Case report

A very rare case of FLT3-D835 positive blastic plasmacytoid dendritic cell neoplasm

Vlad Andrei Cianga[1,2], Cătălin Doru Dănăilă[1,2], Ion Antohe[2], Raluca Oană[3], Mihaela Menţel[4], Iuliu Ivanov[5], Loredana Dragoș[5], Angela Smaranda Dăscălescu*[,1,2]

[1]Grigore T. Popa University of Medicine and Pharmacy, Iași, Romania; [2]Department of Clinical Hematology, Regional Institute of Oncology, Iasi, Romania; [3]Department of Cytology, Regional Institute of Oncology, Iasi, Romania; [4]Department of Immunophenotyping, Regional Institute of Oncology, Iasi, Romania; [5]Department of Molecular Diagnostics, Regional Institute of Oncology, Iasi, Romania

Abstract

Blastic plasmacytoid dendritic cell neoplasms (BPDCNs) are extremely rare and aggressive hematological malignancies that derive from precursors of plasmacytoid dendritic cells (pDC) and frequently involve skin lesions and bone marrow infiltration. They mostly affect the elderly population and the prognosis is poor with the therapeutic choices currently available. Diagnosis is made with the help of tools such as immuno-histochemistry and flow cytometry. Here, we present a particular case of BPDCN with a positive FLT3-D835 mutation and we discuss the possible impact this may have on the evolution of the disease and response to treatment.

Keywords: *blastic plasmacytoid dendritic cell neoplasm; aggressive hematopoietic neoplasm; acute leukemia; flow cytometry; FLT3-D835*

Introduction

Blastic plasmacytoid dendritic cell neoplasms (BPDCNs) are rare and aggressive hematological malignancies that originate from plasmacytoid dendritic cells (pDC) precursors and exhibit skin lesions with possible bone marrow (BM) involvement and leukemic dissemination [1]. Phenotypically, normal pDCs express CD123+, CD303+, CD304+ and CD11c- surface markers [2, 3] and functionally, they secrete proinflammatory cytokines (IL-6, IL-8, IL-12, TNF-α), and high levels of interferon (IFN)α/β, thus exerting an important role in viral infections [4, 5]. No current data are available for Romania, but in the United States, an overall incidence of 0.04

cases per 100.000 people was reported, with a bimodal pattern of distribution: in people younger than 20 and older than 60 years, with a clear predominance in the elderly segment [6, 7]. A slight predisposition for Caucasians and the male sex were also observed (male-to-female ratio of 3.3:1) [1, 6, 7]. Kameoka et al. first mentioned the disease in 1998 when they described 2 particular cases of cutaneous agranular CD4+ CD56+ (NCAM) non-Hodgkin lymphoma (NHL) and the authors proposed they represent a distinct pathological entity [8]. Since then, the nomenclature has changed multiple times due to constant refinement of diagnostic biomarkers and included various names such as agranular CD4+ Natural Killer (NK) cell leukemia and agranular CD4+ CD56+ hematodermic neoplasms/tumors [9, 10]. Chaperot et al. were the first to demonstrate in their study that these leukemic cells exhibit surface markers typical for pDCs and finally established the origin of the malignancy [11, 12]. The disease was
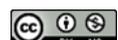
classified, according to the World Health Organization (WHO) 2008 criteria, as a subtype of acute myeloid leukemia and, later in 2016, as a distinct myeloid malignancy [13, 14].

Case report

We present the case of a 74-year-old Caucasian male with cardiovascular (hypertension, permanent atrial fibrillation and chronic heart failure) and metabolic (Diabetes Mellitus type 2) comorbidities that was addressed to the Emergency Department (ED) for persistent fever, dyspnea and productive cough with hemoptysis. Despite a SARS-Cov2 RT-PCR negative test, the chest x-ray described bilateral pneumonia that required antibiotic treatment.

