ETV6-NTRK3 is Associated With Trisomy 8 and Sensitive to TRK Inhibitor in Hematologic Malignancy: Case Report of a Refractory AML and Review of the Literature

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Case report

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Abstract

Background: The *ETV6-NTRK3* fusion transcript has been found to recurrently identified in both solid tumors and leukemias. It has attracted a lot of interest for the clinical targeted therapy and genetic features in *ETV6-NTRK3* positive solid tumors. While the t(12;15)(p13;q25)/*ETV6-NTRK3* is a rare genetic aberration in hematologic malignancies at a low frequency of ≤1%. An accumulation of reported cases would be needed to discuss clinical and cytogenetic characteristics of the important entity. Therefore, it is useful to report every case for clinical implication of prognosis or therapy.

Case presentation: We report the case of a previously healthy 30-year-old female, who was diagnosed as acute myeloid leukemia (AML) and presented with chemoresistance and short survival. The patient was treated with four cycles of chemotherapy but failed to achieve remission. Then the patient underwent a salvage haploidentical stem cell transplantation. Unfortunately, she worsened within 1 month and died of the refractory leukemia 35 days after transplantation. *ETV6-NTRK3* rearrangement was revealed by RNA sequencing but the chromosomal translocation t(12;15)(p13;q25) was cryptic by conventional karyotype analysis. We review the literature and find that the *ETV6-NTRK3* fusion transcript is associated with cryptic karyotype, trisomy 8, aggressive and poor prognosis in hematologic malignancy. The clinical and laboratory characteristics of *ETV6-NTRK3* positive hematologic malignancies are different from those of solid tumors. Nevertheless, tropomyosin receptor kinase (TRK) inhibitor has powerful anti-tumor activity in patients with TRK fusion–driven cancers, regardless of the tumor type.

Conclusions: We demonstrated that TRK inhibitor larotrectinib is an effective treatment on the primary bone marrow (BM) cells derived from the patient described here with *ETV6-NTRK3* positive AML. Our report stresses the importance of screening for *ETV6-NTRK3* fusion transcript in newly diagnosed leukemias and clinical treatment of TRK inhibitor in hematologic malignancies.

Introduction

Acute myeloid leukemia (AML) is a common hematologic malignancy that has highly cytogenetic and molecular heterogeneity.(1, 2) Chromosomal translocations resulting in the generation of fusion genes can be frequently found in AML, constituting the molecular basis of tumor formation and progression, and were referred to divide AML into several special subgroups(3), which in some term informed clinicians of biological and clinical characteristics and prognosis. The chromosomal translocation t(12;15)(p13;q25), through which the N-terminal helix-loop-helix (HLH) dimerization domain of *ETV6* fuses to the C-terminal protein tyrosine kinase (PTK) domain of *NTRK3*, has been implicated in both solid tumors and leukemias.(4–10) Oligomerization of the *ETV6* HLH domain and activation of *NTRK3* PTK domain, which leads to constitutive stimulation of Ras-Erk1/2, PI3K-Akt, and IGF1R signaling pathways(10, 11), are essential for *ETV6-NTRK3*-induced cellular transformation.(12, 13) Transduction of murine BM cells with *ETV6-NTRK3*-expressing retroviruses followed by transplantation results in a rapid and fatal myeloproliferative disease resembling AML.(14) Limited cases of hematological malignancy were described in this important entity and additional cases are needed to delineate the characteristics of this rare entity.(15) We here present the characteristics and outcome of a patient with cryptic t(12;15) from the First Affiliated Hospital of Soochow University and other patients from a comprehensive literature search.

