Case Reports in Oncology

Case Rep Oncol 2023;16:728–732
DOI: 10.1159/000532003
Received: February 9, 2023
Accepted: July 3, 2023
Published online: August 25, 2023

Case Report

Family Aggregation of Hematological Malignancies Discovered from an Acute Myeloid Leukemia Patient with STK11 and THBD Gene Mutation

Nan Zhang Xiao-juan Miao Yan-rong Shuai Hao Yao Fang-Yi Fan Yi-lan Liu

Department of Hematology, People's Liberation Army The General Hospital of Western Theater Command, Chengdu, China

Keywords

Serine/threonine kinase 11 · Family aggregation · Hematological malignancies · Acute myeloid leukemia · Thrombomodulin

Abstract

Acute myeloid leukemia (AML) is a large class of heterogeneous hematological malignancies with the highest incidence rate in acute leukemia. Its pathogenesis is still unclear, which may be related to genetics. According to the latest AML NCCN guidelines, genes involved in AML family genetic changes include RUNX1, ANKRD26, CEBPA. Finding new genes related to AML genetics is of great significance for predicting the prognosis of patients, developing targeted drugs, and selecting transplant donors. Here, we report a case of adult female AML patient whose three relatives suffered from hematological malignancies, including Waldenstrom macroglobulinemia, NK/T-cell lymphoma, and angioimmunoblastic T-cell lymphoma. The screen for genetic susceptibility genes related to blood and immune system diseases was carried out, and the result showed that the patient herself, her son, her daughter, and her two cousins all had STK11 p.F354L and/or THBD p.D486Y mutations. At present, there is no research or case report on the relationship between STK11/THBD and family aggregation of hematological malignancies. We report for the first time that an AML patient with STK11 and THBD mutations has a family aggregation of hematological malignancies, and consider that STK11 and THBD may be related to family genetic changes which ultimately cause the family aggregation of hematological malignancies.

Correspondence to:
Yi-lan Liu, 114978818@qq.com;
Fang-Yi Fan, 834525469@qq.com;
Hao Yao, yaohao9001@163.com

Case Rep Oncol 2023;16:728–732
DOI: 10.1159/000532003

Introduction

Acute myeloid leukemia (AML) is a large class of heterogeneous hematological malignancies with the highest incidence rate in acute leukemia. The overall prognosis is poor, and the 5-year overall survival rate is about 28% [1, 2]. Its pathogenesis is still unclear, which may be related to genetics. According to the latest AML NCCN guidelines, genes involved in AML family genetic changes include RUNX1, ANKRD26, CEBPA, DDX41, ETV6, GATA2, MBD4, MECOM/EVI1, SAMD9/SAMD9L, TERC/TERT, and ATG2B/GSKIP. Finding new genes related to AML genetics is of great significance for predicting the prognosis of patients, developing targeted drugs, and selecting transplant donors.

Here, we report a case of adult female AML patient whose three relatives suffered from hematological malignancies, including Waldenstrom macroglobulinemia, NK/T-cell lymphoma, and angioimmunoblastic T-cell lymphoma. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000532003). During the process of searching for suitable transplant donors, we screened for genetic susceptibility genes related to blood and immune system diseases, and found that the patient herself, her son, her daughter, and her two cousins all had STK11 p.F354L and/or THBD p.D486Y mutations. Since 3 relatives of the patient had hematological malignancies, and this patient herself and her four relatives all had STK11 and/or THBD mutations, we consider that STK11 and THBD may be related to family genetic changes which ultimately cause the family aggregation of hematological malignancies. At present, there is no research or case report on the relationship between STK11/THBD and family aggregation of hematological malignancies. We report for the first time that an AML patient with STK11 and THBD mutations has a family aggregation of hematological malignancies.