The complete blood count (CBC) showed moderate to severe pancytopenia. A hematological malignancy was suspected and the patient was committed to the Hematology Clinic from the Regional Institute of Oncology

in Iasi, Romania, for further investigations. At presentation, a 4 cm singular, violaceous nodule located on the left posterior thorax, and disseminated ecchymotic lesions were evidenced. However, no palpable superficial lymph nodes, nor hepatosplenomegaly were observed. The repeated CBC was consistent with the previous one, showing normochromic, normocytic anemia (Hb=12g/dl), severe thrombocytopenia (PLT=21000/μl) and leucopenia (WBC=2000/μl) with neutropenia (N=670/μl), while blood morphology described 22% medium sized blast cells. The coagulation panel was normal, the erythrocyte sedimentation rate was elevated (ESR=50 mm/h) and biochemistry tests also revealed an elevated lactate dehydrogenase (LDH=423 U/L; reference range 120 – 246 U/L), a marker of tumor cell lysis. Under these circumstances, BM aspiration was performed and morphology analysis identified 27% medium sized blast cells with irregular nuclear outline, lax chromatin and reduced basophilic cytoplasm (Figures 1A and 1B).
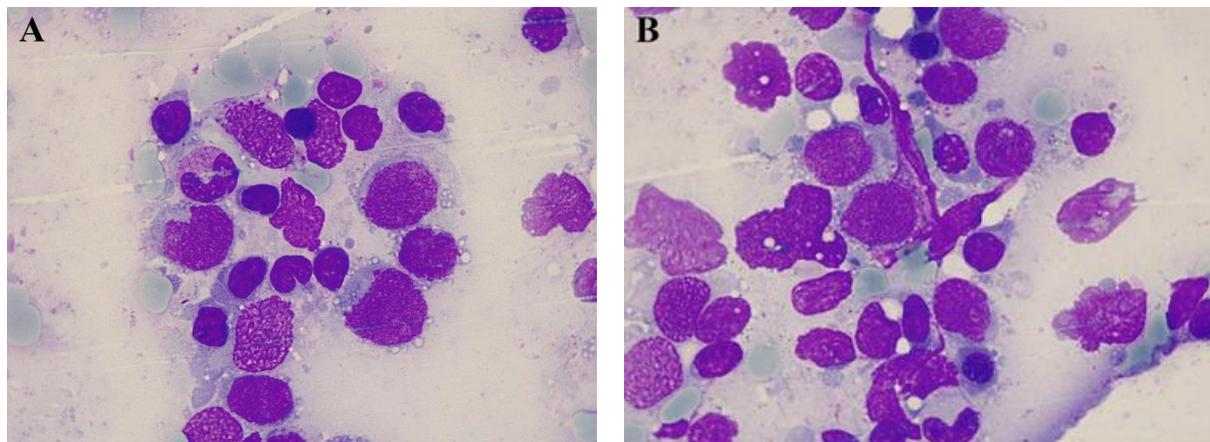
Fig. 1. A, B. Morphology analysis of the BM cells reveals a population of 27% medium sized blast cells that present irregular nuclear outlines, fine chromatin and reduced agranular basophilic cytoplasm.

Flow cytometry described atypical cells, with positivity for CD45, HLA-DR, CD4, CD123, CD56, NG2 and partial positivity for CD117 and CD7. The precursor cell marker CD34 was absent and lineage markers cyMPO, cyCD79a, cyCD3 and CD94 were also negative (Figure 2). Based on clinical findings, morphological characteristics and tumor cells phenotype, a diagnosis of BPDCN was established.

Cytogenetic analysis showed that karyotype was normal 46, XY and subsequent molecular tests investigated the presence of the following mutations: BCR/ABL (p190), BCR/ABL (p210), E2A-PBX1, MLL-AF4, SIL-TAL, AML1-ETO, CBFβ-MYH11, PML/RARα, NPM1, FLT3-ITD and FLT3-D835, out of which only FLT3-D835 was positive.

Due to advanced age and cardiometabolic comorbidities, the therapeutical choice was a

dose adjusted acute lymphoblastic leukemia (ALL) induction regimen based on Vincristine, Cyclophosphamide, Idarubicin, Cytarabine and corticotherapy. Treatment related events were represented by steroid induced hyperglycemia and a 3-week long aplasia, complicated with febrile neutropenia and catheter induced thrombophlebitis with cellulitis. Blood and wound cultures were positive for *Klebsiella pneumoniae* and *Klebsiella oxytoca*, which imposed local and systemic antibiotic therapy, with a favorable evolution. Follow-up BM control identified only 1% residual blasts – complete remission, considered as minimal residual disease (MRD+). One month after chemotherapy completion, the patient was admitted for extreme fatigue, dyspnea and general enlargement of the lymph nodes. Clinical findings revealed generalized lymphadenopathy with tendency to form blocks, discrete splenomegaly and multiple, disseminated violaceous skins lesion in different stages of evolution. Considering the fulminant evolution of the disease, treatment with salvage chemotherapy combining Dexamethasone, Etoposide, Ifosfamide and Carboplatin (DeVIC protocol) was implemented.

