A neonatal case of congenital Blastic plasmacytoid dendritic cell neoplasm with KMT2C gene duplication

jian li[1], Jun wang[1], Liucheng Rong[1], Li Zhou[1], Yue Hong[1], Liwen Zhu[1], and Yongjun Fang[1]

[1]Nanjing Medical University

June 30, 2022

Abstract

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematologic neoplasm derived from plasmacytoid dendritic cell precursors. The malignancy was characterized by cutaneous and bone marrow involvement and leukemic spread,predominantly involving elderly patients. Pediatric cases of BPDCN are much fewer reported in the literature, making the management of pediatric BPDCN challenging. We report a congenital BPDCN patient who manifested with neutropenia and nodular skin lesions. Whole-exome sequencing suggests the presence of kmt2c gene duplication. She died four months after diagnosis. This case report reminds clinicians, especially neonatologists, to consider the possibility of BPCDN when finding neonates present with rash(such as purplish nodules, bruiselike macules) and a cytopenia. In addition, this study suggests that the KMTC2 gene may play a vital role in the pathogenesis of BPDCN.

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Jian Li[1*] , Jun Wang[1*], Liucheng Rong[1], Li Zhou[1],Yue Hong[1], Liwen Zhu[1], Yongjun Fang[1#]

1.Department of Hematology and Oncology, Children's Hospital of Nanjing Medical University, Nanjing, China; Key Laboratory of Hematology, Nanjing Medical University Nanjing, China 210008

Email: Jian Li: wylj25210@sina.com; Jun Wang: wangjun_1008@189.cn; Liucheng Rong: danqifly@sina.com; Li Zhou:zhoulinjey@163.com;Yue Hong:*812833832@qq.com;* Liwen Zhu:15105159029@163.com; Yongjun Fang:fyj322@189.cn.

*Equal contributors.

 # Correspondence to

Dr. Yongjun Fang, Department of Hematology and Oncology, Children's Hospital of Nanjing Medical University, Code 72, Guangzhou Road, Nanjing city, Jiangsu province, China. Tel.:18951769586; E-mail: fyj322@189.cn.

Acknowledgments: We gratefully acknowledge the pathologists in our hospital for their expertise and generous provision of data.

Disclosure of conflict of interest: None

Competing interests: The authors have no competing interests.

Statement: The parents of this infant provided informed consent for publication of the case. The study was approved by the ethics and plan review committee of Nanjing Medical University.

Text word count: 1008;

Abstract word count: 128;

Brief running title: *congenital BPDCN with KMT2C gene duplication*

Key words: Blastic plasmacytoid dendritic cell neoplasm (BPDCN); neonatal; KMT2C gene

Tables: 0

Figures: 2

Abbreviations	Abbreviations
BPDCN	Blastic plasmacytoid dendritic cell neoplasm
KMT2C	lysine-specific methyltransferase 2C
ANC	absolute neutrophil count
WBC	White blood cell
LDH	Lactate dehydrogenase
WHO	World Health Organization
HLA	Human leukocyte antigen

Abstract:

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematologic neoplasm derived from plasmacytoid dendritic cell precursors. The malignancy was characterized by cutaneous and bone marrow involvement and leukemic spread,predominantly involving elderly patients. Pediatric cases of BPDCN are much fewer reported in the literature, making the management of pediatric BPDCN challenging. We report a congenital BPDCN patient who manifested with neutropenia and nodular skin lesions. Whole-exome sequencing suggests the presence of kmt2c gene duplication. She died four months after diagnosis. This case report reminds clinicians, especially neonatologists, to consider the possibility of BPCDN when finding neonates present with rash(such as purplish nodules, bruiselike macules) and a cytopenia. In addition, this study suggests that the KMTC2 gene may play a vital role in the pathogenesis of BPDCN.

Kewords: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) ;**neonatal** ; **KMT2C gene**

Introduction:

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare myeloid malignancy with non-pruritic, violaceous, and papulo-nodular skin lesions, as well as the involvement of the bone marrow and lymph nodes. BPDCN is recognized as a distinct acute leukemia entity by the WHO's 2016 classification of hematological neoplasms[1]. BPDCN is more common among the elderly, with a median age of 65 years, while in children, particularly infants are much rare[2]. Neoplastic cells in BPDCN are now thought to be derived from plasmacytoid dendritic cells, as marked by the co-expression of CD4 and CD56 without any lineage-specific markers other than plasmacytoid dendritic cell antigen-2 (BDCA-2, CD303) and interleukin-3 receptor a chain (CD123), which are markers for plasmacytoid dendritic cells, and the absence of features for B, T, myeloid or monocytic. The etiology and pathophysiology of BPDCN remain mostly unknown due to the scarcity of research reports to date.

Herein, we report a rare case of inherited BPDCN who had cutaneous and peripheral blood and bone marrow involvement and whole-exome sequencing suggesting the presence of a KMT2C gene duplication; the infant died rapidly after the parents abandoned treatment for the diagnosis.

