

Myeloid/Lymphoid Neoplasms with *ETV6::PDGFRB* Fusion Gene: A Rare Case of Poor Response to Imatinib and Possible Transformation Mechanisms from Myeloid Neoplasms of Bone Marrow to T-Cell Lymphoblastic Lymphoma Invasion in Lymph Nodes

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Abstract: The *ETV6::PDGFRB* fusion gene is commonly reported in chronic myelomonocytic leukemia with eosinophilia, yet patients with *ETV6::PDGFRB* presenting myeloid and lymphoid neoplasms successively have not been reported. Here, we report the first case of a 35-year-old man with myeloid and lymphoid neoplasms harboring an *ETV6::PDGFRB* fusion gene who demonstrated poor response to imatinib. The patient was diagnosed with an *ETV6::PDGFRB* fusion gene myeloid neoplasm on initial diagnosis at our hospital. After 5 months of treatment with imatinib, he was diagnosed with T-cell lymphoblastic lymphoma. *ETV6::PDGFRB* turned negative after increasing the dose of imatinib, but enlarged superficial lymph nodes reappeared the following year. Notably, the patient exhibited a worse response to imatinib treatment. This study describes this rare case and speculates on a possible mechanism.

Keywords: *ETV6*, *PDGFRB*, fusion, myeloid/lymphoid neoplasms, imatinib

Introduction

The *ETV6::PDGFRB* fusion gene is commonly associated with myeloid neoplasms with monocytosis (such as CMML), and with eosinophilia.¹ The *PDGFRB* gene, located on 5q33, encodes PDGFR β , a type III tyrosine kinase comprising an extracellular domain consisting of five immunoglobulin (Ig)-like domains, a single-transmembrane helix domain, a juxtamembrane domain, and an intracellular tyrosine kinase domain.² *PDGFRB* can fuse with >30 partner genes (*ETV6* being the most commonly seen) and result in a constitutive activation of the tyrosine kinase domain, despite extracellular signals, and give rise to an uncontrolled proliferation of blood cells, mostly later-stage myeloid cells, and less frequently immature B- or T-lymphoid cells.² The *ETV6::PDGFRB* fusion gene with lymphoid blasts is rarely seen and less frequently reported in the literature.^{1,2}

In the past, the aim of treatment was to limit organ damage by controlling the eosinophil count using drugs like prednisone, hydroxyurea, and IFN α . Since imatinib, a TKI first approved for the treatment of chronic myeloid leukemia by inhibiting ABL kinase activity, was discovered to block PDGF receptors at even lower concentrations in 2002, the prognosis of *PDGFRB*-rearrangement neoplasms was revolutionized.³ Patients with *ETV6::PDGFRB* exhibit an excellent

response to imatinib, with much less frequent transform to blastic crisis phase.^{3,4} It is challenging for clinicians to treat patients with poor response to target therapy, and even disease transformation can occur.

Here, we report a rare case of *ETV6::PDGFRB* that manifested initially as a myeloid neoplasm and was treated with imatinib, but then an invasion of lymphoblastic T cells was found on lymph node (LN) biopsy. The patient got better after a course of chemotherapy and an increasing dose of imatinib, but enlarged superficial LNs reappeared the following year. Notably, the patient exhibited a worse response to imatinib treatment. This study describes this rare case and speculates on a possible mechanism, displays the complexity of targeting fusion genes, and highlights the need for a comprehensive understanding of the molecular basis of neoplasms and personalized therapeutic strategies.

Case Presentation

A 35-year-old man with a history of IgA nephropathy was followed up in our hospital. A bone marrow (BM) aspiration biopsy was done when a significant leukocytosis (WBCs $26 \times 10^9/L$) and eosinophilia (nucleated cells [eosinophils] 12.5%) was observed on complete blood count. A marked myeloid hyperplasia with 5% myeloblasts and 3% eosinophils was found in the BM aspirate smear, while lymphoid was hypoplasia with only 1.5% of mature lymphocytes counted (Figure 1A). A positive *ETV6::PDGFRB* fusion gene and negative *BCR/ABL* was found on RTq-PCR, *PDGFRB* gene breakage of 90% of cells was detected by FISH (Figure 1B), and karyotype analysis showed 46, XY, del(12)(p13p11.2), indicative of a diagnosis of myeloid neoplasms with *ETV6::PDGFRB* fusion gene. After hydroxyurea (Qilu Pharma, China; 1.5 g/day) for 4 days, followed by imatinib (Hansoh Pharma, China) 200 mg/day, his WBCs and eosinophils had normalized within a month, then imatinib was decreased to 100 mg/day. Five months after initial diagnosis, an

