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Blastic plasmacytoid dendritic cell neoplasm

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Abstract

Blastic plasmacytoid dendritic cell neoplasm is an uncommon, aggressive hematologic neoplasm carrying a poor prognosis with a median survival of one year, making early detection vital. Patients present with a number of characteristic cutaneous manifestations and are treated with chemotherapy and hematopoietic stem cell transplantation, which may improve survival. In this case, a 65-year-old man with a history of basal cell carcinoma presented with a nodule on his forehead with a honey-crusted border. Although the patient was treated with intralesional triamcinolone and a 7-day course of cephalexin for concurrent staphylococcal infection, the patient reported rapid growth of the nodule, new ecchymosis and edema involving his right cheek, and erythematous patches of the right temple and neck. Biopsy of lesions and immunohistochemical analysis confirmed the diagnosis of blastic plasmacytoid dendritic cell neoplasm. The patient was referred for further management, leading to sustained complete remission at 18 months after hematopoietic stem cell transplantation. Because blastic plasmacytoid dendritic cell neoplasm has varied cutaneous presentations that often mimic benign disease, particularly when presenting as bruise-like lesions, providers must maintain a high index of clinical suspicion and willingness to biopsy in order to make the diagnosis.

Keywords: BPDCN, HPSCT, CD4, CD56, CD123, immunohistochemistry, Tagraxofusp, IMGN632

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematologic neoplasm that presents with a range of cutaneous findings [1,2]. BPDCN has a poor prognosis with a median survival of 12 months as noted in a retrospective cohort study of 90 patients [2]. However, chemotherapy induced remission followed by allogeneic hematopoietic stem cell transplantation (HPSCT) may improve survival [1,2], making early detection, diagnosis, and treatment crucial in disease management. Since most patients with BPDCN present with cutaneous manifestations [1], which may be the primary reason for seeking care in the absence of other constitutional symptoms, it is vital that dermatologists consider a broad differential diagnosis when confronted with new purpuric, erythematous, or cystic lesions. The case described here details such a presentation in which early biopsy and immunohistochemical analysis led to rapid diagnosis of BPDCN, referral, and treatment of the affected patient. This resulted in improved survival of this patient with sustained complete remission at 18 months following HPSCT and 22 months after initial diagnosis.

Case Synopsis

A 65-year-old man with a history of basosquamous carcinoma of the right nasal sidewall status post Mohs micrographic surgery, presented to clinic with

a complaint of a bump on his forehead (**Figure 1A**).

He reported a two-week history of an erythematous, tender nodule with a honey-crusted border on his medial forehead. The lesion was treated with 2.5mg/ml of intralesional triamcinolone, 0.1ml of 10mg/ml, and a prescription for a 7-day course of cephalexin 500mg twice daily for the concurrent staphylococcal infection. Upon follow-up two weeks later, the patient reported rapid growth of the forehead nodule and a new concern of bruising and swelling on his right cheek along with erythematous patches involving the right temporal region and right anterolateral neck (**Figure 1B**).



Figure 1. A) *Marked size increase of forehead lesion compared to his initial size two weeks prior.* **B)** *Bruising and swelling of the face and neck, erythematous patches involving the right temporal region and right anterolateral neck are visible.*

Induration was also noted within the prior flap from Mohs surgery. Numerous scattered violaceous lesions were also found on the patient's back and chest. We sampled the forehead and neck lesions by punch biopsies, taken for hematoxylin and eosin examination, and tissue culture owing to concern for possible deep fungal infection. Microbial tissue cultures were negative.

Histopathology showed top-bottom heavy mononuclear infiltrate with a periadnexal and perivascular pattern (**Figure 2**).

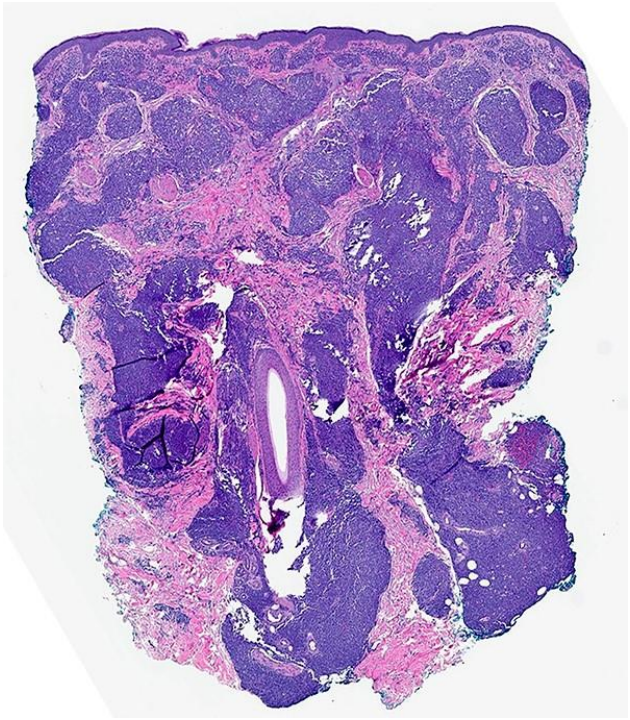


Figure 2. *The histopathology of a nodule, located on the medial forehead, showed top-to-bottom heavy nodular dermal infiltrate with periadnexal and perivascular patterns. Total image magnification: 40x.*

