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Case Study

Blastic Plasmacytoid Dendritic Cell Neoplasm : Report of Two Cases

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Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a clinically aggressive tumor derived from the precursor of plasmacytoid dendritic cells. We describe two cases of BPDCN. In case 1, the patient presented with multiple erythema on the trunk and arms. Histopathology of a skin biopsy specimen and immunohistochemistry demonstrated that the tumor cells were small to medium-sized with a blastoid morphology and positive for CD4, CD56, CD123 and T-cell leukemia-1 (TCL-1). In case 2, the patient presented with a solitary skin nodule and rapidly developed involvement of the bone marrow and peripheral blood. Although immunohistochemistry of the infiltrating tumor cells demonstrated positivity for CD4, CD56, CD123 and TCL-1, the cells were large with a distinct nucleolus, and different from those of typical BPDCN. The atypical morphological features of BPDCN may be diagnostically problematic, and should therefore be recognized correctly. 〔*J Clin Exp Hematopathol 52(1) : 23-29, 2012*〕

Keywords: blastic plasmacytoid dendritic cell neoplasm, CD123, T-cell leukemia-1 (TCL-1), Ki-67, cutaneous lymphoma

INTRODUCTION

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare entity that was recently classified as an acute myeloid leukemia and related precursor neoplasms in the World Health Organization (WHO) classification.[1] It was previously termed 'blastic natural killer cell lymphoma' in the WHO classification for hematopoietic tumors[2] and $CD4^+/CD56^+$ hematodermic neoplasm in the WHO-EORTC classification.[3] BPDCN has a highly aggressive clinical course with a poor prognosis, showing a high incidence of cutaneous involvement and risk of leukemic dissemination. Histopathologically, BPDCN is characterized by non-epidermotropic dense, monomorphous infiltrates of medium-sized blasts with irregular nuclei, fine chromatin, and one to several small nucleoli. The cytoplasm is scant and difficult to visualize, and never exhibits granulation. However, a diverse cell morphology in BPDCN has been described.[4,5]

The immunophenotype of the tumor cells is $CD4^+$, $CD56^+$, $CD8^-$, $CD7^{+/-}$, $CD2^{-/+}$ and $CD45RA^+$, and terminal deoxynucleotidyl transferase (TdT) and CD68 may also be positive. T-and B-cell markers, CD1a, CD10, CD30, CD57, cytotoxic molecules and myeloperoxidase are negative. The cells express CD123 and T-cell leukemia-1 (TCL-1), supporting a possible derivation from a plasmacytoid dendritic cell precursor.[3,6]

Here, we describe two cases of BPDCN with reference to the morphological cellular diversity of this entity. Case 1 showed typical histopathological and immunohistochemical features of BPDCN. In case 2, the tumor consisted of a monomorphous proliferation of large cells with distinct nucleoli and showed unusual histopathological features.

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CASE REPORT

Case 1

An 86-year-old, previously healthy Japanese man was admitted because of a 6-month history of cutaneous lesions located on the trunk and arms. Physical examination showed multiple areas of infiltrating erythema without other symptoms (Fig. 1a & 1b). Superficial lymph nodes were not palpable on physical examination. Histological examination of a biopsy specimen taken from plaque on the trunk revealed the presence of a dermal lymphomatous infiltrate with an alveolar growth pattern, which extended into the subcutis. The epidermis was not involved, and a grenz zone was present between the epidermis and the infiltrate. The monomorphous infiltrat-