A major complication occurred due to the contact with a confirmed COVID-19 patient and infection with SARS-CoV-2, for which he required transfer to the Infectious Diseases hospital. The clinical evolution was apparently favorable and the patient was discharged after 3 weeks. However, he did not later check back to the Hematology Clinic
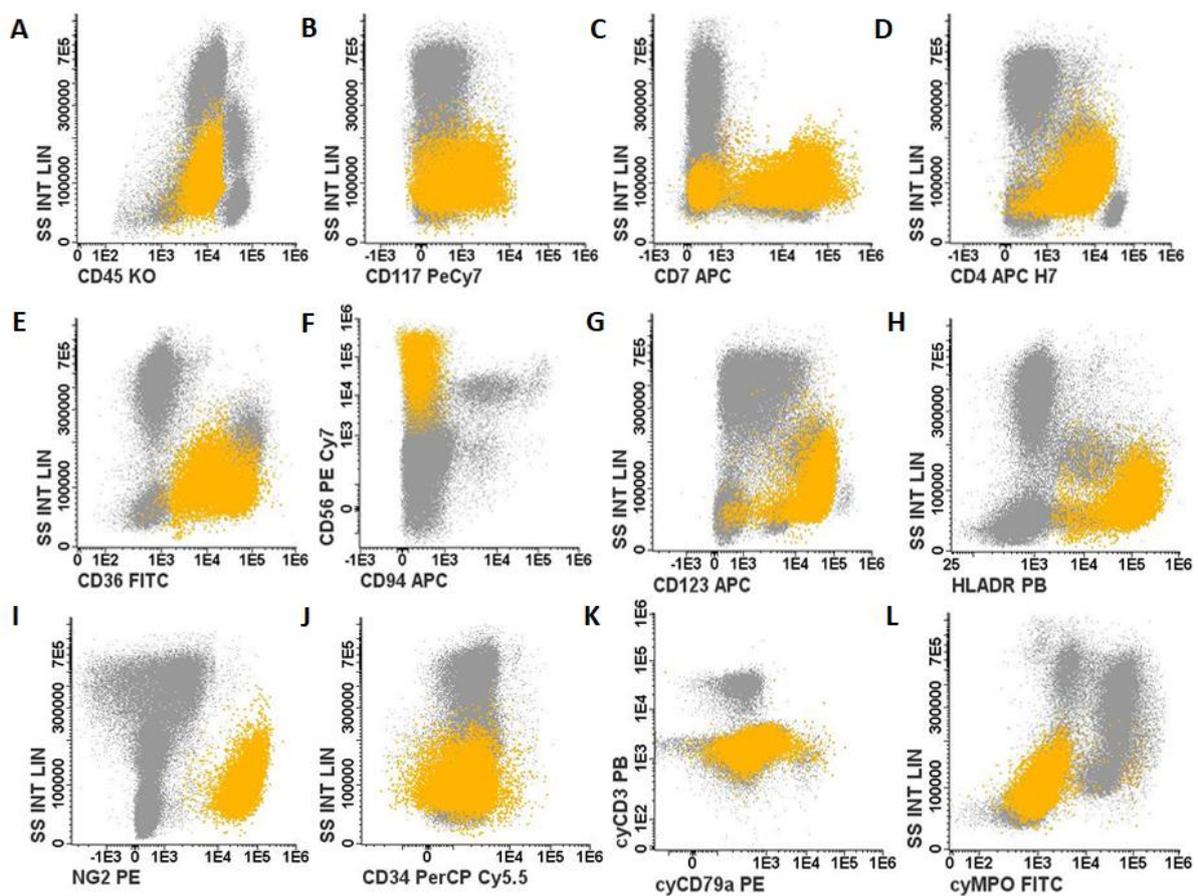
Fig. 2. Flow cytometry was performed on the BM cells. The blastic plasmacytoid dendritic cell population is highlighted in orange. The blasts were intermediate positive for CD45 (a); partially positive for CD117 and CD7 (b, c); positive for CD4, CD36, CD56, CD123, HLA-DR and NG2 (d, e, f, g, h, i) and negative for CD94 (f), CD34 (j), cyCD3 and cyCD79a (k) and cyMPO (l).

Discussions

BPDCNs are extremely rare myeloid malignancies that mostly affect the elderly segment and involve skin tumor lesions, BM infiltration with cytopenias and extra-cutaneous presentation, with possible lymphadenopathy, hepatosplenomegaly and leukemic dissemination [1, 15]. Singular or multiple skin lesions can be found in the majority of BPDCN cases (90%) with either nodular, papular or macular aspect and accompanying erythema or purpura [1, 15, 16].

