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Case presentation

Blastic plasmacytoid dendritic cell neoplasm of the skin associated with myelodysplastic syndrome

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Abstract

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a recently described, rare hematologic malignancy with prominent skin involvement. The prognosis of this disease is poor in most cases, with rapid progression despite chemotherapy administration. The first reported case of this disease was in 1994, and less than 200 cases worldwide have been described in the literature to date. Moreover coexistence of BPDCN and MDS is extremely rare. In this study, we describe a typical patient with BPDCN in China who presented with cutaneous involvement as the first manifestation associated with MDS; a brief review of literature is also given.

Key words: plasmacytoid dendritic cell; neoplasm; CD4+/CD56+/CD123+; myelodysplastic syndrome

Case synopsis

A 62-year-old man presented with a 4-month history of generalized petechia or ecchymosis and subcutaneous nodules. Initially, diffuse petechia or ecchymosis on the upper chest was noted in February 2012, which spread rapidly to the trunk and upper extremities. The patient underwent a bone marrow aspiration that showed atypical cells at a local hospital. A biopsy specimen revealed myelodysplastic syndrome-refractory anemia with excess blasts-2 (MDS-RAEB2). A putative diagnosis of MDS was made and CAG (cytarabine, aclacinomycin, G-CSF) chemotherapy was administered. The patient achieved partial remission after 6 days. After one month, the cutaneous eruption developed again on the anterior/posterior trunk and both thighs. Skin biopsy revealed monotonous lymphocytes infiltrates of the dermis. Immunohistochemical stains demonstrated that tumor cells were positive for CD43 and CD56, but negative for CD3, CD20, and MPO. Based on the histological and immunohistochemical results, T-Lymphoproliferative disease was considered. The patient received the CAG regimen again, achieved complete remission after one month, and subsequently discharged from the hospital. Three days after discharge, the

patient presented with a painless generalized erythematous skin rash of papules and nodules (Figure 1), with abdominal distension. The patient was admitted to our hospital on 12-May, 2012. Upon admission, the blood routine showed white blood cell (WBC) count of $50.3 \times 10^9/L$ ($3.9\text{--}10 \times 10^9/L$); red blood cell (RBC) count of $3.12 \times 10^{12}/L$ ($4\text{--}5.5 \times 10^{12}/L$); reticulocyte count (RTC) of $152.9 \times 10^9/L$ ($24\text{E--}84 \times 10^9/L$); and hemoglobin level of 95 g/L ($120\text{--}160$ g/L). Biochemistry tests noted elevations in serum total bilirubin of 52.4 $\mu\text{mol}/L$ ($0\text{--}19$ $\mu\text{mol}/L$); alanine

aminotransferase (ALT) of 200 U/L ($2\text{--}50$ U/L); aspartate aminotransferase (AST) of

228 U/L ($2\text{--}50$ U/L); alkaline phosphatase of 266 U/L ($50\text{--}172$ U/L); α -hydroxybutyrate dehydrogenase of 1139 U/L ($72\text{--}182$ U/L); lactate dehydrogenase (LDH) of 1437 U/L ($60\text{--}240$ U/L); urea of 9.4 mmol/L ($0\text{--}6.8$ mmol/L); creatinine of 119 $\mu\text{mol}/L$ ($45\text{--}110$ $\mu\text{mol}/L$); and uric acid of 695 $\mu\text{mol}/L$ ($150\text{--}430$ $\mu\text{mol}/L$). Computed tomography of the chest and abdomen showed multiple lymphadenopathies in both axillae, the mediastinum, hepatic hilar region, retroperitoneum, and inguinal region. Splenomegaly, pneumonia, and pleural effusion were also observed. Bone marrow aspiration smear showed hypercellularity, containing 55% blast cells (Figure 2A). The cells were negative for peroxidase (100%), positive for periodic acid-Schiff (PAS, 50%), and strongly positive for non-specific esterase (NSE) staining. Moreover, the marrow biopsy showed bone marrow hyperplasia.

Immunohistochemical analysis revealed that tumor cells were positive for CD43, but negative for CD138, CD20, CD3, and CD79a. Peripheral blood flow cytometry revealed 80.4% of CD45 (+) cells within the nucleated cell; positive immunophenotyping for CD117, HLADR, and CD7; and negative immunophenotyping for CD34, CD33, CD13, CD3, CD19, CD10, CD20, CD5, CD2, CD14, CD64, CD123, and cytoplasmic MPO, CD3 and CD79a. Histopathological analysis of the left upper extremity disclosed BPDCN (Figure 2B). Immunohistochemical analysis demonstrated that tumor cells were positive for CD43, CD4, CD123, TCL1, Tdt, CD56, CD68 (weakly), Mum-1, Bcl-2, and Ki67, and negative for CD3, MPO, CD117, CD34, Granzymes B, Perforin, CD20, CD79a, CD30, CD10, Bcl-6, CKpan, NSE, and EBER (Figures 2C–F). Epstein-Barr virus (EBV) detection was negative. Gene rearrangement analysis for T-cell receptor by Southern blot hybridization showed no clonal rearrangement of the genes. A diagnosis of blastic plasmacytoid dendritic cell neoplasm of the skin associated with myelodysplastic syndrome (MDS) was

