Pathology quiz case: Plasmacytoid dendritic cell neoplasm

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ABSTRACT

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematologic malignancy that possesses a heterogenous clinical and immunophenotypic presentation. The current case report describes an interesting and unique presentation of BPDCN as a primary paranasal sinus tumor without evidence of cutaneous or systemic involvement. As such, the report further contributes to the ongoing debate regarding the true putative origin of the neoplasm, as well as highlights the optimal diagnostic modalities, paramount importance of early diagnosis, and vast heterogeneity exhibited by this fascinating malignancy. The atypical presentation described here indicates the manifestations of BPDCN are more heterogenous than previously documented and thus can not be definitively ruled out in the absence of bone marrow, peripheral blood, or cutaneous involvement. Furthermore, atypical neoplastic presentations mandate flow cytometry and adjunctive immunohistochemistry for the definitive diagnosis of BPDCN, and early diagnosis of such neoplasms are critical for rapid initiation of treatment and improved outcomes.

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CASE PRESENTATION

A 28-year-old man presented with a 1-week history of sudden-onset right-sided frontal pressure and headache. Medical history and review of systems were negative and the patient was a nonsmoker. Physical exam was normal with no neurological deficits. On nasal endoscopy, swelling of the right-sided middle and inferior meatus, as well as purulence at the sphenoethmoidal recess, was noted.

Computed tomography and magnetic resonance imaging showed a soft tissue mass with involvement of the posterior ethmoid and sphenoid sinuses (Fig. 1).

Right endoscopic sinus surgery was performed to obtain pathological tissue. Once frozen sections returned as a small blue cell tumor, the procedure was terminated without further debulking of the tumor because of its suspected origin.

Routine hematoxylin and eosin staining showed a diffuse infiltrate of neoplastic medium-sized cells with slightly irregular nuclear contours, blastic chromatin pattern, inconspicuous nucleoli, and scant agranular cytoplasm (Fig. 2). An immunoperoxidase stain for CD123 was uniformly positive in neoplastic cells (Fig. 3). The Ki-67 showed a high proliferation index of 70–80%. Flow cytometric (FCM) analysis identified a clonal $CD4^+$/$CD56^+$, human leukocyte antigen D-related$^+$ (HLA-DR^+) population that did not coexpress T-cell, B-cell, myeloid, monocytic, natural killer (NK) cell, or plasma cell–specific surface or cytoplasmic antigens. An *in situ* hybridization study for detecting Epstein-Barr–encoded RNA was negative. Staging bone marrow biopsy with FCM studies and peripheral blood examination showed no evidence of a neoplastic population of cells or any other hematologic abnormalities. Positron emission tomography scan showed hypermetabolic activity in the right posterior sinonasal cavities and cervical level 2 lymph nodes. No distant metastatic disease was present. In addition, a comprehensive cutaneous exam was completed by a dermatologist and revealed no lesions. What is your diagnosis?

DIAGNOSIS: BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematologic malignancy provisionally categorized by the 2008 World Health Organization classification under acute myeloid leukemia and related precursor neoplasms, a change from the previous designation of "blastic NK cell leukemia/lymphoma." The diagnosis is provisional due to the heterogenous clinical and immunophenotypic presentation, a testament to the still uncertain lineage and pathophysiology of this malignancy.[1]

BPDCN is a highly aggressive tumor that, controversially, is derived from the precursor of plasmacytoid dendritic cells (pDCs), which in itself is a Th2-type DC precursor. The pDC cells tend to exist in clusters found in T-cell–rich, paracortical areas of peripheral lymphoid tissue. They are also important effector cells that circulate within the blood as veiled, immune responsive cells with the capacity to produce α-interferon and differentiate into DCs. Otherwise, circulating pDCs are scarce under normal conditions.[2]

