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CASE REPORT

Blastic Plasmacytoid Dendritic Cell Neoplasm: Skin and Bone Marrow Infiltration of Three Cases and the Review of the Literature

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Abstract Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a distinct and rare neoplastic entity and was classified as a subgroup of acute myeloblastic leukemia by the WHO in 2008. The median survival of patients was 15.2 months in a large case series. Allogeneic or autologous bone marrow transplantation has been recommended by some reports because of the disease's poor prognosis. We present three patients who presented with both skin and bone marrow infiltration. A 57-year-old man, a 62-year-old woman, a 64-year-old man were admitted to our outpatient clinic because of skin lesions. All of the patient's had bone marrow infiltration with positivity of the CD4, CD56, and CD123 staining. Survival of the patient's were 42, 6 and 12 months, respectively. Two of the patients who presented as blastic form didn't respond to any chemotherapy. BPDCN is a difficult disease to diagnosis and manage. CD4, CD56, CD123, CD303, and T cell leukemia/lymphoma 1. Cutaneous lesions can present as isolated nodules, macules, and disseminated macules and nodules. Positivities are crucial to the diagnosis of the disease in histological examination. Bone marrow infiltration or disease relapse at presentation were related to poor prognosis. Complete immunocytochemical staining must be performed for all patients who have cutaneous lesions with or without blood count abnormalities. Bone marrow (allogeneic or autologous) transplantation should be considered at the first remission.

Keywords Blastic plasmacytoid dendritic cell neoplasm · Bone marrow neoplasms · Skin neoplasms

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Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a distinct and rare neoplastic entity and was classified as a subgroup of acute myeloid leukemia by the WHO in 2008 [1]. BPDCN originates from precursors of plasmacytoid dendritic cells. In pathological examination, the neoplastic cells express typical CD4, CD56, and CD123 [2]. BPDCNs usually present in an elderly patient group (60–70 years) with male predominancy [3]. The median survival of patients was 15.2 months in a large case series [4]. Allogeneic or autologous bone marrow transplantation has been recommended by some reports because of the disease's poor prognosis [3, 5]. BPDCN usually presents with cutaneous and non-cutaneous involvement. According to the Ann-Arbor staging system, stage IV disease is seen in 66 % of cases, and cutaneous lesions are seen in most patients at disease onset [6]. Skin lesions may be in maculopapular, nodule, or plaque form. Non-cutaneous involvement can cause leukemic infiltration of the bone

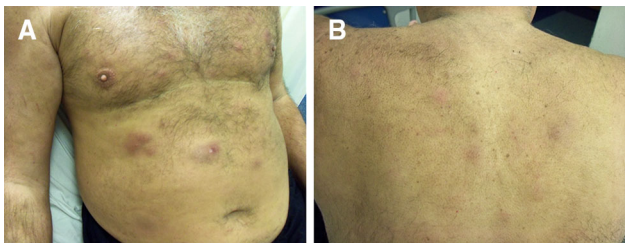

Fig. 1 *Case 1* Cutaneous lesions; **a** multiple erythematous, well demarcated plaques and nodules and a few violeceous small nodules on some plaques; **b** bruise-like and slightly erythematous plaques on the back

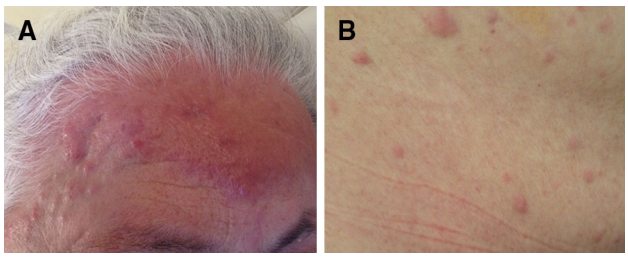

Fig. 2 *Case 2* Cutaneous lesions. **a** Skin-colored and erythematous papules and nodules on the frontal skin; **b** multiple discrete erythematous papules and nodules on the extremities

marrow or enlargement of the lymph nodes [6–8]. We present three patients who presented with both skin and bone marrow infiltration.

