Two cases of blastic plasmacytoid dendritic cell neoplasm

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Objectives

Aim was to investigate the molecular background of blastic plasmacytoid dendritic cell neoplasm (BPDCN) which is an aggressive tumor derived from precursors of plasmacytoid dendritic cells (pDC). BPDCN presents frequently as cutaneous lesions and subsequently progresses to bone marrow (BM) invasion and leukemic dissemination.[1] Most cases show an initial response to chemotherapy, frequently followed however by resistance to any therapy.[1,2]

Case report information

Case 1. A 74-year-old male, without important medical history, was referred to our hospital with anemia, leukocytosis, adenopathy and blue-colored skin papules. Immunophenotyping of blast cells in BM and examination of skin biopsy led to the diagnosis of BPDCN. Treatment with vincristine, cyclophosphamide and doxorubicin was started. After six months, an allogeneic stem cell transplantation was performed with complete remission for 11 months.
Case 2. A 79-year-old female, known with a myelodysplastic syndrome (MDS-EB1), was referred to our hospital with diffuse ecchymosis and worsening pancytopenia. Deterioration of the MDS-EB1 was suspected but examination of BM and skin biopsy led to the diagnosis of BPDCN. Treatment consisted of vincristine and mercaptopurine. She relapsed after a few months and as there were no more therapeutic options, a comfort policy was established.

Methods

Massive Parallel Sequencing (MPS) using a Human Myeloid Neoplasm Qiaseq DNA panel (QIAGEN), was performed with the NextSeq 550 DX (Illumina) aiming to identify variants in 141 myeloid-related genes. Variants were identified with a limit of detection of 2% variant allele frequency (VAF).

Results

Diagnosis of both cases was made based on clinical manifestations, skin biopsy and immunophenotype of the blast cell population, which is characterized by expression of CD4, CD43, CD56, CD123 and TCL1 *(Figure 1.A-B)*. MPS revealed variants in several genes in our cases, including *ASXL1*, *NRAS*, *SRSF2* and *TET2 (Figure 1C)*. These genes, predominantly involved in chromatin regulation and signal transduction, have been identified as recurrently mutated genes in BPDCN.[2,3,4] In one patient, a *IKZF1* variant, which has been described as a key event in BPDCN development, was also found.[4] As this gene is crucial for the differentiation of pDC, it can be expected that its inactivation will disturb the normal development, possibly leading to their clonal expansion.[4]

Conclusion

BPDCN is a rare, poorly understood disease with difficult diagnosis based on morphology and immunophenotyping. Several recurrently mutated genes have recently been identified in BPDCN and these were also found in our two cases. Studies exploring genetic biomarkers, however, are still limited and no common genetic alteration has yet been found explaining the pathogenesis of BPDCN.[2,3,4] In addition, some patients with BPDCN are also affected by other myeloid neoplasms, such as myelodysplastic syndrome and chronic myelomonocytic leukemia, suggesting a clonal relation between those entities.[5] Further exploration of genetic factors determining the origin and clonal evolution is indispensable in the understanding of this disease and could possibly lead to development of more effective treatments.

References:

