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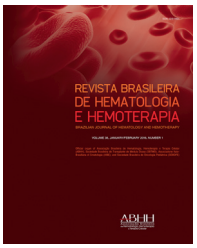

Case Report

Flow cytometry to identify bone-marrow relapse in blastic plasmacytoid dendritic cell neoplasm: a case report

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Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare acute leukemia subtype characterized by clonal expansion of dendritic-lineage cells.[1] These cells are identified immunophenotypically by weak CD45 expression and co-expression of the CD4 and CD56 antigens in the absence of other lineage-specific markers.[2,3] Previously known as blastic natural killer (NK)-cell lymphoma or $CD4^{+}/CD56^{+}$ hematodermic neoplasm, it is currently classified by the World Health Organization (WHO) as a distinct entity, under the acute myeloid leukemia (AML) and related precursor neoplasm group.[4]

Few studies have assessed the incidence of BPDCN in the general population. The limited existing data suggest an extremely low overall incidence, representing 0.44% of all hematological malignancies[3,5] and 0.7% of cutaneous lymphomas.[6] BPDCN mostly affects men, with a 3:1 male-to-female ratio, and usually occurs in patients aged 60–70 years[7,8] although cases have been reported in children and young adults.[9]

BPDCN is particularly difficult to diagnose because of its clinical and biological heterogeneity that overlaps with other clinical malignancies, and frequent lack of chromosomal abnormalities.[5,10] On laboratory testing, the cell morphology can be misleading, with a pseudolymphocytic appearance, abundant cytoplasm with a low nuclear-cytoplasmic ratio, strong basophilia, and no granulation. Microvacuoles are often visible, possibly representing glycogen compounds inclined to form a “pearl necklace” on the nuclear membrane, as well as cytoplasmic extensions similar to pseudopodia.[11,12] The cell lineage must be evaluated by flow cytometry immunophenotyping, which identifies dendritic cells in their three stages of differentiation.[10]

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A recent study showed that, according to their CD34 and CD117 expressions, dendritic cells can be categorized into three maturational stages: (1) in BPDCN, CD34 is expressed in some of the immature blasts; (2) intermediate cells are partially CD117-positive when the expression of CD34 is absent in blast cells; and (3) mature cells do not express CD34 or CD117. These stages of maturation explain the variation in the clinical presentation of BPDCN, as well as its laboratory characteristics.[10]

The most differentiated stage is characterized by cells with weak expression of CD45, no expression of CD34, co-expression of CD4/CD56, presence of HLADR/CD123, and absence of specific markers of myeloid, B and T lymphoid, and NK cells.[13,14] Co-expression of CD2, cytoplasmic CD3, CD5, CD7, CD33, nTdT, CD79a, and/or CD117 can be common.[13,15,16]

CD123 is the α chain of the interleukin-3 receptor, and is a sensitive and specific marker of plasmacytoid dendritic cells (pDC). However, although CD123 is currently the most important marker in the diagnosis of BPDCN, it is not unique to the plasmacytoid dendritic cell lineage. CD4 and CD56 are expressed in other hematological malignancies, and are not enough to establish diagnosis.[17,18]

Clinically, this disease manifests with isolated cutaneous involvement in the form of single or multiple lesions, and, despite initial indolent behavior, it is characterized by aggressive, rapid systemic dissemination.[19,20] Many patients have cytopenia, particularly thrombocytopenia, as a result of extremely variable rates of dendritic-cell infiltration of the bone marrow. Although there is an initial response to systemic chemotherapy, the disease relapses as a matter of course, and survival ranges from 12 to 14 months.[19]

Currently, there is no consensus as to the ideal treatment for BPDCN.[1,21] Retrospective studies have evaluated different treatment strategies, including multi-agent chemotherapy according to established protocols for acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML), while a few cases have been submitted to allogeneic hematopoietic stem cell transplantation (HSCT).[1,21] The neoplastic cells are initially sensitive to chemotherapy agents which are typically active against lymphoblasts, such as steroids, vincristine, and asparaginase. Therefore, it is recommended that ALL protocols be followed, with subsequent HSCT when appropriate.[1,20] It is important to highlight that the effectiveness of this procedure still needs to be investigated by clinical studies, and the role of transplantation has yet to be defined.[1] The Martín-Martín et al. study demonstrated that this strategy (ALL therapy plus HSCT) was associated with the best prognosis.[10]

Within this context, the aim of this paper is to report a case of this rare, difficult-to-diagnose neoplasm in which flow cytometry immunophenotyping contributed to the correct identification of leukemic cell lineage.

