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# Blastic Plasmacytoid Dendritic Cell Neoplasm without Cutaneous Manifestation: A Case Report

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**Financial support:** None declared  
**Conflict of interest:** None declared**Patient:** Male, 85-year-old  
**Final Diagnosis:** Blastic plasmacytoid dendritic cell neoplasm  
**Symptoms:** Dizziness • leg pain • malaise • weakness  
**Medication:** —  
**Clinical Procedure:** Bone marrow biopsy • lumbar puncture  
**Specialty:** Hematology • Oncology**Objective:** Rare disease**Background:** As an uncommon malignancy with the highest prevalence in the elderly population, blastic plasmacytoid dendritic cell neoplasm or BPDCN is a hematologic disorder with unknown pathogenesis and devastating outcomes. This neoplasm usually manifests in the skin but can also involve the bone marrow, and less frequently the central nervous system (CNS). However, it does not exclude other organs and can even be associated with other malignancies.**Case Report:** Here, we discuss an interesting case of BPDCN in an 85-year-old man who mainly presented with dizziness and weakness. Physical examination revealed splenomegaly, laboratory tests showed pancytopenia, and peripheral blood smear depicted metamyelocytes. Further workup including bone marrow biopsy revealed atypical cells and flow cytometry disclosed 84% blasts positive for cluster of differentiation (CD) 4, CD53, and CD156 suggestive of BPDCN. Moreover, cerebrospinal fluid (CSF) studies came back positive for tumor plasmacytoid dendritic cells. The patient underwent chemotherapy with CHOP, mini-CHOP regimens, and venetoclax, as well as treatment for CNS involvement. He achieved remission, but unfortunately had a recurrence of the disease. Later he was admitted due to pneumonia with concomitant recurrent pulmonary effusions complicated by multiorgan dysfunction and subsequently died.**Conclusions:** The diagnosis of BPDCN can be very challenging, and high clinical suspicion and intuition are required to reach the diagnosis, especially when patients do not present with cutaneous involvement. Concerning treatment options, novel therapies such as tagraxofusp, a CD123-directed cytotoxin, are emerging in the hope of decreasing the rate of mortality for this aggressive malignancy.**Keywords:** Bone Marrow Neoplasms • Dendritic Cells • Hematologic Neoplasms • Leukemia • Rare DiseasesFull-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/932887> 1625  —  1  22

## Background

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an uncommon aggressive hematologic malignancy with a high mortality rate. BPDCN accounts for 0.5% of all hematologic cancers and it is more prevalent in older men. It mainly presents with cutaneous lesions and it can invade or spare the bone marrow [1]. Diagnosis of BPDCN is often based on specific clinical characteristics and histopathology of the involved tissue along with immunophenotypic markers. The classical triad of tumor markers is CD4, CD56, and CD123 [2]. Treatment recommendations have evolved in the last years, and medications such as tagraxofusp, a CD123-directed cytotoxin, emerged as novel therapeutic modalities with promising outcomes [3]. This report presents an interesting case of BPDCN which manifested with pancytopenia and central nervous system (CNS) involvement, while excluding the skin.

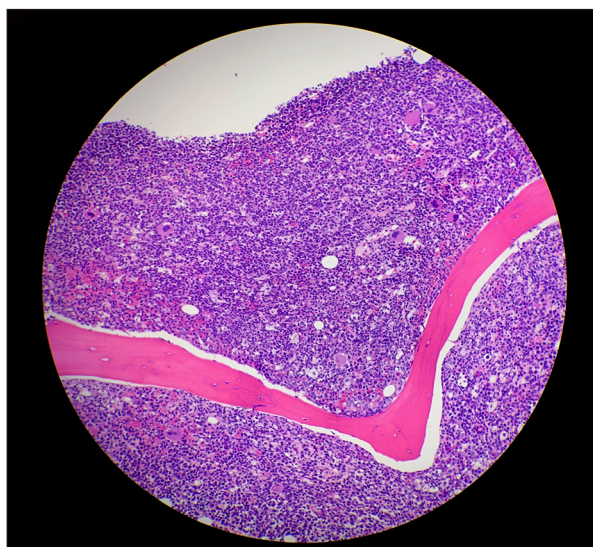
## Case Report

An 85-year-old man with a past medical history of 30-pack-year smoking and peripheral vascular disease presented with 3 days of dizziness, general weakness, malaise, and progressive severe pain in the left lower extremity. The patient denied any rectal bleeding, hematuria, hematemesis, or skin changes.