Case Presentation

A 38-year-old female patient was diagnosed as having "CBFbeta-MYH11-positive AML with NRAS/LNK mutation" in May 2021. Bone marrow smears showed 20% of primordial granulocytes and 24.5% of promyelocytes. Flow cytometry of bone marrow showed that 39.5% of the nuclear cells were abnormal primitive cells. The karyotype was 46, XX, inv (16) (p13q22) [20]. The fusion gene was found to be CBFbeta-MYH11-positive. NRAS and LNK were mutated, with mutation frequencies of 43.2% and 47.9%, respectively. After a course of IDA (idarubicin and cytarabine) chemotherapy, the patient was evaluated as morphologically complete remission and minimal residual disease (MRD) positive (CBFbeta-MYH11 quantitative was 0.09%). After 2 cycles of high-dose cytarabine and 1 cycle of BCL2 inhibitor + azacitidine chemotherapy, MRD was still positive (CBFbeta/MYH11 quantitative was 0.2%). After the follow-up oral treatment of BCL2 inhibitor + dasatinib, MRD turned negative and then became positive again. Twice lumbar puncture and intrathecal injection operations were performed during this period, and no abnormal cells were found in the cerebrospinal fluid.

In the process of asking about the family history of the patient, we found that there were 3 patients with hematological malignancies in the patient's family, including two sisters and 1 brother of the patient's father. The patient's father's two sisters have Waldenstrom macroglobulinemia and NK/T-cell lymphoma, respectively, and one brother has angioimmunoblastic T-cell lymphoma (Fig. 1). Considering the possible family aggregation history of hematological malignancies of this patient, we screened genetic susceptibility genes related to blood and immune system diseases in order to find suitable transplant donors, and found that

Case Rep Oncol 2023;16:728–732
DOI: 10.1159/000532003

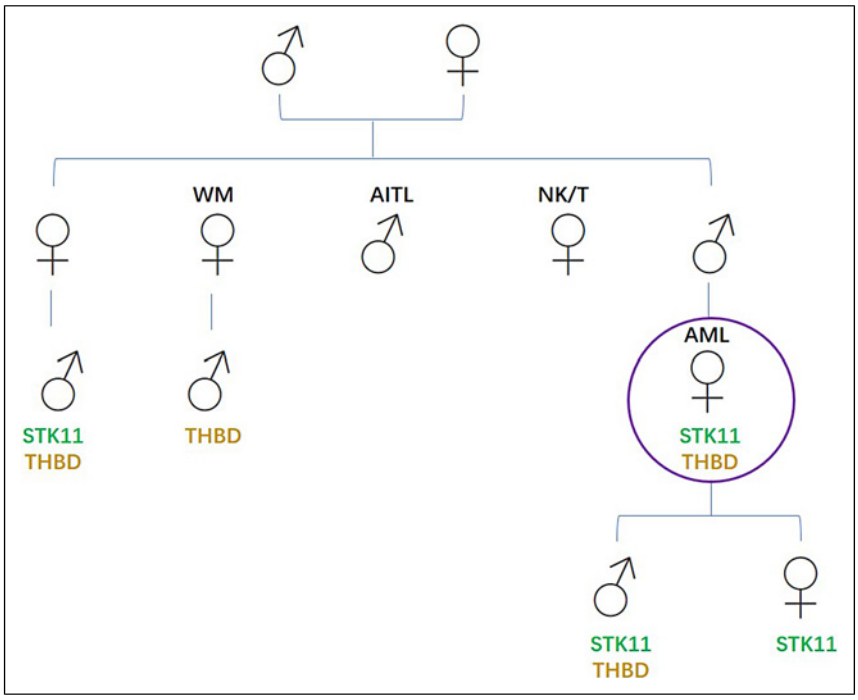

Fig. 1. Genetic map centered on the AML patient. The AML patient's father's two sisters have WM and NK/T, respectively, and one brother has AITL. The patient herself, her son, her daughter, and her two cousins had STK11 p.F354L and/or THBD p.D486Y mutations. The female with purple circle is this AML patient. WM, Waldenstrom macroglobulinemia; NK/T, NK/T-cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma.

the patient herself, her son, her daughter, and her two cousins all had STK11 p.F354L and/or THBD p.D486Y mutations (Fig. 1). At present, the patient is undergoing continuous treatment and preparing for allogeneic hematopoietic stem cell transplantation.

