Letter to the Editor
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The First Case of Acute Myeloid Leukemia With a Novel Five-way Variant Translocation of *RUNX1–RUNX1T1*

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Dear Editor,

The translocation (8;21) is a common mutation observed in 1–5% of patients with AML and is associated with a good prognosis, with a high rate of complete remission and long-term disease-free survival [1, 2]. Approximately 4% of t(8;21) mutations show variant translocations, and most of these rearrangements involve a third and, rarely, a fourth chromosome, including chromosomes 8 and 21 [3-6]. The prognostic effects of variant translocations have not been evaluated [3, 5, 7-9]. We report the first case of a novel five-way variant t(5;10;10;21;8) in AML, a complex form of the variant t(8;21) involving multiple chromosomes. This case study was approved by the Institutional Review Board of Soonchunhyang University Bucheon Hospital (SCHBC 2022-08-001), Bucheon, Korea and was exempted from informed consent.

An 80-year-old man with no specific medical history presented at our hospital with general weakness in January 2022. Complete blood count showed an Hb level of 54 g/L, white blood cell count of 8.21×10^9/L with 60% circulating blasts, absolute neutrophil count of 0.66×10^9/L, and platelet count of 12×10^9/L. Bone marrow biopsy showed hypercellularity (80%), with leukemic blast infiltration. In bone marrow aspirates, up to 74% of cells were blasts, which were large cells with dispersed chromatin, abundant cytoplasm, and prominent nucleoli, some with Auer rods (Fig. 1A). Flow cytometry results indicated that the blasts were positive for CD13, CD33, CD34, CD38, CD117, HLA-DR, and cMPO, indicating AML. G-banding analysis using the bone marrow sample revealed a complex variant translocation of 46, XY,t(5;10;10;21;8)(q22;q22;?p15;q22;q22),del(11)(q14q23) [20] (Fig. 1B). FISH analysis with probes for *RUNX1–RUNX1T1* dual color, dual fusion translocation (Abbott, Abbott Park, IL, USA) showed that 98.4% of cells had one red, one green, and two fusion signals (Fig. 1D). The *RUNX1/RUNX1T1* fusion signals were observed on chromosomes 5 and 8 in metaphase cells (Fig. 1C and D). Multiplex nested reverse transcription PCR confirmed the presence of *RUNX1/RUNX1T1*.

A next-generation sequencing panel targeting 49 genes associated with myeloid malignancy detected variants *FLT3* (internal tandem duplications; 1–2% variant allele frequency [VAF] and NM_004119.2:c.2503G>C, p.Asp835His; 21% VAF), *KIT* (NM_005896.3:c.2447A>T, p.Asp816Val; 14% VAF), and *CBL* (NM_005188.3:c.1150T>C, p.Cys384Arg; 5% VAF). Induction chemotherapy using decitabine, a demethylating agent for the treat-

