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The formation of an aberrant PAX5 transcript in a patient with mixed phenotype acute leukemia harboring der(9)t(7;9)(q11.2;p13)

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ABSTRACT

We experienced the case of a 56-year-old male with B-lymphoid/myeloid lineage mixed phenotype acute leukemia (MPAL). A cytogenetic analysis of the patient's bone marrow revealed a complex karyotype, including der(9)t(7;9)(q11.2;p13). We identified an aberrant *PAX5* transcript, including the exons 1A to 5 and the contiguous intron 5/6 sequence using the 3′ rapid amplification of cDNA ends-polymerase chain reaction method, and confirmed their expression in the leukemic cells. Our case suggests that der(9)t(7;9)(q11.2;p13) can cause the truncation of the *PAX5* transcript, which is supposed to contribute to the generation of MPAL, in addition to three previously reported types of *PAX5* fusion.

1. Introduction

Mixed phenotype acute leukemia (MPAL) is a rare hematological malignancy which is characterized by the generation of leukemic blasts with multilineage potential. Genetic analyses revealed that the *BCR-ABL1* and *KMT2A* (*MLL1*) gene rearrangement in B-lymphoid/Myeloid MPAL are frequently detected, resulting in the formation of each subtype of MPAL. In addition, deletion 6 and 12p11.2 abnormalities have been observed in multiple cases [1,2]. On the other hand, the frequency and significance of *PAX5* gene alteration located on 9p13.2, which have been reported in B-progenitor acute lymphoblastic leukemia (B-ALL), remains unknown in MPAL.

We herein report an MPAL patient with der(9)t(7;9)(q11.2;p13) which generated a truncated PAX5 transcript.

2. Case report

A 56-year-old male was referred to our hospital for evaluation of leukocytosis ($29{,}800 \times 10^9$/L). A bone marrow examination showed a marked proliferation of blasts (88.3%) that were negative for myeloperoxidase (MPO) staining. These blasts were uniformly positive for CD19, CD10, TdT, CD34, MPO and HLA-DR based on the findings of flow cytometry (Fig. 1**A**), thus suggesting the presence of biphenotypic acute leukemia. A chromosomal analysis of the bone marrow cells revealed a complex karyotype including the derivative chromosome der(9)t(7;9)(q11.23;p13) (Fig. 1**B**). Transcripts of *BCR-ABL1*, *ETV6-RUNX1*, *E2A-PBX1*, *MLL-AF4*, *MLL-AF6*, *MLL-AF9* and *MLL-ENL* were not detected. The patient was therefore diagnosed with MPAL of B-lymphoid/myeloid lineage (not otherwise specified).

3. Result and discussion

Three types of PAX5 fusion in B-ALL with t(7;9)(q11.2;p13) and der(9)t(7;9)(q11.2;p13), including *PAX5-ELN*, *PAX5-AUTS2* and *PAX5-POM12*, have been reported thus far [3]. In order to analyze the alteration of the *PAX5* gene in the present case, we utilized the 3′ RACE-PCR method. We detected an aberrant *PAX5* transcript, including exons 1A to 5 and the contiguous intron 5/6 sequence. The presumably truncated PAX5 protein was composed of 256 amino acids. It preserved the paired domain for DNA binding at the N-terminus and acquired an aberrant C-terminus, instead of the transactivation and inhibitory domains for transcription regulation. The expression of this transcript and wild-type transcript (derived from a wild-type allele) in the leukemic blasts was confirmed by reverse transcription (RT)-PCR (Fig. 2).

