. Partial remission (PR) was achieved. He refused follow up and further treatments. Patient no.4 was first patient diagnosed with BPDCN. Treatments involved fludarabine, cyclophosphamide and mitoxantrone (FCM) were given to him. He died due to progressive disease (PD). Patient no.5 who had CNS involvement, was treated with CHOP chemotherapy and intrathecal (IT) treatment with methotrexate, cytosine arabinoside, dexamethasone. PD was observed. Patients no.6,7 and 8 were given 6 cycles of CHOP chemotherapy and CR was obtained as response to first line therapy in all patients. Patients 6 and 8 had full match sibling donors so proceeded with AHSCT in CR1. One of them was conditioned with thiotepa—fludarabine-busulfan—ATG due to CNS involvement and other one with Cy-TBI. Patient no.9 was 80 years-old gentlemen so he was treated with cyclophosphamide, etoposide and methylprednisolone (CEP). CR was achieved after first line treatment but, he relapsed a year later. Venetoclax at a dose of 400 mg daily was initiated with the approval of the health authority and

Table 1 Clinical and laboratory features of the patients at diagnosis

Patients no.	Gender/ age (yr)	Skin involvement	Bone marrow involvement	Involved other tissues	Peripheral blood (10^9/L)	Cytogenetics	Flow cytometry (bone marrow)	Antigenic profile of the neoplastic BPD cells by IHC on tissue biopsies
1	M/20	−	+	−	WBC:2.3 × 10^9/L HB:4.9 g/dl HTC:13.7% PLT:28 × 10^9/L	NV	CD45 + , CD19, HLADR + , CD33 + , MPO − , CD13 − CD14 − CD15 − NG2 ± CD16 − CD11b − CD2, CD7CD4 + , CD56bright + , CD123 + , CD38 + , CD34 − CD117−	CD45, CD56, CD123, CD4, TCL1
2	M/58	nodules	+	Spleen, LN	WBC:5.9 × 10^9/L HB:13.6 g/dl HTC:39.9% PLT:95 × 10^9/L	46, XY[20] del 13q +[17/200]	CD45 weak + , HLA DR + , CD19 − , CD13 − CD33 −/ weak + CD117∓, MPO − , CD2 + , CD4 + CD7 + , CD5 − CD16 − CD56∓, CD64 − CD71 + CD34 − , CD24 − CD123 + , tdt + CD43+	TCL1, CD123, CD4, CD56
3	M/76	patches	+	Spleen, LN	WBC:15.7 × 10^9/L HB:12.7 g/dl HTC:39.9% PLT:87 × 10^9/L	45, 49, XY, +X, der (5), 9, der(9), 10, 12, der(13), +20, +21, +mar1, +mar2, +mar3, inc[cp5]/ 46, XY[4]	CD45 weak + , HLA DR +CD19, CD33weak ± MPO − CD13 − , CD34, CD123 + , CD15 − , CD71 − CD117 − CD11b, CD24 −CD36 + CD64 −, CD9 −CD4 + CD2 − CD3 − , CD43 + CD7 weak ± , NG2 −CD56 bright +	TCL1, CD123, CD4, CD56
4	M/70	−	+	−	WBC:116 × 10^9 HB:15 g/dl HTC:43% PLT: 70 × 10^9	NV	CD45 +, HLA DR ± , CD19 −, CD33 ± , MPO − CD34 − , CD123 + , CD56 +, CD15 − , CD7 − , CD5 − CD8 −, CD4 + CD2 + , CD3 − , TCR−	CD123, TCL1, CD56
5	M/67	−	+	LN, CNS	WBC:3.4 × 10^9 HB:10 g/dl HTC:31.2% PLT: 30 × 10^9	47, XY, der(1) add(1)(p), der(9) add (9)(q), der(12), der(15), der(7) [cp9]/46, XY[1]	CD45 + HLA DR + CD33 + MPO − CD19 − CD2 + CD4 + CD56 + CD123 + sCD3 − cCD3 − CD8 − CD7 + CD5 − TCRab − TCRgd − CD36 + CD11b − CD64 − CD24−	CD45, CD56, CD123, TCL1
6	M/47	patches	−	LN, CNS	WBC:6.6 × 10^9 HB:15.7 g/dl HTC:44.3% PLT: 201 × 10^9	46, XY	No involvement	TCL1, CD56, CD4, CD123
7	M/64	nodules and patches	−	−	WBC:3.9 × 10^9 HB:14.1 g/dl HTC:43.3% PLT: 203 × 10^9	46, XY	No involvement	TCL1, CD56, CD4, CD123