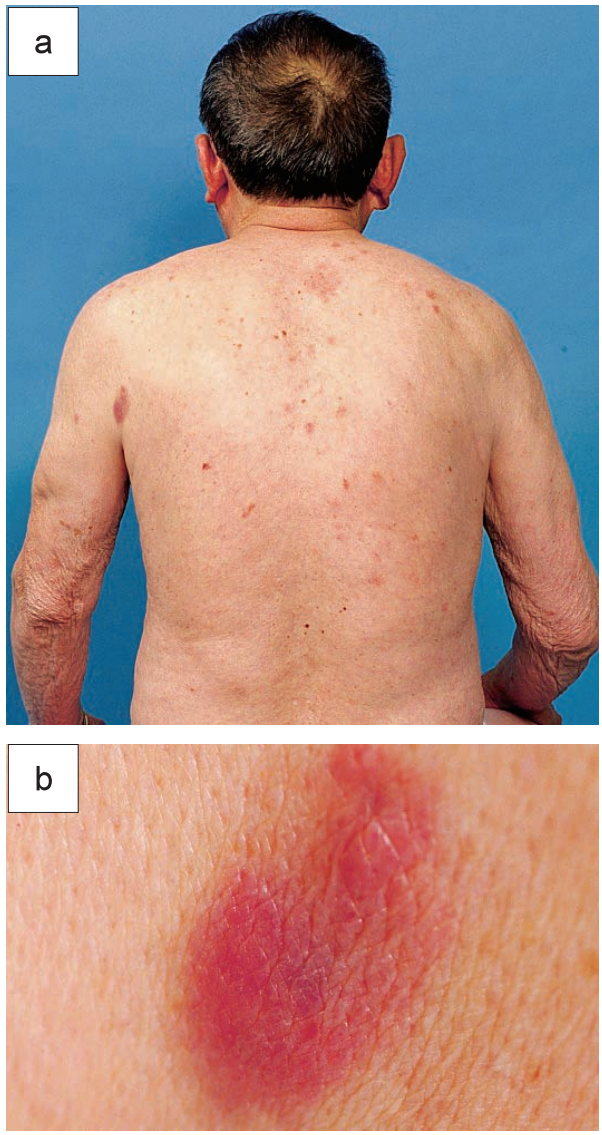

Fig. 1. Case 1. Macroscopic view of the skin tumors. Multiple infiltrating erythemas on the trunk and arms (*1a* & *1b*).

ing cells were medium-sized cells with finely dispersed chromatin and absent or indistinct nucleoli (Fig. 2a & 2b). The cytoplasm was scant and appeared grey-blue and agranular upon Giemsa staining. Neither angiocentrism nor angiodestruction was evident. Immunohistochemical studies, performed on formalin-fixed, paraffin-embedded tissue, revealed positive immunoreactivity of the cells for CD4, CD56, CD123 and TCL-1 (Fig. 2c, 2d, 2e & 2f) and negativity for cCD3, CD5, CD7, CD8, CD10, CD43, CD45, CD20, CD30, CD34, CD45RO, CD68, CD79a, HLA-DR, T-cell restricted intracellular antigen-1 (TIA-1), perforin, granzyme B, TdT, anaplastic lymphoma kinase (ALK) and myeloperoxidase (MPO). *In situ* hybridization for Epstein-Barr virus was negative. The Ki-67 labeling index of the tumor cells was 40% (Fig. 5a). On the basis of clinical and histopathological findings, the cutaneous lesion was diagnosed as BPDCN. At this point, the patient's peripheral blood and chemistry values were within the normal ranges, and systemic involvement was not apparent on computed tomography. The patient refused chemotherapy and was followed without any therapy. Leukemic change was not evident at the final follow-up examination 12 months after diagnosis.

