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Case Study

Leukemic Manifestation of Blastic Plasmacytoid Dendritic Cell Neoplasm Lacking Skin Lesion : A Borderline Case between Acute Monocytic Leukemia

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Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematologic malignancy with a poor prognosis. We encountered a unique case of BPDCN that was leukemic at presentation without skin lesion and expressed CD33 antigen. A 74-year-old man was admitted because of dyspnea. Physically, hepatosplenomegaly, but not skin lesions and superficial lymph node swelling, was noted. The white blood count was 33.6×10^9/L with 19% giant abnormal cells. These cells were positive for CD4, CD86, CD123 (bright), BDCA-2, and HLA-DR, but negative for CD1a, CD3, CD11b, CD11c, CD13, CD14, CD19, CD64, and CD68. From these findings, a diagnosis of BPDCN was made. In terms of unusual expression, these tumor cells were positive for CD33 but negative for CD56. The karyotype was 47, XY, t(6;8) (p21;q24), + r. We performed combination chemotherapy (Ara-C + VP-16 + MIT), which resulted in a marked reduction of tumor cells and improvement of the dyspnea. On day 16, however, he died of sepsis due to *Bacillus cereus*. The clinical picture of this patient is unusual and may provide new information on the clinicopathology of BPDCN. 〔*J Clin Exp Hematopathol 52(2) : 107-111, 2012*〕

Keywords: blastic plasmacytoid dendritic cell neoplasm, leukemic manifestation, skin lesion, CD33, CD56

INTRODUCTION

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematologic malignancy with a poor prognosis. The normal counterpart of BPDCN has been proposed to be plasmacytoid dendritic cells (pDC). PDC exert antiviral immunity and autoimmunity *via* type I interferon production mediated by stimulation through toll-like receptor 9 in the palatine tonsil and T-zone of lymph nodes.[1–4] The cellular origin of pDC, however, is still controversial. We encountered a unique BPDCN patient who initially presented with a leukemic condition without skin and lymph node involvement. As an unusual pattern of antigen expression, the BPDCN cells expressed CD33 but lacked CD56. In addition, the BPDCN cells carried a rare cytogenetic abnormality of 47, XY, t(6;8) (p21;q24), + r. The unusual clinical picture, the unique antigen profile, and the characteristic karyotype of BPDCN may provide new information regarding diagnostic criteria and tumor biology of this neoplasm.

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CASE REPORT

A 74-year-old man was referred and admitted to our hospital because of dyspnea, general fatigue, and leukocytosis with 2% abnormal cells in October 2009. His medical history was significant for hyperlipidemia, colon cancer, and inferior wall myocardial infarction. On admission, his body temperature was 36.9℃ and oxygen saturation (SpO_2) 90%. Physically, bilateral wheezing was heard, and the liver and spleen were palpable 4.5 cm and 2 cm below the costal margin, respectively. He showed neither superficial lymphadenopathy nor skin lesions. Hematologic examination revealed

a white cell count of 33.6 × 10^9/L with 19% abnormal large cells (Fig. 1a), a hemoglobin concentration of 11.7 g/dL, and a platelet count of 2.4 × 10^9/L. Serum lactate dehydrogenase and C-reactive protein were elevated to 1,652 IU/L (normally 120 to 250 IU/L) and 12.4 mg/dl (normally below 0.5 mg/dL), respectively. Computed tomography scanning showed hepatosplenomegaly, splenic infarction, bilateral ground-glass opacity of the lung, and plate-like atelectasis in the left lower lobe due to marked splenomegaly. A bone marrow aspirate, which was obtained with difficulty, showed similar giant abnormal cells with abundant and basophilic cytoplasm (Fig. 1a), which comprised 21.6% of nucleated cells. These cells exhibited monocyte-like properties because they were negative for peroxidase staining and weakly positive for α-naphthyl butyrate esterase with susceptibility to sodium fluoride (Fig. 1b, 1c & 1d). Flow cytometric analysis revealed that these abnormal cells were positive for CD4, CD45RA, CD86, HLA-DR, and ILT-3 (CD85k), but negative for CD3, CD11b, CD11c, CD13, CD14, CD19, CD64, and CD68 antigens. Furthermore, they expressed CD123 (bright) and BDCA-2 (CD303), but not CD1a. From these findings, a diagnosis of BPDCN was made. It is noteworthy that these BPDCN cells were positive for CD33 but negative for CD56. The karyotype of peripheral blood cells was 47, XY, t(6;8) (p21;q24), + r (Fig. 2) in all divided cells. Electron microscopy of the tumor cells showed dendritic cytoplasmic projections on the surface membrane and moderately developed cytoplasmic laminar rough endoplasmic reticulum (Fig. 3), supporting the diagnosis of BPDCN. Serum concentrations of cytokines such as tumor necrosis factor-α), interleukin-1β, interleukin-6, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, and macrophage colony-stimulating factor were elevated to 32.1, 0.41, 111, 71.1, 7.3, and 3,920 pg/mL, respectively, in accordance with the fever, high concentration of C-reactive protein, and granulocytosis in the present patient. On day 3 after admission, he needed the assistance of a nonin-