Table 1 continued

Patients no.	Gender/ age (yr)	Skin involvement	Bone marrow involvement	Involved other tissues	Peripheral blood (10^9/L)	Cytogenetics	Flow cytometry (bone marrow)	Antigenic profile of the neoplastic BPD cells by IHC on tissue biopsies
8	M/37	–	–	LN	WBC:4.2 × 10^9 HB:14.1 g/dl HTC:44.3% PLT: 272 × 10^9	46, XY	No involvement	CD4, CD45, CD123, CD56, TCL1
9	M/80	nodules and patches	–	LN	WBC:4.9 × 10^9 HB:13.1 g/dl HTC:43.3% PLT: 376 × 10^9	46, XY	No involvement	CD4, CD123, CD56, TCL1

M male, *yr* year, *Bx*: biopsy, *WBC* white blood cell, *HB* hemoglobin, *HTC* hematocrit, *PLT* platelet, *LN* lymph node, *CNS* central nervous system, *IHC* immunohistochemistry, *LN* Lymph node, *NV* not valid

CR was provided 6 months after venetoclax onset (Table 2).

As first line therapy, 2 (22.2%) patients received hyper-CVAD regimen due to leukemic presentation, 5 (55.6%) patients treated with CHOP chemotherapy like lymphoma, 1 (11.1%) patient treated with FCM and 1 patient received CEP chemotherapy. After first line therapy, CR was achieved in 6 (66.6%) patients and PR in 1 (11.1%) patient, while PD was observed in 2 (22.2%) patients. Four (44.4%) patients underwent AHSCT, 3 patients with HLA full match sibling donor, 1 patient with HLA 9/10 MUD in CR1. Three of them conditioned with Cy-TBI, 1 of them with thiotepa based regimen due to CNS involvement. CR was achieved in all patients after AHSCT. Venetoclax was given to a patient with relapsed disease, who was not eligible for transplant. At last visit, PD was observed in 5 (55.5%) patients and 4 (44.5%) patients were in CR (Table 2).

The median follow-up time was 15.9 months (3–48.6 months). Estimated median overall survival (OS) was 15.9 + 1.6 (95% CI 12.7–19.1) months. Factors such as age (≥ 60 years), consolidative AHSCT, bone marrow, skin, lymph node, CNS and spleen involvement that could affect OS and progression free survival (PFS) were analyzed. Cutaneous involvement was associated with better OS ($p = 0.04$) but had no effect on the PFS ($p = 0.3$). All other factors had no effect on the OS and PFS ($p > 0.05$) (Fig. 4).

Discussion

In this report, main clinical and biological characteristics, management and outcomes of 9 BPDCN patients were retrospectively analyzed. Clinical features of our patients were similar with the previous reports. All our patients were male, median age was 64 (21–81). Elderly male predominance was observed as mentioned in previous reports except one of 20 years old patient [13].

A small number of cases are presented with leukemia without skin involvement [9, 14]. In our patient group, 3 patients had BPDCN with leukemic presentation, lacking cutaneous involvement. Two patients had bruise-like brown to violaceous infiltrated patches, 1 patient had purple nodular lesions and 2 patients had mixed lesions. A retrospectively analysis of 90 patients revealed that 73% of the patients had brown or purple nodular lesions, 12% of the patients had bruise-like brown to violaceous infiltrated patches, and %14 of the patients had disseminated and mixed lesions. [15]. Atalay et al. reported conjunctival and gingival infiltration in one of 3 cases [16] which was not seen in our series.