Discussion

THBD gene is located in the first band of the short arm 1 region of chromosome 20 and encodes thrombomodulin, which is an endothelium-specific type 1 membrane receptor. The junction of thrombomodulin and thrombin lead to the activation of protein C, which in turn degrades coagulation factors Va and vllla. The abnormal function of thrombomodulin is related to the susceptibility to atypical hemolytic uremic syndrome (aHUS) and thrombosis. Among them, the susceptibility of aHUS is mostly manifested as autosomal dominant inheritance. THBD p.D486Y mutation can cause aspartic acid at 486 position to become tyrosine, which is related to the susceptibility of aHUS. Besides aHUS, a study reported that THBD mutation exists in families with bleeding events [3]. In AML, it has been reported that recombinant human soluble thrombomodulin can be used to treat AML patients with DIC [4–6]. Kojima et al. [7] reported that recombinant human soluble thrombomodulin can prevent retinoic acid-related differentiation syndrome. At present, there is no report on the correlation between THBD and the pathogenesis of AML.

STK11 gene is located in the third band of the short arm 1 region of chromosome 19, and it encodes a protein that is a member of the serine/threonine kinase family. STK11 gene plays a role in cell metabolism, polarity, apoptosis, and DNA damage response, and its functional abnormalities are related to breast cancer, ovarian cancer, NSCLC, melanoma, juvenile polyp syndrome, and Peutz-Jeghers syndrome (PJS) [8]. Among them, PJS is clinically autosomal dominant inheritance. STK11

p.F354L mutation can cause phenylalanine at 354 position to become leucine. STK11 p.F354L mutation was detected in PJS patients, which led to the loss of cell polarity and the decrease of AMPK activity, thus affecting the downstream pathway of AMPK [9]. It is speculated that this mutation is related to the development of malignant tumors [9]. Besides PJS, STK11 has also been reported to be genetically related to pancreatic cancer [10, 11] and breast cancer [12] families.

A clinical retrospective analysis has reported that a pathogenic polymorphism Phe354Leu of STK11 is detected in 7% of 85 AML patients, and patients with Phe354Leu polymorphism diagnosed at younger ages had a worse overall survival [13]. Some basic studies have also reported the role of STK11 in AML. For example, Green et al. [14] reported that STK11/AMPK/TSC tumor suppressor axis can be activated by the biguanide molecule metformin, resulting in a specific inhibition of mammalian target of rapamycin catalytic activity. The inhibition of mammalian target of rapamycin reduces the translation of mRNA molecules encoding oncogenic proteins, resulting in a strong antileukemic activity against primary AML cells. Christian Marinaccio found that loss of STK11 leads to stabilization of HIF1a and promotes the disease progression of the myeloproliferative neoplasms to AML, indicating that STK11 is a tumor suppressor in the myeloproliferative neoplasms [15]. By contrary, Yusuke Tarumoto reported that STK11 and its salt-inducible kinase effectors (SIK3) plays an essential role to maintain MEF2C function which is an essential transcription factor for the proliferation of leukemia cells [16]. Huihan Wang found that LKB1 downregulation can suppress the long-term proliferation of leukemia stem cells (LSCs), induce LSCs into G2/M phase, and enhance the sensitivity of LSCs to chemotherapy [17].

At present, there is no research or case report on the relationship between STK11/THBD and family aggregation of hematological malignancies. We report for the first time that an AML patient with STK11 and THBD mutations has a family aggregation of hematological malignancies, and consider that STK11 and THBD may be related to family genetic changes which ultimately cause the family aggregation of hematological malignancies. More clinical case studies and basic experiments are needed.

Statement of Ethics

This study protocol was reviewed and the need for approval was waived by the Ethics Committee of People's Liberation Army, the General Hospital of Western Theater Command. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. The authors certify that they have obtained all appropriate patient consents. The patient knows that his name and initial will not be published, and the author will try to hide the patient's identity, but anonymity cannot be guaranteed. The authors all agree to publication.

Conflict of Interest Statement

The authors declare no conflict of interest.

Funding Sources

We gratefully acknowledge the financial support provided by the Natural Science Foundation of Sichuan Province (Grant No. 2022NSFSC1330 and 2021YJ0145); The incubation program of General Hospital of Western Theater command (Grant No. 2021-XZYG-C46) and The general program of General Hospital of Western Theater Command (Grant No. 2021-XZYG-B32).

Author Contributions

N.Z. performed the clinical data. X.-J.M. performed clinical treatment. Y.-R.S. and F.-Y.F. performed the public dataset analysis. H.Y. and Y.-L.L. supervised the whole study and wrote the paper. The author(s) read and approved the final manuscript.