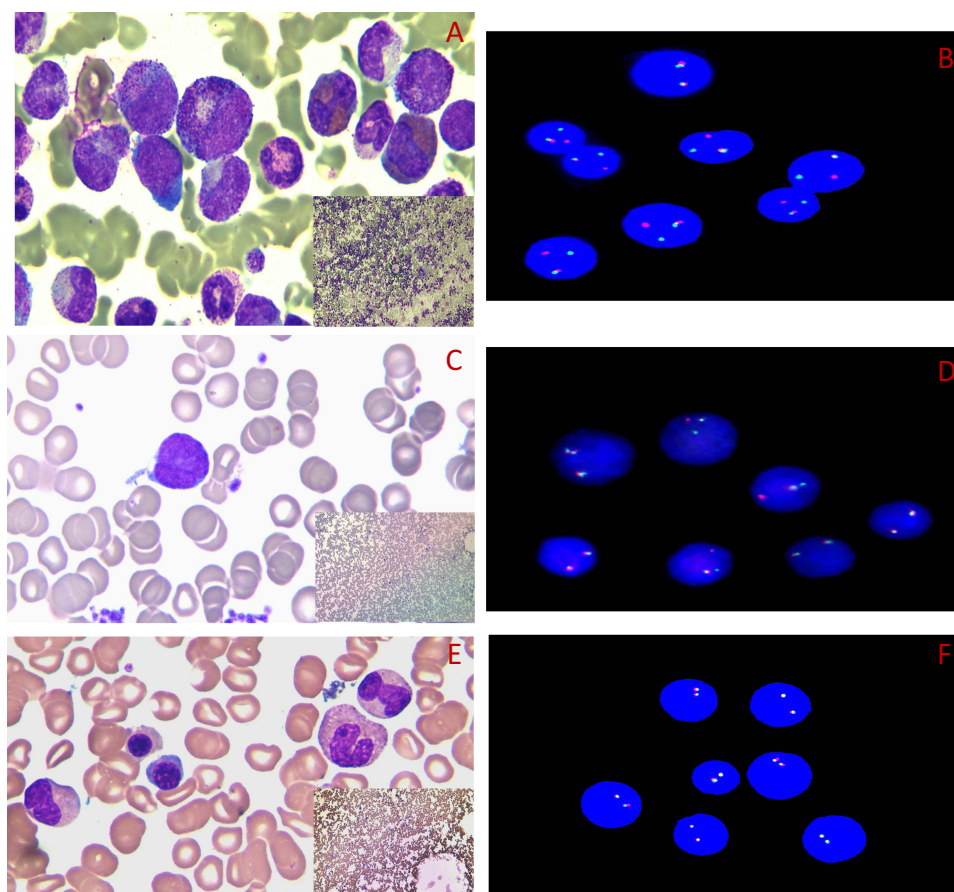


Figure 1 (A and B) Bone marrow at first diagnosis; (C and D) bone marrow during lymph-node invasion of lymphoblastic T cells; (E and F) bone marrow at complete response. (A, C and E) Wright's stain (100×, 10×). (B, D and F) Interphase FISH results: red (*CSF1R*), green (*PDGFRB*), 2 yellow (*PDGFRB* no breaking), 1 red, 1 green, 1 yellow (*PDGFRB* breaking detected).

enlargement of LNs was found after a cold in his bilateral neck, axilla and groin. Ultrasound examination showed the max LN was 3.7×1.5 cm in zone II of the right neck with a regular shape and clear border. Biopsy of the max LN revealed intermediate blastoid infiltration by neoplastic lymphocytes. Immunohistochemical analysis of lymphoma cells showed CD34⁺, CD10⁺, CD3⁺, CD7⁺, and Tdt⁺ scattered, leading to a diagnosis of T-LBL. At the same time, the BM aspirate showed a hypocellularity with 11.5% blasts (Figure 1C), and 24% *PDGFRB* breakage cells on FISH (Figure 1D). The karyotype was normal at this time.