Case 2

A 74-year-old Japanese man presented with a reddish skin

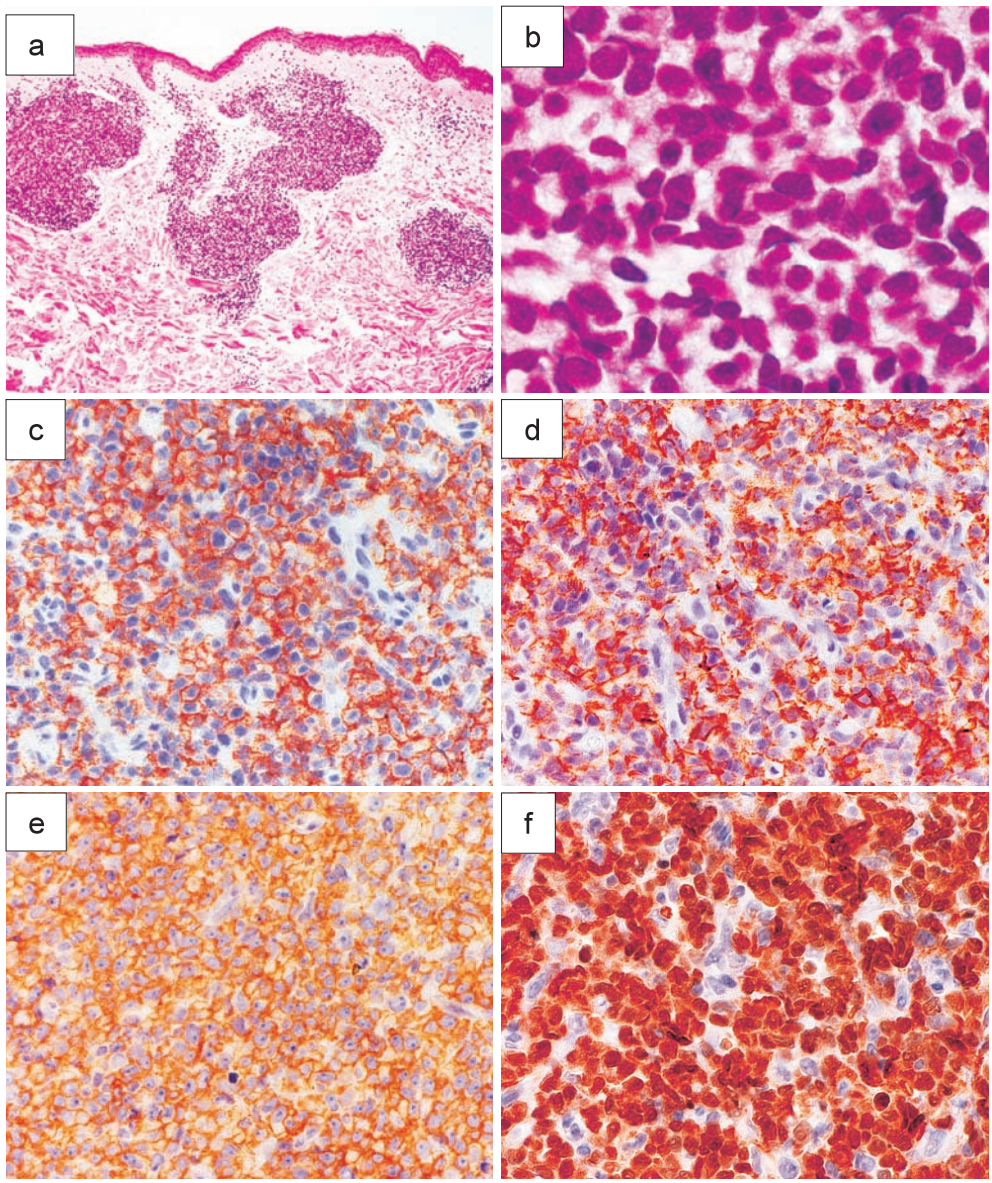

Fig. 2. Case 1. (***2a***) Skin biopsy sample showing dermal lymphocytic infiltrates extending into the subcutis and separated by a grenz zone (H&E stain, ×40). (***2b***) The infiltrating cells are medium-sized with fine dispersed chromatin and absent or indistinct nucleoli (H&E stain, ×1,000). (***2c-2f***) The infiltrating cells are positive for CD4 (*2c*), CD56 (*2d*), CD123 (*2e*) and T-cell leukemia-1 (*2f*) (×400).

tumor, measuring 36.6 × 19.2 mm, which had appeared two weeks earlier in the right post-auricular region (Fig. 3). Histopathological examination of a skin biopsy specimen demonstrated non-epidermotropic, diffuse, monotonous infiltrates of large cells, each with a distinct nucleolus, in the superficial and deep dermis, separated from the epidermis by a small grenz zone (Fig. 4a & 4b). Angiocentrism and angiodestruction were not evident.