Case presentation

A 48-day-old female infant was firstly hospitalized at Nan children Hospital of Nanjing medical University (Nanjing, China) in April, 2021, with a complaints of increasing pallor sign from birth. Her mother had a history of PIH during pregnancy. On the first day after birth, the newborn was treated for fever in a local hospital. Blood routine tests showed neutropenia with absolute neutrophil count (ANC) $0.04 \times 109/l$ with no periodic changes, mild anemia, and normal platelet count. She also presented with non-pruritic, ecchymosis skin lesions on the head,chest, trunk, and extremities after birth but got a self-remission soon. At this time,

laboratory evaluation demonstrated marked neutropenia again with severe anemia (WBC, 0.91 × 109 /L; ANC ,0.02 × 109 /L,hemoglobin, 3.3 g/dL; platelets, 212 × 109 /L). Coombs test were negative. LDH level was normal. Physical examination revealed severe anemia, while no skin lesions and lymphadenopathy were found.

She was treated by infusion of erythrocytes but complicated with a severe allergic reaction. Blood transfusion was immediately stopped, epinephrine and hydrocortisone were given, and transferred to ICU for other life-supporting treatment.Anemia screening revealed ferritin 524ng/ml, folic acid and vitamin B12 at normal levels; reticulocyte ratio and absolute count were within the normal range;We performed bone marrow biopsy and without positive result. Based on the above examination and the past medical history of the infant, we first ruled out hemolytic anemia and nutritional deficiency anemia and chronic disease anemia;We also completed peripheral blood whole exon gene sequencing to rule out inherited metabolic diseases; while waiting for the gene results, we continued the infant's red blood cell transfusion treatment and administered methylprednisolone before the transfusion to prevent allergic reactions; the patient's granulocyte deficiency status gradually returned to normal after glucocorticoid administration. Therefore, the infant was discharged from our hospital for the first time and was instructed to be followed up on an outpatient basis. One week after discharge, the child's anemia worsened again. During this recurrence, he was treated with methylprednisolone 10mg once a day daily for four weeks, and hemoglobin gradually recovered again .At this point, the whole-exon gene sequencing results suggested a mutation in the KMT2C gene[**Figure2**] , but this was not sufficient to explain the symptoms of allocytopenia in the infant.

She experienced a worsening bruise-purple nodular skin rash, and pancytopenia two months later. BM smears demonstrated that blastic or abnormal cells accounted for 3.5% of the nucleated cells[**Figure1 C/D**] . Flow cytometry revealed a small population of blasts in the dim CD45 positive blast gate that were positive for CD4, CD56, CD123, and HLA-DR but the negative expression of B, T, myeloid marker, and TdT[**Figure2**] . A skin biopsy was done, and the results revealed diffuse dermal infiltrate with blast-like cells extending to the hypodermis. Immunohistochemistry revealed cells positive for CD4, CD31,CD68,CD43,CD56, and CD123 but negative for CD3,CD20, MPO, TDT, CD34, and EBER, confirming the blastic plasmacytoid dendritic cell neoplasm diagnosis[**Figure1**] . Her parents disregarded the advice to take chemotherapy, and she died just a month after being diagnosed.

Discussion

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare myeloid malignancy with non-pruritic, violaceous, and papulo-nodular skin lesions, as well as the involvement of the bone marrow and lymph nodes. The WHO's 2016 classification of hematological neoplasms recognizes BPDCN as an unique acute leukemia entity. BPDCN has been reported in infants and children, even though it primarily affects older persons with a median age of 65 years. It is typically characterized by involvement of the skin that rapidly evolves and compromise organs such as bone marrow, lymph nodes, viscera, and, to a lesser extent, the central nervous system (CNS)[3].

With just a few research reports to date, the etiology and pathophysiology of BPDCN are largely unclear. BPDCN is frequently linked with a complicated karyotype, numerous tumor suppressor gene deletions, and abnormalities in the DNA methylation or chromatin remodeling pathways.[4]. In the case of Congenital Blastic Plasmacytoid Dendritic Cell Neoplasm, Kiriko Tokuda et al. described an infant with CLTC-ALK Fusion, which is considered a primary event[5].

In various epithelial and myeloid cells, the lysine-specific methyltransferase 2C (KMT2C/MLL3) is a possible tumor suppressor. KMT2C has also played a tumor suppressor role in acute myeloid leukemia (AML) and urothelial carcinogenesis in mice[6-7]. Its involvement in BPDCN carcinogenesis, however, is mainly unknown. Toya T et al. reported the first MLL-ENL rearrangement in a 45-year-old male patient in 2012[8]. In 2015, Naery Yang et al. said the first pediatric case of BPDCN with a *KMT2A (MLL)-MLLT1* rearrangement[9]. Four juvenile patients of BPDCN with KMT2C gene mutation were recently described by Chan Liao et al., emphasizing the possible critical roles of KMT2 family genes in BPDCN[10].