The nodular infiltrate, centered in the dermis, extended deeper to the subcutis, as it was transected above base as the deep tissue edge. High-power examination revealed a diffuse monotonous infiltrate of medium-sized immature-appearing monocytes with obvious mitotic figures (**Figure 3**).

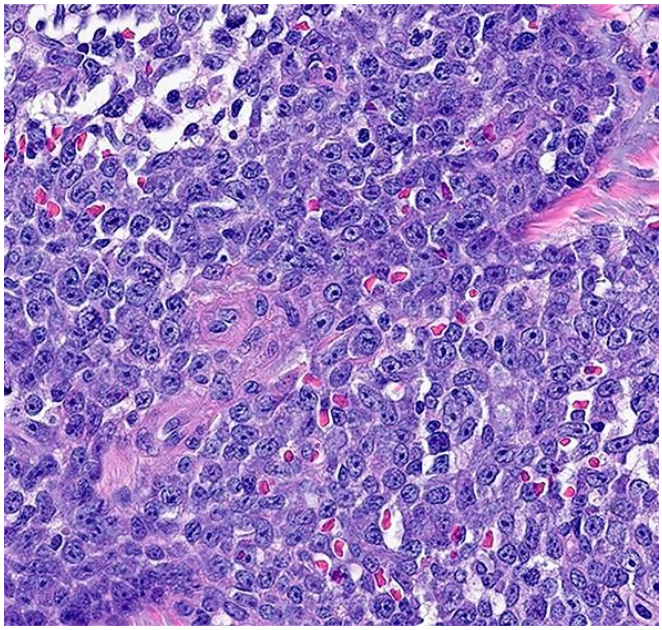


Figure 3. *Closer examination revealed diffuse nodular growth of neoplastic cells with scanty cytoplasm, eccentric nuclei, irregular nuclear contour, fine chromatin, and conspicuous nucleoli with*

easily found mitotic figures. Total image magnification: 400x.

The neoplastic cells possessed scanty cytoplasm and eccentric nuclei with irregular, thickened contour, fine chromatin, and conspicuous nucleoli, imparting an immature, blastic cytology. An extensive panel of immunohistochemistry with appropriate controls was performed. The results showed strong and diffuse expression of *CD4* (**Figure 4**), *CD56* (**Figure 5**), *CD123*, and *CD43*. *CD2*, *CD3*, *CD10*, *CD20*, *CD34*, *CD79a*, activin receptor-like kinase 1, and terminal deoxynucleotidyl transferase were negative.

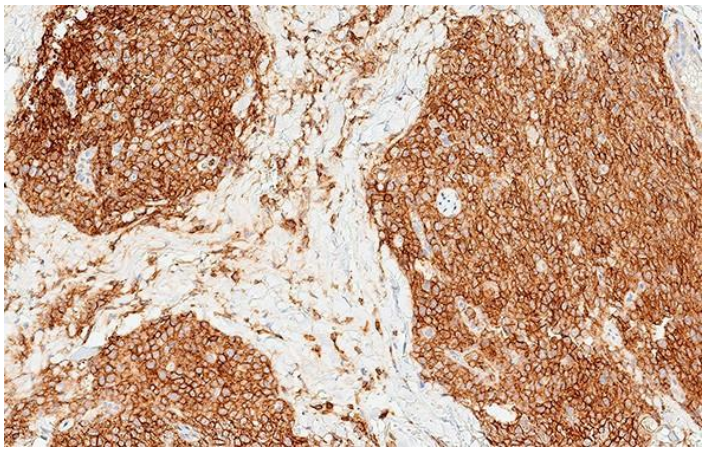


Figure 4. *By immunohistochemistry, the neoplastic cells diffusely expressed CD4. Total image magnification: 200x.*