Imatinib was increased to 400 mg/d, and induction chemotherapy with PCIOD (asparaginase, cyclophosphamide, idarubicin, vindesine, dexamethasone) was begun. Shrunken LNs after chemotherapy, but a severe pulmonary fungal infection occurred in the process, and an impaired renal function arose, then imatinib was decreased to 200 mg/day (after 1 month of 400 mg/day). WBC and eosinophil counts reached normality gradually. The BM aspirate was normal, and hypocellularity and *PDGFRB* breakage detection in BM was negative on FISH 1 year after initial diagnosis and remained negative on follow-up (Figure 1E and F). However, 14 months after initial diagnosis, an enlargement of his LNs was detected in his bilateral neck, axilla, and groin again. Maximum sizes were 1.4–1.8×0.6–0.9 cm on ultrasound. Impacted by the COVID-19 situation in our city, 200 mg/day imatinib was continued. Enlarged LNs kept stable relative to 1 month before manuscript submission (20 months after initial diagnosis). For further treatment decisions and understanding the pathogenesis of this disease, more experiments were done.

Methods

Serial BM and LN samples were collected for FCM, FISH, and DNA and RNA sequencing at three time points: (A) first diagnosis of myeloid/lymphoid neoplasm, abbreviated as diagnosis; (B) lymphoblastic T-cell invasion in LNs, abbreviated as invasion; and (C) 1 year after diagnosis, when *PDGFRB* breakage cells in BM had turned negative on FISH, abbreviated as CR. FCM immunophenotyping analyses were performed using 10-color flow cytometry (Navios, Beckman Coulter, USA). FISH analyses were performed on unstimulated interphase cells using dual-color break-apart probes (D-FISH, Jinpujia, China; CSF1R signal red, *PDGFRB* signal green, two yellow signals represent *PDGFRB* without breakage, one red, one green, and yellow signals represent one *PDGFRB* breakage detected) according to the manufacturer's instructions. Targeted DNA sequencing and RNA sequencing were performed with the NovaSeq 6000 sequencing platform (Illumina, USA) and high-throughput Sanger sequencing using an ABI 3730 automated DNA sequencer (Applied Biosystems, USA). Total genomic DNA and RNA was extracted from BM and LN samples for target sequencing, and 38 genes commonly mutated in myeloid neoplasms were investigated with a custom-designed next-generation sequencing approach for library construction (Yuanqi, China). RNA-sequencing libraries were prepared using the TruSeq Stranded Total RNA Library Prep Kit (Illumina, USA) following the manufacturer's instructions. $P < 0.05$ and $\log_2$ -fold change > 2 were considered to be significantly differentially expressed. GO and KEGG pathway enrichment analysis was performed using KOBAS (<http://kobas.cbi.pku.edu.cn>) and DAVID (<https://david.ncifcrf.gov>).

Results

At diagnosis, FCM analysis showed one progenitor-cell population with CD34^{par}+CD38⁺+CD117⁺+CD7⁻-CD56^{par}+cMPO⁺+CD123^{dim}HLA-DR⁺+cCD3⁻ in the BM sample (Figure 2A). Upon invasion, progenitor-cell populations were CD34⁺+CD38⁺+CD117^{par}+CD7⁺+CD56⁺+cMPO^{par}+CD123⁺HLA-DR⁺+cCD3⁻ in the BM sample (Figure 2B) and CD34⁺+CD38⁺+CD117[±]+CD7⁺+CD56⁺+cMPO^{few}+ CD123⁺ HLA-DR⁻-cCD3⁺ in the LN sample (Figure 2C). Once it was found blast cells coexpressed cMPO and cCD3 simultaneously in the LN sample upon invasion, a CD117 gate was used, and the results showed CD117-positive cells (red cells, accounting for 13.93% of nuclear cells) were positive for cMPO and cCD3 (a mixed T and myeloid phenotype), CD117 negative cells were cMPO-negative and cCD3-positive (blue cells, accounting for 69% of nuclear cells) (T-LBL phenotype) (Figure 2C). In LNs during invasion, the imprint cytology image showed intermediate blastoids with intermediate-to-condensed chromatin and scant cytoplasm (Figure 2D). FISH detected a break in 64% of the cells from the invaded LNs (Figure 2E).

