












The First Case of B-lymphoblastic Leukemia Associated With t(7;8)(q34;p11.2) and *FGFR1* Rearrangement

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Dear Editor,

According to the 2016 WHO classification, myeloid/lymphoid neoplasms associated with clonal eosinophilic disorders are associated with specific genes, such as *PDGFRA*, *PDGFRB*, *FGFR1*, and *PCM1-JAK2* [1]. *FGFR1* rearrangement has been reported in myeloid/lymphoid neoplasms of various disease groups and associated with various partner genes [1, 2]. We report a rare case of B-lymphoblastic leukemia associated with t(7;8)(q34;p11.2) and *FGFR1* rearrangement. This report was approved by the Institutional Review Board of Kyung Hee Medical Center, Seoul, Korea (KHUH 2019-09-057) and granted a waiver of informed consent as this was a retrospective study using residual samples.

A 24-month-old male patient was admitted to our hospital in January 2019 with fever up to 39°C, which started eight days before the visit, and petechiae on the upper chest. A complete blood count revealed white blood cell (WBC) count $7.32 \times 10^9/L$, Hb 91 g/L, and platelets $36 \times 10^9/L$. Initial WBC differential counts were 10% segmented neutrophils, 67% lymphocytes, 9% monocytes, 6% atypical lymphocytes, 1% metamyelocytes, 1% myelocytes, and 6% blasts. A bone marrow (BM) aspirate showed a hypercellular marrow with an increased number of blasts (86.2%

of all nucleated cells) (Fig. 1).

In a biopsy section of the BM, the estimated cellularity was 80%–90%. A BM chromosome study revealed 46,XY,t(7;8)(q34;p11.2),i(9)(q10) in 16 out of 20 metaphase cells analyzed (Fig. 2A). The patient was suspected of having *FGFR1* rearrangement. Therefore, FISH analysis (MetaSystems, Altlußheim, Germany) using an *FGFR1* probe was performed, and break-apart signals were observed in 106 out of 300 interphase cells (35.3%) (Fig. 2B). Genetic rearrangement was not detected by multiplex reverse transcription PCR using cDNA, mastermix and split-out PCR primer mix from the HemaVision kit (DNA Diagnostic A/S, Risskov, Denmark) on the SimpliAmp thermal cycler (Thermo Fisher Scientific, Waltham, MA, USA), following the manufacturer's instructions.

Flow cytometric analysis (Navios EX Flow Cytometer and Kaluza Analysis Software, Beckman Coulter, Miami, FL, USA) of BM specimens performed per the manufacturer's instructions revealed that blasts expressed CD34, CD10, CD19, CD33, CD20, CD38, cCD22, cCD79a, and TdT. Finally, the patient was diagnosed as having B-lymphoblastic leukemia with *FGFR1* rearrangement. The patient was transferred to another hospital immediately after diagnosis and no further clinical and laboratory

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results were obtained.

FGFR1 is associated with clonal eosinophilic disorders and can undergo various gene rearrangements with at least 44 partner genes [2]. Gene rearrangement associated with *FGFR1* has been termed “8p11 myeloproliferative syndrome (EMS)” in the past because of the chromosomal location of *FGFR1*, (8p11-12) [3]. Currently, it is classified as an independent myeloid/lymphoid neoplasm group [1]. The clinical features of myeloid/lymphoid neoplasm with *FGFR1* rearrangement can take many forms, including chronic eosinophilic leukemia, AML, T-cell lymphoblastic lymphoma, and occasionally, precursor B-lymphoblastic leukemia/lymphoma [1, 4]. Patients in the chronic phase of myeloid/lymphoid neoplasm with *FGFR1* rearrangement usually show eosinophilia and neutrophilia and sometimes, monocytosis

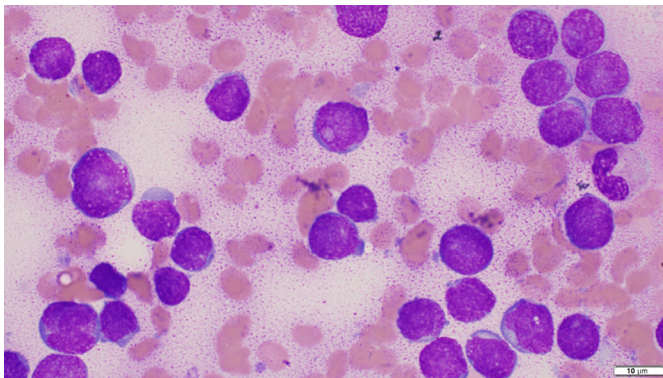


Fig. 1. Wright-Giemsa staining of a bone marrow aspirate smear ($\times 1,000$) showing an increased number of blasts with a high nuclear:cytoplasmic ratio, round to oval, indented nuclei, and scanty cytoplasm.

[4]. The most common *FGFR1* rearrangement is related to t(8;13) (p11.2;q12.1), where the *ZMYM2-FGFR1* fusion gene can be detected at the molecular level [5]. In addition, *FGFR1* rearrangement associated with approximately 10 different partner genes is listed in the 2016 WHO classification [1].

To the best of our knowledge, t(7;8)(q34;p11.2) is a very rare *FGFR1* rearrangement and has been reported in only one AML case in a 49-year-old Italian female patient [6]. Furthermore, our case is the first report of t(7;8)(q34;p11.2) in lymphoid malignancies. In the Italian AML patient, a *TRIM24-FGFR1* fusion gene was identified at the molecular level [6]. However, our patient was transferred to another hospital and was lost to follow-up. *TRIM24* (also known as *TIF1 α*) encodes a nuclear protein that contributes to polymerization and ubiquitylation and thus, regulates developmental and physiologic processes [7, 8]. *TRIM24* proteins have various functions in transcription, cell differentiation, mitosis, and DNA repair, and functional abnormalities can lead to tumorigenesis [7, 9]. Malignant disorders associated with *TRIM24* abnormalities include thyroid, breast, lung, liver, colorectal, and prostate cancers [7-9]. In most cancers, overexpressed *TRIM24* acts as an oncogene associated with cancer progression; however, in hepatocellular carcinoma, it functions as a tumor suppressor [8, 9]. *TRIM24* abnormalities in hematologic malignancies have not been sufficiently studied and further studies will be necessary.

Until recently, the prognosis of hematologic malignancy associated with *FGFR1* rearrangement was very poor, and stem cell transplantation was the only treatment option [4, 5]. However, tyrosine kinase inhibitors have enabled molecular targeted ther-



Fig. 2. Cyto-genetic analysis of a bone marrow specimen. (A) G-banded karyogram of bone marrow cells revealing 46,XY,t(7;8)(q34;p11.2), i(9)(q10). The arrows indicate the chromosomes involved in this translocation. (B) FISH analysis using an *FGFR1* break-apart probe (XL *FGFR1* probe; MetaSystems, Altlußheim, Germany). The arrows indicate split signals related to *FGFR1* rearrangement.

apy in *BCR-ABL1*-positive chronic myeloid leukemia, which was incurable in the past [10]. Similarly, we believe that consistent clinical reporting of rare gene rearrangements will facilitate the development of personalized treatments in future.

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AUTHOR CONTRIBUTIONS

Cho H and Han Y coordinated the drafting of the manuscript and wrote the manuscript. Lee JJ collected the data. Park KS, Kim YJ, and Cho SY interpreted the data. Yoon HS managed the patient and provided the clinical information. Lee WI reviewed and commented on the draft. Park TS designed and supervised the study. All authors have accepted their responsibility for the entire content of this manuscript and approved submission.

CONFLICTS OF INTEREST

None declared.

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