

Case Report

Complete Remission with α -Interferon in a Poor Risk Patient with Blastic Plasmacytoid Dendritic Cell Neoplasm: A Case Report and Review of Literature

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Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN), due to its biological and clinical features, could be classified as an intermediate disease between acute myeloid leukemia (WHO 2008) [1] and non Hodgkin lymphomas (WHO-EORTC 2005) [2].

In the first BPDCN case published in 1994 [3], authors reported the lack of a lineage specific antigen and the co-expression of CD4 and CD56 suggesting a natural killer (NK) cell-lineage origin. This entity was firstly defined as blastic NK cell lymphoma (BNKL) [4]. Later, the discovery of CD123 (interleukin-3 receptor) and BDCA2 (blood dendritic cell antigen 2) expression allowed to identify these cells as plasmacytoid dendritic cells. Blastic cells appear to secrete α -Interferon (INF) [5-7] and thus are immunophenotypically and functionally identified as immature dendritic cells. For the above mentioned reasons, the tumor was renamed blastic plasmacytoid dendritic cell neoplasm [1].

Plasmacytoid dendritic cells (pDCs) develop in bone marrow, reside primarily in the lymphoid organs (nodes and thymus) in steady state and can be mobilized, in response to some stimuli including G-CSF and FLT-3, into peripheral blood, where they are poorly represented (< 1% of the mononuclear cells).

In lymph nodes pDCs are detectable in T-cell rich areas [8,9] as round or oval cells with an eccentric nucleus and a well developed endoplasmic reticules (ER).

Fred Siegal and Yong-Jun Liu [10] demonstrated that these secretory cells produced large amounts of IFN and identified them with the IFN-producing cells previously described [11-13].

As components of the innate immune system, pDCs detect viral acid nucleic through toll-like receptor 7 (TLR7) and toll-like receptor 9 (TLR-9), inducing the IFN secretion. This protein is responsible for

Abstract

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and clinically aggressive haematologic malignancy caused by neoplastic transformation and clonal proliferation of plasmacytoid dendritic cell precursors. Current treatment approaches are not effective and the outcome remains poor in the majority of patients even after chemotherapy and bone marrow transplantation. In this report we consider the use of interferon alpha for old unfit patients not candidate for intensive strategies.

Keywords: Blastic plasmacytoid dendritic cell neoplasm; Interferon alpha; NK

the resistance to viral infections and promotes NK, DC, T and B cell functions [14].

IFN signaling promotes the survival of *ex vivo* pDCs [15,16], but *in vivo* studies [17] have demonstrated that IFN mediates pDCs death through caspase activation, creating a proapoptotic loop.

Limited data are available to guide the management of BPDCN. Response to conventional chemotherapy is commonly poor and survival correspondingly short (mean survival of 12-14 months) [18].

Several Authors suggest the effectiveness of allogeneic hematopoietic stem cell transplantation (AHSCT) [19-21].

Case Presentation

A 74-year-old man was admitted on our chemotherapy ward because of BPDCN with initial skin involvement.

At diagnosis, in November 2013, the patient showed 2-3 cm purplish eruptive nodules, neither painful nor itchy, preferentially located on his trunk and legs (Figure 1).

A biopsy specimen taken from thigh skin lesion revealed a dermo-epidermal infiltrate of small sized cells (Figure 2) reactive to CD4 and CD56. Immunostaining for CD8, CD30, CD20, CD79a, CD3, CD5, CD10, CD23, Bcl-6, TdT, myeloperoxidase, D1 cyclin, CD34, CD117 and CD138 was negative. Mib-1 proliferation index was 70%.

All these features were consistent with the diagnosis of BPDCN.

The patient underwent staging with complete blood counts, blood chemistry, total body computer tomography scan and bone marrow biopsy. Blood counts and serum chemistry were within normal range and CT imaging was negative for lymph nodes involvement or other noteworthy. Bone marrow appeared infiltrated (15%) by medium-sized blast-like cells with basophilic cytoplasm and irregular nuclei.