Initial vital signs were blood pressure: 124/54 mmHg; pulse: 115/min; respiratory rate: 19/min; temperature: 97.8°F (36.6°C), and oxygen saturation of 97% on room air. On the physical exam, the patient had mild left pedal edema, diminished dorsalis pedis pulses, splenomegaly, and no lymphadenopathy. His lab results showed leukopenia with white blood cells (WBC) count of  $2.7 \times 10^3/\text{mL}$  (normal range  $3.6\text{-}11 \times 10^3/\text{mL}$ ), neutropenia  $1.3 \times 10^3/\mu\text{L}$  (normal range  $1.8\text{-}8 \times 10^3/\mu\text{L}$ ), lymphopenia  $1.2 \times 10^3/\mu\text{L}$  (normal range  $1.5\text{-}3.5 \times 10^3/\mu\text{L}$ ), red blood cells (RBC) count of  $1.58 \times 10^6/\mu\text{L}$  (normal range  $3.8\text{-}5.6 \times 10^6/\mu\text{L}$ ), hemoglobin (HGB) of 5 g/dL (normal range 11.6-16.8 g/dL), and platelet count of 108 K/ $\mu\text{L}$  (normal range 150-372 K/ $\mu\text{L}$ ).

Due to severe anemia and concomitant pancytopenia, Hematology-Oncology was consulted. Iron studies came back normal. Furthermore, peripheral blood smears showed pancytopenia with relative lymphocytosis, and CBC with differential showed increased metamyelocytes 2% (normal 0%). HIV Ag/Ab 4<sup>th</sup> generation, CMV IgM, and direct Coombs (DAT) polyspecific were requested and came back negative. ESR, vitamin B12, folate, LDH, haptoglobin, and bilirubin were ordered and were in the normal range. Additionally, complete abdominal sonography and computed tomography (CT) abdomen revealed splenomegaly.

Moreover, as per Hematologist recommendation, the patient underwent bone marrow biopsy. Bone marrow smear showed



**Figure 1.** Bone marrow biopsy showing hyperfractionated infiltration of blastoid cells.

atypical cells that represented 90% of total cells; they had high nuclear-cytoplasmic (NC) ratio, prominent nucleoli, and slightly vacuolated cytoplasm (Figure 1). Iron staining on bone marrow aspirate smears showed increased ringed sideroblasts. Additionally, flow cytometry of bone marrow showed 84% blasts positive for Cluster of Differentiation (CD) 2, CD4, CD10, CD38, CD43, CD56, and CD123, and HLA-DR indicative of BPDCN. Cytogenetic analysis showed normal male karyotype, and FISH analysis showed no translocations in chromosomes 5,7,8,11.

Hematology-Oncology opted to transfer the patient to a tertiary cancer center for further management. He underwent lumbar puncture and CSF (cerebrospinal fluid) studies, which came back positive for tumor plasmacytoid dendritic cells. The diagnosis of BPDCN with CNS involvement was made. Given the patient's advanced age, while considering his optimum quality of life and his family's refusal, more aggressive interventions such as hematopoietic stem cell transplantation were not deemed appropriate.

The patient started chemotherapy with CHOP regimen, which consisted of cyclophosphamide 750 mg/m<sup>2</sup>, doxorubicin 50 mg/m<sup>2</sup>, vincristine 1.4 mg/m<sup>2</sup>, and prednisone 100 mg [4]. For his CNS involvement, he received twice-weekly intrathecal chemotherapy with methotrexate until negative leukemic involvement was observed and then the regimen was switched to weekly intrathecal (IT) chemotherapy. He also received prophylaxis with acyclovir, fluconazole, and Bactrim. The patient's course was complicated by several hospitalizations due to severe anemia and thrombocytopenia. Consecutively, due to delayed blood cell count recovery and significant transfusion requirements, he was then switched to a mini-CHOP regimen

which consisted of cyclophosphamide 400 mg/m<sup>2</sup>, doxorubicin 25 mg/m<sup>2</sup>, vincristine 1 mg, and prednisone 40 mg/m<sup>2</sup> [5]. This treatment was tolerated better in terms of myelosuppression. After receiving 2 cycles of CHOP and 2 cycles of mini-CHOP regimen, bone marrow showed no morphologic or flow cytometric evidence of BPCDN and CSF studies remained negative. Following 2 more cycles of mini-CHOP, a repeat of bone marrow biopsy revealed minimal residual disease and CSF studies came back positive. Considering the latest approved medications available at that time, the Hematology-Oncologist started the patient on venetoclax 400 mg daily treatment. However, the patient did not achieve remission in the consecutive CSF analysis and the mini-CHOP regimen was added again. Four weeks later, the patient was admitted to the hospital with respiratory distress and was diagnosed with severe pneumonia and pulmonary edema with pleural effusion. His condition deteriorated, and he was transferred to the Intensive Care Unit due to severe respiratory failure and later died due to cardiopulmonary arrest.