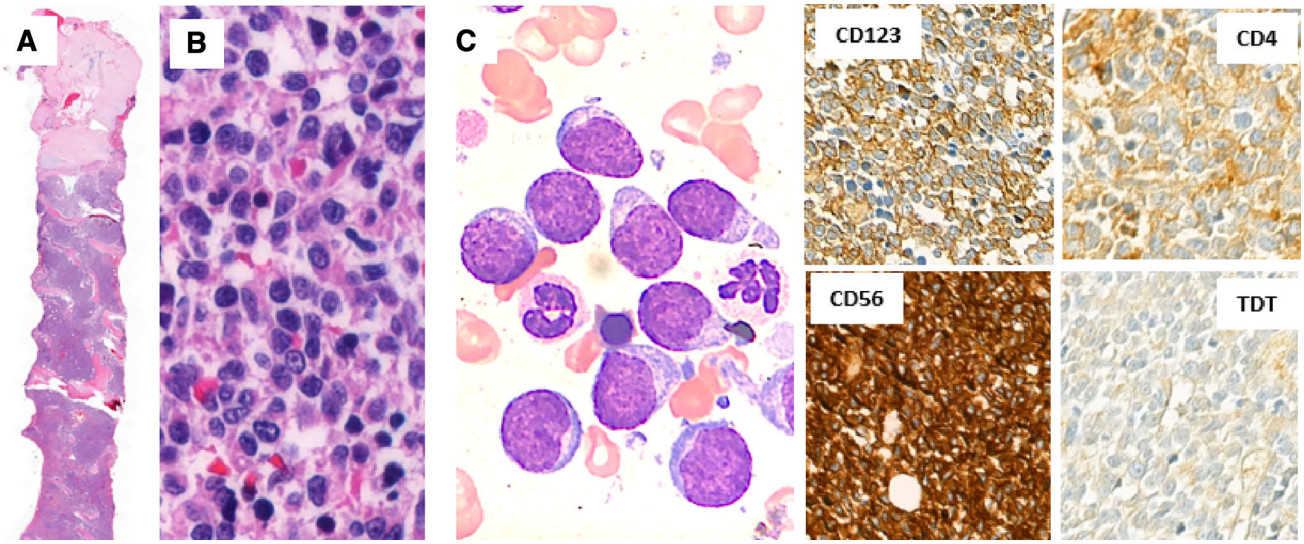

Fig. 1 Case number 1: **a** Diffiuse bone marrow (BM) involvement with atypical blastic cells. **b** The neoplastic cells' nuclei have fine granular chromatin and the cytoplasm does not have granules or vacuoles. The characteristic phenotype as CD123, CD56 and CD4 expression and TdT negativity was helpful for making the diagnosis

