Letter to the Editor
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First Case of Double T-Cell Receptor Alpha/Delta Rearrangements of t(11;14) and inv(14) and Subsequent *JAK2* Rearrangement in a Patient With T-cell Acute Lymphoblastic Leukemia

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Dear Editor,

Primary cytogenetic abnormalities of T-cell ALL (T-ALL) frequently involve rearrangements between oncogenic transcription factor genes and T-cell receptor (TCR) loci. These are usually mutually exclusive and associated with specific genetic subgroups [1, 2]. We report the first case, to our knowledge, of T-ALL showing distinct and rare abnormalities of sequential TCR alpha/delta (*TRA/D*) locus rearrangements associated with t(11;14)(p13;q11.2), inv(14)(q11.2q32), and clonal evolution of *JAK2* rearrangement. This report was approved by Asan Medical Center Institutional Review Board, Seoul, Korea (S2019-1375-0001).

A 21-years-old man was admitted to Asan Medical Center in September 2017, with chest discomfort, petechiae, and oral bleeding. The study period was six months from admission. On admission, his hemogram showed a white blood cell count of 55×10^9/L with 68% lymphoblasts, 141 g/L Hb, and 71×10^9/L platelets. Computed tomography revealed a mediastinal mass, and a bone marrow (BM) examination showed that 90% of nucleated cells were lymphoblasts (Fig. 1A). The immunophenotype of the lymphoblasts by four-color flow cytometric analysis (BD FACSCanto II; BD Biosciences, San Jose, CA, USA) was positive for CD2, CD7, CD8, terminal deoxynucleotidyl transferase, and cytoplasmic CD3. The karyotype of the BM cells was 47,XY,del(6)(q13q23),+8,t(11;14)(p13;q11.2),inv(14)(q11.2q32)[13]/46,XY[22] (Fig. 1B). Metaphase fluorescence *in situ* hybridization (FISH) analysis using the Vysis LSI *TRA/D* Dual Color Break Apart Rearrangement Probe (Abbott Laboratories, Abbott Park, IL, USA) showed double *TRA/D* rearrangements associated with t(11;14) and inv(14) (Fig. 1C), while interphase FISH revealed a single *TRA/D* rearrangement in 12.5% of the cells and double *TRA/D* rearrangements in 74.0% of the cells (Fig. 1D).

The patient received two cycles of cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) for a month and achieved partial remission on day 47. Three weeks later, he was readmitted with disease progression. The follow-up BM examination showed 57.4% lymphoblasts, increased eosinophils (4%), and focal fibrosis (MF-1) (Fig. 2A and 2B). The BM karyotype was 47,XY,del(6)(q13q23),+8,t(8;9)(p22;p24),t(11;14)(p13;q11.2),inv(14)(q11.2q32)[20]/46,XY[10] including clonal evolution of t(8;9)(p22;p24) (Fig. 2C). The t(8;9)(p22;p24) component showed a *JAK2* rearrangement by FISH analysis using the JAK2 Break Apart FISH Probe (Empire Genomics LLC, Buffalo,