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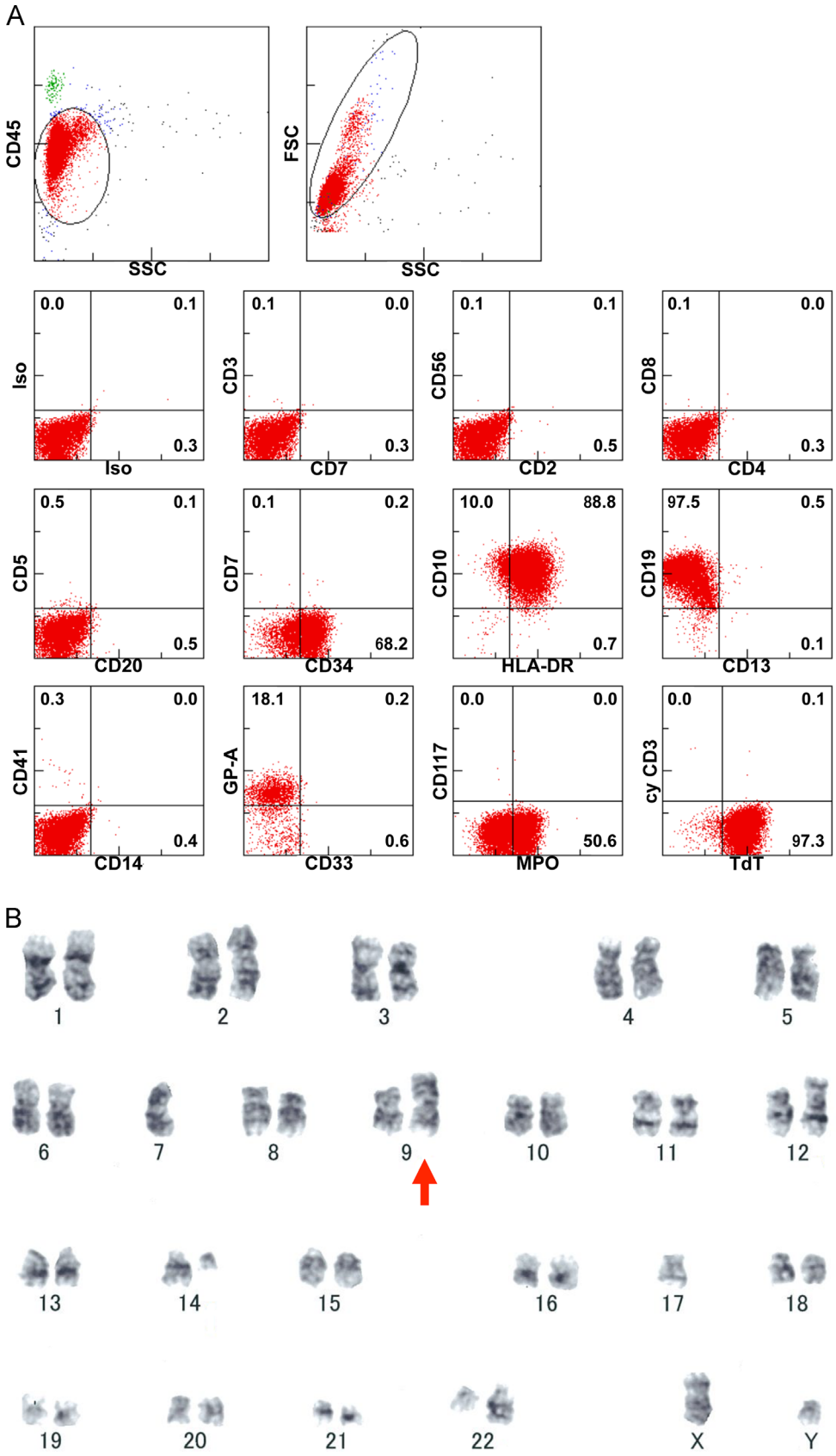

Fig. 1. The characterization of leukemic cells. A. A flow cytometry analysis of the cellular surface markers. The blasts were found to be positive for CD19, CD10, TdT, CD34, MPO and HLA-DR, while they were negative for CD13, CD33 and CD3. B. The cytogenetic analysis of our case. The karyotype panel shows 44, XY, -7, der(9)t(7;9)(q11.2;p13), dic(12;17)(p11.2;p11.2), ?t(14;22)(q13,q13). The red arrow indicates the derivative chromosome der(9)t(7;9)(q11.23;p13). (For interpretation of the references to color in this figure legend,the reader is referred to the web version of this article.)