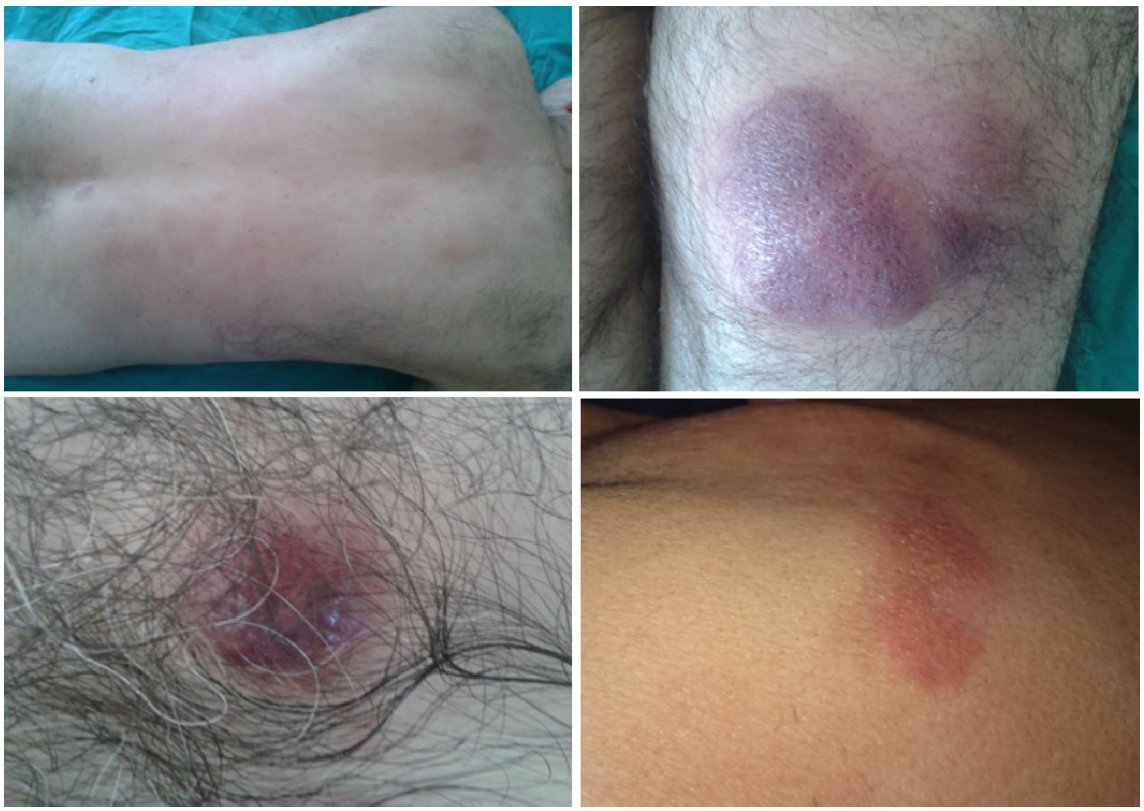

Fig. 2 Bruise-like brown to violaceous infiltrated patches and erythematous nodules

In our cohort, 1 patient had 13q deletion (34% of the cells) with FISH and 2 patients had complex cytogenetic abnormalities in chromosome 7, 9, 12, 13 and 15. Lucioni et al. reported that the deletion of 9p21.3 locus was the most recurrent event in their series and homozygous loss of locus 9p21.3 was as a basically independent adverse prognostic factor [17]. Karyotype analysis frequently demonstrate complex cytogenetic abnormalities, but

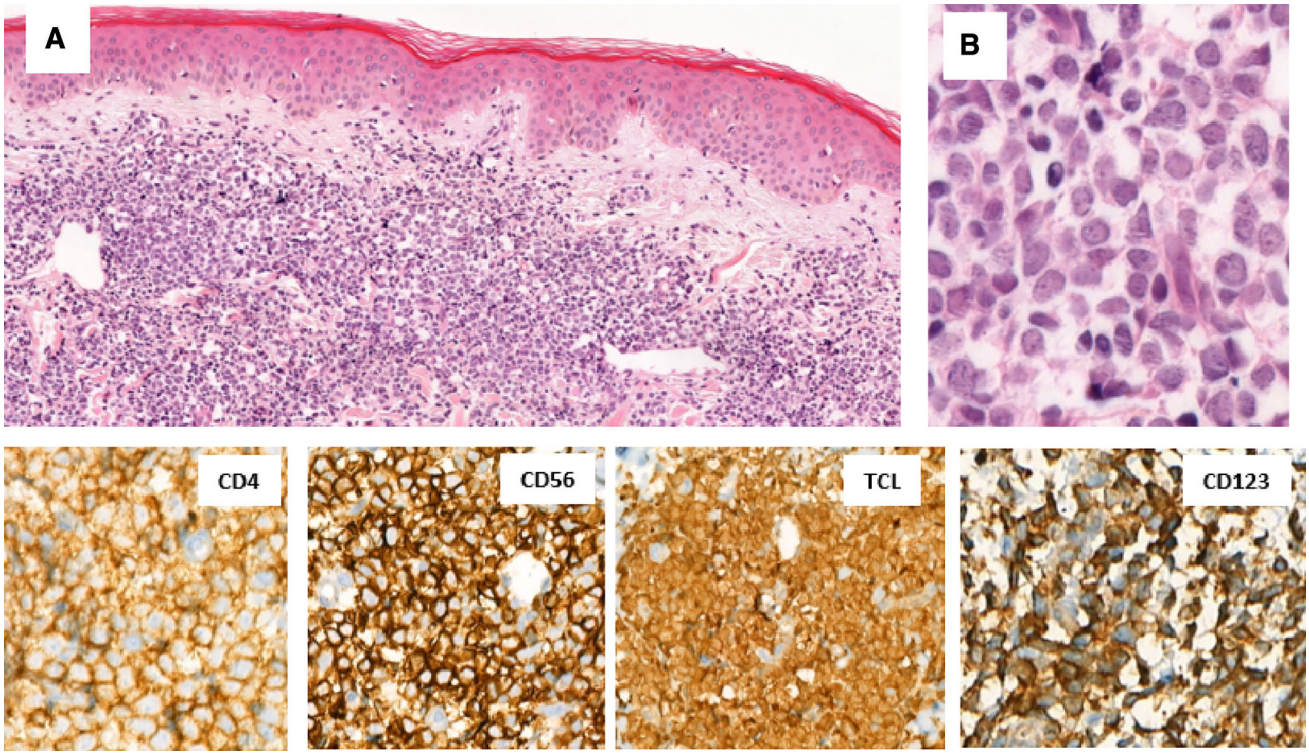

Fig. 3 The skin involvement is characterised by diffuse infiltration of dermis (**a**), by the neoplastic immature cells round and oval nucleated cells with the fine granulated chromatin and invisible cytoplasm (**b**). The characteristic phenotype with CD4, CD56, TCL and CD123 expressions are the most helpfu findings for making the diagnosis