NPM1 and *TET2* mutations were positive at diagnosis and negative at invasion in the BM sample, while *TET2* mutation was positive at invasion in LN samples. NOTCH3 p. R2031H mutation kept positive but changed the VAF at diagnosis, while VAFs of *CHD8*, *MUC16* and *PLCG2* remained close to 50% in samples at diagnosis and invasion.

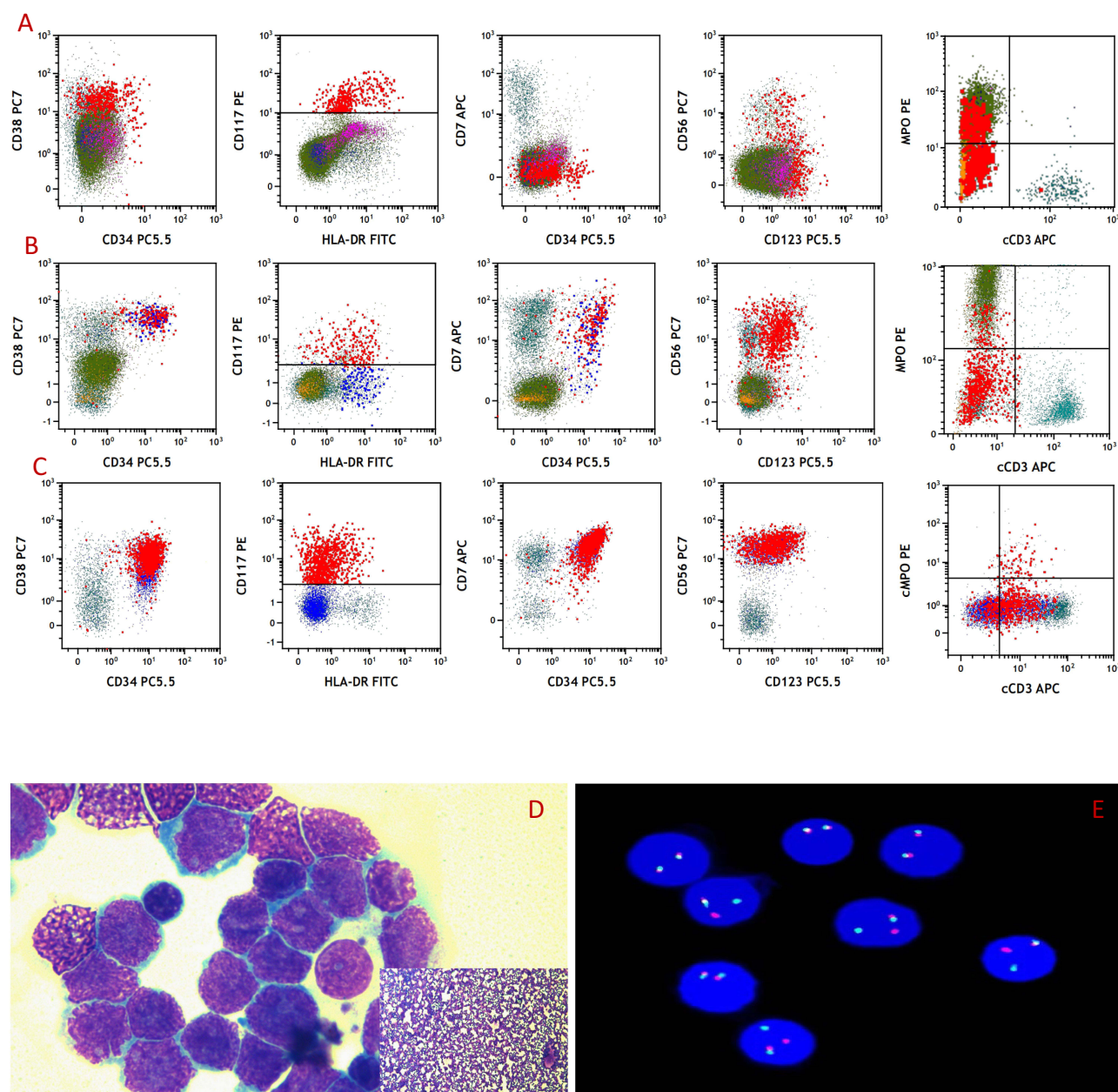


Figure 2 (A and C) Flow-cytometry histograms at different stages. (A) Bone marrow at first diagnosis; (B) bone marrow at times of lymph-node invasion of lymphoblastic T cells; (C) lymph node during lymph-node invasion of lymphoblastic T cells; (D) inprint of lymph-node invasion; (E) interphase FISH results of lymph node during lymph-node invasion of lymphoblastic T cells.

