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A Very Incongruous Ecchymotic Macules and Nodules Revealing a Blastic Plasmacytoid Dendritic Cell Neoplasm

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Abstract **Case Report**

Blastic plasmacytoid dendritic cell neoplasm previously known as CD4+/CD56+ blastic NK cell tumors or hematodermic tumors. We report a case of a A76-year-old women presented with disseminated violaceus nodular, 'bruise like' patches and macules of the trunk and subconjunctival hemorrhage. Immunohistochemistry showed a CD4+/CD56+ expression which confirmed the diagnosis of BPDCN was made. We emphasize that careful analyses should be performed to make the correct diagnosis.

Keywords: hematodermic tumors, Immunohistochemistry, CD4+/CD56+, BPDCN.

INTRODUCTION

Blastic plasmacytoid dendritic cell neoplasm previously known as CD4+/CD56+ blastic NK cell tumors or hematodermic tumors. They were reclassified as a neoplastic entity in the 2008 World Health Organization classification [1].

This leukemia is regarded as an orphan tumor due to its rareness and usual clinical aggressiveness with poor response to conventional chemotherapies [2].

It derives from precursors of plasmacytoid dendritic cells (pDCs), also known as professional type I interferon- producing cells or plasmacytoid monocytes. In the Revised WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues, BPDCN is quoted after acute myeloid leukemia [3].

CASE REPORT

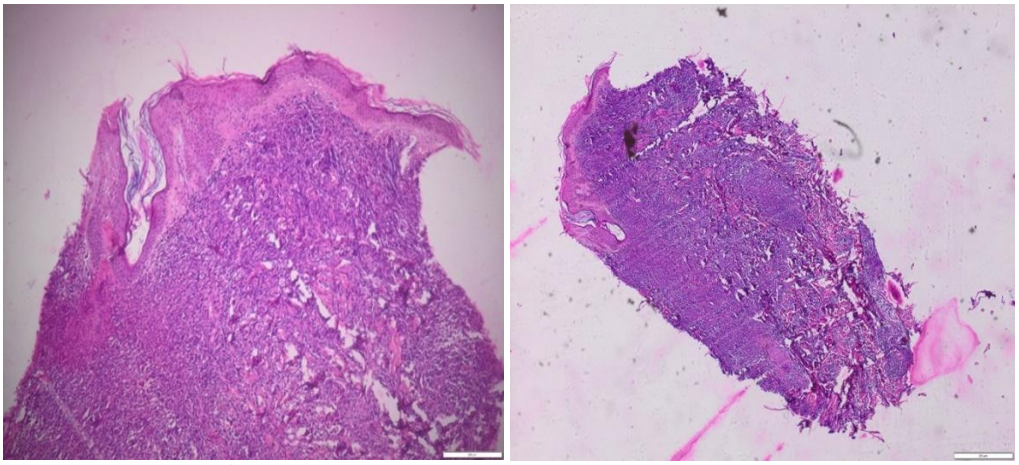
A76-year-old women presented with disseminated violaceus nodular, 'bruise like' patches and macules with variable size involving the trunk, the left shoulder and subconjunctival hemorrhage. Pain and itching were absent (Figure-1).

Fig-1: Characteristic violaceous nodules and papules of cutaneous involvement by blastic plasmacytoid dendritic cell neoplasm with subconjunctival hemorrhage

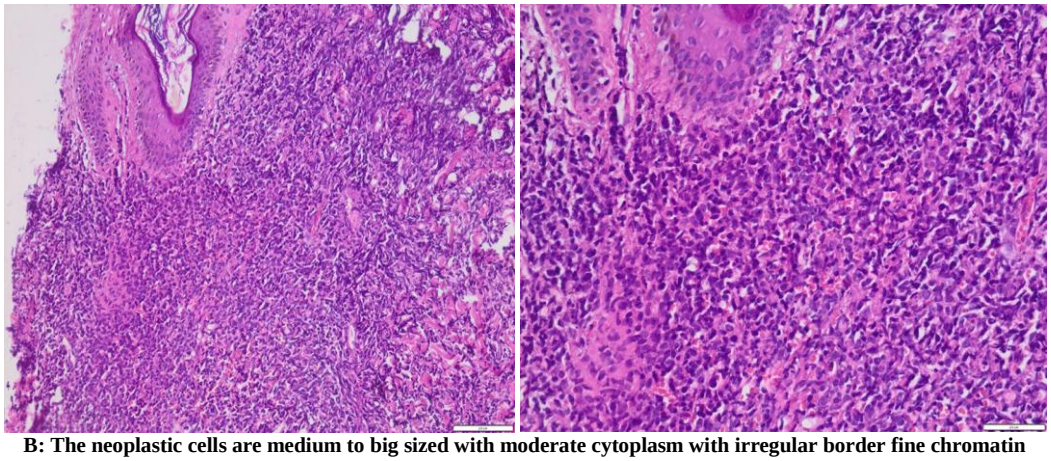
The lesions had been present for more than 4 months without any other symptoms. Hematologic explorations revealed a hemoglobin concentration of 6 g/dL. Serum lactate dehydrogenase (LDH) was elevated to 500 IU/L.