## Discussion

BPDCN is considered is a rare hematologic malignancy with aggressive behavior. Our understanding of this condition and its biological characteristics has improved in recent years. There have been multiple changes in its nomenclature until 2008, when BPDCN was classified by the World Health Organization or WHO under the category “Acute myeloid leukemia (AML) and related precursor neoplasms” [6] and it was reclassified in 2016 as its own category [7].

BPDCN arises from the precursors of myeloid-derived resting plasmacytoid dendritic (PD) cells, but the pathogenesis is still unclear [8]. In contrast to the classical dendritic cell, the PD cell functions as type 1 interferon producing cells or plasmacytoid monocytes in response to viruses and play a role in the innate immune system [9].

BPDCN incidence is unknown, but it accounts for 0.5% of all hematologic cancers [1] and 0.7% of primary cutaneous skin lymphomas [10]. It is more prevalent in the elderly population, with a median age of 53 to 68 years and a male predominance [11]. It can occur as a primary malignancy or associated with other hematologic malignancies such as myelodysplastic syndrome, acute myeloid leukemia, and chronic myelomonocytic leukemia in up to 10% of cases [1].

BPDCN presents with cutaneous lesions in 77-83% of patients at diagnosis and it may or may not invade the bone marrow. Skin lesions can be heterogeneous in size, shape, and color and are usually nonpruritic nodular or plaque infiltrations. Moreover, bone marrow infiltrations manifest as cytopenias,

particularly thrombocytopenia, in 78% of patients, splenomegaly (in 44%), and lymphadenopathy (in 56%). CNS involvement occurs in 10% of patients, even without neurological symptoms [1,12,13]. Involvement of lung, breast, eye, tongue, gallbladder, and paranasal sinuses has also been reported.

Diagnosis of BPDCN requires high clinical intuition and is often based on specific clinical characteristics, histopathology of the involved tissue, and immunophenotypic markers. In histology, biopsies are characterized by a dense monomorphic infiltrate of medium to large blast cells with scant cytoplasm, fine chromatin, and irregular single or multiple nuclei [14]. On aspirate, dendritic cells can have a unique cytoplasmic vacuolation pattern similar to a “pearl necklace” and cytoplasmic pseudopod extensions [12]. Immunophenotyping is similar to that of PD cells but with abnormal expression of CD56. The classical triad of tumor markers is CD4, CD56, and CD123 (also called interleukin-3 receptor subunit alpha), without the presence of markers for specific lineage, including myeloid, B-lymphocytes, T-lymphocytes, and NK cells. Overexpression of CD123 occurs in almost all cases but is not specific to BPDCN. Additionally, other specific PD cells-associated antigens like CD303, CD2-associated protein (CD2AP), T-cell leukemia/lymphoma protein 1 (TCL1), and transcription factor-like TCF4 can help differentiate BPDCN from similar malignancies [2].

Furthermore, 50-66% of patients have been reported to have abnormal karyotypes, which frequently represents loss of genetic material in 5q, 12p, 13q, 6q, 15q, and 9 in both lymphoid and myeloid neoplasms [15]. Diagnosis of BPDCN remains challenging as it can have overlapping characteristics with other diseases, as well as heterogeneity in clinical presentation. Immunohistopathology may also show either the absence of the main markers or the presence of additional markers indicative of other lineages, which can result in confounding.

Treatment recommendations have changed in recent years. Non-Hodgkin's lymphoma regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), ALL-type regimens such as hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with cytarabine and methotrexate, or less-used AML induction regimens were utilized until recently [16]. Additionally, CNS prophylaxis with intrathecal treatment is recommended regardless of the treatment chosen [13], as CNS involvement is more common in disease recurrence [1,12]. Tagraxofusp, a CD123-directed cytotoxin, is a new promising agent with high response rates and acceptable toxicity. After this treatment, subsequent allogeneic hematopoietic stem cell transplantation or HSCT needs to be followed for consolidation and potential cure [3,17-20]. Other CD-123-based targeted therapies are under study, and novel therapies are emerging such as venetoclax, a bcl-2 inhibitor that has shown clinical response and

prolonged survival as BPDCN is highly bcl-2-dependent and therefore sensitive to venetoclax [21]. The historical prognosis has been poor; patients tend to relapse after treatment and the median survival of patients is less than 2 years [22].

## Conclusions

We identified challenges in the diagnosis and treatment of BPDCN, a rare aggressive hematopoietic malignancy that has a high mortality rate. BPDCN mostly presents with nonspecific cutaneous findings, but dissemination to bone marrow, blood, or lymph nodes is also common. In the nontypical presentation, such as those excluding the cutaneous tissue, high clinical suspicion along with biopsy and immunophenotyping are the main keys in diagnosis. It is crucial to use a panel of tumor markers suitable to identify BPDCN.

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