Additionally, *MED12* mutation was detected at invasion in the LN sample (Table 1). RNA sequencing demonstrated the same break points in *ETV6::PDGFRB* fusion (12:12006495:++5:149510225:-) between the BM sample and LN sample.

RNA sequencing revealed some important expression changes in BM samples between diagnosis and CR (Figure 3). GO functional enrichment analysis revealed that stem cell-related genes had higher expression at diagnosis, such as embryonic organ development and morphogenesis, cell-fate commitment, and signaling pathways regulating pluripotency of stem cells. Neutrophil-related genes in terms of neutrophil activation, neutrophil-mediated immunity, and neutrophil degranulation were more highly expressed during CR. Additionally, KEGG functional analysis revealed that some signaling pathway conduction had also changed, with more gene expression related to the NOTCH pathway, MAPK signaling, PI3K signaling, and less gene expressions related to NF- κ B signaling at diagnosis.

Table 1 Major gene mutations detected in the disease course

	2021/9/14	2022/3/28	2022/3/28	2022/9/14
Stage	Diagnosis	Invasion	Invasion	CR
Sample	BM	BM	LN	BM
Method	Target DNA-seq and RNA-seq	Sanger-seq	Target DNA-seq and RNA-seq	Target DNA-seq and RNA-seq
Gene	NPM1	NPM1	NPM1	NPM1
AA change	W288fs	W288fs	W288fs	W288fs
VAF%	1	0	0	0
Gene	TET2	TET2	TET2	TET2
AA change	L1151V	L1151V	L1151V	L1151V
VAF%	30	0	32	0
Gene	NOTCH3	NOTCH3	NOTCH3	NOTCH3
AA change	R2031H	R2031H	R2031H	R2031H
VAF%	35	+	70	73
Gene	MED12	/	MED12	MED12
AA change	V319FS/S849FS	/	V319FS/S849FS	V319FS/S849FS
VAF%	0	/	61/12	0

Abbreviations: BM, bone marrow; LN, lymph node; seq, sequencing.

Discussion

ETV6::PDGFRB was first reported in a CMML patient in 1994, and in the 2022 WHO and ICC classification, neoplasms associated with *ETV6::PDGFRB* were classified as myeloid/lymphoid neoplasm with eosinophilia and tyrosine kinase gene fusions (M/LN-eo-TK), a specific entity and an updated name.⁵⁻⁷ Although the category name includes myeloid and lymphoid neoplasms, *ETV6::PDGFRB*-associated neoplasms with both myeloid and lymphoid cells in one patient had never been reported in the literature. Fusions of *PDGFRB* with partners like *DIAPH1*, *SART3*, *RABEP1*, and *CBORF204*