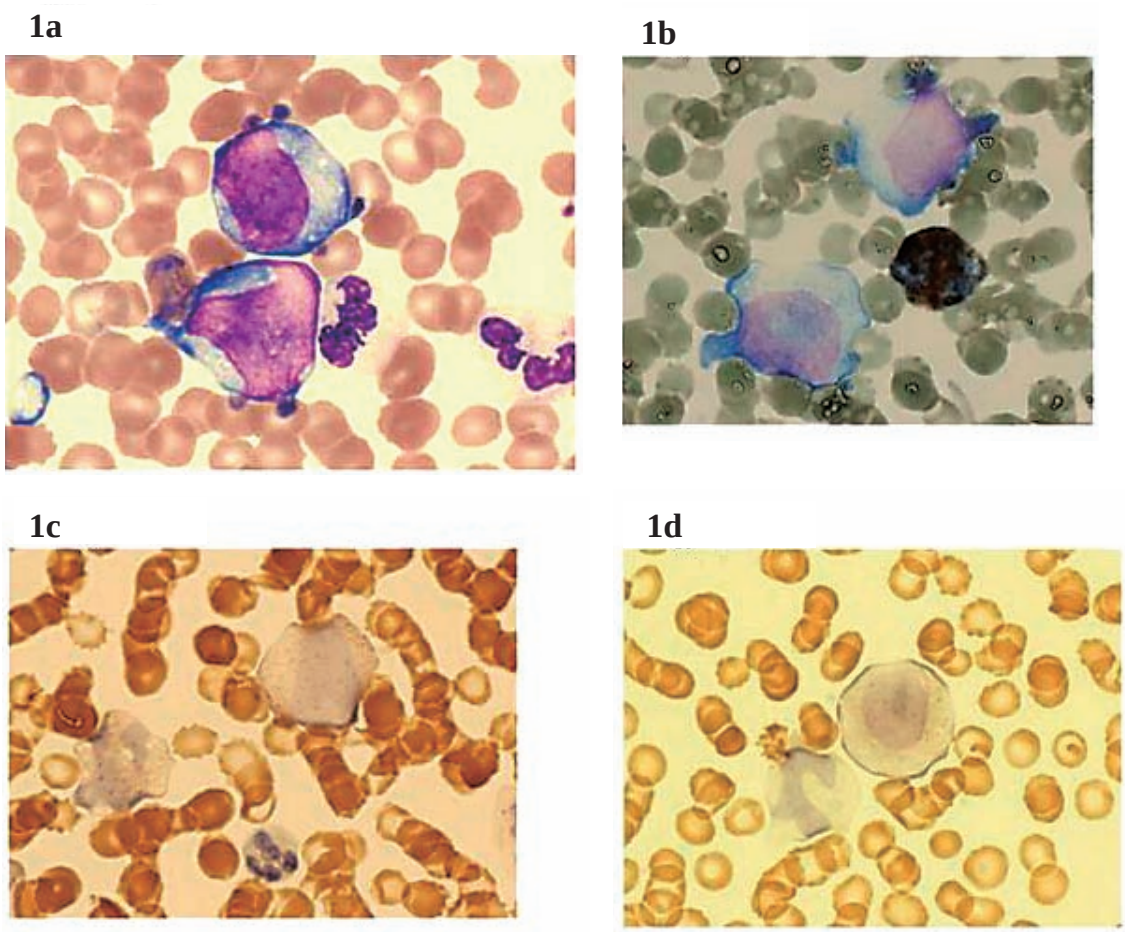

Fig. 1. Smear preparation of peripheral blood on admission. (***1a***) Wright-Giemsa staining : Giant cells with abundant, basophilic cytoplasm and small vacuoles. The nucleus contains clear nucleoli (× 1,000). (***1b***) Peroxidase staining (× 1,000). (***1c***) Esterase staining : These cells are weakly positive for α-naphthyl butyrate esterase (× 1,000). (***1d***) The esterase shows susceptibility to sodium fluoride (× 1,000).