Case report

A 51-year-old previously healthy female presented with a 3-month history of progressively disseminating cutaneous lesions, with no defined diagnosis and no clinical response to topical treatments. Immunohistochemistry skin biopsy was performed and revealed blast-appearing cells, positive for CD45 and CD123, and negative for TCL1 related to the CD3 and CD20 antigens, indicating BPDCN. Bone marrow aspiration and biopsy did not show bone-marrow involvement at the time of diagnosis. Treatment was performed with cytarabine and daunorubicin (7 + 3 protocol – induction, re-induction, and three consolidations). Three months after completing high-dose cytarabine maintenance, a cutaneous relapse was detected (Figure 1A) with central nervous system (CNS) involvement. At this time, bone marrow biopsy identified 80% immature cells with lymphoblast appearance (Figure 1B) and an anatomopathological study revealed diffuse infiltration by blast cells of lymphoid origin (Figure 1C). Bone marrow immunophenotyping by flow cytometry (Figure 2) using the FACSCanto II system (Becton Dickinson, San Jose, CA, USA) showed 62% of cells with expression of the antigens CD4, HLADR, CD38, weak and heterogeneous CD56 expression,

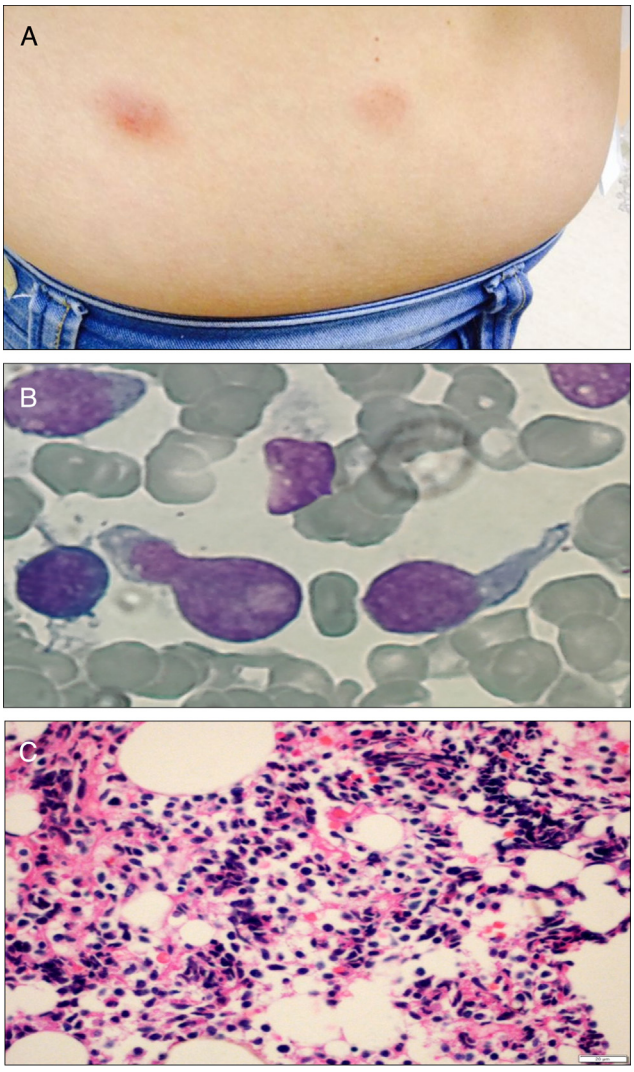

Figure 1 – Physical and morphologic features of blastic plasmacytoid dendritic cell neoplasm. Cutaneous lesions on the patient's abdomen (A); morphology of leukemic blasts in the bone-marrow aspirate smear (B); anatomopathological study showing infiltration by blast cells (C).

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