Abstract

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, aggressive hematologic malignancy that typically affects elderly men. It presents predominately in the skin, with subsequent or concurrent bone marrow, blood, or lymph node dissemination. Cutaneous findings are commonly described as asymptomatic, variably pruritic papules, tumors, or nodules, and less frequently as ecchymotic in appearance. BPDCN is derived from plasmacytoid dendritic cells, and the diagnosis is made by characteristic immunohistochemical findings: CD4+, CD56+, CD123+, TCL1+, blood dendritic cell antigens 2 and 4 (BDCA2+, BDCA4), and CD2-associated protein (CD2AP+). The prognosis for BPDCN is grim. Patients initially respond to chemotherapy regimens but usually relapse, with survival rates averaging between 12 and 16 months. We present a case of an elderly man in assisted living who was diagnosed with BPDCN and chose a conservative treatment approach.

Introduction

In 2008, the World Health Organization listed BPDCN under the classification of “acute myeloid leukemia and related neoplasms.” Due to the uncertainty regarding the cell-type involved, BPDCN was previously referred to as blastic natural killer-cell lymphoma; agranular CD4+ natural killer cell leukemia; and agranular CD4+ CD56+ hematodermic neoplasm. It is now accepted that BPDCN is a neoplasm derived from plasmacytoid dendritic cells. While the incidence of BPDCN is unknown, it is estimated to account for only 0.44% of all hematologic malignancies and 0.7% of cutaneous lymphomas. BPDCN has a male-to-female ratio of 3:1 and a median age of diagnosis in the sixth decade. Cutaneous findings are variable, with descriptions of painless, singular to numerous, erythematous to violaceous papules, nodules, or plaques. Treatment recommendations include acute lymphocytic leukemia (ALL)-type chemotherapy followed by allogeneic stem-cell transplant in patients healthy enough to undergo the procedure.

Case Report

An 82-year-old Caucasian male presented with a three-month history of an eruptive macular rash on the bilateral lower extremities. The cutaneous eruption was an erythematous macular rash, with some areas coalescing into plaques (Figures 1, 2). The erythematous macules and patches were targetoid in appearance with a subtle, violaceous, dusky center (Figures 3, 4). The patient stated that the eruption was minimally pruritic and overall asymptomatic. The patient's past medical history included sepsis, pneumonia, respiratory failure, acute renal failure, sinus tachycardia, urine incontinence and altered mental status. He resided in an assisted-living facility and had no known drug allergies. His medications included atorvastatin, carvedilol, aspirin, clopidogrel, finasteride, sertraline, tamsulosin, phenytoin, vitamin D and vitamin B-1. A review of systems was negative, and there were no other contributory physical findings.

The differentials included cutaneous T-cell lymphoma (CTCL), mycosis fungoides, B-cell lymphoma, and drug-induced pseudo lymphoma. Upon presentation, a punch biopsy was performed on the left upper leg. The biopsy results came back as a poorly differentiated blastic neoplasm. The case was reviewed by a dermatopathology colleague in addition to the original reading dermatopathologist. The biopsy revealed a diffuse infiltrate of irregular hematopoietic cells with elongated, twisted nuclei in the superficial and mid dermis without epidermal involvement (Figures 5, 6). Immunohistochemistry stains were positive for CD4 and CD56, while immunostains for CD3, CD8, CD5, CD20, CD34, myeloperoxidase and CD15 were negative.

Our patient was referred to a hematology/oncology specialist for further evaluation and treatment of his condition. Due to the condition's refractory response to conventional medications, the patient was offered experimental therapies. The patient's...
power of attorney decided on a more conservative treatment approach using topical tacrolimus. This treatment was chosen due to its possible anti-IL3 activity. Due to the patient's poor health and lack of transportation, we received only verbal follow-up from the patient's power of attorney. The POA reported that while the patient's skin had responded positively to the topical tacrolimus, he had died due to his comorbidities.