Immunohistochemical staining, performed on formalin-fixed, paraffin-embedded tissue, revealed that the infiltrating cells were positive for CD4, CD56, CD123 and TCL-1 (Fig. 4c, 4d, 4e & 4f), but negative for cCD3, CD5, CD7, CD8, CD10, CD43, CD45, CD20, CD30, CD34, CD45RO, CD68, CD79a, HLA-DR, TIA-1, perforin, granzyme B, TdT, ALK and MPO. The Ki-67 labeling index was 75% (Fig. 5b). There was no rearrangement of the *T-cell receptor* gene. *In situ* hybridization for Epstein-Barr virus was negative. On the basis of these findings, the lesion was diagnosed as

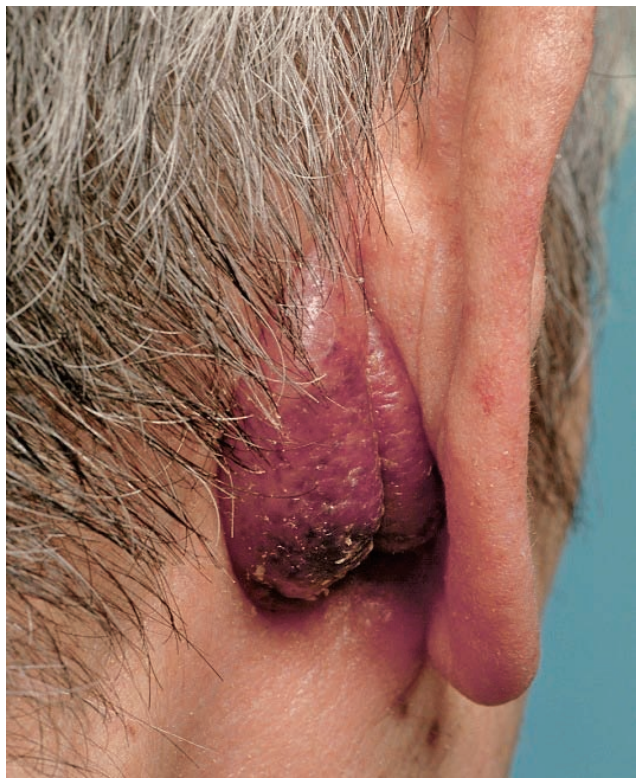

Fig. 3. Case 2. Macroscopic view of the skin tumor. The reddish tumor is present in the right post-auricular region.

BPDCN. The patient's peripheral blood and chemistry values were within the normal ranges, and no systemic involvement was apparent by computed tomography. Bone marrow aspiration cytology disclosed no infiltration. He received electron beam irradiation therapy with a total dose of 27 Gy, and the skin tumor disappeared. Two months later, the patient presented with general fatigue. Hematological examination revealed a white blood cell count of $23.7 \times 10^3/\mu L$ with a differential count of 40.5% tumor cells. Bone marrow aspiration cytology disclosed monotonous infiltrates of large tumor cells with a distinct nucleolus and suppression of normal hematopoiesis. A clot section of a bone marrow aspirate revealed infiltrating tumor cells with the same morphology and immunocharacteristics as those in the skin tumor. Flow cytometric analysis of the bone marrow aspirate demonstrated a population of tumor cells that were positive for CD4, CD56, CD33 and HLA-DR. Cytochemically, the tumor cells in bone marrow aspirate smears were negative for α-naphthyl butyrate esterase and naphthol ASD chloroacetate esterase. Although the patient underwent chemotherapy with adriamycin, vincristine and prednisone (AdVP), he died due to neoplastic progression on the 9th day after chemotherapy. Autopsy was not performed.

DISCUSSION

BPDCN is a clinically aggressive tumor with a high frequency of cutaneous and bone marrow involvement and leukemic dissemination. Histopathologically, the neoplastic cells are characterized by monotonous non-epidermotropic infiltration of uniform medium-sized cells with round nuclei and finely dispersed chromatin and absent or indistinct nucleoli, resembling lymphoblasts or myeloblasts. The cytoplasm is scant and difficult to visualize, and never exhibits granulation.[4,5] Immunohistochemical studies are of critical diagnostic importance, and the characteristic immunophenotypic profile is positivity for CD4, CD56 and CD43, and variable positivity for TdT and CD68.[7] The cells express CD123 and TCL-1, both of which support a relationship to plasmacytoid dendritic cells. However, the neoplastic cells of BPDCN show a greater variability of morphologic and immunophenotypic features.[4,5]

Here we have reported two cases of BPDCN in male patients aged 86 and 74 years. In case 1, the patient showed multiple erythema on the trunk and arms. Histopathology of a skin biopsy specimen and immunohistochemistry of the tumor cells were consistent with typical BPDCN. The tumor cells were medium-sized with a blastoid morphology and showed positive immunoreactivity for CD4, CD56, CD123