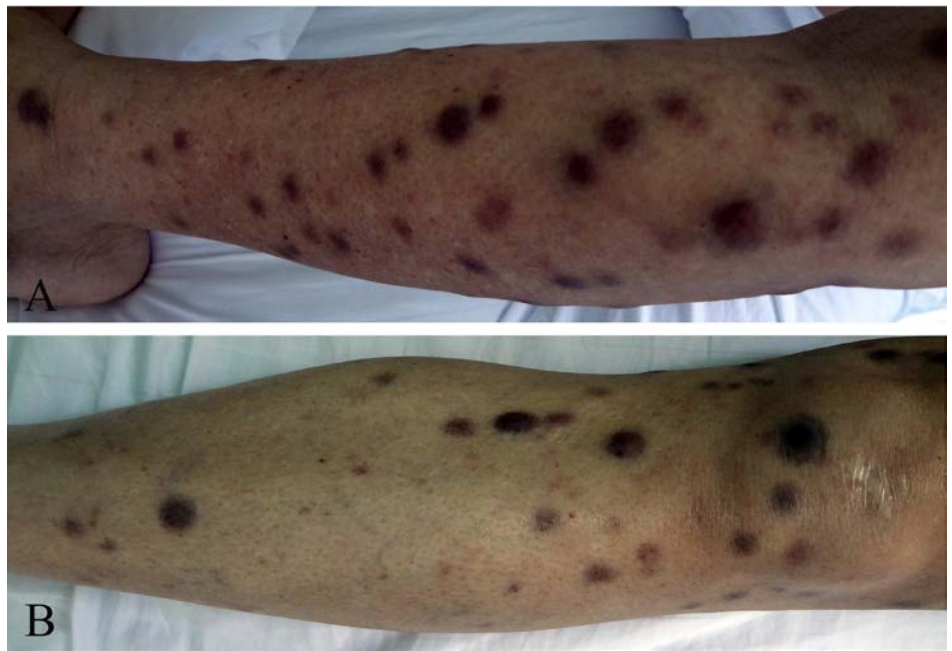
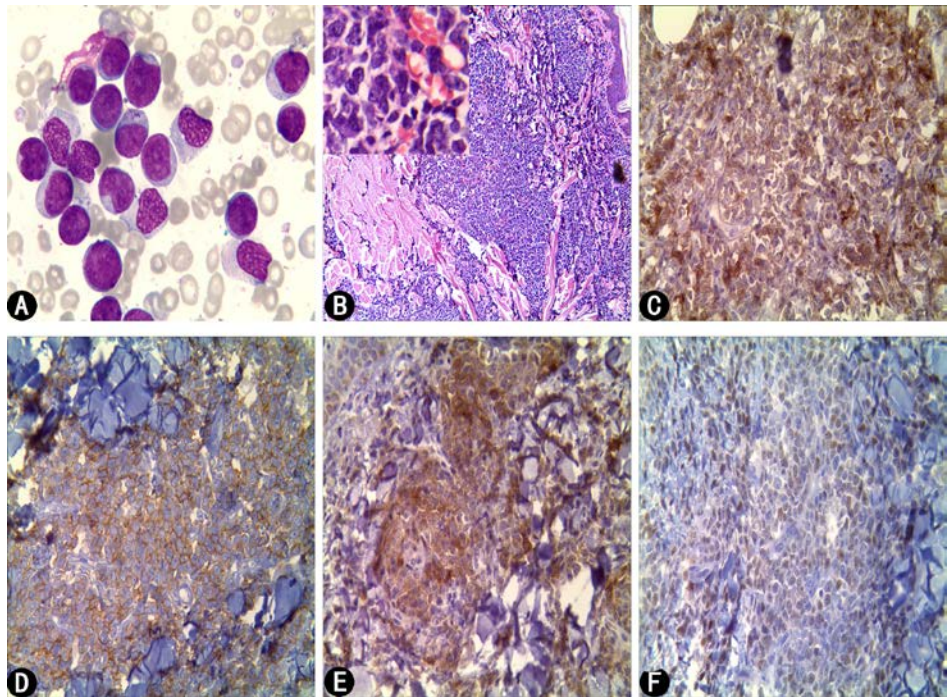


Figure 1. Clinical picture. Erythematous nodules on the upper extremity (A) and lower extremity (B).



