Case Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(2) 1–6

DOI: 10.1177/0300060520982667
journals.sagepub.com/home/imr
SAGE

Blastic plasmacytoid dendritic cell neoplasm with genetic mutations in multiple epigenetic modifiers: a case report

Xinmei Dang*, Di Zhou*, Lingjun Meng and Lintao Bi

Abstract

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, aggressive hematodermic malignancy derived from plasmacytoid dendritic cell precursors. Despite advances in our understanding of tumor cell surface markers, the pathogenesis of BPDCN remains largely unknown. No standard or optimal treatments are available for BPDCN, and the prognosis is usually poor. We report herein a case of BPDCN that harbored multiple genetic mutations in epigenetic modifiers such as *TET2* and *ZRSR2*. Genetic studies in patients with BPDCN may provide insights into the underlying pathogenesis, prediction of clinical prognosis, and development of better targeted therapeutics for this rare clinical entity.

Keywords

Blastic plasmacytoid dendritic cell neoplasm, epigenetic modifier, genetic mutation, methylation, *TET2*, *ZRSR2*

Date received: 24 July 2020; accepted: 1 December 2020

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, clinically aggressive hematodermic neoplasm characterized by skin lesions and bone marrow infiltration with progression to acute leukemia.[1] Several names, including acute agranular

Department of Hematology and Oncology, China-Japan Union Hospital of Jilin University, Changchun, Jilin, China

*These authors contributed equally to this work.

Corresponding author:
Lintao Bi, Department of Hematology and Oncology, China-Japan Union Hospital of Jilin University, 126 Xiantai St, Changchun, Jilin 130033, China.
Email: bilt@jlu.edu.cn

$CD4^+$ natural killer (NK) cell leukemia, blastic NK cell lymphoma, and agranular $CD4^+CD56^+$ hematodermic neoplasm/tumor, have been used to describe this clinical entity as our understanding of the underlying pathogenesis has increased over the last two decades.[2] Following confirmation that the tumor cells were derived from plasmacytoid dendritic cells, the current nomenclature—BPDCN—was recommended by the 2008 World Health Organization classification of myeloid neoplasms and acute leukemia, and BPDCN was listed under the category of acute myeloid leukemia and related neoplasms in 2008.[3] BPDCN was listed as its own category in the 2016 World Health Organization revision.[4] In addition to classical BPDCN, plasmacytoid dendritic cell expansion is frequently observed in patients with acute myeloid leukemia characterized by a high frequency of *RUNX1* mutations.[5] CD123-targeted therapies have been developed or are in development for treatment of BPDCN.[6–8] Despite these advances, the pathogenesis of BPDCN remains elusive.[9] Pathogenic mutations in several genes have been linked to BPDCN.[10–12] Genetic studies may provide insight into the mechanisms underlying the development of BPDCN and the development of better clinical evaluation and therapeutic strategies. We report a case of BPDCN with genetic mutations in multiple epigenetic modifiers.

Case report

A 57-year-old man presented with a 5-month history of multiple nodular lesions over his neck and chest. The nodules were progressively enlarging, and the patient had a fever 2 weeks before admission. He was otherwise well but had a 30 pack-year smoking history. A physical examination on admission found multiple 1- to 2-cm violaceous nodules and reddish papules over his chest (Figure 1a and 1b). Enlarged, nontender lymph nodes up to 2 cm in diameter were palpable in the cervical, inguinal, and axillary areas. Hepatosplenomegaly was also detected by palpation. A complete blood count revealed pancytopenia (hemoglobin of 6.2 g/dL, white blood cell count of 0.45×10^9/L, and platelet count of 8.0×10^9/L) with an increased percentage (53.3%) of lymphocytes. Computed tomography (CT) scans showed multiple pulmonary and mediastinal nodules (Figure 1c) and hepatosplenomegaly with enlarged intra-abdominal lymph nodes (Figure 1d). A lymph node biopsy showed that the tumor cells were positive for CD4, CD56, and CD123. A bone marrow aspirate demonstrated markedly hypercellular marrow with blasts accounting for 89.5% of the nucleated cells. Cytochemical staining revealed that the cells were negative for peroxidase. Flow cytometry of the bone marrow sample revealed 73.8% blasts within the nuclear cell gate. The blasts were positive for CD123, CD38, CD33, CD56, CD303, CD304, HLA-DR, cell leukemia/lymphoma protein 1 (TCL1), and terminal deoxynucleotidyl transferase (TdT), and negative for CD4 and CD13. Chromosome analysis showed a normal male karyotype (46,XY). On the basis of these findings, the patient was diagnosed with BPDCN. Next-generation sequencing of DNA from bone marrow cells showed multiple genetic mutations in epigenetic modifiers, including mutations in *NRAS* (p.G12D), *TET2* (p.C237X and p.K1422S), *NOTCH2* (p.N319S), *SMC3* (p.E688Q), and *ZRSR2* (p.G268D) (Table 1).

