Blastic Plasmacytoid Dendritic Cell Neoplasm With Skin and Bone Marrow Involvement:three Case Reports and Literature Reviews

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Case report

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Abstract

Background Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and highly aggressive hematopoietic malignancy. BPDCN is difficult to diagnose because of the overlap in morphologic and immunophenotypic features with various cutaneous lymphatic hematopoietic tumors.

Case presentation All cases were characterized by skin nodules and examined by histology, immunohistochemical detection, *in situ* hybridization for Epstein -Barr virus, and follow-up, and the relevant literatures were reviewd. Two patients involved the bone marrow. Immunohistochemical detection showed CD56 were positive, EBER were negative. Chemotherapy is the main treatment for BPDCN, but case 1 showed bone marrow suppression; and case 2 developed recur after chemotherapy.

Conclusions An accurate pathological diagnosis is a precondition for treatment, and the diagnosis of BPDCN should be based on a combination of clinical symptoms, pathological characteristics, immunophenotype, and other auxiliary examinations. It is necessary to clarify the clinicopathological features and biological behavior of BPDCN to improve the understanding of BPDCN by both clinicians and pathologists. A cytotoxin directed against CD123(tagraxofusp) may bring new future.

Introduction

BPDCN is a highly aggressive lymphoid hematopoietic system tumor derived from precursors of plasmacytoid dendritic cells, with no racial or ethnic predisposition. BPDCN is difficult to diagnose because of the overlap in morphologic and immunophenotypic features with various cutaneous lymphatic hematopoietic tumors. We retrospectively reported the clinicopathological data, histological and morphological characteristics, immunophenotype, and differential diagnosis in three cases of BPDCN, in order to raise awareness of the condition and provide evidence for its clinical treatment and prognosis. In addition, we briefly review previous cases of BPDCN.

Case Presentation

All patients underwent skin biopsy. The biopsy tissues were stained with hematoxylin and eosin, immunohistochemically stained for CD56, CD4, CD123, CD68, etc and used for *in situ* hybridization to detect Epstein-Barr virus (EBV; EBER). The patients were then followed-up from diagnosis until death.

Case 1

Patient 1 was a 59-year-old man who was admitted to the Department of Hematology at Shanxi Cancer Hospital in February 2013. He found a nodule in his right inner thigh in November 2012, and unequal nodules gradually appeared on his trunk and limbs, followed by multiple tender enlarged lymph nodes in his neck, armpits and groin. The tumors grew rapidly. Lactate dehydrogenase (LDH) levels were normal (156 U/L). A 2.0-cm lymph node biopsy from the right upper arm showed the absence of normal lymph node structure, and medium-sized diffuse lymphoid cells. Immunohistochemically, lymphocytes were positive for CD56, CD123 (Fig. 1A), CD38, LCA, CD43, CD99, and Ki67(60%), and negative for CD4, CD68, myeloperoxidase(MPO), CD3, CD20, CD21, CD10, CD5, CyclinD1, CD23, CD15, CD30, CD138, S-100, Pax-5, MUM1, CD34, Granzyme B, TIA-1, and TdT. The EBER test was negative. Bone marrow biopsy revealed diffuse lymphoid cells between the bone trabeculae, with medium-sized heterotypic nuclei. (Fig. 1B). Immunohistochemical analysis of lymphocytes indicated positivity for CD56, CD123, CD43 and Ki67 (30%), and negativity for CD4, CD68, MPO, CD3, CD20, TIA-1, and TdT. Chemotherapy was administered as the main treatment for BPDCN, but the patient developed bone marrow suppression after VDLD treatment. One month later, he was treated with CAM chemotherapy, and again showed bone marrow suppression. He subsequently developed pulmonary infection in May 2013 and central infiltration on August 8, and finally died at 7 months after his diagnosis.