Case Presentation

We identified 14 cases with *ETV6-NTRK3* fusion genes from the literature (Table 1), including 5 patients with AML, 1 patient with chronic eosinophilic leukemia (CEL), 1 patient with AML transformed from myelodysplastic syndromes (MDS), and the other 7 patients with B-cell acute lymphoblastic leukemias (B-ALL). The majority were males (62.3%, 9/14). There is a remarkable male predominance in B-ALL patients (85.7%, 6/7), and most cases were children or adolescents and young adults (AYA). Patients diagnosed as AML were older (range 45 to 69-year-old). Data on cytogenetic analysis were available in 9 of the 14 patients; all of the nine patients had a cryptic t(12;15) abnormality; six patients had complex karyotype; five patients had trisomy 8; two patients with AML-M0 and CEL, respectively, had monosomy 7; three patients diagnosed as B-ALL had trisomy 21 and two of them had del (17p), both of which were not found in AML or CEL. Relatively complete data were described in 7 of the 14 patients; three patients with AML were reported refractory and died of disease progression in a short time without remissions. The AP-1060 cell line derived patient and two patients with B-ALL suffered from frequent relapse and refractory(R/R), but the two R/R B-ALL were sensitive to TRK inhibitor, larotrectinib and remained long-term remission. The patient diagnosed as CEL failed to response to symptomatic treatment with prednisone and hydroxyurea.

Table 1
ETV6-NTRK3 is associated with trisomy 8 in hematologic malignancy.

Case	Age	Sex	Diagnosis	Karyotype	Therapy	Clinical outcome	Breakpoint of ETV6	Reference
1	59	F	AML-M2	48,XX,add(6)(q27),+8,inv(12)(p13q15), add(15)(q25),+add(15)(q25)	Chemotherapy	Refractory, died at 4 months.	Exon4	5, 29
2	ND	ND	AML-M0	trisomy 13*	ND	ND	Exon4	20,45
3	69	M	MDS-AML	47,XY,add(4)(p16),add(7)(q35),+8,add(12)(p13),add(18) (p11)[10]	Chemotherapy	Progression to AML five months after diagnosis of MDS-RAEB and resistant to chemotherapy, refractory, died at 2 months after transformation to AML.	Exon4	27
4	55	M	AML-M0	Monosomy7,t(10;12)(q24;p13)	Chemotherapy	Refractory, a short period.	Exon5	8
5	45	M	AML-M3	46,XY,t(3;14)(p21;q11.2),add(5)(q33),del(6)(q25),add(12)(p13), t(15;17)(q22;q21)	ATRA + ATO chemotherapy	Forth relapse at 20 months later, Refractory.	Exon4	21,30
6	54	F	AML	ND	ND	ND	Exon4	22
7	82	F	CEL	46,XX,-7,+8	Prednisone, hydroxyurea	Died at 29 days after the CEL diagnosis.	Exon5	23
8	adolescent	M	B-ALL	ND	Crizotinib-PDX model	More sensitive to crizotinib than imatinib.	Exon5	18
9	9	M	B-ALL	49,Y,del(X)(q22q28),add(1)(p36.1),add(2)(q11.2),r(3),add(6)(p21),del(7)(q32q36),add(8)(q24),der(12)t(3;12)(q21;q24),der(13;17)(q10;q10),add(15)(q24),del(16)(p11.2p13),del(17)(p11.2p13),+21,+21,+21,+21[14]/49,sl,add(22)(q11.2)[4]/46,XY[1]/49,sl,+del(X)(q22q28),+11,-21,-22[1]	ND	ND	Exon5	12
10	26	M	B-ALL	ND	ND	ND	Exon5	19
11	6	M	B-ALL	47,XY,+15[19]	Larotrectinib	CNS, high MRD, relapsed at fifty days post-HSCT (ocular, CNS, bone marrow), Larotrectinib successful, in remission.	ND	26
12	61	M	B-ALL	50,XY,+8,+15,del(17)(p11.2),+21,+22	Larotrectinib	Refractory, crizotinib failure. Relapse, Larotrectinib successful, in remission.	Exon4	24
13	16	M	B-ALL	93,XXYY,-3,+5,+5,+8,+8,-9,-15,-18,+21,-22[17]/46,XY[3]	ND	ND	ND	25
14	11	F	B-ALL	ND	ND	ND	Exon5	22
15	30	F	AML	49,XX,t(1;12)(q11;q11),inv(3)(p21q26),+8, +12,+15,19p+[10]	Chemotherapy	Refractory, died at 5 months.	Exon5	this article

Abbreviation: ND, not detected; AML, acute myeloid leukemia; ALL, acute lymphoid leukemia; MDS, myelodysplastic syndromes.