Case 1 Presentation

A 57-year-old man presented to our hematology outpatient clinic in December 2010 with multiple erythematous, well demarcated plaques and nodules on his body. There were a few violeceous small nodules on some of the plaques (Fig. 1a). There were also bruise-like and slightly erythematous plaques on the patient's back (Fig. 1b) and other areas of his body (Fig. 1c). He had no prior medical history and did not take medications. The lesions appeared about 1 month before diagnosis. The pathological examination of the skin biopsy showed that a patchy infiltration was concentrated in the lower half of the dermis. In the immunohistochemical staining, the CD4, CD56, CD68 and CD123 were positive and the Ki-67 proliferation index was 60 % and the CD68-PGM1, CD1a, S-100, CD138, CD25 were negative. He had no other symptoms. There were no significant abnormalities in the biochemical values, except for an elevated lactate dehydrogenase (LDH) level of 566 U/L. The bone marrow biopsy showed a 6 % neoplastic cell infiltration which was same immunophenotypic and morphologic properties with the skin lesions. There was not lymph node enlargement in computerized tomography scanning. Hyper-CVAD chemotherapy (CT) protocol was applied. His skin lesions improved after 1 course of CT, and bone marrow infiltration disappeared after 2 courses of CT. He was released and received no further CT in March 2011. In February 2014, the patient was again admitted to the hematology clinic because of severe weakness, pallor, and dyspnea without skin lesions. His laboratory values were Hemoglobine (Hb) 9.03 g/dL, white blood cells (WBC) 35,000/mm [3], platelet (PLT) 116,000/mm [3], and PNL (polymorph nucleated leucocytes) 3,500/mm [3]. In addition, 80 % of the cells were blastic in the peripheral blood and diffuse blastic infiltration of the bone marrow. A conventional karyotypic analysis of the bone marrow revealed monosomy 5q−. He was determined to have a leukemic form of BPDCN. After 1 course of hyper-CVAD and high-dose methotrexate and cytarabine, the patient's laboratory findings did not improve and he was accepted as refractory. Unrelated donor screening was started because he had no siblings. We applied fludarabine–cytarabine–granulocyte colony stimulating factor (FLAG CT) protocol. He was refractory to the FLAG CT and take hydroxyurea only. The patient rejected any other CT or transplantation. He died 2 months after the last CT. He survived 42 months but he survived 5 months after leukemic for of the BPDCN.

Case 2 Presentation

A 62-year-old woman was referred to our hematology outpatient clinic in June 2013. She had hyperleukocytosis and multiple skin lesions on her head and extremities (Fig. 2). She had multiple asymptomatic skin-colored and erythematous papules and nodules on the front of the head skin (Fig. 2a). The patient also had multiple discrete erythematous papules and nodules on her extremities (Fig. 2b). Her laboratory values were Hb 10.3 g/dL, WBC 18,000/mm [3], PLT 35,900/mm [3], PNL 20 %, Monocyte 15 %, lymphocyte 20 and 45 % of the cells were blastic in the peripheral blood and diffuse blastic cell infiltration of the bone marrow. A bone marrow biopsy and skin biopsies were done and showed diffuse neoplastic cell infiltration. Immunohistochemical staining of the biopsy materials showed CD34, TdT, CD117, CD8, CD10, and myeloperoxidase (MPO) negativity and CD4, CD56, CD123, and CD68 positivity (Fig. 3a, b). She was diagnosed by our department of pathology as BPDCN. The karyotypic analysis of the bone marrow was normal. We administered AML-like regimens. Her disease (skin lesions and laboratory values) did not improve with 4 courses of azacitidine,