The first biopsy revealed undifferentiated lymphoma and the second one performed with immunohistochemistry showed that neoplastic cells expressed CD43. They were positive for CD56, CD4 and KI67 was 80%.

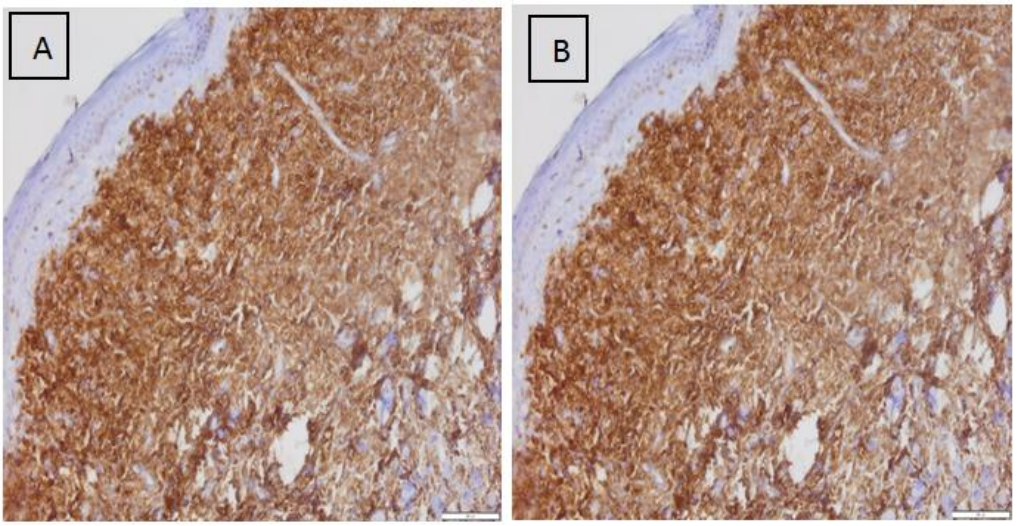
Morphologic features of blastic plasmacytoid dendritic cell neoplasm:

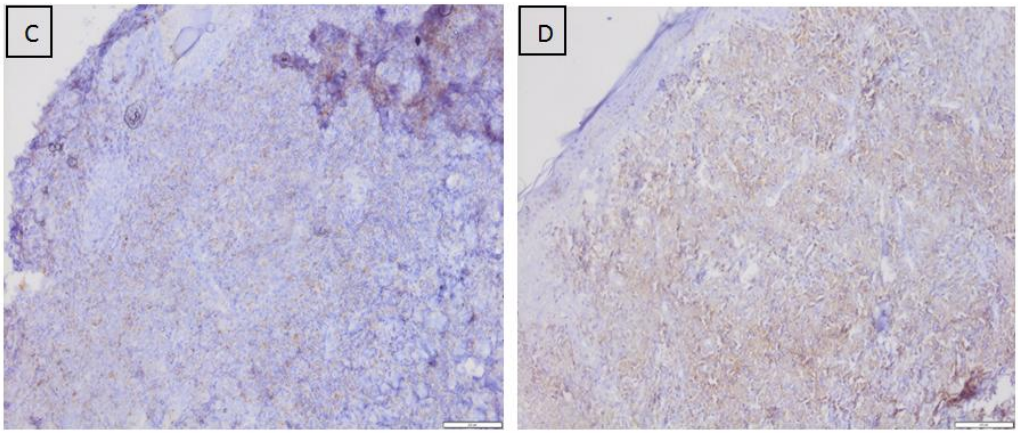


A: Dense neoplastic infiltrate in the dermis with a patchy periadnexal accentuation. The epidermis is intact

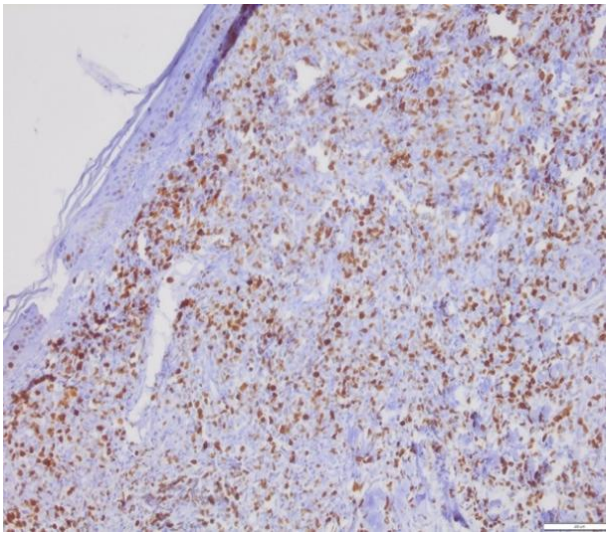


B: The neoplastic cells are medium to big sized with moderate cytoplasm with irregular border fine chromatin





Tumor cells show immunoreactivity for CD43(A), CD4 (B), CD68 « en dot » (C) et le CD56 (D) IHC x 200



High Ki-67 expression in 76%

The bone marrow expressed 54% of lymphoid cells with different size and shape with lymphoplasmacytic and undifferentiated cells. The plasma cells were expressed in 4%.