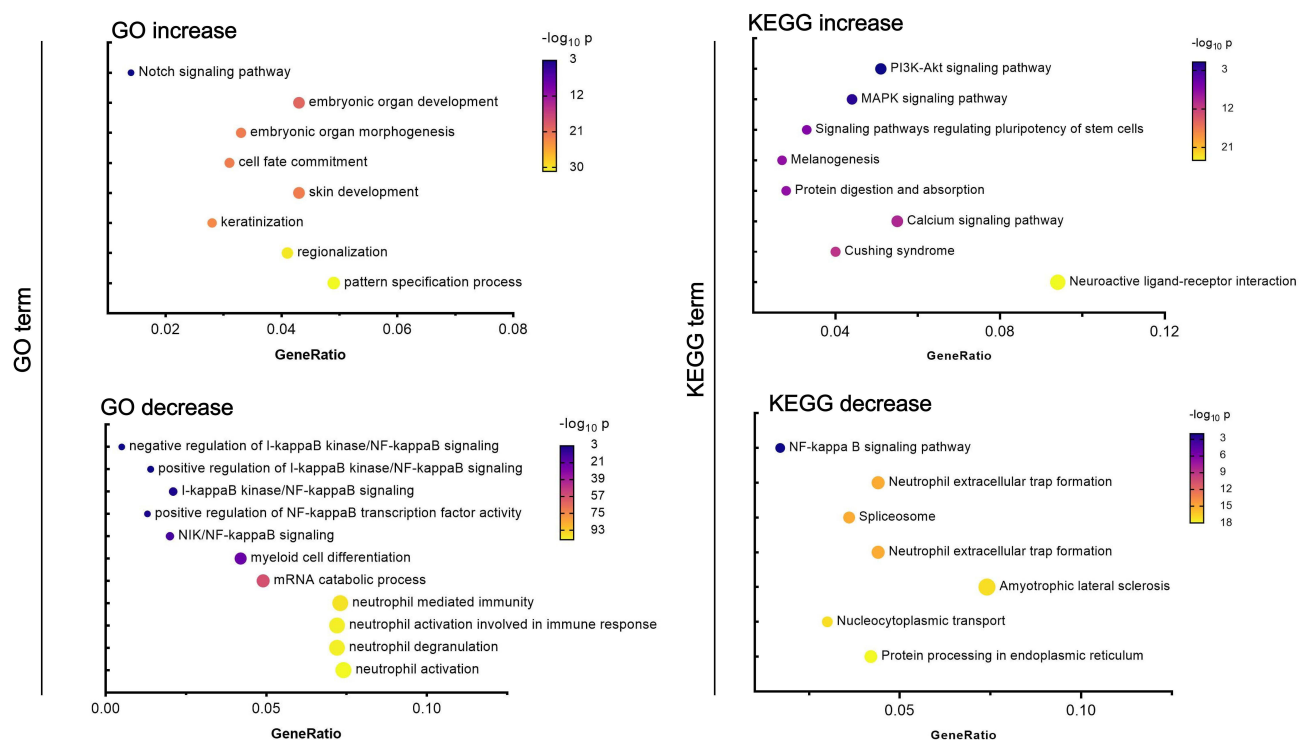


Figure 3 Gene-expression changes between diagnosis and CR detected by RNA sequencing. This shows the five most significantly changed expression pathways, as well as GO terms. Some pathways we focused, increase or decrease were indicated as diagnosis of CR.

were reported to be associated with chronic myeloid neoplasms in BM and T-cell lymphoid neoplasms in LNs.^{8,9} The *ETV6* gene, located on 12p13, encodes a transcriptional repressor playing a crucial role in hematopoietic regulation and can also fuse with >30 partners in myeloid and lymphoid leukemia, among which *ETV6::PDGFRB* in CMML and *ETV6::RUNX1* in acute lymphoblastic B-cell leukemia (ALL) are well known.¹⁰ *ETV6::LYN* and *ETV6::NCOA2* have been reported to be related to T-cell lymphoid and myeloid-mixture leukemia.^{11,12}

PDGFRB-rearranged patients demonstrated good response to imatinib at 100–400 mg/day: 96% response rate, 90% 10-year overall survival,¹³ and median duration of 6.6 years.¹⁴ In non-AML cases, a low imatinib dosage (100–200 mg) is sufficient to induce and maintain long-term hematological, cytogenetic, and molecular remissions.⁴ In blastic crisis patients, whether to proceed with HSCT can only be made on an individual basis.¹⁵ In one study, all three patients with allogeneic HSCT relapsed. Patients may only be offered TKI monotherapy, rather than intensive chemotherapy.⁸ Three patients with chronic myeloid neoplasms and lymphoblastic T-cell lymphoma neoplasms received chemotherapy: two had a poor outcome, and the other transplant patient survived >3 years with complete molecular remission.^{8,9} For this young male patient in this study, the neoplasm cells were controlled by 200 mg/day imatinib, but were partly controlled by 200 mg/day imatinib again. The dose of imatinib is very important, and may show better outcomes with 200–300 mg/day imatinib continuously. Overall, there was a poor response to imatinib, whether at diagnosis or used alone after chemotherapy.