Table 2 Treatment protocols and responses

Patients no.	Induction therapy regimen	Response to first-line therapy	Relapse	Salvage treatment	Pre-AHSCT disease status	Donor type	Conditioning regimen	Response to AHSCT	Disease status at last visit
1	Hyper-CVAD	CR	No	–	CR1	Full match sibling	Cy-TBI	CR	PD
2	Hyper-CVAD	CR	No	–	CR1	9/10 mismatch unrelated	Cy-TBI-ATG	CR	PD
3	CHOP	PR	Yes	Denied further treatment	–	tx ineligible	–	–	PD
4	FCM	PD	–	Palliative care	–	tx ineligible	–	–	PD
5	CHOP	PD	–	Palliative care	–	tx ineligible	–	–	PD
6	CHOP	CR	No	–	CR1	Full match sibling	THIO + FLU + BU + ATG	CR	CR
7	CHOP	CR	No	–	–	tx ineligible	–	–	CR
8	CHOP	CR	No	–	CR1	Full match sibling	Cy-TBI	CR	CR
9	CEP	CR	Yes	Venetoclax	–	tx ineligible	–	–	CR

CR, complete remission, CR1, first complete remission, PR, partial remission, PD, progressive disease, AHSCT, allogeneic hematopoietic stem cell transplant, tx, transplantation, FCM, fludarabine–cyclophosphamide–mitoxantrone, Cy-TBI, cyclophosphamide-total body irradiation, ATG, anti-thymocyte globin, THIO + FLU + BU, thiotepa–fludarabine–busulfan, CEP, cyclophosphamide–etoposide–methylprednisolone

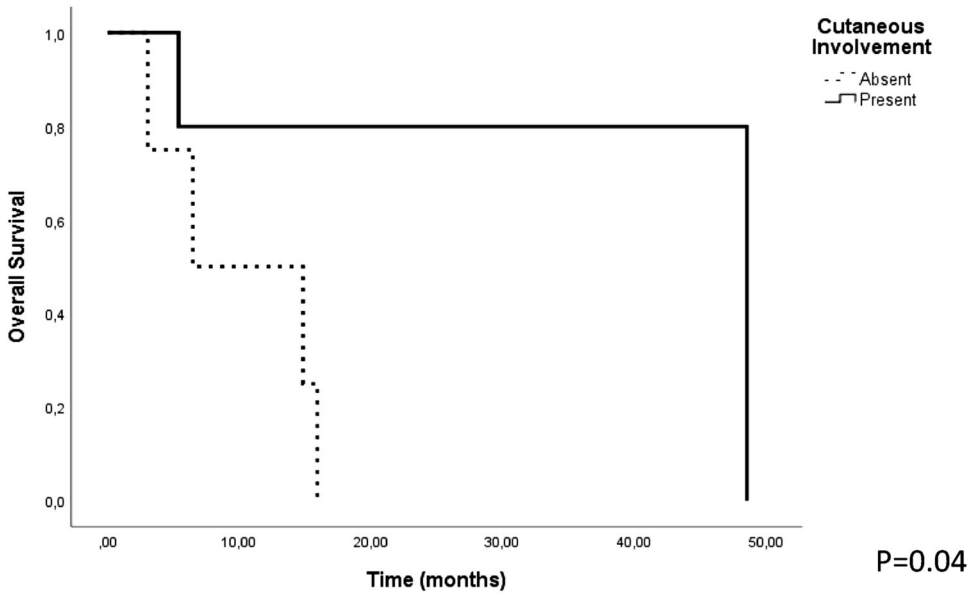

Fig. 4 The relationship between OS and cutaneous involvement

diagnostic or pathogenic value of these abnormalities is still unknown [3]. Leroux et al. reported the results of conventional cytogenetic and FISH analyses in 21 patients whereas 66% had complex cytogenetic abnormalities with predominance of genomic losses. They revealed six major recurrent aberrations affecting 5q, 12p, 13q,6q, 15q, and 9, which were involved in 72% (5q), 64% (12p and 13q), 50% (6q), 43% (15q), and 28% (monosomy 9) of their cases [18].