Data Availability Statement

The data supporting the conclusions of this article are provided in this article. In addition, all data from this study can be obtained from the corresponding author upon reasonable request.

References

1 Newell LF, Cook RJ. Advances in acute myeloid leukemia. BMJ. 2021;375:n2026.
2 Aureli A, Marziani B, Sconocchia T, Del Principe MI, Buzzatti E, Pasqualone G, et al. Immunotherapy as a turning point in the treatment of acute myeloid leukemia. Cancers. 2021;13(24):6246.
3 Maclachlan A, Dolan G, Grimley C, Watson SP, Morgan NV; On Behalf Of The UK Gapp Study Group. Whole exome sequencing identifies a mutation in thrombomodulin as the genetic cause of a suspected platelet disorder in a family with normal platelet function. Platelets. 2017;28(6):611–3.
4 Ikezoe T. Pathogenesis of disseminated intravascular coagulation in patients with acute promyelocytic leukemia, and its treatment using recombinant human soluble thrombomodulin. Int J Hematol. 2014;100(1):27–37.
5 Asakura H, Takahashi H, Tsuji H, Matsushita T, Ninomiya H, Honda G, et al. Post-marketing surveillance of thrombomodulin alfa, a novel treatment of disseminated intravascular coagulation: safety and efficacy in 1,032 patients with hematologic malignancy. Thromb Res. 2014;133(3):364–70.
6 Matsushita T, Watanabe J, Honda G, Mimuro J, Takahashi H, Tsuji H, et al. Thrombomodulin alfa treatment in patients with acute promyelocytic leukemia and disseminated intravascular coagulation: a retrospective analysis of an open-label, multicenter, post-marketing surveillance study cohort. Thromb Res. 2014;133(5):772–81.
7 Kojima S, Nishioka C, Chi S, Yokoyama A, Ikezoe T. In vitro studies on the role of recombinant human soluble thrombomodulin in the context of retinoic acid mediated APL differentiation syndrome. Leuk Res. 2017;63:1–9.
8 Park JG, Kim IJ. [Hereditary colorectal cancer]. Korean J Gastroenterol. 2005;45:78–87.
9 Bourouh M, Marignani PA. The tumor suppressor kinase LKB1: metabolic nexus. Front Cell Dev Biol. 2022;10:881297.
10 Hruban RH, Canto MI, Griffin C, Kern SE, Klein AP, Laheru D, et al. Treatment of familial pancreatic cancer and its precursors. Curr Treat Options Gastroenterol. 2005;8(5):365–75.
11 Hruban RH, Klein AP, Eshleman JR, Axilbund JE, Goggins M. Familial pancreatic cancer: from genes to improved patient care. Expert Rev Gastroenterol Hepatol. 2007;1:81–8.
12 Wendt C, Margolin S. Identifying breast cancer susceptibility genes: a review of the genetic background in familial breast cancer. Acta Oncol. 2019;58(2):135–46.
13 Yang MY, Hsiao HH, Liu YC, Hsu CM, Lin SF, Lin PM. Phe354Leu polymorphism of LKB1 is a potential prognostic factor for cytogenetically normal acute myeloid leukemia. In Vivo. 2017;31(5):841–7.
14 Green AS, Chapuis N, Maciel TT, Willems L, Lambert M, Arnoult C, et al. The LKB1/AMPK signaling pathway has tumor suppressor activity in acute myeloid leukemia through the repression of mTOR-dependent oncogenic mRNA translation. Blood. 2010;116(20):4262–73.
15 Marinaccio C, Suraneni P, Celik H, Volk A, Wen QJ, Ling T, et al. LKB1/STK11 is a tumor suppressor in the progression of myeloproliferative neoplasms. Cancer Discov. 2021;11(6):1398–410.
16 Tarumoto Y, Lu B, Somerville TDD, Huang YH, Milazzo JP, Wu XS, et al. LKB1, salt-inducible kinases, and MEF2C are linked dependencies in acute myeloid leukemia. Mol Cell. 2018;69(6):1017–27.e6.
17 Wang H, Wang X, Xin N, Qi L, Liao A, Yang W, et al. Live kinase B1 maintains CD34(+)CD38(−) AML cell proliferation and self-renewal. Mol Cell Biochem. 2017;434(1–2):25–32.