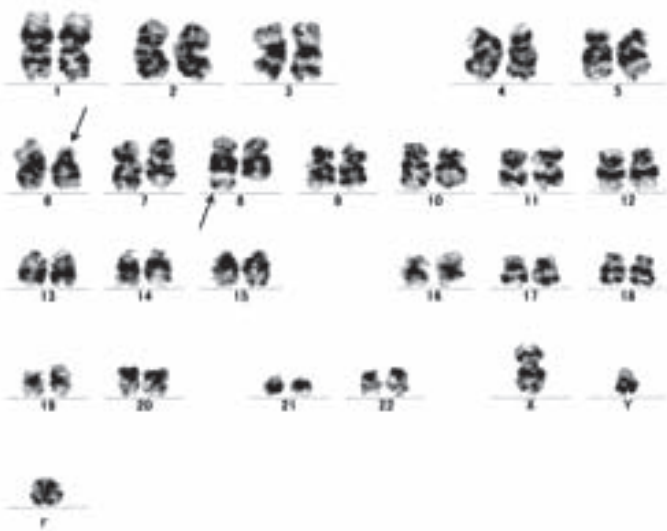

Fig. 2. Cytogenetic analysis of bone marrow cells. All 20 dividing cells analyzed show an abnormal karyotype of 47, XY, t(6;8) (p21;q24), + r.

vasive positive pressure ventilator because of worsening dyspnea and SpO_2. Chest X-ray revealed severe bilateral interstitial infiltrates (Fig. 4), which were considered to be the pulmonary invasion of tumor cells. We performed combination chemotherapy (Ara-C : 140 mg, days 1-5 ; VP-16 : 120 mg, days 1-3 ; mitoxantrone : 8 mg, days 3-5). The treatment rapidly improved the dyspnea, and the patient no longer required oxygen inhalation on day 10. Tumor cells in the peripheral blood disappeared on day 8. On day 15, however, he showed a high fever, followed by progressive consciousness disturbance, and died of septic shock on day 16. *Bacillus cereus* was detected from the blood culture. An autopsy revealed multiple ulcers of the transverse colon with colonies of gram-positive *Bacillus*. A small number of residual tumor cells were observed in the spleen and bone marrow.

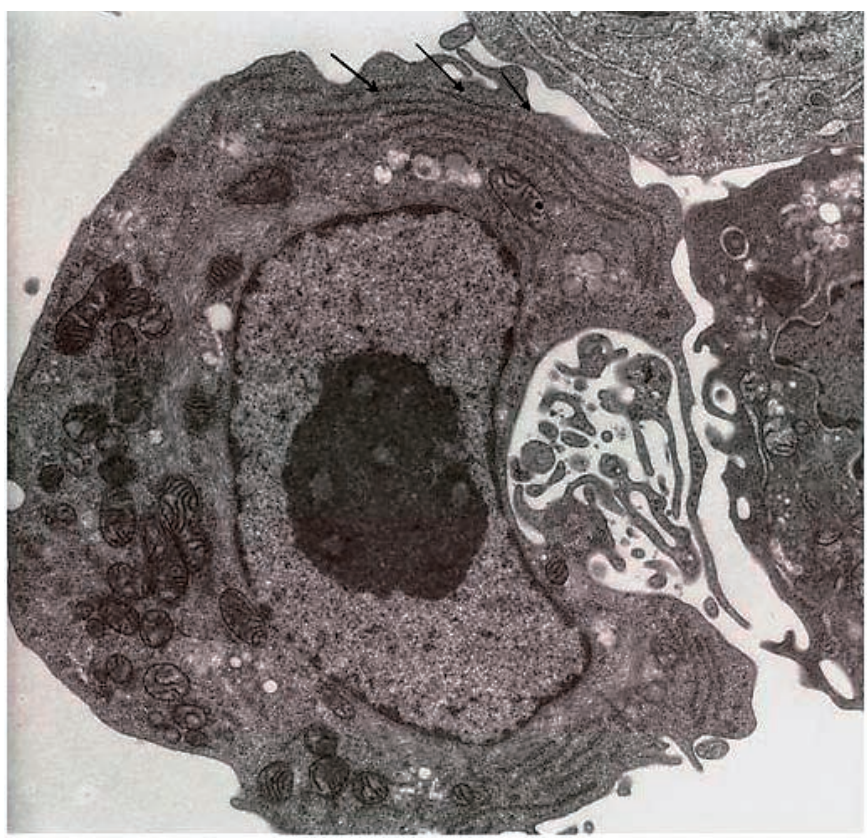

Fig. 3. Electron microscopy of the tumor cells shows that they have dendritic cytoplasmic projections on the surface membrane and moderately developed cytoplasmic laminar rough endoplasmic reticulum (*arrows*).