Our study reports the first newborn BPDCN patient with KMT2C gene duplication. It is crucial to understand the pathophysiology of this rare disease, and more research into the gene expression profile and pathogenesis of BPDCN in pediatric patients may drastically enhance prognosis.

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Figure legend

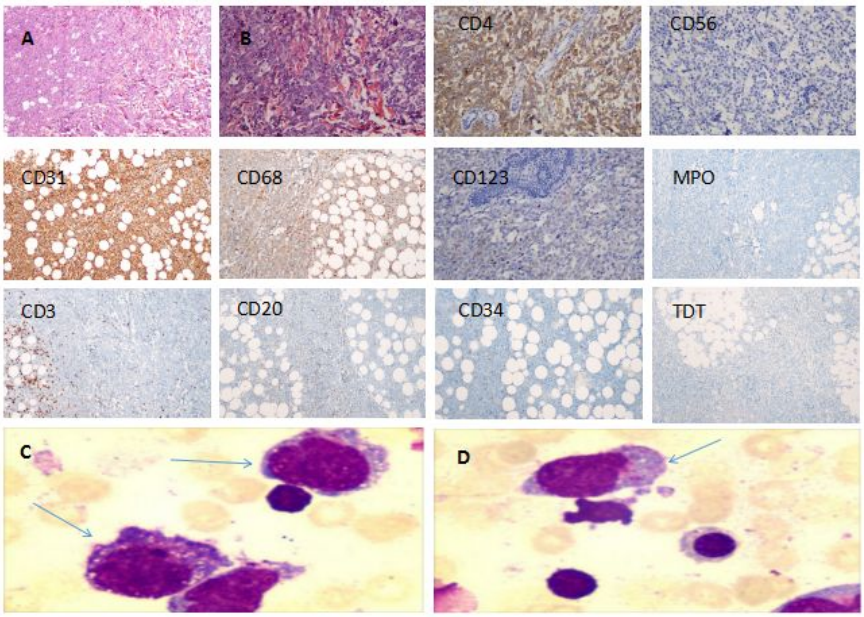

Figure 1: Skin biopsy H&E showed diffuse dermal infiltrate with blast-like cells extending to the hypodermis(A40x and B100x). Bone marrow aspirate (100*10x) showing infiltration with atypical cells with an eccentric nucleus, fine nuclear chromatin, and weakly basophilic, easily visible vacuoles in the cytoplasm, agranular cytoplasm with pseudopods (C/D); Immunohistochemistry tumor cells expressed CD4、CD56、CD31、CD43, CD68, BCL-2(not shown), and CD123 but were negative for myeloperoxidase (MPO), CD3, CD20, TDT, CD34, and EBV-encoded RNA (EBER in situ hybridization, not shown).

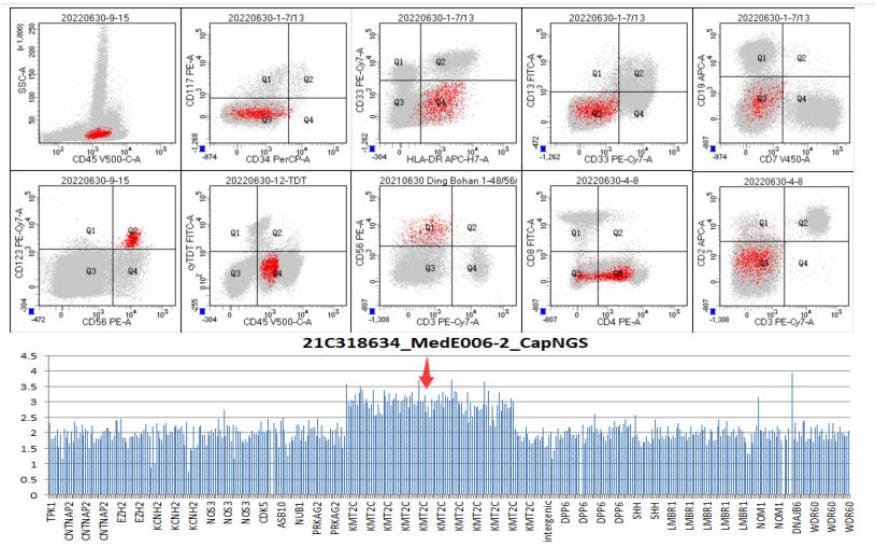

Figure 2:

Flow cytometry profile of blasts coexpressing CD45/CD4/CD56/CD123/HLA-DR; NGS results showed a duplication in the KMT2C gene.

Foundation: This research was supported by Natural Science Foundation of Jiangsu Province (BK20211009)

and Nanjing Medical Science and technique Development foundation(No.QRX 17074)

Author contributions

Patient Management and Data curation: Jian Li,Jun Wang, Yue Hong, Liwen Zhu and Li Zhou. Project administration:Yongjun Fang. Writing—original draft: Jian Li and Jun Wang;Writing—review and editing: Yongjun Fang. All authors contributed to the article and approved the submitted version.