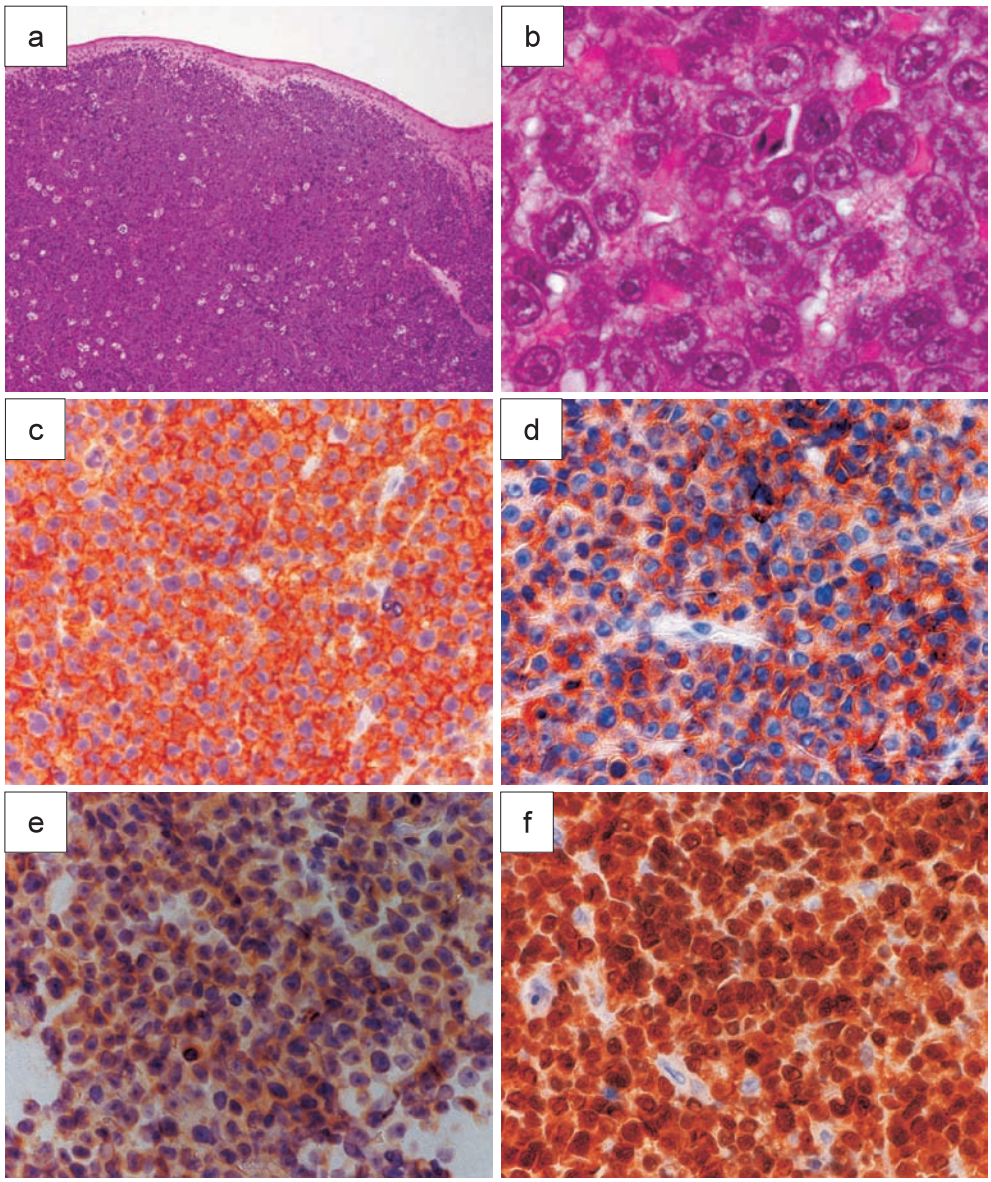

Fig. 4. Case 2. (***2a***) Skin biopsy sample showing non-epidermotropic, diffuse, monotonous infiltrate separated from the epidermis by a small grenz zone (H&E stain, ×100). (***2b***) The infiltrating cells are large, each with a distinct nucleolus (H&E stain, ×1,000). (***2c-2f***) The infiltrating cells are positive for CD4 (*4c*), CD56 (*4d*), CD123 (*4e*) and T-cell leukemia-1 (*4f*) (×400).