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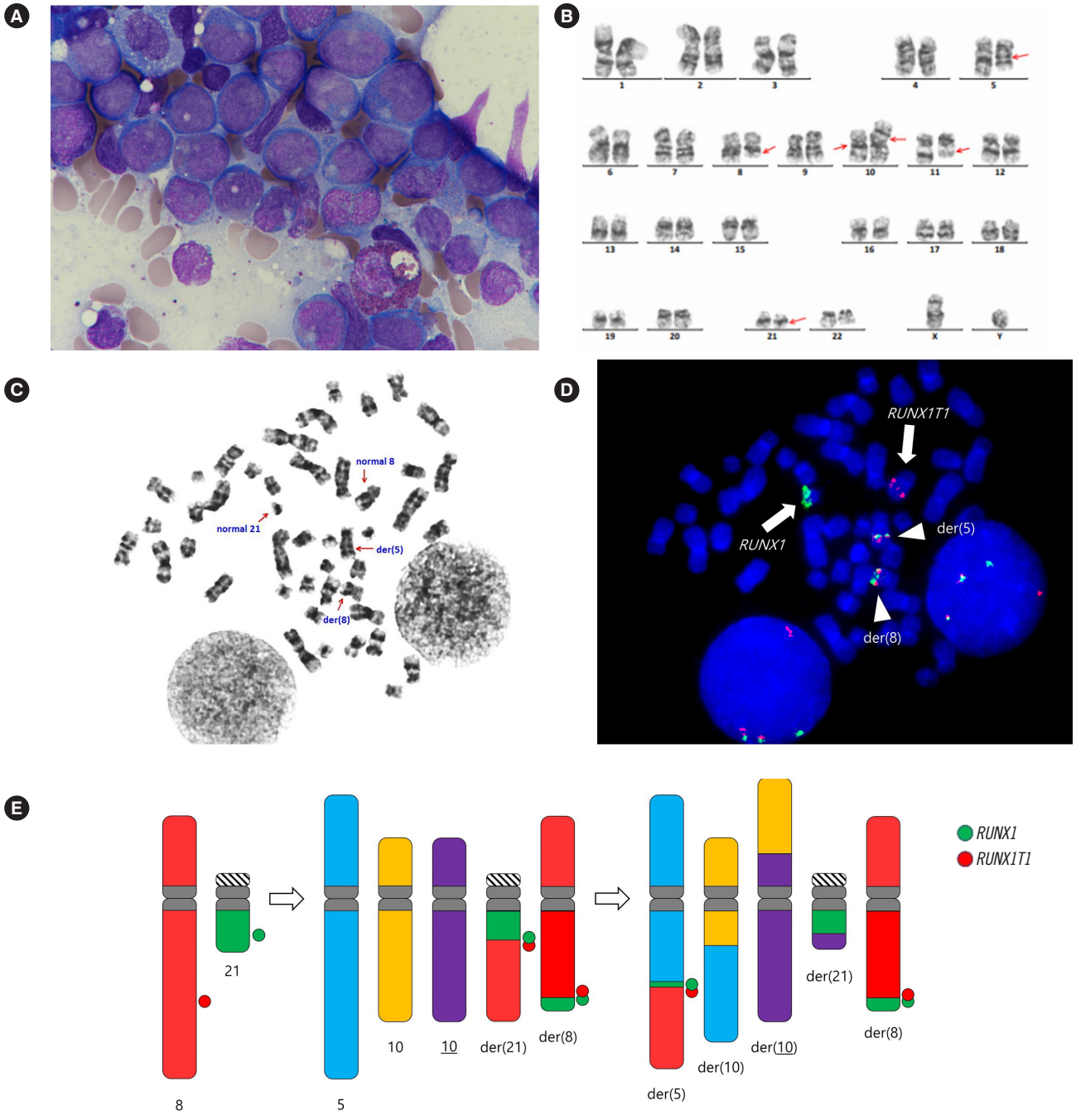

Fig. 1. Hematological and cytogenetic characteristics of the AML patient with novel complex *RUNX1–RUNX1T1* translocation. (A) Bone marrow aspirate (Wright–Giemsa stain, magnification, ×400) and (B) G-banding karyotyping showing t(5;10;10;21;8) (q22;q22;?p15;q22;q22) and del(11)(q14q23). Arrows indicate translocated regions. (C) G-banding metaphase. (D) Dual-color FISH analysis using *RUNX1* (green)- and *RUNX1T1* (red)-specific probes (arrows). One fusion signal is present on der(8), the other on der(5) (arrow heads). (E) Idiogram of G-banding indicating that the mutation likely occurred through a two-step mechanism in which t(8;21)(q22;q22) occurred first, and then the genetic material of der(21) was translocated to chromosome 5.

ment of elderly patients with newly diagnosed AML who are not eligible for standard chemotherapy, was administered five times. Six months after diagnosis, the patient had continuing illness (circulating blasts, 22%) and eventually died of neutropenic fever and sepsis.