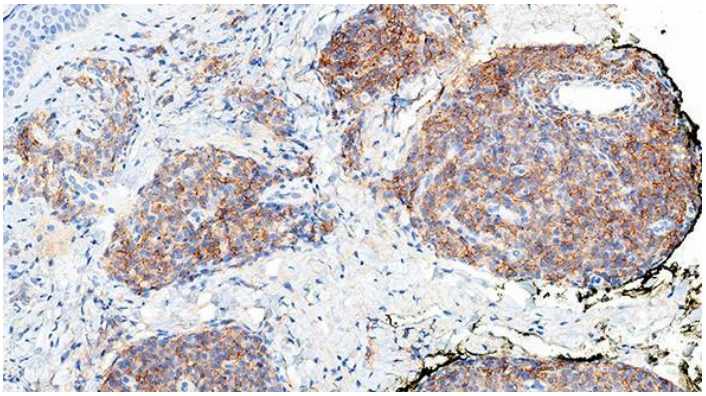


Figure 5. *By immunohistochemistry, the neoplastic cells diffusely expressed CD56. Total image magnification: 200x.*

In situ hybridization for Epstein-Barr Encoded RNA was negative. Kappa and Lambda light chain studies did not demonstrate a monoclonal plasma cell population. Although the histologic differential diagnosis could include an immature B-cell neoplasm, the immunohistochemical panel, along with blastic cytomorphology supported a diagnosis of BPDCN. Moreover, these initial findings were confirmed on a repeat biopsy (not shown). Bone marrow aspirate and core biopsy and the results of flow cytometry revealed the presence of neoplastic cells with large, pleomorphic nuclei, fine chromatin, and conspicuous nucleoli. The tumor cells displayed positive expression for *CD4*, *CD56*, *CD123*, and T-cell leukemia /lymphoma protein 1, confirming bone marrow involvement by blastic plasmacytoid dendritic cell neoplasm.

The patient was referred to Dana Farber Cancer Institute Leukemia center 5 months after his initial presentation to the dermatology clinic at which time repeat biopsies were taken which were consistent with BPDCN. Complete blood count showed normal differentiation. However, rare circulating BPDCN cells were noted on flow cytometry of peripheral blood. Full body positron emission tomography-computed tomography was also consistent with the diagnosis with a fluorodeoxyglucose (FDG) avid soft tissue nodule in the midline forehead. Multiple FDG avid lymph nodes were seen in several locations including the bilateral cervical, supraclavicular, axillary, mediastinal, and hilar regions. FDG avid lymph nodes were also observed above and below the diaphragm and in the right retrocrural, porta hepatis, retroperitoneal, pelvic, and bilateral inguinal regions. Additionally, diffuse heterogeneous marrow uptake was evident. At that time, the patient reported associated symptoms of night sweats and worsening fatigue; his bone marrow biopsy was consistent with BPDCN. The patient was then treated with his first cycle of IMGN632, 0.045mg/kg, as a participant in a clinical trial, resulting in complete remission by bone marrow biopsy three weeks later. IMGN632 is an antibody drug conjugate comprised of a high affinity anti-*CD123* antibody coupled to an indolinobenzodiazepine DNA-alkylating agent [3]. After three cycles of induction chemotherapy and 6 doses of intrathecal methotrexate, lasting remission was achieved and no features of involvement of BPDCN were seen on bone marrow biopsy or positron emission tomography-computed tomography. Next, the patient underwent reduced intensity conditioning haploidentical stem cell

transplantation from his donor nephew. He continues to remain in complete remission at 18 months post-transplantation and 22 months from initial diagnosis. Flow cytometric analysis of bone marrow specimen revealed no population of cells expressing *CD4*, *CD56*, or *CD123*. Positron emission tomography-computed tomography also showed no evidence of FDG-avid malignancy. The only post-transplant complication the patient experienced was a gout flare which was successfully treated with a prednisone taper and allopurinol.

Case Discussion

BPDCN was first described in 1995 when it was known as blastic natural killer cell lymphoma and accounts for 0.8% of primary cutaneous skin lymphomas. The disease was renamed in the 2008 World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissue to BPDCN, reflecting the origin of malignant cells from plasmacytoid dendritic cell precursors [1,2]. According to the 5th edition WHO classification, these cells characteristically express *CD4*, and/or *CD56*, *CD123*, and at least one other plasmacytoid dendritic cell marker such as T-cell leukemia/lymphoma protein 1, transcription factor 4, *CD303*, or *CD304*. Cells may also express any three plasmacytoid dendritic cell markers while also having absent expression of all expected negatives [4]. In this case, the patient's skin biopsy immunohistochemistry profile is positive for *CD4*, *CD56*, and *CD123*. This supports the diagnosis of BPDCN when taken together with hematoxylin and eosin findings and the clinical presentation without being fully diagnostic per the WHO 5th edition criteria above. However, immunohistochemical analysis of the patient's bone marrow specimen showed positivity for *CD4*, *CD56*, *CD123*, and T-cell leukemia/lymphoma protein 1 and therefore meets the full diagnostic criteria.