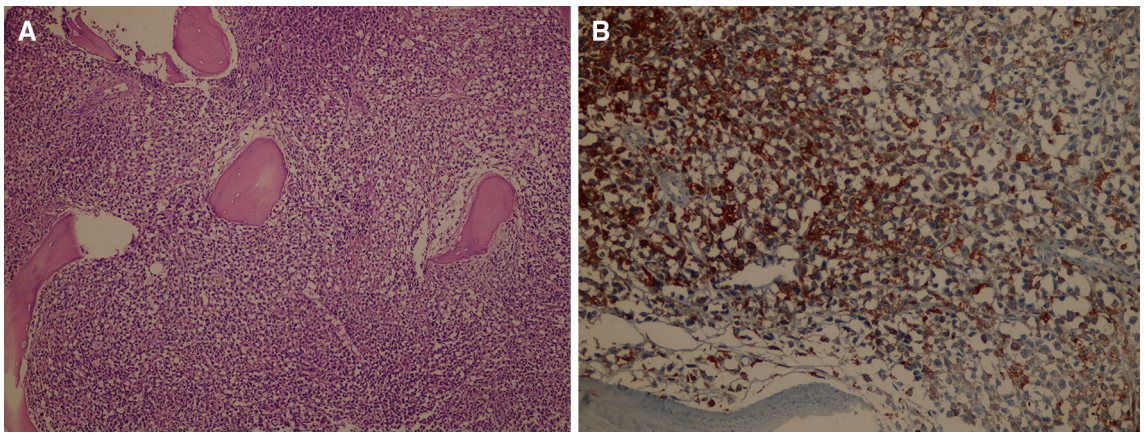

Fig. 3 *Case 2* Pathological findings. **a** The cytomorphology of the immature tumor cells in blastic plasmacytoid dendritic cell neoplasm shows medium-size immature cells with variable amounts of cytoplasm (H+E, ×50) **b** CD68 strongly expressed (Immunoperoxidase, ×200)

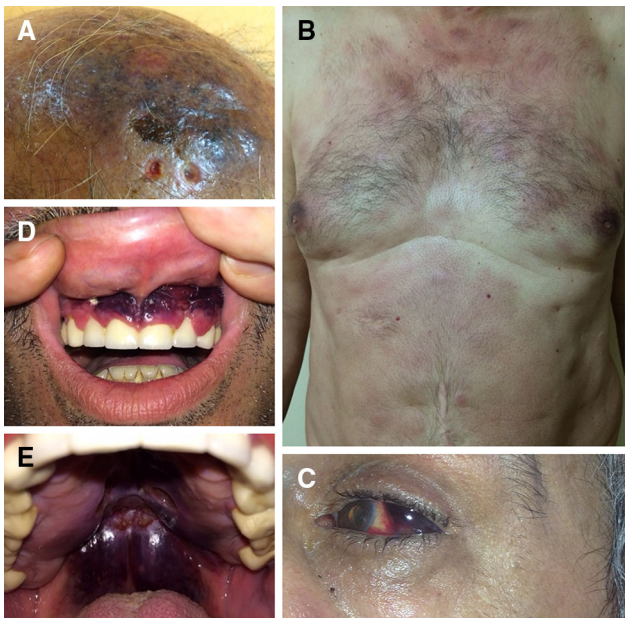

Fig. 4 Cutaneous lesions in Case 3. **a** Slightly indurated, erythematous–violaceous plaque on the scalp; **b** multiple erythematous patches and indurated plaques on the trunk; **c** conjunctival hematoma located on the temporal side; **d** violeceous plaque located on the upper gingiva; **e** edematous violeceous plaque on the soft palate

1 course of cytarabine (100 mg/m^2/day for 7 days), idarubicin (12 mg/m^2/day for 3 days) CT protocol, and 1 course FLAG CT protocol, respectively. She was accepted as refractory after these treatments. The patient died 2 months later from pulmonary sepsis after the last CT. She survived only 6 months following diagnosis.

Case 3 Presentation

A 64-year-old man was admitted to our outpatient clinic because of skin lesions. The condition began as a small nodule on his back 9 months prior to his admission to the clinic and was treated with topical clobetasol 17-propionate ointment with some improvement. Later, the patient experienced disease progression with the development of multiple new lesions. A dermatological examination revealed 8 × 5 cm, slightly indurated erythematous–violeceous plaques on his scalp (Fig. 4a), as well as multiple erythematous patches and indurated plaques involving his trunk (Fig. 4b). A conjunctival hematoma was located on the temporal side of his left eye (Fig. 4c). A violaceous plaque was located on his upper gingiva (Fig. 4d) and an edematous violaceous plaque was on the soft palate (Fig. 4e).

Skin biopsies were taken from the lesion and a bone marrow biopsy was done. CD4, CD56, and CD123 were positive, and CD3, CD5, CD7, CD8, CD34, CD117, pax5, and TdT were negative by immunohistochemical staining in both the skin and bone marrow. Complete blood count and liver and renal function tests were normal. He did not have organomegaly or lymph node enlargement. The karyotypic analysis of the bone marrow was normal. Based on the histocytochemical features of the biopsies, he was accepted as BPDCN, and hyper-CVAD CT protocol was started. After 1 course of CT, his skin lesions almost improved. He has full-matched HLA sibling and we are planning allogeneic bone marrow transplantation at first remission for him.