Most of the variant t(8;21) cases reported to date contain three

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Table 1. Summary of patients with AML carrying complex *RUNX1–RUNX1T1* translocation

Variable	Vieira, *et al.* [8]	Isik, *et al.* [10]	Huang, *et al.* [6]	Albano, *et al.* [9]	This study
Age at diagnosis, yr	15	39	12	62	80
Sex	Male	Male	Male	Female	Male
Complete blood count					
Hb, g/L	106	131	110	86	54
WBC, 10^9/L	10.6	13.8	1.1	9.0	8.2
Platelet, 10^9/L	105	64	158	155	12
Bone marrow features					
Blasts, %	63	20	15	80	74
Blasts with Auer rods	Yes	Yes	Yes	ND	Yes
Karyotype	45,X,-Y, t(8;17;15;21)(q22;q23;q15;q22)	45,X,-Y, t(8;5;21;4)(q21;q13;q22;q31)	45,X,-Y, t(4;21;8;12)(q31.3;q22;q22;q15)	46,XX, t(8;11;16;21)(q22;q14;q12;q22)	46,XY, t(5;10;10;21;8)(q22;q22;?p15;q22;q22), del(11)(q14q23)
Gene mutation	NA	*KIT* p.Asp820Gly and p.Asn822Lys	NA	NA	*FLT3* ITD and p.Asp835His, *KIT* p.Asp816Val, and *CBL* p.Cys384Arg
Induction chemotherapy	Cytosine arabinoside and mitoxantrone	Cytosine arabinoside and daunorubicin	Daunorubicin, cytarabine, 6-thioguanine	Cytosine arabinoside and mitoxantrone	Decitabine
Remission after induction chemotherapy	Yes	No	Yes	Yes	No
Transplantation	Not done	Done	Done (2 times)	Not done	Not done
Outcome/follow-up	Dead/20 months	Alive/four months	Alive/26 months	Alive/32 months	Dead/six months

Abbreviations: WBC, white blood cell; NA, not available; ITD, internal tandem duplication.

chromosomes and, rarely, four [3-6, 10]. Clinical features, karyotype, and molecular data of variant t(8;21) cases involving four or more chromosomes, including the present case, are summarized in Table 1 [6, 8-10]. Among these cases, three patients achieved complete remission with induction chemotherapy [6, 8, 9], whereas the remaining patient with Y chromosome loss and a *KIT* mutation did not [10]. As our patient received decitabine chemotherapy because of his old age, it is difficult to compare his outcome with those of previously reported patients who received standard chemotherapy. However, the multiple mutations in *FLT3, KIT,* and *CBL* along with the complex karyotypic abnormalities may have adversely affected his prognosis.

The current case showed a novel five-way complex translocation variant involving t(5;10;10;21;8) and relocalization of the *RUNX1–RUNX1T1* fusion gene. Although the mutation mechanism cannot be definitively determined, we expect that the mutation occurred through a two-step mechanism. The first step likely was the occurrence of the standard t(8;21)(q22;q22). This was followed by the translocation of genetic material of der(21) t(8;21) to chromosome 5, which is supported by the fusion signals observed on chromosomes 5 and 8 (Fig. 1E). In two previous cases, *RUNX1–RUNX1T1* fusion signals appeared on chromosomes other than 8 or 21, as in our case, i.e., on chromosome 1 [5] and chromosome 5 [10]. The clinical significance of the fusion gene relocalization remains to be elucidated.

In conclusion, we report the first case worldwide of *RUNX1–RUNX1T1*-associated AML with a novel variant translocation involving five chromosomes, which was associated with a poor prognosis. Further clinical observations and comprehensive cytogenetic and molecular data are needed to determine the importance of variant translocations on prognosis and to elucidate the complex mechanisms of their origin.

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AUTHOR CONTRIBUTIONS

Jo YH collected the data and wrote the manuscript. Park SK was involved in clinical evaluation. Han EA and Jeon BR performed the cytogenetic analysis. Jang MA supervised the study and ed-

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CONFLICTS OF INTEREST

None declared.

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