Diagnosis of BPDCN can be made either by tumor skin biopsy immunohistochemistry or by BM cells flow cytometry. A combination of CD4+, CD123+, HLA-DR+ and CD56+ antigens, in the absence of B-cell, T-cell or myeloid/monocytoid lineage markers establishes the pDC origin and helps discriminate BPDCN from other malignancies, such as NK/T-cell lymphoma nasal type, ALL and acute myeloid leukemia (AML)/myeloid sarcoma [9, 17-19]. Neuron-glial antigen 2 (NG2) is a marker expressed in AMLs and mixed-lineage leukemias (MLL) that is typically associated with extramedullary invasion, high number of circulating blasts and overall poor prognosis, with increased resistance to therapy [20, 21]. Its positivity in this case represented a predicting factor for the early relapse of the patient after induction chemotherapy.

The pathological mechanisms that lead to BPDCN are still poorly understood and the few available studies could not pinpoint the main molecules and pathways that are involved. The cytogenetic abnormalities identified so far appear to be complex and unspecific, mainly involving chromosomes 5q, 12p, 17p, 13q, 6q and 15q and affect almost 2 out of 3 patients [22, 23]. However, we like to highlight the fact that the patient we present had no such cytogenetic abnormalities. Gene expression profiling, whole genome sequencing and target sequencing allowed researchers to identify recurrent somatic mutations that include TET2, ASXL1, NPM1, NRAS, SF3B1, ZRSR2, CUX1 and EZH2; upregulated pathway mutations, such as nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB); loss of cell cycle

checkpoint inhibitors results in enhanced G1/S transmission, as observed in MYC rearrangements on 8q24 [15, 25-28].

In our case, we were able to identify a mutation (D835) in the tyrosine kinase domain (TKD) of the fml tyrosine kinase 3 (FLT3) that causes constitutive activation of this receptor [29]. To the best of our knowledge, there are no literature data showing an association between BPDCN and this mutation in the FLT3-D835. In AML, FLT3 mutations come as either internal tandem duplications (ITD), which are more common and have a well-established prognostic significance by the European leukemia network (ELN) [30], or point mutations, such as TKD, which are rarer and with an unclear prognosis. In a study on 3082 AML patients, Baher et al reported an incidence of only 4.8% of FLT3-TKD positive cases. Thus, they concluded that the impact on overall survival (OS) and event free survival (EFS) was rather influenced by the association with other mutations, while FLT3-D835 did not carry any prognostic relevance itself [31]. However, owing to the rapid evolution of this patient and the aggressiveness of the tumor, we consider that this molecular abnormality may carry a worse prognosis in BPDCN than in AML, but in order to confirm this suspicion, more studies are needed.

In regards to treatment options, there is no current consensus for a standard option at the moment, owing to the low incidence of the disease and lack of prospective studies. Most experts agree though that ALL and non-Hodgkin lymphoma (NHL) based chemotherapy regimens, such as hyper-CVAD (hyperfractionated Cyclophosph-amide, Vincristine, Doxorubicin and Dexamethasone) or CHOP (Cyclophosph-amide, Doxorubicin, Vincristine and Dexamethasone) proved better than AML treatment options, with reported complete remission (CR) rates varying between 50-80% [9, 15, 17, 29]. However, the event free survival is usually short (average of 5 months) and longer remissions were reported only amongst patients who underwent allogenic stem cell transplant (ASCT) [29]. As in our case, it is difficult to perform this procedure in unfit, elderly patients. Advanced age, the important cardiac dysfunction and diabetes were important

factors to take into consideration when electing the chemotherapy regimen. Even with dose adjusted agents, the aplasia lasted for 3 weeks and was complicated by febrile neutropenia and infection.

Conclusions

BPDCNs are extremely rare hematopoietic malignancies, with rapid evolution and severe prognosis. Immunohistochemistry and immunephenotyping are the best diagnostic tools able to discriminate BPDCN from more common myeloid malignancies and set an accurate diagnosis.

Our unusual finding of the FLT3-D835 mutation in the absence of cytogenetic abnormalities brings proof of this disease complexity and demonstrates that the BPDCN entity is far from being fully understood. Unraveling the intimate mechanisms leading to this particular pathology would directly impact the therapeutical approach.

Consent
Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

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