The histologic differential diagnosis may include leukemia cutis, B-cell lymphoma (mucosa-associated lymphoid tissue-type or follicle-center cell lymphoma), neuroendocrine (Merkel cell) carcinoma (either primary or metastatic from lung or other sites), and lymphoblastic lymphoma (either B- or T-lymphoblastic). Myeloperoxidase-negative, *CD34*-negative, and *CD123*-positive expression can typically exclude leukemia cutis. The lacked expression of B-cell markers can help exclude a B-cell neoplasm; this, along with *CD123*-positive expression, can exclude B- or T-lymphoblastic lymphomas. The lack of expression of chromogranin, synaptophysin, and cytokeratin markers (e.g., cytokeratin 20 and epithelial membrane antigen) helps exclude a neuroendocrine carcinoma [4]. Moreover, the plasmacytoid histopathology along with *CD4* and *CD123* coexpression could raise the possibility of mature plasmacytoid dendritic cell proliferation associated with myeloid neoplasm. However, a strong and diffuse expression of *CD56* and lack of chronic myelomonocytic leukemia in our patient excluded this possibility, according to the latest WHO 5th edition.

BPDCN is clinically aggressive with a poor prognosis and affects patients of all ages and ethnicities with no identified predisposing genetic or environmental risk factors [1,2,5]. However, older male patients are more likely to be diagnosed with a male to female ratio of 3:1 and median age of 61 to 67 [1,2]. Most patients present with one of three cutaneous manifestations with or without leukemic dissemination: 1) brown or purple nodules, 2) bruise-like brown to violaceous infiltrated patches, 3) disseminated mixed nodules or macules [2]. BPDCN may have varied dermatologic presentations often mimicking benign disease, particularly when presenting as bruise-like lesions.

The clinical differential diagnosis for this presentation ranges from benign processes such as nummular eczema, traumatic ecchymoses, contact dermatitis, and lichen planus to malignant manifestations including *CD56*+ acute myeloid leukemia, nasal-type extranodal natural killer/T-cell lymphoma, cutaneous T cell lymphoma,

subcutaneous panniculitis-like T cell lymphoma, plasmacytoma, and angiosarcoma [1,6]. Therefore, a high index of clinical suspicion and a low threshold for biopsy of lesions along with flow cytometry or immunohistochemical analysis is essential for early diagnosis. Additionally, bone marrow aspirate and peripheral blood may be evaluated by flow cytometry for malignant cells as these sites are also frequently involved [1].

Treatment of BPDCN involves induction of remission followed by allogenic HPSCT which may improve survival when performed after first remission [1,7]. Tagraxofusp (SL-401), a *CD123*-directed cytotoxin comprised of human interleukin-3 fused to truncated diphtheria toxin is the treatment of choice to induce remission. Tagraxofusp is administered intravenously at a dosage of 12mcg/kg daily from day one through 5 of a 21-day cycle and is approved by the US Food and Drug Administration as compared to acute myeloid leukemia and acute lymphocytic leukemia chemotherapeutic regimens classically used for the treatment of BPDCN [1,3,8]. As highlighted by this case in which the patient remains in remission at 18 months post HPSCT, when induction is followed by hematopoietic stem cell transplantation, patients experience durable remission with improved survival rates at four years compared to observation alone for which median survival is approximately one year. Interestingly, durable remission has been observed regardless of the induction regimen used [7]. Lastly, clinicians should confirm remission with repeat skin biopsy to differentiate between residual disease and hyperpigmentation as an adverse effect of chemotherapeutic treatment [1].

Conclusion

In conclusion, BPDCN is a rare and aggressive hematologic neoplasm with medial survival of one year with tumor cells derived from plasmacytoid dendritic cell precursors that are positive for *CD4*, and/or *CD56*, *CD123*, and at least one other plasmacytoid dendritic cell marker such as T cell leukemia/lymphoma protein 1, transcription factor 4, *CD303*, or *CD304* [1,2,4]. Treatment is with chemotherapy induced remission followed by HPSCT which may improve survival, making early detection necessary [1,2,7]. However, arriving at the diagnosis may be challenging because BPDCN manifests with a range of cutaneous presentations including: 1) brown or purple nodules, 2) bruise-like brown to violaceous infiltrated patches, 3) disseminated mixed nodules or macules [2]. These presentations can mimic benign dermatologic conditions such as nummular eczema, traumatic ecchymoses, contact dermatitis, and lichen planus or malignant diseases including *CD56*+ acute myeloid leukemia, nasal-type extranodal natural killer/T-cell lymphoma, cutaneous T-cell lymphoma, and subcutaneous panniculitis-like T-cell lymphoma [1,6].

Therefore, dermatologists should entertain a broad differential diagnosis, high index of clinical suspicion, and low threshold for biopsy and immunohistochemical analysis of appropriate lesions in order to make the diagnosis and improve patient outcomes. As demonstrated in this case, early detection of BPDCN led to improved survival of the patient with sustained complete remission at 18 months post HPSCT and 22 months from initial diagnosis.

Potential conflicts of interest

The authors declare no conflicts of interest.

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