*We presented a vague and incomplete karyotype of M0-91 cell line according to the submitted title by Okabe M., et al: Establishment and characterization of a trisomy 13-positive leukemic cell line, M0-91, expressing flt3/flk2 gene and novel phosphotyrosyl proteins.

A 30-year-old female was admitted to our hospital in October 2019 for headache and anemia. The peripheral blood (PB) values were; white blood cells 11.55 × 10^9/L; hemoglobin 64 g/L, and platelets 56 × 10^9/L. PB smear showed 23% circulating blasts, 5% promyelocytes, 1% myelocytes, 4% metamyelocytes, 19% neutrophils, 19% lymphocytes, 11% eosinophils, 15% monocytes, and 3% basophils. Clinical examination revealed splenomegaly but no signs of lymph nodes swelling and central nervous system leukemia. BM aspiration was failed due to dry tap and subsequent BM biopsy showed markedly hypercellular with 30% blasts and diffuse myelofibrosis (MF-3). (Fig. 1A) Immunophenotyping analysis of PB sample by flow cytometry showed a 24.7% blasts population positive for CD34, CD13, CD14, CD33, CD11b, and CD64. Cytogenetic analysis of the PB cells observed a karyotype of 49,XX,t(1;12)(q11;q11),inv(3)(p21q26),+8,+12,+15,19p+[10]. (Fig. 1B) Multiplex reverse transcription-polymerase chain reaction (RT-PCR) detected no common leukemia-related fusions. (Table S1) Next-generation sequencing identified somatic mutations in *BCOR* and *ETV6*. (Table S2-3) The clinical examinations of the patient were consistent with a diagnosis of AML, NOS according to the WHO classification.

She was treated with two cycles of idarubicin (IDA), combined with cytarabine (Ara-c) (IA regime) and two courses of chidamide, decitabine, IDA and low does Ara-c and granulocyte colony-stimulating factor (G-CSF) (DC-IAG regime). Unfortunately, no remission was achieved. Then the patient received an allogeneic PB stem cell transplantation from a healthy HLA-matched sibling donor after a modified busulfan and cyclophosphamide conditioning regimen. Cyclosporine and short course methotrexate were given as a graft-vs-host disease–prevention regimen. However, the condition of the patient worsened 15 days after transplantation and she died of refractory leukemia 35 days after transplantation. RNA-sequencing of the diagnostic PB sample was performed and revealed an *ETV6-NTRK3* fusion with no reciprocal fusion detected. RT-PCR and subsequent sanger sequencing confirmed the *ETV6-NTRK3* fusion. (Fig. 1C) The *ETV6-NTRK3* fusion transcript involved HLH and entire central domain (exon 1 to exon 5) of *ETV6* and PTK domain of *NTRK3*. The breakpoints were located in exon 5 of the *ETV6* gene and exon 15 of the *NTRK3* gene. (Fig. 1D)

Different studies have suggested that oncogenic TRK aberrations are amenable to targeted inhibition.(16, 17) Primary BM cells derived from our patient were cultured ex vivo and treated with serial concentration of larotrectinib for 8 and 16 hours, respectively. Immunoblotting examination of cell lysates showed that phosphorylation of TRK downstream signaling targets, STAT3, AKT and PLCγ1, were inhibited in a dose-dependent manner. Larotrectinib induced cell death in a time and dose-dependent manner, which was observed by Caspase 3 activation and PARP cleavage. (Fig. 2C) We also evaluated the anti-proliferative ability of larotrectinib, ponatinib and PKC412 against the patient-derived BM cells. Cell viability was measured following 48-hour treatment with serial concentration of larotrectinib. The TRK fusion-driven primary BM cells was more sensitive to larotrectinib with the IC50 value of 3.151 nM in contrast with 18.55 nM for ponatinib and 74.14 nM for PKC412. (Fig. 2A) In addition, larotrectinib was much more potent against BM cells carrying TRK fusion than Kasumi-1 cell line (3.151 nM versus > 1000 nm) (Fig. 2B), which expressed the fusion protein *AML1-ETO*.(18) Larotrectinib induces cell apoptosis, inhibits cell proliferation and TRK signaling in *ETV6-NTRK3*-rearrangement patient derived primary BM cells. These in vitro data support that larotrectinib is an effective treatment for TRK fusion-driven AML.