BPDCN is rare aggressive neoplastic disease which involves most frequently skin, bone marrow and lymphoid tissues. When the skin is the first involved area, the diagnosis may be challenging especially for the pathologists who are not experienced in hematopathology [33]. The neoplastic cells characteristically express CD4, CD56, CD123, TCL1 and CD303. Except CD303 none of these markers are specific for BPDC and at least 4 of them is expected to be positive for the confident diagnosis [8]. CD303 is recently described as a lectin type cell membrane receptor selectively expressed on normal BPDC involved in antigen capture and IFN production [19]. Skin biopsies are characterized by diffuse, monotonous dermal infiltration by medium-sized cells with round nuclei and narrow cytoplasm [20]. At the initial presentation bone marrow may not be involved as it is seen four of our patients. When the bone marrow is involved, flow cytometry helps for the diagnosis.

No consensus on treatment of the patients with BPDCN has been published yet. Although patients respond to intensive chemotherapy-based induction regimens, relapse is common and OS ranges from 8 to 14 months [21, 22]. The rarity of disease does not allow prospective clinical trials to define well-established treatment strategies.

In Italian cohort CR was achieved in 7 of 26 patients after AML-type regimens and 10 of 15 patients after ALL/lymphoma type regimens. ALL/lymphoma-type chemotherapy was significantly better than AML like therapies ($p = 0.02$). The median OS of the AHSCT recipients was significantly longer compared to the non-transplanted patients with median 22.7 months (range 12–32.9) [9]. ALL like induction chemotherapy including Hyper-CVAD yielded higher response rate as 90% but remission duration was short with median OS rates ranged between 12 and 16 months [23].

In our cohort, AHSCT was performed to 4 (44.4%) patients in CR1. Consolidative AHSCT was not associated with better OS and PFS and estimated median overall survival was 15.9 +1.6 (95% CI 12.7–19.1) months. In a review including 97 patients, the authors reported that age $\geq$ 60 years was a negative prognostic factor, skin restricted disease was not associated with better OS compared with advance disease and median OS was only 13 months for all patients [24]. We found that cutaneous involvement was associated with better OS ($p = 0.04$) but had no effect on the PFS ($p = 0.3$).

Two of our patients had CNS disease without neurological symptoms at diagnosis. One of them had very poor prognosis despite treated with both IT treatment and CHOP regimen. Martín et al. reported occult CNS involvement in 6/10 cases at diagnosis despite none of the patients presented with neurological symptoms. They suggest that treatment of occult CNS involvement may lead to a dramatically improved outcome of BPDCN [25].

New targeted agents have been developed recently with early encouraging results in BPDCN. Tagraxofusp, a CD123-directed cytotoxin, was the first drug to be

specifically approved for the treatment of BPDCN [26, 27]. Venetoclax, a BCL-2 inhibitor, is another promising drug in patients with relapsed refractory BPDCN [27]. BCL-2 is overexpressed in most blastic plasmacytoid dendritic-cell neoplasms, however it is not expressed in normal plasmacytoid dendritic cells [28, 29]. There are reports about successful outcome of venetoclax in relapsed refractory BPDCN patients who were not provided to AHSCT [30, 31]. In our series venetoclax was given to a relapsed refractory 81 years old patient who was presented with cutaneous lesions. The patient continues to do well at 6 months follow-up, with no new skin lesions or evidence of recurrence.

Conclusion

Clinical presentation of BPDCN can be ambiguous and diagnosis of BPDCN needs experienced hematopathologist. There is still no consensus on the treatment of these cases but chemotherapy regimens for aggressive lymphoproliferative diseases followed by AHSCT in CR1 still remains to be the most appropriate choice. New targeted therapies are emerging with promising outcomes in BPDCN, however patients eligible for transplantation still should be offered AHSCT.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, there was no conflict of interest.

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

Informed consent Informed consent was obtained form all individual participants included in this study.

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