{fig 2}. Cytology of bone marrow cells and biopsy of skin lesions. (A) Bone marrow was packed with large blast cells. The percentage of blast cells amounted to 50%. (B) Skin biopsy revealed lymphoid infiltration of the dermis, consisting of medium-sized monomorphic neoplastic cells (H&E, original magnification: $\times 100$; inset: $\times 400$). (C–F) The neoplastic cells were immunohistochemically positive for CD4(C), CD56 (D), CD123 (E) and Tdt(F), respectively, ($\times 400$).

established. The patient received one cycle of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and achieved partial remission.

Discussion

BPDCN was first defined in the 2008 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissue and less than 200 cases have been reported [1, 2]. The previous names of this disease include blastic natural killer-cell lymphoma, agranular CD4+ natural killer-cell leukemia, and CD4+/CD56+ hematodermic neoplasm, which reflect the evolving understanding of the disease.

BPDCN primarily afflicts elderly adults with a median age of approximately 65 years, although it can occur at any age, even in infants [3]. This disease is highly aggressive, with a clinical presentation characterized by early skin involvement and rapid dissemination. Approximately 85% of the reported cases demonstrated cutaneous involvement at presentation, whereas a lack of cutaneous involvement is rare, with approximately 30 cases that have been reported [4, 5]. Atypical presentation has been described; some patients presented with early liver metastasis [6] or with a renal mass [7].

Histologically, these neoplasms are composed of non-epidermotropic, monotonous infiltrates of medium-sized cells with finely dispersed chromatin and absent or indistinct nucleoli. BPDCN is a disease with specific immunophenotype. This disease is typically positive for CD4, CD56, and CD123 (IL-3 receptor α -chain, strong), with CD68 immunoreactivity and/or TdT (terminal deoxynucleotidyl transferase) expression in a subset of cases. It lacks NK cells, T cells, B-lineage-specific markers, or myeloid or monocytic markers, such as myeloperoxidase, lysozyme, and CD14 [8]. Coexpression of CD7 or CD33, or less commonly, CD2, may be observed [9]. Expression of CD3 should raise suspicion for a T-lineage malignancy, although rare cases of BPDCN with cytoplasmic CD3 expression have been reported. Furthermore, the proliferative rate is extremely increased in BPDCN (30% to 90% Ki-67 proliferative index), which is also the case in this study. CD34, CD8, myeloperoxidase, lysozyme, CD20, CD79a, EPV, and T-cell receptor protein are consistently negative and the expression of such markers should exclude the diagnosis of BPDCN.

Neither CD4 nor CD56 positivity may be absolutely necessary for diagnosis and either marker can vary in intensity from weak and focal to diffuse and strong. CD4 (–) cases are rarely observed, and rare CD56 (–) cases have been reported [10]. Strong CD123 expression is not entirely specific for BPDCN because basophils that normally express high levels of CD123 and CD123 expression may also be detected in histiocytic sarcoma and Langerhans cell histiocytosis.

Our patient fulfilled the WHO criteria for the diagnosis of blastic plasmacytoid dendritic cell neoplasm, but the discordance between bone marrow and skin immunophenotypes suggests coexistence of BPDCN and MDS. We reviewed similar cases reported in the literature and found that Kazakov DV [11] reported two similar patients and reviewed the relevant literature. Approximately 100 similar cases were reported; they believed that the association of BPDCN and various myelodysplastic/myeloproliferative disorders seen in a subset of patients (\approx 15–20%) is more than coincidental and may indicate their common origin.

The clinical course of BPDCN is aggressive and generally dismal at best, with the median survival time of 12–24 months. Several reports have described a better prognosis for cases with skin involvement alone, whereas Reimer et al. [12] concluded that patients with disease initially restricted to skin progressed less than those with disseminated disease at presentation; age was identified as an adverse prognostic factor. The clinical course in most cases has been characterized by an initial response to chemotherapy, followed by relapse and subsequent death. As the outcomes of many therapeutic attempts have been reported to be quite variable, no standard treatment for BPDCN is available. Dalle et al. [13] asserted that only stem cell transplantation can significantly prolong survival regardless of the initial extent of the disease. Although our patient has shown a partial response to CHOP chemotherapy, the ultimate prognosis looks grim. The simultaneous occurrence of MDS makes the therapeutic approach even more complicated.

Our case exhibits the fact that BPDCN should be considered in the differential diagnosis of erythematous purpuric nodules, particularly when there is relapse soon after chemotherapy treatment. Biopsy of a patch or a nodule is generally referred to the pathologist with a clinical suspicion of lymphoma. The diagnosis, particularly in its early phase, relies almost exclusively on an accurate laboratory evaluation, indicating that dermatopathologists in particular must be cognizant of this entity.

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