**Discussion**

BPDNC is a rare, hematologic malignancy derived from plasmacytoid dendritic cells. It frequently presents with cutaneous findings initially, but often has accompanying bone-marrow, lymph-node, and blood dissemination at the time of diagnosis. Cutaneous findings vary, with three main clinical presentations: solitary to multiple purple nodules, ecchymotic-appearing macules, or disseminated lesions. Isolated purple nodules on the head or lower limbs are believed to be the most common presentation of BPDNC. A multi-center study by Pagano et al. found that at the time of presentation, 56% of BPDNC patients presented with lymphadenopathy, 44% with splenomegaly, and 42% with hepatomegaly.

BPDNC has a known predominance in elderly men. Few case reports in the literature cite disease in the pediatric population. There is a 3:1 ratio of men to women diagnosed with BPDNC. New research indicates that loss-of-function mutations in ZRSR2 splicing factor on chromosome Xp22.1 may explain the prevalence of BPDNC in older males.

The diagnosis of BPDNC is based upon clinical morphology and immunophenotype studies such as flow cytometry and immunohistochemistry. Characteristic immunohistochemical findings include: CD4+, CD56+, CD123+ (interleukin 3α chain receptor), TCL1+ (T-cell leukemia 1), blood dendritic cell antigens 2 and 4 (BDCA2+, BDCA4), and CD2-associated protein (CD2AP+). Terminal deoxynucleotidyl transferase (TdT) is inconsistently expressed. The differential diagnosis of BPDNC includes acute myelogenous leukemia (AML); however, BPDNC can be distinguished from AML by the former’s unique expression of CD123, TCL1, BDCA2, and CD2AP. Pathologically, skin biopsy shows atypical, medium-sized, monomorphic blastoid cells in the dermis that do not penetrate the epidermis. Varying levels of mitoses are present, with no angiogenesis or coagulatative necrosis.

Although there are no karyotype abnormalities considered to be pathognomonic for BPDNC, multiple chromosomal abnormalities have been elucidated, including 5q, 12p, 13q, 6q, 15q, and monosomy 9. There is no association of BPDNC with Epstein-Barr virus.

Treatment regimens are similar to those for acute lymphocytic leukemia (ALL) and acute myelogenous leukemia (AML), with better remission rates seen in those receiving ALL-like treatment. Remissions are usually short-lived, so consolidation therapy with hematopoietic stem-cell transplantation is typically performed post-remission. Retrospective results from the Japan Society for Hematopoietic Cell Transplantation showed four-year overall survival rates of 82% for those undergoing auto-hematopoietic stem-cell transplantation (HSCT) versus 53% for those undergoing allo-HSCT. Azacytidine, a DNAhypomethylating agent used for the treatment of myelodysplastic disorders and AML, has shown stabilization of hematologic disease and regression of skin disease in a small number of elderly patients. SL-401, a recombinant fusion protein comprised of diphtheria toxin fused to interleukin-3 (IL-3), has shown promise in clinical trials by targeting IL-3 receptors, which are overexpressed in BPDNC.

Of nine BPDNC patients undergoing a single treatment of SL-401, five showed complete remission and two showed partial remission in all involved sites, including lymph nodes, bone marrow, spleen, and skin. In elderly patients who may not be candidates for aggressive treatment, palliative therapy with oral prednisone may be indicated to induce skin healing and thus improve quality of life.

**Conclusion**

BPDNC is a rare, aggressive hematologic malignancy favoring elderly men. BPDNC has nonspecific cutaneous findings, making it difficult to diagnose, and the practitioner must have a high index of suspicion. Early recognition and diagnosis is critical and often happens after a biopsy is performed. Cutaneous involvement is the most frequent initial finding, but subsequent or concurrent bone-marrow, blood, or lymph-node dissemination is common. Once the diagnosis is made, it is crucial that hematology and oncology physicians are consulted to help manage possible extracutaneous involvement. Diagnosis of BPDNC is classically made by morphology alongside classic immunohistochemical findings. ALL-like or AML-like chemotherapy followed by allo or auto-HSCT is the most widely accepted treatment regimen, but novel therapies are currently under study.

**References**


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