and TCL-1. In case 2, the patient presented with a solitary skin nodule and rapidly developed involvement of the bone marrow and peripheral blood. Although immunohistochemistry of the infiltrating tumor cells revealed positivity for CD4, CD56, CD123 and TCL-1, morphologically the tumor cells were large, with distinct nucleoli, and different from those of typical BPDCN. On the basis of the morphological features of the tumor cells in case 2, the differential diagnosis included primary cutaneous anaplastic large-cell lymphoma (ALCL) and primary cutaneous diffuse large B-cell lymphoma (DLBCL). ALCL frequently involves both lymph nodes and extranodal tissue. Extranodal sites include skin, bone and soft tissues. Although the hallmark of primary cutaneous ALCL cells is expression of CD30, the infiltrating cells in case 2 were negative for CD30 and the cytotoxic-granule-associated proteins (perforin and granzyme B). Primary cutaneous DLBCL preferentially affects the lower legs, but 10-15% of cases arise at other sites. Negativity for B-cell lineage

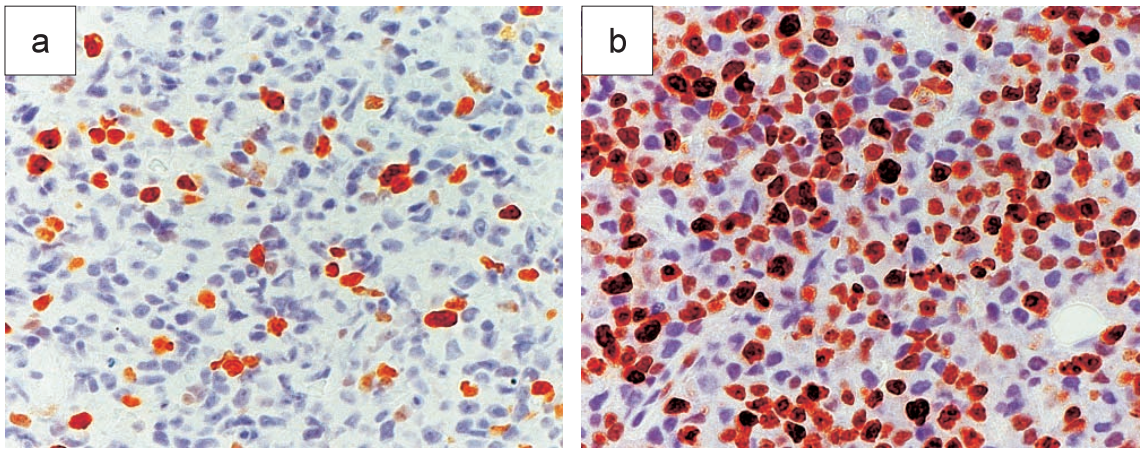

Fig. 5. Immunostaining for Ki-67. (***5a***) Case 1. Ki-67 labeling index was 40% (×400). (***5b***) Case 2. Ki-67 labeling index was 75% (×400).

Table 1. List of antibodies, source and immunohistochemical results

Antigen	Clone	Source	Immunopositivity	
			Case 1	Case 2
CD3	PS1	Nichirei, Tokyo, Japan	−	−
CD4	1F6	Novocastra, Newcastle upon Tyne, UK	+	+
CD5	4C7	Novocastra	−	−
CD7	CD7-272	Novocastra	−	−
CD8	C8/144B	DakoCytomation, Glostrup, Denmark	−	−
CD10	56C6	Novocastra	−	−
CD30	Ber-H2	DakoCytomation	−	−
CD34	NU-4A1	Nichirei	−	−
CD43	MT-1	Seikagaku Kogyo, Tokyo, Japan	−	−
CD45RO	UCHL1	DakoCytomation	−	−
CD56	1B6	Novocastra	+	+
CD68	PGM1	Nichirei	−	−
CD79a	JCB117	DakoCytomation	−	−
CD123	6H6	Biolegend, CA, USA	+	+
ALK	ALK1	DakoCytomation	−	−
Granzyme B	GrB-7	Nichirei	−	−
MPO	Polyclonal	DakoCytomation	−	−
Perforin	5B10	Novocastra	−	−
TCL-1	27D6/20	MBL, Nagoya, Japan	+	+
TdT	SEN28	Novocastra	−	−
TIA-1	Polyclonal	Abcam, Cambridge, UK	−	−
EBER	(DNA probe)	DakoCytomation	−	−
MIB-1 index	MIB1	DakoCytomation	40%	75%