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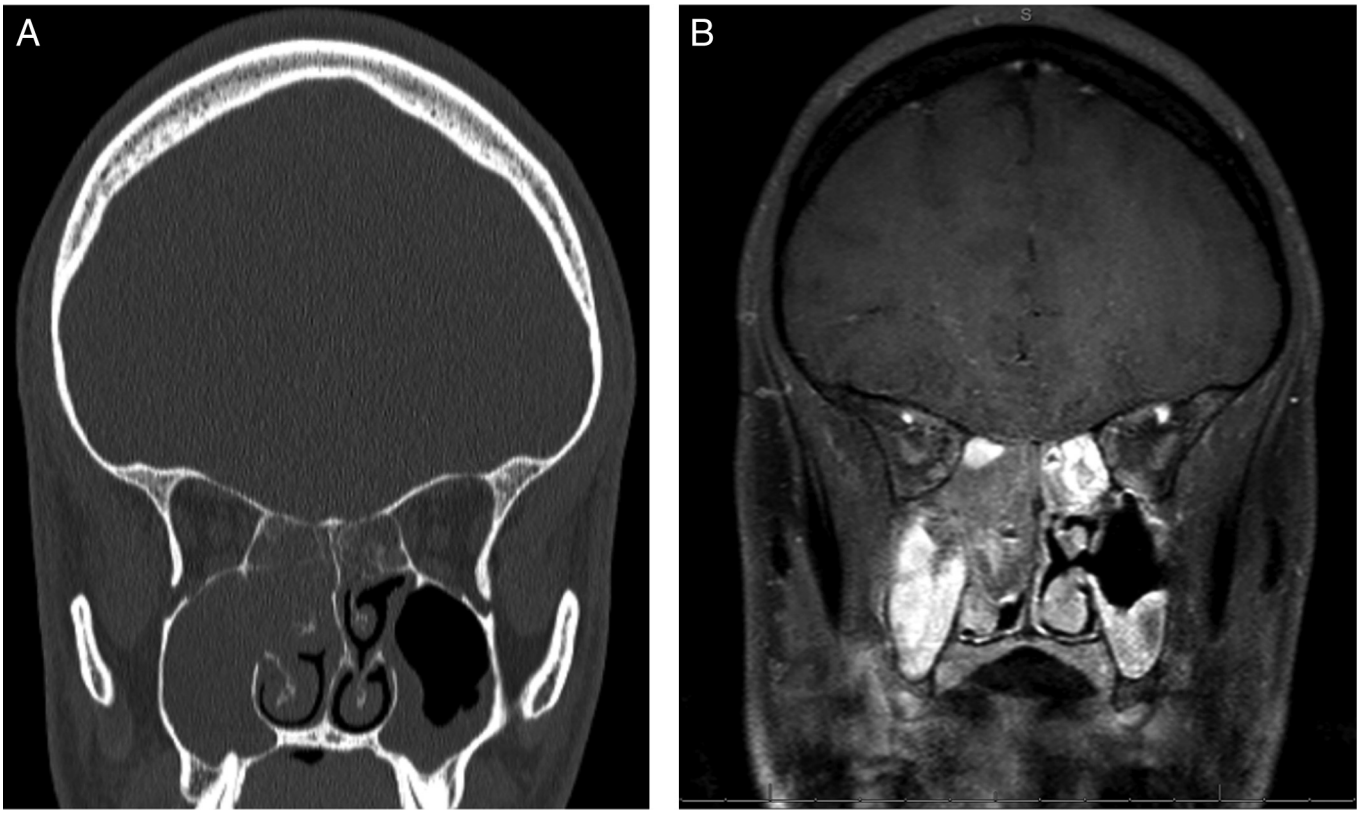

Figure 1. *Coronal CT (A) and T1 fat suppressed MRI with gadolinium (B) images demonstrating a soft tissue mass in the posterior ethmoid sinuses.*

Among hematologic malignancies, the overall incidence of BPCDN is extraordinarily low (0.4–0.7%), with two-thirds of all cases affecting elderly persons >55 years of age, including an increased susceptibility in male subjects (3:1).[3–6] Frequently an initial finding, skin lesions are almost always (90–99%) present in BPDCN prompting otherwise asymptomatic patients to seek medical attention and treatment. Evaluation of these patients reveals variable involvement of bone marrow, peripheral blood, spleen, lymph nodes, and extrahematopoietic sites, highlighting the phenotypic heterogeneity of this neoplasm.[3–7] Without immediate initiation of appropriate treatment, rapid dissemination and systemic symptoms appear. Despite an often indolent initial presentation, BPDCN is almost invariably a highly aggressive disease with median survival ranging from 12 to 20 months from time of diagnosis.[2,3,5] Therefore, early detection and diagnosis is paramount in successful treatment of this condition.

Results from the Hellenic Dendritic Cell Study Group suggest that the most sensitive and specific method for diagnosis of BPDCN is FCM, because of the superior ability to simultaneously detect numerous antigens, including some not routinely tested for by immunohistochemistry.[3] Still, immunohistochemistry is an effective confirmatory adjunct, and testing for pDC antigens, most commonly CD123, is often critical. Regardless of the testing modality, an immunophenotypic profile including a $CD4^+/CD56^+/CD123^+$ population of cells in the absence of expression of B-cell (CD19, CD20, and CD79a), T-cell (CD3, cCD3, and CD5), or myelomonocytic (myeloperoxidase, lysozyme, CD14, and CD64)-specific antigens is needed for a diagnosis of BPDCN.[1,2,4,5] Critical to ruling out an aggressive NK cell neoplasm, which can also be $CD4^+/CD56^+$, tumor cells of BPDCN will not display the nucleic acid material of the Epstein-Barr virus when tested for by *in situ* hybridization studies using a probe