The patient received cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy (CHOP), which eliminated most of the skin papules and shrank the cutaneous nodules and lymph nodes. The serum level of lactate dehydrogenase decreased from 261.82 U/L at admission to 193.5 U/L (within the reference range: 80–248 U/L). Treatment also reduced the

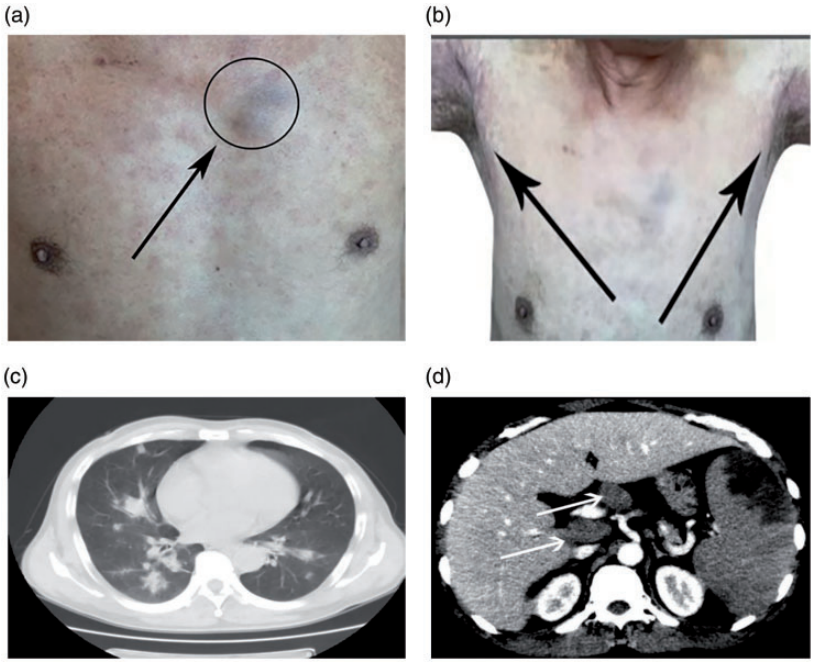

Figure 1. Cutaneous lesions and images of the patient with blastic plasmacytoid dendritic cell neoplasm (BPDCN) Multiple cutaneous nodules and papules were observed over the chest (a) and around the armpits (b). High-resolution computed tomography images showed multiple pulmonary and mediastinal nodules (c) and enlarged intra-abdominal lymph nodes (d).

Table 1. Hot-spot mutation sites closely related to blastic plasmacytoid dendritic cell neoplasm (BPDCN).

Gene	Transcript	Protein change	SNP accession no.	Frequency (%)
NRAS	NM_002524	p.G12D	rs121913237	30.8
TET2	NM_001127208	p.C237X	–	47.1
TET2	NM_001127208	p.K1422Sfs*3	–	46.9
NOTCH2	NM_024408	p.N319S	rs144936899	48.6
SMC3	NM_005445	p.E688Q	rs201162818	49.3
ZRSR2	NM_005089	p.G268D	–	80.9

Transcript numbers refer to GenBank sequences (https://www.ncbi.nlm.nih.gov/).

liver and spleen enlargement, and the patient was discharged. A CT scan performed 1 month after discharge, following development of a limb movement disorder, found multiple intracranial masses, indicating invasion of the central nervous system. The patient refused further treatment and died 1 month later.

Discussion

BPDCN is an exceedingly rare aggressive hematodermic neoplasm that usually occurs in elderly patients.[13] The tumor cells of BPDCN are often positive for CD4, CD56, CD43, CD7, CD68, CD2, and HLA-DR.[14] BPDCN tumor cells are

also usually positive for plasmacytoid dendritic cell-specific surface markers such as CD123, CD303, and CD304.[15] Overexpression of plasmacytoid dendritic cell markers, especially CD303, is valuable for the differential diagnosis. Although the origin and surface biomarkers of BPDCN tumor cells are well established, the underlying pathogenesis remains unclear.