No lymphadenopathy, splenomegaly or hepatomegaly were palpable. Based on skin lesions, monomorphic and diffuse infiltrate in the dermis composed of medium and big sized cells with blastic appearance and phenotypic (CD4+, CD56+) features the diagnosis of BPDCN was made.

Three week later the initial diagnosis the patient presented general fatigue and dyspnea. The staging investigations were not done, the patient died 4 weeks after.

DISCUSSION

BPDCN is a very rare form of lymphoma-like disease, reported in 1994, for the first time, in a patient with violaceous nodules on the skin [4].

The 2008 update of the WHO classification of Tumors of Haematopoietic and Lymphoid Tissue included the title 'blastic plasmacytoid dendritic cell neoplasm (BPDCN) [5]. Less than 100 cases of BPDCN have been reported in the English literature.

Immunophenotypical studies have confirmed the expression of CD123 by tumor cells, suggesting that hematological neoplasm derives from plasmacytoid dendritic cell (PDC) precursor [6, 5, 7].

The few available data reported that its extremely rare, accounting from 0,44% of all hematological malignancies [28] to 0 ,7% of cutaneous lymphomas [29]. The leukemic form of disease represents less then 1% of acute leukemia cases [30].

BPDCN typically affects older males, with a median diagnostic age of 67 years [8]. In the pediatric population, BPDCN is exceedingly rare, with only 33 cases published cases to date [9].

According to the literature, almost 85% of cases of BPDCN show cutaneous involvement at presentation [10, 11]. Cutaneous lesions typically present with asymptomatic, solitary or multiple nodules , plaques or bruise-like infiltrates with variable shape and color and size associated or not with purpura or hyperpigmentation [12].

Lymphadenopathy, splenomegaly and cytopenia due to bone marrow involvement can be present at diagnosis or may occur at disease progression [13].

To our knowledge this is the first study to describe the aggressiveness of BPDCN presenting with subconjunctival hemorrhage, disseminated lesions and fatal outcome.

Mucosal involvement has rarely been described in the literature. Two cases with pharynx involvement have been reported [14].

Disseminated cutaneous lesions are characterized by the association of nodules, papules and purpuric generalized macules.

Diagnosis is made on skin biopsy, which shows an infiltration of the dermis by a population of monomorphous intermediate size cells, with fine chromatin without necrosis or vascular infiltration. Bone marrow aspiration may show or not atypical blast cells.

The presence of more than 20% of blast cells infiltrating the bone marrow confirms leukemia of plasmacytoid dendritic cell lineage diagnosis. Phenotypic features have recently been confirmed [15, 16].

The diagnosis must be confirmed by either immunohistochemistry or by flow cytometry, depending on the material available.

The diagnosis relies on the demonstration of CD4 and CD56 positivity by tumor cells, together with markers more restricted to plasmacytoid dendritic cells, CD123, TCL1.

BPDCN has been assessed by array comparative genomic hybridization (CGH) analyses confirm that loss of genetic material is much more frequent than presence of additional genetic material [17-19].

It was suggested in recent study that genes CDKN2A/CDKN2B on 9p21.3 is frequently lost [13, 20]. The clinical course of BPDCN is aggressive leukemia median overall survival ranging from 12 to 16 months [21, 6]. Because of its low incidence, prospective data are lacking and the few series published so far rarely exceed 15 cases [13].

The best treatment for BPDCN is unknown. In general, intensive induction regimens (hyperCVAD)are considered more effective compared to standard therapies (CHOP-like) .In general, ALL-like treatments seem to be more effective in term of response rates than AML-like induction therapies [21-24].

There are several reports suggesting better results with allogeneic-stem cell transplantation (allo-SCT) compared to auto-SCT in BPDCN therapy.

These studies demonstrated durable complete remissions with allo-SCT at 3 years depending on the follow-up period. With chemotherapy, prognosis is still poor, and median overall survival often remains inferior to 2 years [13] .

Targeted therapies are currently under development with promising results [2]. Recent studies show that BPDCN survival depends on the anti-apoptotic protein BCL-2, which is highly expressed in BPDCN compared to normal plasmacytoid dendritic cells [25].

The BCL-2 inhibitor venetoclax is currently under evaluation in combination with induction chemotherapy and hypomethylating agents [26, 27].

Several experiences show that venetoclax seems safe, effective and adapted in treatment of BPDCN, in elderly patients with skin involvement. In conclusion BPDCN is a rare disease with a poor prognosis underdiagnosed and underreported.

Given this aggressiveness multiple analysis including genetic, molecular and immunohistochemical are needed to make an exact and quick diagnosis of BPDCN and to optimize the therapeutic management of this disease.

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