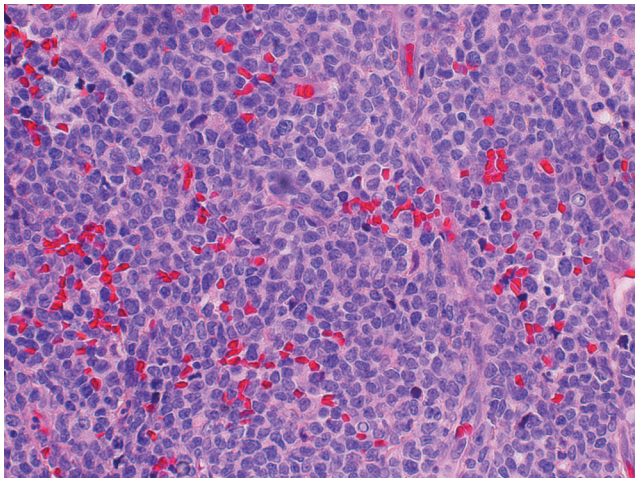

Figure 2. *Hematoxylin and Eosin staining demonstrates diffuse infiltrate of neoplastic cells with blastic chromatin pattern.*

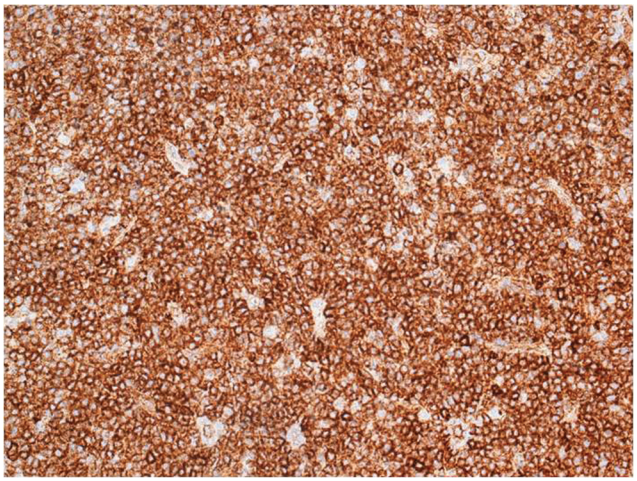

Figure 3. Positive staining for CD123.

for Epstein-Barr–encoded RNA.[3,7] Other markers such as HLA-DR, CD68, CD36, Tdt, CD33, CD117, and CD7, although not uncommonly expressed in BPDCN, are nonspecific, as they are expressed in a variety of myeloid and lymphoid neoplasms.[3]

Treatment protocols vary and are still evolving. Several studies have concluded that the current optimal treatment of BPDCN consists of an intensive polychemotherapy protocol usually administered for acute lymphocytic leukemia (ALL), accompanied by intrathecal chemotherapy with the goal of achieving complete remission. Use of the ALL treatment protocol is based on a retrospective multicenter study evaluating outcomes of acute myelocytic leukemia- and ALL-based chemotherapy. Patients treated with ALL chemotherapy had significantly increased median survival time. Prospective clinical trials to evaluate a better therapeutic strategy are prohibitive because of the rarity of this disease.[8] Although complete remission is achieved in the vast majority of cases treated with chemotherapy, almost all remissions are followed by relapse within 1 year. Therefore, in adults and if a candidate, the patient subsequently receives an allogeneic bone marrow transplantation during the first complete remission, hopefully avoiding the rapid deterioration and death that would otherwise follow complete remission. Even with allogeneic bone marrow transplant, the only true chance at a complete cure, survival outcomes remain very poor.[2,3,5,6]

This case is a fascinating and strikingly unique presentation of a BPDCN. As a young adult, this patient presented with an isolated BPDCN of the paranasal sinuses without evidence of cutaneous or systemic involvement. Only rare cases of BPDCN with systemic involvement and without skin lesions have been documented in the literature,[4,5] and even fewer have been reported that lack both systemic and cutaneous involvement. Such a presentation does not neatly fit prevailing theories regarding the site of origin of BPDCN, a topic currently fueling research and debate. One theory hypothesizes that the tumor originates from the bone marrow and secondarily involves the skin, similar to cutaneous involvement by myelomonocytic leukemia. However, a cutaneous origin can not be excluded, considering that instances of cutaneous involvement without bone marrow, lymph node, or peripheral blood involvement are well reported. Lymph node involvement within lymphatic draining areas of an associated cutaneous tumor further promotes this theory.[7] Although this case presentation does not resolve the ongoing debate regarding the putative cell or organ of derivation, it does suggest that the clinical manifestations of BPDCN are more heterogenous than previously documented. In summary, absent bone marrow, peripheral blood, or cutaneous involvement at the time of clinical presentation does not absolutely rule out BPDCN. When a presentation is atypical, such as in this case, the confirmation of the diagnosis of BPDCN relies indispensably on FCM and adjunctive immunohistochemistry. These methods, by using antibodies against recently described and better-characterized antigens, allow for a more sensitive and specific diagnosis of an otherwise phenotypically heterogeneous and easily misdiagnosed neoplasm of undetermined lineage, as well as allow for appropriate potentially lifesaving treatment. The patient in the current case report received three rounds of ALL-based chemotherapy (hyper–cyclophosphamide, vincristine, doxorubicin, and prednisone/methotrexate-cytarabine) followed by an allogeneic bone marrow transplant with an excellent response. He is disease free over a year after transplant.

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