Figure 1: Multiple nodules on the (A) trunk and (B) leg.

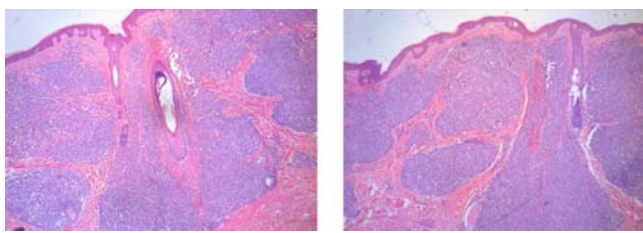


Figure 2: Skin biopsy: haematoxylin and eosin staining shows a dermo-epidermal infiltrate of small sized cells.

Flow cytometry identified a low percentage (3%) of immature elements CD34+/CD38+/CD56+ and molecular characterization showed a clonal T cell receptor delta (TCR) gene rearrangement. The patient underwent active surveillance until April 2014, when he developed clinical progression with enhanced skin involvement, occurrence of enlarged neck lymph nodes, tonsil involvement and increased bone marrow infiltration (blasts CD4+/CD56+ 35%)(Figure 3).

Age and comorbidities (dysmetabolism and previous nephrectomy for a kidney malignancy) did not candidate the patient for intensive chemotherapy followed eventually by allotransplant.

The patient underwent therapy with subcutaneous administration of α -INF 3.0 MUI three times per week for two months and oral administration of dexametasone 20 mg on day 1-4 of each month. He was monitored monthly by measuring the diameter of the skin lesions and repeated bone marrow blast count with molecular analysis at +3 and +6 months (Figure 4).

Skin nodules and lymph nodes progressively reduced within 4 weeks from therapy beginning. After a year and a half from the diagnosis our patient is alive, without major side effects and in complete response with respect to bone marrow and lymph node diseases. Bone marrow analysis shows complete morphologic, immunophenotypic and molecular response (TCR delta rearrangement negativity). Skin lesions are now present in the form of small dyschromic alterations.

Discussion

BPDCN is a rare, aggressive and incurable malignancy, derived from plasmacytoid dendritic cells precursors and characterized by co-expression of CD4 and CD56. Its incidence in the population is unknown due to the lack of defining criteria. Literature reports very low incidence (0.44% of all hematologic malignancies) and rare leukemic presentation: <1% of cases of acute leukemia. BPDCN affects males prevalently, with a male/female ratio of 3.5/1, and generally occurs in older adults, with a median age of 60 years at diagnosis [22].

In the majority of cases patients present solitary or multiple non-

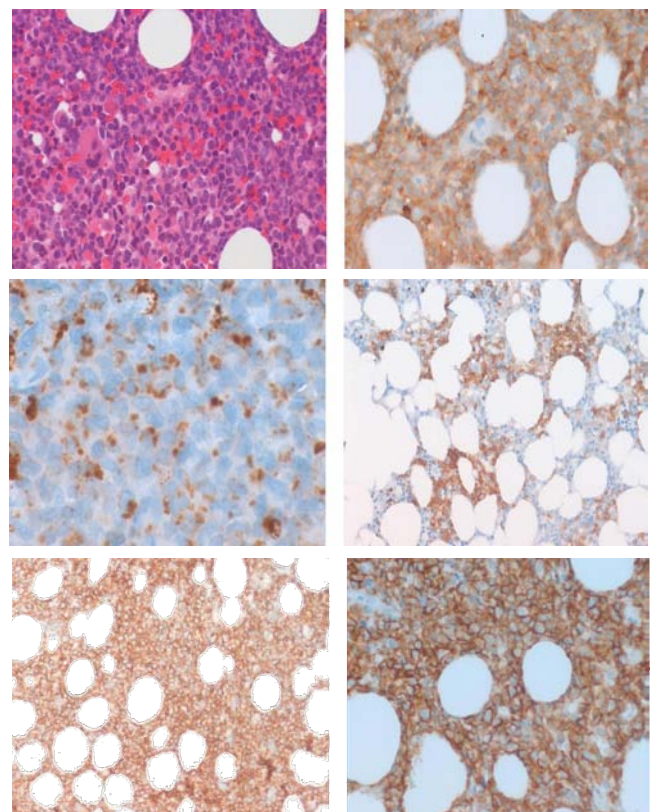


Figure 3: (A) Haematoxylin and eosin staining and immunohistochemical staining for (B) CD4+ 200x (C) CD68+ (D,E) CD56+ 200x (F) CD56+ 400x.