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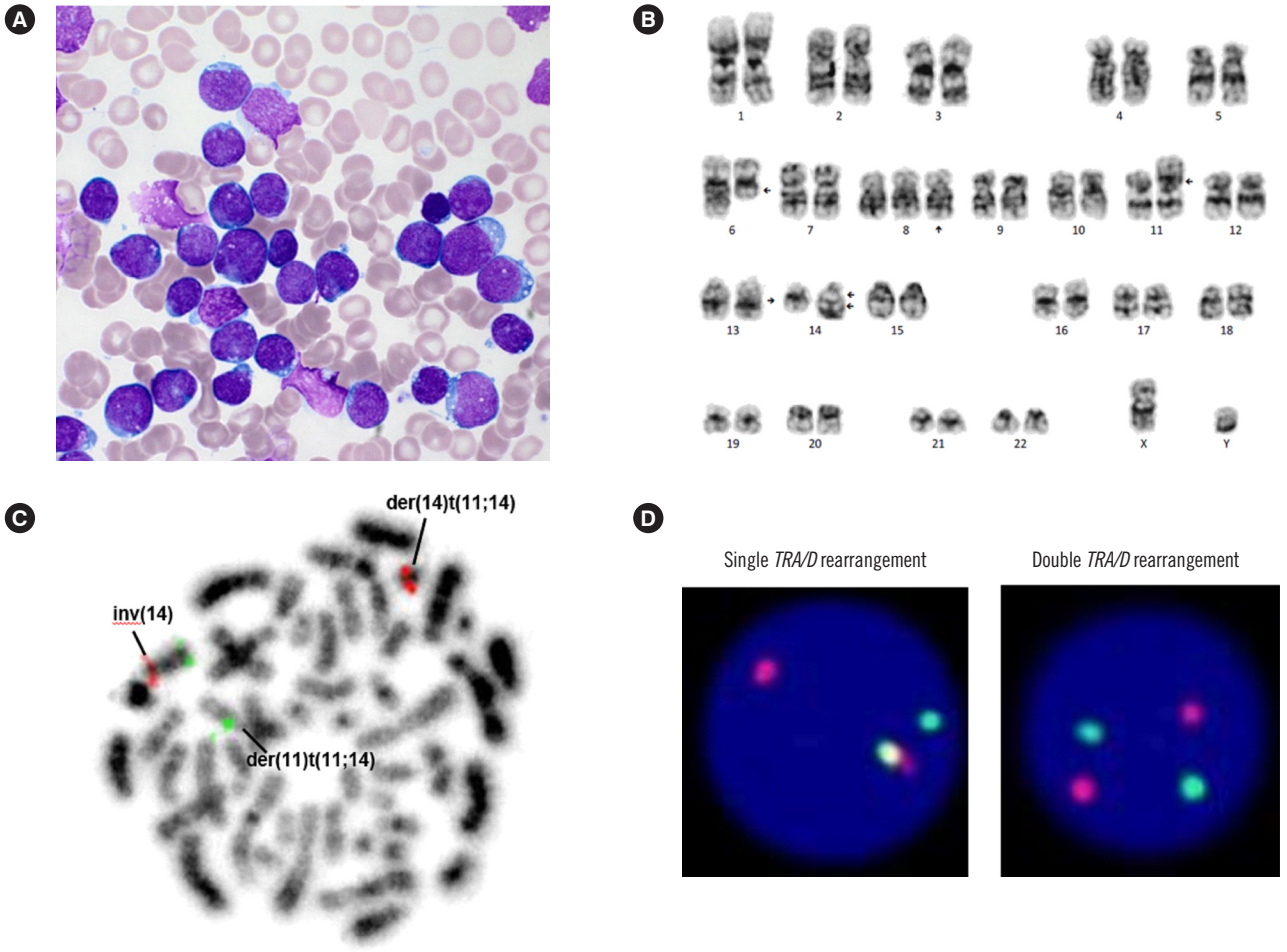

Fig. 1. BM examination, karyotyping, and FISH analysis at diagnosis. (A) Lymphoblasts on the BM aspirate smear (Wright-Giemsa, ×1,000). (B) BM karyogram. (C, D) Metaphase and interphase FISH analyses with TRA/D Dual Color Break Apart Rearrangement Probe for 14q11.2 (5′*TRA/D*: SpectrumRed, 3′*TRA/D*: SpectrumGreen).
Abbreviations: BM, Bone marrow; FISH, fluorescence *in situ* hybridization; inv, inversion; der, derivative chromosome; *TRA/D*, T-cell receptor alpha/delta.