Recently, the genetic mutations associated with BPDCN have received increasing attention.[15] Previous studies showed that patients with BPDCN often have complex karyotypes and chromosomal aberrations, including abnormalities in chromosome regions 5q, 12p13, 13q21, and 6q23-ter.[11,16] Genetic studies have reported that inactivation of tumor suppressors (*RB1*, *TP53*, *CDKN1B*, and *CDKN2A*), activation of oncogenes (*KRAS*, *NRAS*, *HES6*, *RUNX2*, and *FLT3*), and mutations in epigenetic modifiers (*TET2*, *TET1*, *DNMT3A*, *IDH1*, and *IDH2*) are frequently observed in BPDCN.[10,16–19] Our patient had a normal karyotype but mutations in multiple epigenetic modifiers, including *NRAS*, *TET2*, *NOTCH2*, *SMC3*, and *ZRSR2*. This mutational pattern supports a myeloid lineage derivation of this neoplasm.[20] As reported in previous studies,[17] *TET2* and *ZRSR2* are the most mutated genes in BPDCN. An epigenetic modifier, *TET2* encodes the protein Tet methylcytosine dioxygenase 2, which catalyzes the conversion of methylcytosine to 5-hydroxymethylcytosine.[16] Imbalance between DNA methylation and demethylation may contribute to the development of BPDCN.

BPDCN has no uniform or standard treatment. CHOP was chosen for this patient on basis of the clinical presentation and comorbidities. The patient initially responded well to the treatment, but relapse occurred quickly after discharge. Mutations in DNA methylation genes indicate a poor prognosis in patients with BPDCN.[10] In our case, mutations in multiple genetic modifier genes likely contributed to the patient's poor prognosis and short survival.

Mutations in genetic modifiers are not only useful to predict prognosis but also to help in development of targeted therapeutics. Deletion of *TET2* leads to a dramatic reduction in the 5-hydroxymethylcytosine levels and a concomitant increase in 5-methylcytosine.[21] The hypomethylating agents azacytidine and decitabine have been shown to inhibit disease progression and improve survival in models of BPDCN.[22] Several clinical trials have found that hypomethylating agents achieved promising clinical outcomes in relapsed or refractory patients with BPDCN.[23–25] Therefore, hypomethylating agents might be a better choice for BPDCN patients harboring mutations in *TET2*.

In conclusion, we report a case of BPDCN that was associated with mutations in multiple epigenetic modifiers. Genetic studies on BPDCN may provide insights into the underlying pathogenesis, prediction of clinical prognosis, and development of better targeted therapeutics for this rare clinical entity.

Authors' contributions

LB planned the research; XD, DZ, LM, and LB collected the data; LB wrote the manuscript; and all authors read and approved the manuscript.

Ethics statement

The study was approved by the ethics committee of the China-Japan Union Hospital of Jilin University. The patient provided written consent for publication of this case report.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This work was supported by the Science and Technology Development Project of JiLin Province (20180101124JC), the Special Project

for Health Research of JiLin Province (2018SCZ031, 2019SCZ055), and the Health Technology Innovation Project of JiLin Province (3D517ED43430).