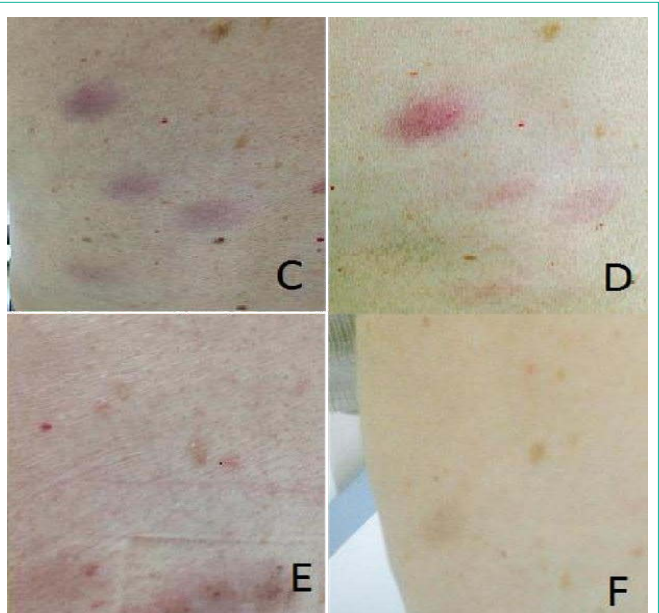


Figure 4: Clinical response. (C) Diagnosis, (D) +1 months, (E) +3 months, (F) +8 months from the beginning of therapy.

pruritic skin lesions and lymph nodes enlargements, with subsequent or rarely simultaneous leukemic spread.

In the last two decades many efforts were made in order to

understand the underlying biology of BPCDN, indentifying DCs as the normal counterpart of CD4+CD56+ malignant cells [23,24]. Still little is known about cancer initiation, promotion and leukemic progression making a pathogenesis-based therapy not available. Moreover the absence of prospective data makes treatment of this neoplasm a great challenge to physicians.

In agreement with literature, intensive strategies [19-21] possibly followed by allogeneic transplantation should be considered the best choice in order to produce deep and prolonged responses.

Responses obtained after front-line therapy are variable ranging from 40-50% for CHOP-like chemotherapy [25] to 80-90 % for AML/ ALL like regimens [26]. However, independently of the frontline chemotherapy, responses are short-lived [18-20,27] and clinical course is usually characterized by an initial response followed by relapse.

In this work we present a case of BPDCN with typical skin lesions at presentation, followed by bone marrow involvement and leukemic progression. Due to patient's age and comorbidities he didn't undergo multiagent chemotherapy and allogeneic HSCT.

In the absence of a standard of care, awareness of the aggressive behavior of BPDCN and of the need for ongoing treatment, we have considered the use of α -INF in this disease.

This drug is easy to administer, doesn't require hospitalization and it is charged by infrequent minor side effects (flu-like symptoms, hematological toxicity, elevated transaminases, nausea) usually adequately handled by dose adjustment.

Alpha IFN administration in BPDCN appears to have a biological rationale. Some *in vivo* [17] studies have shown that when skin-DCs are exposed to high concentrations of α -IFN, they undergo apoptosis. On the basis of these results and considering the effectiveness of IFN in several lymphoid and myeloid diseases, our patient underwent α -IFN therapy. Considering mean survival reported in the literature after intensive strategies, this drug in our patient demonstrated to be no less effective.

We suggest that α -IFN could be an option to consider for old unfit patients that cannot be exposed to conventional multidrug chemotherapy.

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