NY, USA) (Fig. 2D). Metaphase and interphase FISH at diagnosis was negative for *JAK2* rearrangement. Reverse transcriptase -PCR analysis using several primer sets for hotspot breakpoints of *PCM1* (exons 23, 26, 36) and *JAK2* (exons 3, 9, 11, 17) failed to detect the *PCM1-JAK2* fusion transcript; these are most commonly associated with t(8;9)(p22;p24) [3, 4]. Sequencing of *NOTCH1* revealed an in-frame deletion of the heterodimerization (HD) domain (NM_017617.5:c.4732_4734delGTG (p.V1578del)) and a nonsense mutation in the proline/glutamic acid/serine/threonine (PEST) domain (NM_017617.5:c.5707C>T (p.Q2503*)). We further investigated malignant clones, using a bacterial artificial chromosome FISH probe for RP11-162F6 (Aqua, 11p13), which covers the *LMO2* gene. FISH analysis using the RP11-162F6 and *TRA/D* probes showed that *LMO2* was fused with 5′*TRA/D* in all cells with a single *TRA/D* rearrangement as well as double *TRA/D* rearrangements (Fig. 2E). This indicated that t(11;14) was probably the primary event, rather than inv(14), as a single *TRA/D* rearrangement was associated with *LMO2* rearrangement.

The patient was refractory to chemotherapy regimens. He died four months later, after disease progression.

The t(11;14)(p13;q11.2) component is associated with *LMO2* on 11p13 and *TRA/D* on 14q11.2 and is found in 6% of T-ALL patients [1]. Nevertheless, inv(14)(q11.2q32) is very rare in T-ALL. In cases of T-ALL with inv(14)(q11.2q32), possible coexistence with rearrangements of other TCR loci, such as add(7)(q34), t(11;14)(p13;q11.2) and t(8;14)(q24;q11.2), has been reported, indicating that inv(14)(q11.2q32) could constitute a combined cytogenetic abnormality causing T-ALL [5, 6]. *BCL11B* and *TRD* may be associated with inv(14)(q11.2q32) [7].