Discussion And Conclusions

ETV6-NTRK3 was a rare but recurrent molecular event in hematological malignancies.(19–22) Limited number of hematopoietic tumors have so far been reported, including AML(5, 8, 17, 23, 24), CEL(25), B-ALL(12, 17, 21, 22, 26–28) and MDS transformed AML.(29, 30) The very aggressive clinical characteristics of this patient described here was similar to the firstly reported *ETV6-NTRK3* positive patient diagnosed as AML-M2.(31) Both of the two patients (Case 1 and 15) were presented with splenomegaly and accompanied by severe fibrosis of the BM samples at the time of diagnosis, and died in a short period with no remissions achieved. The manifestation was also observed in the patient (Case 7) with a diagnosis of CEL and previous history of breast and pancreatic carcinomas. We speculate that this distinct manifestation might be associated with *ETV6-NTRK3* fusion gene. The AML-M3 cell line AP-1060 was obtained from the patient (Case 5), who had relapsed for the fourth time resistant to all-trans retinoic acid and arsenic trioxide.(24, 32) The patient (Case 3) initially diagnosed as MDS aggressively progressed to AML and was died for persistent resistant to chemotherapy soon after the transformation.(29) In addition, four patients introduced in Case 1, 3, 4, 15, respectively, were refractory to each treatment cycle with a short survival time, indicating primary drug resistance and poor outcome of the *ETV6-NTRK3* fusion gene in AML. Furthermore, eosinophilia was described in Case 7 and 15, suggesting that *ETV6-NTRK3* fusion gene may be associated with myeloid neoplasms with eosinophilia. *ETV6-NTRK3* positive B-ALL is associated with relapse and/or refractory diseases (Case 11 and 12). B-ALL harboring an *ETV6-NTRK3* fusion gene accounts for approximately 1% of the Philadelphia-like cases(21), and is characterized by rapid proliferation and infiltration of central nervous system in preclinical models.(27) However, *ETV6-NTRK3* was relatively frequently detected in some rare non-hematologic malignancies/solid tumors, like congenital fibrosarcoma (CFS), congenital mesoblastic nephroma (CMN) and secretory breast carcinoma (SBC).(9) The presence of the *ETV6-NTRK3* fusion gene indicate an excellent prognosis and highly sensitive to typical chemotherapy in some solid tumors as CFS and cellular CMN.(33)

There was a correlation between the expression of the *ETV6-NTRK3* fusion gene and trisomy 11 in CMN as well as CFS, among which the polysomies of chromosomes 8 and 17 were also well known.(6, 34) We found a striking correlation between trisomy 8 and *ETV6-NTRK3* fusion gene expression in hematological malignancies with available karyotypes (6/10 in total, 4/6 in AML/CEL and 2/4 in B-ALL, Table 1). Trisomy 8 is one of the most common numerical aberrations in AML, with an incidence between 10% and 15%.(20, 35) Trisomy 8 is rarely observed in ALL. Notably, Valentina Nardi et al demonstrated that the patient (Case 12) relapsed due to an expansion of an *ETV6-NTRK3* rearranged subclone that also carried trisomy 8, confirming the association described above. Furthermore, FISH analysis showed that 93.8% of the *ETV6-NTRK3* positive SKK-1 cells, derived from the patient 3, carried trisomy 8, which was considered to gradually expand and have a growth advantage.(29) AML with trisomy 8 is classified as intermediate risk according to the European Leukemia Net (ELN) classification.(36) In the 11q23/*MLL*-rearranged AML, which implied an adverse prognosis, the addition of chromosome 8 seem to independently predicted a more favorable outcome.(37) However, *CBFB/MYH11* rearrangement AML with trisomy 8 had an inferior OS.(38) Here, the co-occurrence of trisomy 8 does not change the adverse prognosis of the *ETV6-NTRK3* fusion gene.