ALK, anaplastic lymphoma kinase ; MPO, myeloperoxidase ; TCL-1, T-cell leukemia-1 ; TdT, terminal deoxynucleotidyl transferase ; TIA-1, T-cell restricted intracellular antigen-1 ; EBER, Epstein-Barr virus encoded small RNAs

markers (CD20 and CD79a) distinguishes it from primary cutaneous DLBCL. From the clinical course, the skin lesion in case 2 appeared histologically indistinguishable from leukemia cutis, which occurs in the setting of acute myeloid leukemia. Extramedullary leukemic infiltration may precede acute myeloid leukemia in some cases. In acute monoblastic and monocytic leukemia, there is generally expression of CD4 and aberrant expression of CD56 in 25-40% of cases.[8] In case 2, tumor cells in bone marrow aspirate smears were negative for α-naphthyl butyrate esterase and naphthol ASD chloroacetate esterase. Immunohistochemistry of a skin biopsy specimen and a clot section of a bone marrow aspirate showed that the tumor cells were negative for CD68 and MPO.

Morphologic and immunophenotypic were reported variability in a series of 45 cutaneous biopsy specimens of

BPDCN, the typical monomorphous, blastic neoplastic cell morphology being evident in only 44.4% of cases. A pleomorphic infiltrate of blastoid cells admixed with elongated, twisted and hyperchromatic cells, some of them with a centrocyte-like appearance, was observed in the majority of cases (55.6%), indicating a greater morphologic variability of BPDCN. A heterogeneous population comprising a mixture of small, medium and large tumor cells has also been reported. The cell morphologic diversity of BPDCN may be diagnostically problematic in a minority of cases.[4,5] Monomorphous infiltration of large cells in BPDCN, like that seen in case 2, has not been reported previously. In addition, immunophenotypic variations have been observed in occasional cases. Ascani *et al*.[9] and Aragrakos *et al.*[10] reported cases of a CD4-negative variant of BPDCN. Cases of CD56-negative BPDCN have also been reported. Cota *et al*.[4] examined negativity of CD4, CD56, CD123 and TCL-1 in BPDCN and reported that CD4 was negative in 20% of cases, CD56 in 8.9%, CD123 in 4.4% and TCL-1 in 10.2% of cases. Here, the Ki-67 labeling indexes of the tumor cells were 40% in case 1 and 75% in case 2. The Ki-67 labeling index of BPDCN reportedly ranges from 20% to 90%, and varies among cases.[4] Although the morphological cellular diversity may be related to the proliferation activity of the tumor cells, the diagnostic value of the Ki-67 labeling index must be examined further in a large number of BPDCN cases.

The prognosis of BPDCN is poor, with a median survival period of 14 months, and 2- and 5-year overall survival rates of 33% and 6%, respectively.[11] There is no consensus on the optimal treatment for BPDCN. The therapeutic approaches described in the literature are very different and not standardized. Initially, most patients show a good response to treatment, but relapse quickly.[12] In the present case 2, the skin tumor disappeared after electron beam irradiation therapy of 27 Gy. However, bone marrow and peripheral blood involvement appeared after 2 months after the therapy. Despite AdVP chemotherapy, the patient died due to progression of the neoplastic process.

BPDCN needs to be considered in the differential diagnosis of hematopoietic tumors involving the skin. Accurate diagnosis requires careful histologic examination and appropriate immunohistochemical and flow cytometry panels, including CD4, CD56, TCL1 and CD123. In addition, case 2 indicates that BPDCN can show considerable diversity of cell morphology. This variant should be clearly recognized to allow an early diagnosis of BPDCN to be made, and patients with this aggressive hematological disorder should be managed properly.

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