Case 2

Patient 2 was a 15-year-old girl who was admitted to the Department of Hematology at Shanxi Cancer Hospital in July 2016. She inadvertently found scattered hard subcutaneous nodules on her back in May 2016. Her LDH level was increased to 348 U/L. Biopsy showed dense heteromorphic lymphoid cells throughout the dermis (Fig. 2A). Immunohistochemically, the lymphocytes were positive for CD56, CD4 (Fig. 2B), CD123, Bcl-2 and Ki67 (80%), but negative for CD68, MPO, CD3, CD20, CD30, CD43, CD5, MUM-1, CD34, TIA-1, Gramm B and CD10. An EBER test was negative. Posterior iliac puncture revealed diffuse lymphoid cells between the bone trabeculae and bone marrow, with medium-sized heterotypic nuclei, and bone marrow infiltration. Immunohistochemistry revealed that the lymphocytes were positive for CD56, CD4, CD123, and Ki67 (20%-30%), and negative for CD68, MPO, CD3, CD20, and CD38. The subcutaneous nodules subsided after anti-infective treatment but subsequently reappeared and became more severe, gradually involving the limbs and body. She was treated with CHOP and VDCLP for BPDCN, with improvement of the subcutaneous nodules and a complete bone marrow response. The patient was followed up for 17 months from diagnosis to death, after stopping treatment for economic reasons.

Case 3

Patient 3 was a 70-year-old woman who was hospitalized in another hospital. Immunohistochemical and *in situ* hybridization examinations were performed in the Department of Pathology of Shanxi Cancer Hospital. A biopsy from her inner left thigh demonstrated diffuse infiltrating plasmacytoid cells with nuclear deviation. Immunohistochemically, the lymphocytes were positive for CD56, CD68, and Ki67 (10%), and negative for CD4, CD123, CD3, CD20, CD10, MUM1, AE1/AE3, Desmin, S-100, and CD30. The patient was treated in another hospital and died 9 months after her diagnosis. (The main test results are shown in Table 1)

Table 1
Main test results in the three patients

Case	Site	CD56	CD4	CD123	CD68	MPO	CD3	CD20	Ki67	EBER	LDH	Follow-up
1	Skin	+	-	+	-	-	-	-	60%	-	156U/L	7 months
	Bone marrow	+	-	+	-	-	-	-	30%	-		
2	Skin	+	+	+	-	-	-	-	80%	-	348U/L ↑	17 months
	Bone marrow	+	+	+	-	-	-	-	20%-30%	-		
3	Skin	+	-	-	+	*	-	-	10%	-	*	9 months

* Not checked.

Discussion

BPDCN accounts for only 0.7% of primary lymphatic hematopoietic tumors of the skin[1]. It can occur in any age group[2, 3], but is most common in the elderly. The male: female ratio is 3.3:1. Jegalian et al.[2] reported that children and young patients had a relatively good prognosis. About 76%-85% of cases[4] have skin involvement, with asymptomatic isolated or multiple nodules, plaques, or bruises. Some cases only involve the skin, but multiple parts may be affected. The current cases of BPDCN included one man and two women, and although two were elderly, case 2 was unusually only 16 years old, and she had a relatively good prognosis (17 months). In the present study, all three cases were characterized by skin nodules.

The diagnosis of BPDCN is based on pathological biopsy. Kerr et al.[5] showed that tumor cells invading the dermis and adipose tissue of the skin, with no tumor cells in the epidermis. When the lesion involves the bone marrow, it may show as an interstitial infiltration or as a mass of tumor cells, like infiltrating leukemia, often accompanied by hematopoietic tissue dysplasia[6]. In the current study, the pathological features of all three patients showed no tumor cells invading the epidermis, and morphology consistent with that reported in the literature. In addition, the bone marrow was involved in cases 1 and 2, and numbers of diffuse lymphoid cells could be observed.

The immunological phenotype of BPDCN is important. Julia et al.[7] proposed five specific immunological markers for BPDCN: CD56, CD4, CD123, TCL1, and CD303, and suggested that positivity for at least four of these indicated a diagnosis of BPDCN. Overexpression of CD123 or interleukin-3(IL-3) receptor subunit alpha occurs in essentially all cases of BPDCN[8–10]; however, individual CD123-negative cases of BPDCN have also been reported[11]. CD68 is expressed in 50% of tumor cells, and such patients are prone to leukaemia transformation[2]. In contrast, the cytotoxic markers CD23, CD30, and CD138 are negative. In this study, tumor cells expressed CD56 in all three cases, CD4, CD123, CD68 were positive in one, two, and one cases, respectively. Tumor cells were positive for CD68 expression in case 3, but she did not develop acute leukemia. Laboratory examinations are also essential for diagnosing BPDCN, and LDH was significantly elevated in case 2.