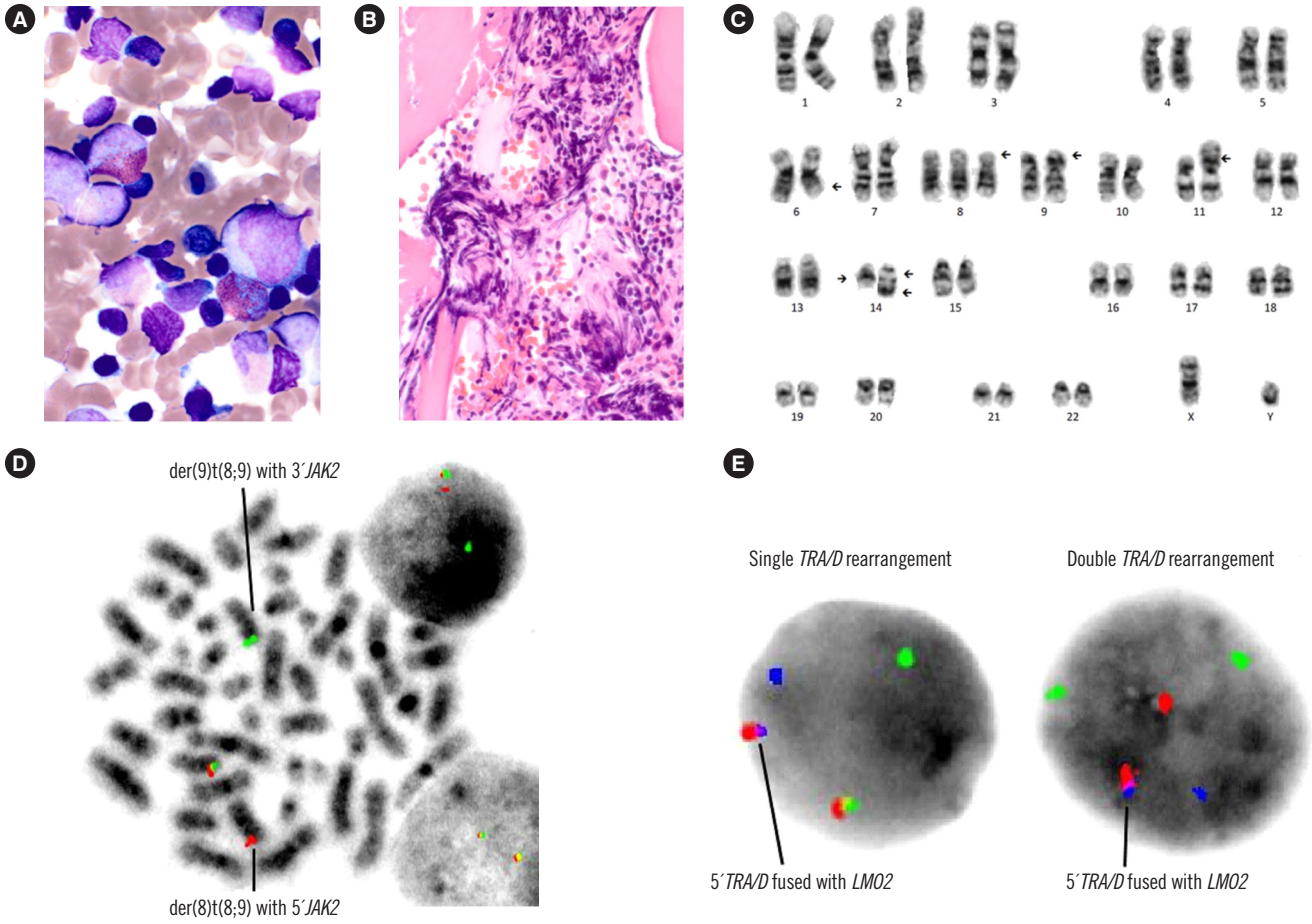

Fig. 2. BM examination, karyotyping, and FISH analysis at follow-up. (A) Eosinophils (Wright-Giemsa, ×1,000) and (B) focal fibrosis (HE, ×400). (C) BM karyogram. (D) Metaphase and interphase FISH analyses with JAK2 Break Apart FISH Probe for 9p24.1 (5´*JAK2*: Red, 3´*JAK2*: Green). (E) Interphase FISH analysis with RP11-162F6 (LMO2) for 11p13 (Aqua) and TRA/D Dual Color Break Apart Rearrangement Probe for 14q11.2 (5´*TRA/D*: SpectrumRed, 3´*TRA/D*: SpectrumGreen).
Abbreviations: BM, Bone marrow; HE, hematoxylin and eosin; FISH, fluorescence *in situ* hybridization; der, derivative chromosome; TRA/D, T-cell receptor alpha/delta.

Most cases in a provisional category of myeloid/lymphoid neoplasms associated with t(8;9)(p22;p24.1) and *PCM1-JAK2* are considered myeloid neoplasms, and only a few cases are B-cell ALL (B-ALL) or T-cell lymphoma [8]. A recent study reported that hematopoietic neoplasms with *JAK2* rearrangement are extremely rare, and most are associated with *PCM1-JAK2* rearrangement [9]. Our patient, who had a *JAK2* rearrangement of t(8;9)(p22;p24.1) as a clonal evolution, shared the characteristics of the entity with *PCM1-JAK2* rearrangement such as eosinophilia and fibrosis on follow-up BM examination. A *JAK2* inhibitor, such as ruxolitinib, would be effective for treating patients with ALL involving *JAK2* rearrangement [10].

The t(11;14)(p13;q11.2) component was probably the primary cytogenetic event, with inv(14) and t(8;9) occurring successively. Clonal evolutions, dual *NOTCH1* mutations, and additional chromosomal abnormalities may contribute to a rapidly progressive clinical course. Follow-up cytogenetic evaluations and supporting tests, including FISH, are important to detect cytogenetic clonal evolution.

Author Contributions

All authors equally contributed to this study. All authors have accepted their responsibility for the entire content of this manuscript and approved submission.

Conflict of Interest

None declared.

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