ORCID iD

Lintao Bi https://orcid.org/0000-0003-2931-5762

References

1. Pagano L, Valentini CG, Grammatico S, et al. Blastic plasmacytoid dendritic cell neoplasm: diagnostic criteria and therapeutical approaches. *Br J Haematol* 2016; 174: 188–202.
2. Laribi K, Denizon N, Besancon A, et al. Blastic plasmacytoid dendritic cell neoplasm: from origin of the cell to targeted therapies. *Biol Blood Marrow Transplant* 2016; 22: 1357–1367.
3. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood* 2009; 114: 937–951.
4. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016; 127: 2391–2405.
5. Xiao W, Chan A, Waarts MR, et al. Plasmacytoid dendritic cell expansion defines a distinct subset of RUNX1 mutated acute myeloid leukemia. *Blood* 2020: blood.2020007897.
6. Testa U, Pelosi E and Castelli G. CD123 as a therapeutic target in the treatment of hematological malignancies. *Cancers (Basel)* 2019; 11: 1358.
7. Pemmaraju N, Lane AA, Sweet KL, et al. Tagraxofusp in blastic plasmacytoid dendritic-cell neoplasm. *N Engl J Med* 2019; 380: 1628–1637.
8. Pemmaraju N and Konopleva M. Approval of tagraxofusp-erzs for blastic plasmacytoid dendritic cell neoplasm. *Blood Adv* 2020; 4: 4020–4027.
9. Sapienza MR, Pileri A, Derenzini E, et al. Blastic plasmacytoid dendritic cell neoplasm: state of the art and prospects. *Cancers (Basel)* 2019; 11: 595.
10. Menezes J, Acquadro F, Wiseman M, et al. Exome sequencing reveals novel and recurrent mutations with clinical impact in blastic plasmacytoid dendritic cell neoplasm. *Leukemia* 2014; 28: 823–829.
11. Tang Z, Tang G, Wang SA, et al. Simultaneous deletion of 3'ETV6 and 5'EWSR1 genes in blastic plasmacytoid dendritic cell neoplasm: case report and literature review. *Mol Cytogenet* 2016; 9: 23.
12. Ladikou E, Ottolini B, Nawaz N, et al. Clonal evolution in the transition from cutaneous disease to acute leukemia suggested by liquid biopsy in blastic plasmacytoid dendritic cell neoplasm. *Haematologica* 2018; 103: e196–e199.
13. Pileri A, Delfino C, Grandi V, et al. Blastic plasmacytoid dendritic cell neoplasm (BPDCN): the cutaneous sanctuary. *G Ital Dermatol Venereol* 2012; 147: 603–608.
14. Lim MS, Lemmert K and Enjeti A. Blastic plasmacytoid dendritic cell neoplasm (BPDCN): a rare entity. *BMJ Case Rep* 2016; 2016: bcr2015214093.
15. Sapienza MR, Abate F, Melle F, et al. Blastic plasmacytoid dendritic cell neoplasm: genomics mark epigenetic dysregulation as a primary therapeutic target. *Haematologica* 2019; 104: 729–737.
16. Alayed K, Patel KP, Konoplev S, et al. TET2 mutations, myelodysplastic features, and a distinct immunoprofile characterize blastic plasmacytoid dendritic cell neoplasm in the bone marrow. *Am J Hematol* 2013; 88: 1055–1061.
17. Jardin F, Ruminy P, Parmentier F, et al. TET2 and TP53 mutations are frequently observed in blastic plasmacytoid dendritic cell neoplasm. *Br J Haematol* 2011; 153: 413–416.
18. Jardin F, Callanan M, Penther D, et al. Recurrent genomic aberrations combined with deletions of various tumour suppressor genes may deregulate the G1/S transition in CD4+CD56+ haematodermic neoplasms and contribute to the aggressiveness of the disease. *Leukemia* 2009; 23: 698–707.
19. Sapienza MR, Fuligni F, Agostinelli C, et al. Molecular profiling of blastic plasmacytoid

dendritic cell neoplasm reveals a unique pattern and suggests selective sensitivity to NF-kB pathway inhibition. *Leukemia* 2014; 28: 1606–1616.
20. Abdel-Wahab O and Levine RL. Mutations in epigenetic modifiers in the pathogenesis and therapy of acute myeloid leukemia. *Blood* 2013; 121: 3563–3572.
21. Li Z, Cai X, Cai CL, et al. Deletion of Tet2 in mice leads to dysregulated hematopoietic stem cells and subsequent development of myeloid malignancies. *Blood* 2011; 118: 4509–4518.
22. Kalac M, Scotto L, Marchi E, et al. HDAC inhibitors and decitabine are highly synergistic and associated with unique gene-expression and epigenetic profiles in models of DLBCL. *Blood* 2011; 118: 5506–5516.
23. DiNardo CD, Rausch CR, Benton C, et al. Clinical experience with the BCL2-inhibitor venetoclax in combination therapy for relapsed and refractory acute myeloid leukemia and related myeloid malignancies. *Am J Hematol* 2018; 93: 401–407.
24. Grushchak S, Joy C, Gray A, et al. Novel treatment of blastic plasmacytoid dendritic cell neoplasm: A case report. *Medicine (Baltimore)* 2017; 96: e9452.
25. Agha ME, Monaghan SA and Swerdlow SH. Venetoclax in a patient with a blastic plasmacytoid dendritic-cell neoplasm. *N Engl J Med* 2018; 379: 1479–1481.