Clinicopathologically, the differential diagnosis of BPDCN includes myeloid sarcoma or leukemia, T-lymphoblastic lymphoma and NK/T cell lymphoma. Both myeloid sarcoma or leukemia and BPDCN can show skin, lymph node and bone marrow involvement. However, applying a series of markers (such as CD56, CD4, CD123, and TCL-1) can better distinguish these diseases[12]. MPO is a specific immunological marker of AML. In the current study, MPO was negative in cases 1 and 2, and BPDCN could be confirmed by a combination of morphology and immunological positivity for CD56, CD4, and CD123 and MPO negativity. Compared with BPDCN, T-lymphoblastic lymphoma usually occurs in adolescents or young adults, with more frequent mediastinal involvement. It is important to note that patients with BPDCN without skin involvement may have a younger onset age, and may have mediastinal involvement and CD34-positive tumor cells, which may be more easily confused with T-lymphoblastic lymphoma. Although case 2 was an adolescent, all three patients had skin involvement and no mediastinal involvement; furthermore, CD34 was negative in cases 1 and 2, and T-lymphoblastic lymphoma could thus be excluded. BPDCN and NK/T cell lymphoma can be distinguished by morphology, immunohistochemistry, and EBER testing. Tumor cells in NK/T cell lymphoma have various forms, often invade the vascular wall and are accompanied by necrosis, and cytotoxic markers such as TIA-1 and Granzyme B are often positive. Furthermore, NK/T cell lymphoma is associated with EBV infection, and the EBER test is thus positive in patients with NK/T cell lymphoma. Although CD56 was expressed in BPDCN, serum EBV and *in situ* hybridization EBER were negative, indicating that BPDCN was not related to EBV infection[1]. In this study, TIA-1 and Granzyme B were negative in cases 1 and 2, and all three patients were EBER-negative, thus excluding a diagnosis of NK/T cell lymphoma.

Given the lack of consensus, BPDCN has been treated with regimens used for other acute leukemias. Most case reports indicated that the majority of patients who received initial treatment with acute lymphoblastic leukemia, AML, or lymphoma CHOP chemotherapy achieved complete remission but had a high recurrence rate[13, 14]. In this study, case 1 received successive VDLD treatment and CAM chemotherapy, but both caused significant bone marrow suppression. VDCLP has since been used to replace VDLD. Notably, CHOP and VDCLP resulted in improvement of the subcutaneous nodules and complete bone marrow response in case 2; however, as reported in previous studies, the duration of the response was short and the patient relapsed quickly. Recent, new treatment options have been developed. A cytotoxin directed against CD123 (tagraxofusp, formerly DT-IL3 and SL-401) has received United States Food and Drug Administration approval specifically for BPDCN in adults and in children aged 2 years or older[15].

Conclusions

In summary, BPDCN is a rare and highly aggressive hematopoietic malignancy. Skin involvement is the most common initial clinical manifestation, but it is not specific, and the bone marrow can also be affected. CD56, CD4, and CD123 are important diagnostic makers for BPDCN. The diagnosis of BPDCN should thus be based on a combination of clinical symptoms, pathological characteristics, and other auxiliary examinations, to minimize the risk of a missed or delayed diagnosis. These cases highlight the need to improve the understanding of BPDCN by both clinicians and pathologists.

Declarations

Availability of data and material

All data and materials are available.

Ethics approval and consent to participate

Written informed consent was obtained from our patient to publish this case report and its accompanying images.

Consent for publication

All the authors are qualified for authorship and agree to submit this paper.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

Jinfen Wang for data collection. Hongwei Zhang for the treatment of the patients. Li Wang,Yaling Li and Wei Bai for data analysis. Yanfeng Xi and Jiang Chang conducted the literature review. Jianghong Guo wrote the manuscript. All authors read and approved the final manuscript.