However, trisomy 11 and 17 was absent in hematological malignancies, which was obviously different from non-hematological malignancies. We also found that *ETV6-NTRK3* fusion gene was related to complex karyotype with a cryptic t(12;15)(p13;q25) translocation, which has never been detected in hematological malignancies using a conventional technique. Nevertheless, the chromosome translocation could be detected in several cases of solid tumors. (39) Monosomy 7 was noted in myeloid leukemias harboring non-complex karyotype (Case 4 and 7, 2/2). Trisomy 21 and deletion 17p (containing the *TP53* gene) were recurrent in *ETV6-NTRK3* positive B-ALL (Case 9, 12 and 13, 3/4 and 2/4 proportion respectively).

Various breakpoints of *ETV6-NTRK3* have been identified. It was previously considered that exon 1 to exon 5 of the *ETV6* were retained in the *ETV6-NTRK3* fusion product of solid tumor, but leukemic fusion variant contained exon 1 to exon 4, excluding exon 5 of the *ETV6*.(8, 23–25, 40, 41) We here found that the breakpoints of *ETV6* were not specific to distinguish solid tumors from leukemias. The two variants of fusion transcripts identified in leukemias may function differently in cell transformation due to the entire central domain encoded by partly of exon 4 and the entire exon 5, enabling further protein-protein interactions. There are no differences in clinical outcome between the two fusion variants. The reciprocal *NTRK3-ETV6* fusion gene was not detected in all reported leukemias but could be detected in solid tumors as CFS.(42)

All the patients treated with traditional chemotherapy had disease progression while on treatment or persistent chemo-resistant, clearly highlighting that leukemia with *ETV6-NTRK3* fusion is not chemo-sensitive. These observations are in contrast with the excellent clinical response on the larotrectinib, a highly selective TRK inhibitor. It has shown robust and durable anti-tumor activity in solid tumors and also in two single cases of B-ALL related to relapse/refractory. (4, 26, 28, 43–46) It has been demonstrated that larotrectinib was effective on AML cell lines carrying TRK rearrangements (IMS-M2, M0-91) as well as primary BM cells of the patient reported here. (27, 47)

In conclusion, we identified the *ETV6-NTRK3* fusion gene in a patient with AML remaining refractory and surviving for a short term. Moreover, we present a study of this rare entity from a comprehensive literature search as a specific and important subgroup of hematological malignancies with poor outcome and usually an additional copy of chromosome 8, which were different from solid tumors with good prognosis and always trisomy 11. Most importantly, the translocation t(12;15)(p13;q25) is highly cryptic and easily overlooked in conventional cytogenetics. Newly diagnosed AML presented with myeloproliferative neoplasm clinal features such as splenomegaly, myelofibrosis, eosinophilia or trisomy 8 cytogenetic abnormality, may harbor *ETV6-NTRK3* fusion transcript. Our study highlights the significance of combining multiple molecular techniques to early identify the cryptic t(12;15)(p13;q25)/ *ETV6-NTRK3* in hematological malignancies and also emphasizes the value of TRK inhibitors on patients with *ETV6-NTRK3* positive hematological malignancies.

Abbreviations

AML: acute myeloid leukemia; TRK: tropomyosin receptor kinase; BM: bone marrow; HLH: helix-loop-helix; PTK: protein tyrosine kinase; CEL: chronic eosinophilic leukemia; MDS: myelodysplastic syndromes; B-ALL: B-cell acute lymphoblastic leukemias; AYA: adolescents and young adults; PB: peripheral blood; RT-PCR: reverse transcription-polymerase chain reaction; IDA: idarubicin; Ara-c: cytarabine; G-CSF: granulocyte colony-stimulating factor; CEL: chronic eosinophilic leukemia; CFS: congenital fibrosarcoma; CMN: congenital mesoblastic nephroma; SBC: secretory breast carcinoma; ELN: European Leukemia Net.

Declarations

Ethical approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the First Affiliated Hospital of Soochow University committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. This article does not contain any studies with animals performed by any of the authors.

Consent for publication

Written informed consent for research and publication from the patients was obtained.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare no competing financial interests.

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Author contributions

ANS designed this study. XFY and ANS wrote the manuscript; LZ, LJW and ZW analyzed RNA-seq data and performed research; ZZ and YX analyze the research data; JLP and SLX collected clinical data and samples; SNC and DPW gave advices for the study design and paper writing.

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