The existence of *ETV6::PDGFRB* fusion within the cells with T-cell and myeloid-cell biomarkers in the LNs revealed the same origin as the tumor cells in BM. CD34+CD117+CD7+CD56+ cell populations appeared simultaneously in invasive BM, and lymphatic samples confirmed it. Once the N-terminal part of the transcription repressor *ETV6* is joined to the kinase domain of *PDGFRB*, the kinase domain is constitutively activated despite PDGF, resulting in the increased activation of several signaling pathways, including PI3K, STAT, MAPK and NF-B.¹⁶ NF-KB is critical for the cell growth and differentiation of *ETV6::PDGFRB*.¹⁷ NF-B signaling was not activated in this case, revealing that further mechanisms may go beyond the known role of *ETV6::PDGFRB*. Deregulated *NOTCH3* and pre-TCR signaling contribute to the development of leukemia and lymphoma.¹⁸ Mutated *MED12* can increase NOTCH signaling in CLL patients and was mutated in 10% pediatric T-ALL.^{19,20} The mutated *NOTCH3* and activated NOTCH signaling in this case may be associated with the T-cell phenotype, especially in LN cells that have passed the pre-TCR signaling process.

ETV6::PDGFRB is capable of transforming lymphocytes in mice expressing it, although it is usually displayed as a myeloproliferative disease in mouse models.^{21,22} The break point in intron 8 of *PDGFRB* was special in the *ETV6::PDGFRB* fusion gene in this case and in intron 10 in most cases, resulting in the retention of the fifth Ig domain expressed by exon 9 and exon 10, which may also be associated with the special phenotype of this case, likely abnormal increased activating ability of *PDGFRB*.² Notably, the karyotype at diagnosis favored a cryptic variant translocation, which was consistent with the atypical break point of *PDGFRB*. Several mechanisms have been proposed for the transformation of leukemia lineage, including stem-cell plasticity in which common myeloid/lymphoid progenitor cells were present expression of myeloid and B/T-lymphoid antigen, and clonal selection in which subclones with different phenotypes exist such that major clones could change under selection of drugs.^{23,24} *ETV6::NCOA2* fusion can cause lymphoid specification while sustaining myeloid potential, and then cooperate with mutated *NOTCH1*, resulting in a T/My MAL.¹² This case manifested as a phenotype of T/My MAL in the disease process. Both stem-cell plasticity and clonal selection were assumed to function, and in the background of multiple gene mutations, drugs like imatinib play an important role in accelerating the manifestation of T-LBL.

Fortunately, the LN size was still under control, but for this young patient, choosing whether to increase doses of imatinib, second/third generation of TKIs, or combine with chemotherapy while LNs enlarge again is challenging. TKI targets the kinase domain of *ETV6::PDGFRB* protein and blocks the constitutive activation of signaling pathways.²⁵ Due to the atypical activated signaling pathway in this patient, single administration of TKIs may have had limited efficacy. Combined with target therapy on NOTCH signaling, chemotherapy and HSCT may be tried in the future.²⁶ It is regretful that imatinib plasma levels were not measured in this patient, and the LN was not biopsied during the second enlargement. Meanwhile, there are some limitations of this study, such as the potential influence of individual genetic variability on treatment response and the limitations of using a single case to draw broad conclusions, which could be partly controlled by expanding case numbers in future studies.

Abbreviations

LN, lymph node; CMML, chronic myelomonocytic leukemia; TKI, tyrosine kinase inhibitor; BM, bone marrow; WBC, white blood cell; RTq-PCR, real-time quantitative polymerase chain reaction; FISH, fluorescence in situ hybridization; T-LBL, T-cell lymphoblastic lymphoma; FCM, flow cytometry; CR, complete response; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; VAF, variant allele frequency; WHO, World Health Organization; ICC, International Consensus Classification; HSCT, hematopoietic stem-cell transplantation; T/My MAL, T/myeloid mixed phenotype acute leukemia.

Ethics Approval

This study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Army Medical University.

Consent to Participate

The patient provided their written informed consent to participate in this study.

Consent for Publication

All authors have seen and approved the final version of the manuscript being submitted.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas, took part in drafting, revising, or critically reviewing the article, gave final approval to the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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