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[2]*Menezes J., Acquadro F., et al. Exome sequencing reveals novel and recurrent mutations with clinical impact in blastic plasmacytoid dendiritic cell neoplasm. Leukemia. 2014;28:823-829.*
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[4]*Torres A.N.B., Cats D., et al. Whole-genome analysis uncovers recurrent IKZF1 inactivation and aberrant cell adhesion in blastic plasmacytoid dendritic cell neoplasm. Genes Chromosomes Cancer. 2020;59:295-308.*
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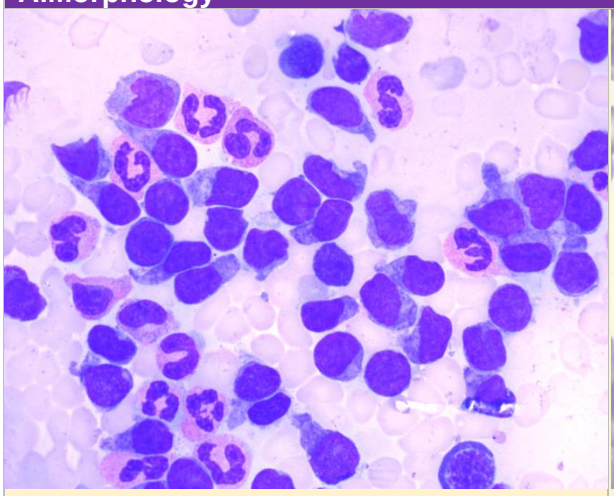
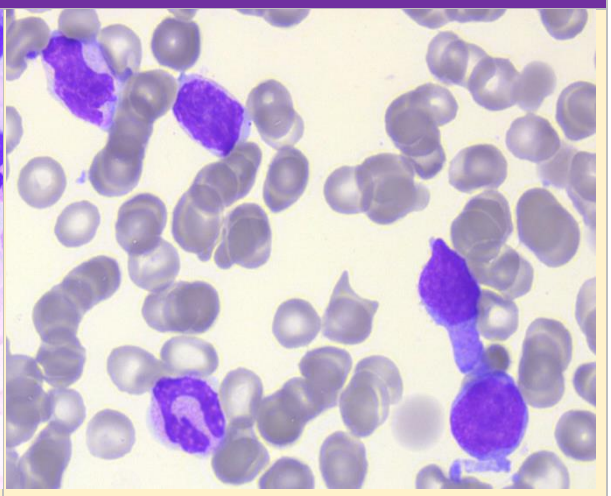
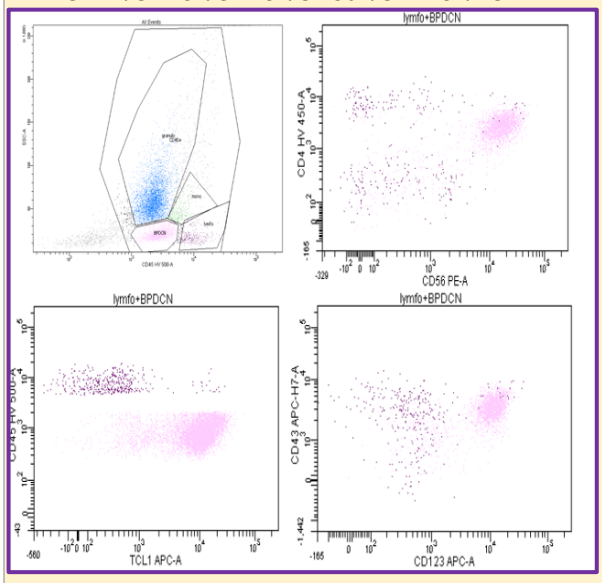
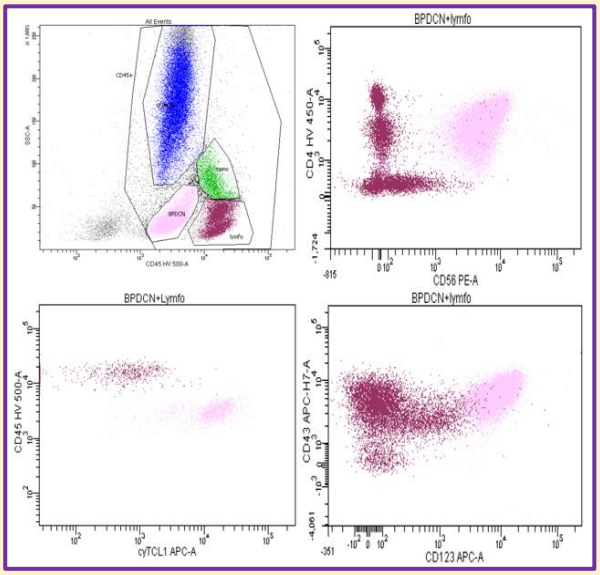
Figure .1: Morphological (A), immunophenotypic (B) and molecular (C) features of blastic plasmacytoid dendritic cell neoplasms: bone marrow of two cases.

Case 1	Case 2
A.Morphology	
	
B.Immunophenotype	
CD4+/CD43+/CD45+/CD56+/CD123+/TCL1+	*CD4+/CD43+/CD45+/CD56+/CD123+/TCL1+*
	
C.Molecular biology	
Two pathogenic variants: ▪ **SRSF2** (c.284C>A p.(Pro95His) 43% VAF) ▪ I**KZF1** (c.1313_1314dupTG p.Arg439Cysfs*22 12% VAF) Two likely pathogenic variants: ▪ **ASXL1** (c.1772dupA p.(Tyr591Ter) 46% VAF) ▪ **NRAS** (c.64C>A p.(Gln22Lys) 30% VAF) Two VUS (variant of unknown significance): ▪ **TET2** (c.5720T>G p.(Met1907Arg) 46% VAF) ▪ **TET2** (c.5582G>T p.(Gly1861Val) 42% VAF) ***(in bold: recurrently mutated genes in BPDCN)***	Three pathogenic variants: ▪ **SRSF2** (c.284C>T p.Pro95Leu 43% VAF) ▪ STXBP2 (c.1444C>T p.Gln482Ter 50% VAF) ▪ **TET2** (c.2877_2883del p.Lys959Asnfs*46 89% VAF) Four likely pathogenic variants: ▪ CBL (c.1212_1223dup p.Cys404_Ser407dup 15% VAF) ▪ **NRAS** (c.175G>A p.Ala59Thr 25% VAF) ▪ **NRAS** (c.176C>G p.Ala59Gly 3.2% VAF) ▪ **TET2** (c.3892T>A p.Cys1298Ser 4.8% VAF) One VUS (variant of unknown significance): ▪ IDH1 (c.301A>T p.Asn101Tyr 47% VAF)