Discussion

BPDCN is a difficult disease to diagnosis and manage [9]. While neoplastic cells infiltrate the dermis at disease onset, neoplastic cell infiltration spreads to perivascular areas as the disease progresses [2]. Neoplastic cells infiltrated the dermis layer in our three patients. The expected pathological findings of BPDCN are characterized by diffuse,

monotonous infiltration of the dermis by medium-sized cells with round nuclei [8]. CD4, CD56, CD123, CD303, and T cell leukemia/lymphoma 1 (TCL1) positivities are crucial to the diagnosis of the disease in histological examination [4, 10]. Julia et al. reported that only 50 % of cases had positivities in all five markers [4]. $CD4^{+}/CD56^{+}$ co-expression is important in the diagnosis of BPDCN, as well [4]. In the same study, Julia et al. detected that 99 % of patients were positive in CD4, CD56, CD123, CD303, and TCL1 in histochemical staining (98, 92, 97,63, 99 %, respectively) [4]. CD56 and CD123 were positive in the bone marrow biopsies of our three patients; however, we lacked laboratory resources to examine other markers. Cutaneous lesions with typically immunohistochemical staining helped us to establish exact diagnoses.

The bone marrow conventional cytogenetic chromosome analyse of three of our patients were initially normal. When the first patient relapsed, monosomy 5q− cytogenetic abnormality was seen as leukemic presentation. Chromosome abnormalities are frequently encountered in BPDCNs. The most common are 5q (72 %), 12p and 13q (64 %), 6q (50 %), 15q (43 %), and monosomy 9 (28 %), as in our first patient [11].

According to a recently published large case series, cutaneous lesions can present as isolated nodules, macules, and disseminated macules and nodules. Purplish nodules were the most common lesions (73 %) in the patients diagnosed with BPDCN [12]. Our patients cutaneous lesions were usually plaques, nodules, and papules. The third patient's lesions were localized atypically. However we didn't reveal any biopsy from gingival lesions, the lesions disappear after CT. To the best of our knowledge, there are no case reports in the literature about presentations of BPDCN in the gingiva, soft palatum, and conjunctiva.

The application of multi-agent CT protocols is recommended; however, the effective application of this treatment is not usually possible due to the patients' older ages [2, 13]. Chemotherapy protocols for acute lymphoblastic leukemia have slightly longer survival than CT protocols for acute myeloid leukemia [6]. The complete remission rate was 90 % with hyper-CVAD CT protocol [14], as in our two patients who did not present in the leukemic phase. Gruson et al. reported that L-asparaginase–methotrexate and dexamethasone combination therapy can be an alternative treatment strategy with good tolerability and high efficacy for older and otherwise unfit patients [15]. Despite the high response rates to the multi-agent CT protocols, remission duration is still limited in BPDCN [16]. Bone marrow infiltration or disease relapse at presentation were related to poor prognosis as did our first and second patients. Patients who have isolated cutaneous lesions tend to survive longer [6]. However, in another study of 33 patients, bone marrow infiltration did not affect the prognosis [17]. Weil et al. reported that allogeneic bone marrow transplantation in first remission was related to 3-years longer progression-free survival and overall survival (33 and 41 %respectively) [5]. A patient who underwent reduced intensity transplantation had a 4-year survival [16]. In another recent report, autologous hematopoietic stem cell transplantation was a good option for patients with BPDCN without available donors [3].

Our patients were elderly, making it difficult to administer multi-agent CT protocols. A high number of infectious complications were seen in all three. None of the patient underwent allogeneic transplantation. Case 1 rejected any additional therapy, Case 2 had no response to any CT protocol, including FLAG, and transplantation planning for case 3 after completion of remition induction CT protocol.

Conclusion

We share our three patients which have BPDCN here. BPDCN is a rare disease that is difficult for pathologists to diagnose and for clinicians to manage. Complete immunocytochemical staining must be performed for all patients who have unexplained, atypical cutaneous lesions with or without blood count abnormalities. Bone marrow infiltration of BPDCN is related to very short overall survival and to lower response rates. Bone marrow (allogeneic or autologous) transplantation should be considered at the first remission.

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