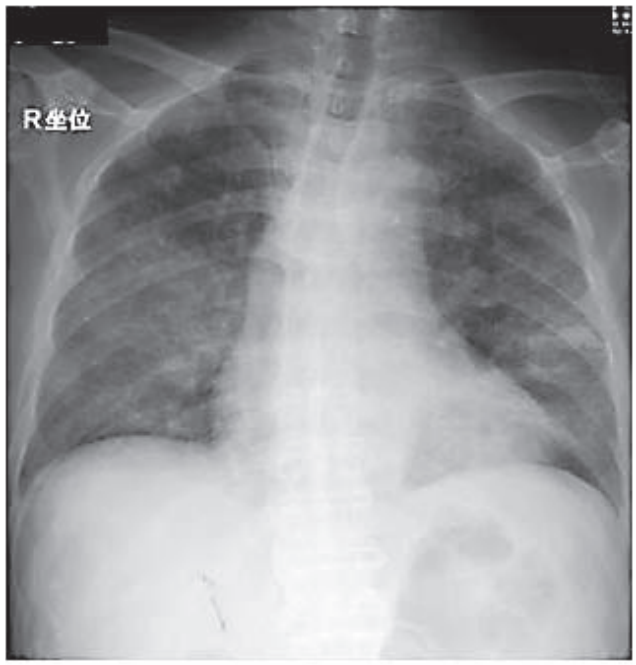

Fig. 4. Chest X-ray on day 3 after admission reveals severe bilateral interstitial infiltrates.

DISCUSSION

BPDCN is a highly aggressive hematologic malignancy, leading to a median survival of 12-14 months.[5] Initially, BPDCN almost exclusively affects the skin, then involves lymph nodes and the bone marrow, and ultimately proliferates in the peripheral blood.[5–6] Therefore, the leukemic condition involving a lack of skin lesions at presentation in the present patient is quite exceptional. Indeed, only 8 such cases have been documented.[7]

BPDCN usually expresses CD4, CD43, CD45RA, CD56, CD123 (bright), HLA-DR, BDCA-2, BDCA-4, and TCL1 antigens without other lineage markers.[6–8] A scoring system for pDC leukemia/BPDCN based on surface antigen expression has been proposed by Garnache-Ottou *et al*. (Table 1).[9] They gave a definitive diagnosis of pDC leukemia/BPDCN when a case is assigned more than 2 points. According to this system, the present case scored 4 ; therefore, the diagnosis of BPDCN may be definitive regardless of the exceptional phenotype of positive CD33 and negative CD56 expressions. Regarding the CD56 antigen, only 6 cases of CD56-negative BPDCN have been reported.[9–14] A lack of CD56 expression, however, may not exclude the diagnosis of BPDCN because pDC themselves do not express CD56,[15] although this opinion is based on the assumption that BPDCN originates from pDC. CD33-positive BPDCN may also be rare, given that only 8 cases have been described in the literature.[16] Similarly, normal pDC are weakly positive for CD33 ;[16] therefore, the finding regarding CD33 may also not exclude the diagnosis of BPDCN in the present case.

The abnormal karyotype of 47, XY, t(6;8) (p21;q24), + r, which was observed in the present patient, may be exceptional in BPDCN because t(6;8) (p21;q24) has been described only in one patient.[17] Furthermore, commonly affected chromosomal loci include 5q, 12p, 13q, 6q, 15q,[17] and 9p21[18] in BPDCN. The chromosomal translocation of t(6;8) in the present patient does not involve these regions.

The developmental origin of pDC remains controversial. PDC have long been considered to be differentiated from lymphoid progenitor cells because several arguments have focused on the expression of the pre-T cell receptor α gene by human pDC and immunoglobulin heavy chain gene rearrangement in murine pDC.[19–21] A recent study demonstrated that pDC develop randomly from both myeloid- and lymphoid-committed progenitors.[22] According to this finding, tumor cells in the present patient might have developed from a myeloid progenitor because they expressed CD33 and weakly expressed non-specific esterase. More recently, research has shown that T-cell progenitors preserve the developmental potential in the myeloid lineage.[23,24] This suggests that T-cell and myeloid progenitors originate from a common progenitor. On the basis of this hypothesis that pDC develop from this common progenitor, we can reasonably understand the cause of various phenotypes of BPDCN including CD33 and non-specific esterase expressions, as observed in the present case. Further accumulation of BPDCN cases and investigation of pDC themselves will shed more light on this issue.

Table 1. Scoring system for pDCL diagnosis

Markers	Present	Absent
Profile: $CD4^+$, $CD56^{+/-}$, $CD11c^-$, MPO^-, $cCD79a^-$, $cCD3^-$	1	pDCL excluded
CD123	1 ($CD123^{+or\ high}$)	0 ($CD123^{neg\ or\ dim}$)
BDCA-2	2	0
BDCA-4	1	0

MPO, myeloperoxidase ; pDCL, plasmacytoid dendritic cell leukemia

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