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Figures

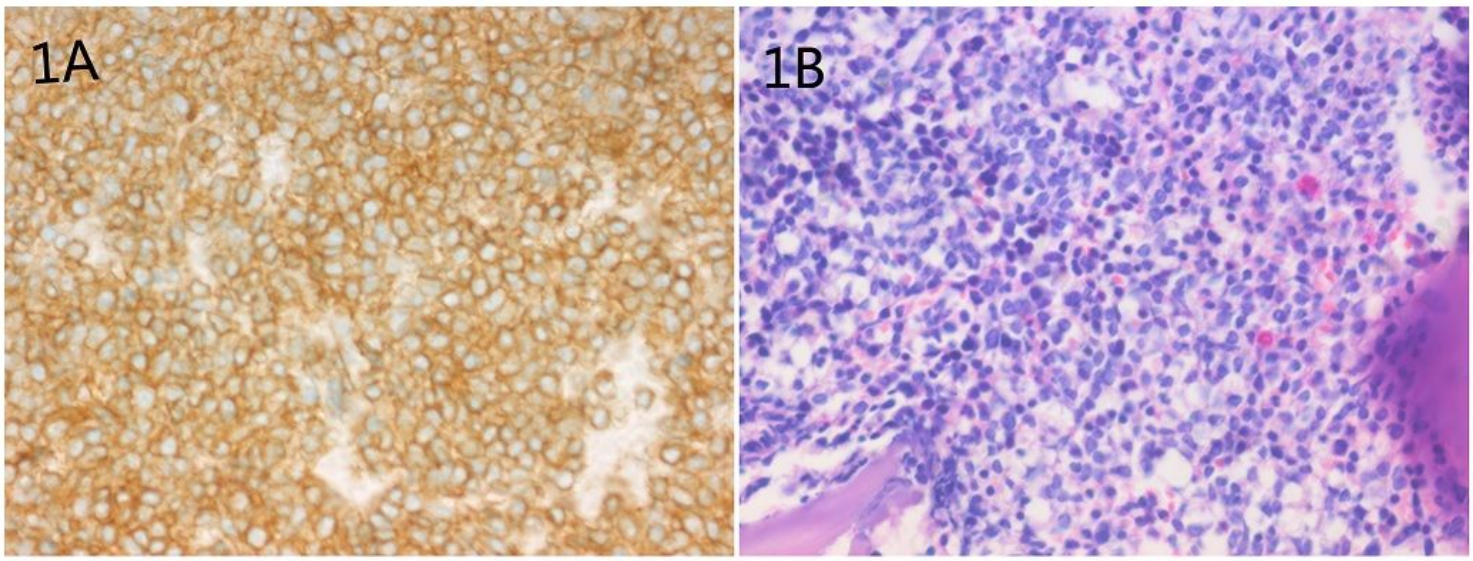

Figure 1

A 2.0-cm lymph node biopsy from the right upper arm showed the absence of normal lymph node structure, and medium-sized diffuse lymphoid cells. Immunohistochemically, lymphocytes were positive for CD56, CD123 (Fig.1A) Bone marrow biopsy revealed diffuse lymphoid cells between the bone trabeculae, with medium-sized heterotypic nuclei. (Fig.1B).

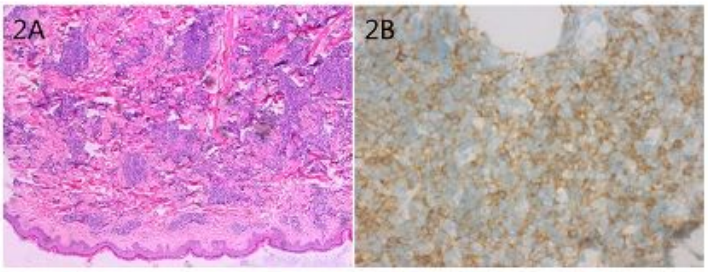

Figure 2

Biopsy showed dense heteromorphic lymphoid cells throughout the dermis (Fig.2A) Immunohistochemically, the lymphocytes were positive for CD56, CD4 (Fig.2B)