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The First Korean Case of Childhood Acute Myeloid Leukemia with Inv(11)(p15q22)/*NUP98-DDX10* Rearrangement: A Rare but Recurrent Genetic Abnormality

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Inv(11)(p15q22)/*NUP98-DDX10* rearrangement is a rare but recurrent chromosomal translocation associated with myeloid malignancies. Structural chromosomal rearrangements of the nucleoporin 98 gene (*NUP98*) at 11p15.4 produce *NUP98* fusions with the DDX10 DEAD (Asp-Glu-Ala-Asp) box polypeptide 10 (*DDX10*) gene on chromosome 11q22 [1]. To date, only 15 such cases, except the present case, with *de novo* or therapy-related myeloid disorders have been reported [1-8]. Three *NUP98-DDX10* fusion isoforms, types I, II, and III, have been reported. The type I fusion, which fuses *NUP98* exon 12 (NM_139131.1) with *DDX10* exon 6 (NM_004398.2), has been reported in 2 adult therapy-related AML patients [1, 8]. The type II fusion, which fuses *NUP98* exon 14 with *DDX10* exon 7, has been reported in 12 cases. The type III fusion, which fuses *NUP98* exon 15 and *DDX10* exon 7, has been reported in 1 adult *de novo* AML patient with a concurrent case of type II fusion [7]. Herein we report a *de novo* childhood AML patient with inv(11)(p15q22)/*NUP98-DDX10* rearrangement for the first time in Korea.

A 4-yr-old boy presented with petechiae and easy bruising. His complete blood count revealed the following: Hb, 7.7 g/dL; leukocyte count, 7.64×10^9/L (absolute neutrophil count, 0.32×10^9/L); and platelets, 42×10^9/L. Additional analysis of the peripheral blood revealed 15% myeloblasts and leukoerythroblastic features. The bone marrow (BM) study showed 55% blasts with dysplastic erythropoiesis and megakaryopoiesis, suggesting AML with myelodysplasia-related changes. The estimated cellularity of the BM section was variable at 10-100% (overall 50%). Flow cytometry revealed that the blasts were positive for CD13, CD33, CD64, CD11c, CD117, cMPO, HLA-DR, and CD34 (CD64 and CD34 were weakly expressed). Chromosomal analysis performed on a short-term culture of BM cells using the Giemsa banding technique revealed that the patient's karyotype was 46,XY,inv(11)(p15q22)[19]/46,XY[1] (Fig. 1). FISH analysis with probes for EGR1 (5q-), D7S522 (7q-), TP53/CEP17 [i(17q)/t(17p)], and MLL [t(11q23)] (Vysis, Downers Grove, IL, USA) showed no cytogenetic abnormalities. The HemaVision (DNA Technology, Aarhus, Denmark) screen was negative for all detectable fusion transcripts. Mutation analyses for *NPM1* and internal tandem duplications of *FLT3* and *CEBPA* were negative. One microgram of total RNA was reverse transcribed for reverse transcription (RT)-PCR experiments for further evaluation of cytogenetic abnormalities. The *NUP98-DDX10* fusion transcript was detected by using previously described primers [1], and

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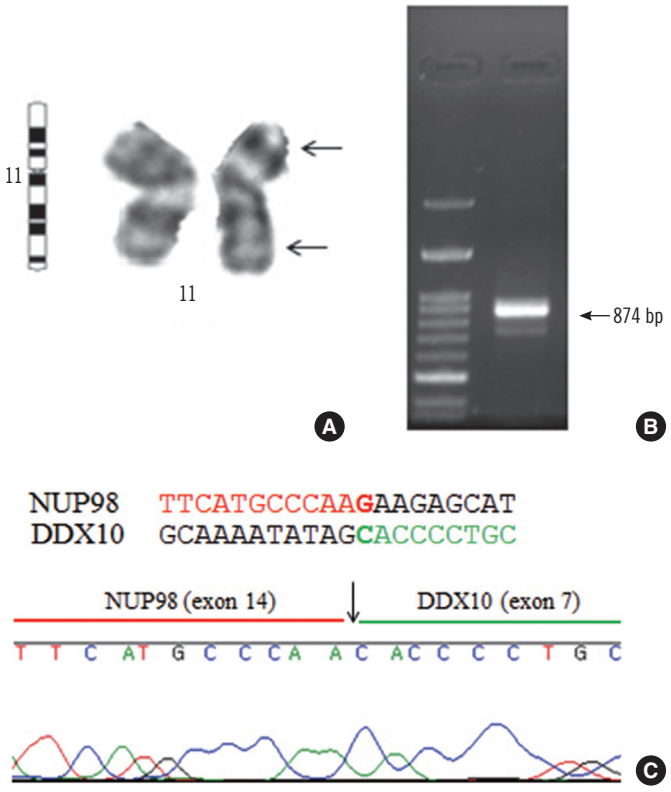

Fig. 1. Karyotyping, reverse transcription (RT)-PCR, and sequence analyses of the *NUP98-DDX10* fusion transcripts in the present case. (A) Giemsa-band karyotype with 400-band resolution showing inv(11)(p15q22). (B) RNA samples from the patient's leukemic cells were amplified by RT-PCR using *NUP98* and *DDX10* primers; molecular weight marker, 100-bp ladder (left); patient's results showing the 874-bp *NUP98-DDX10* fusion transcripts (right). (C) Direct sequencing of the RT-PCR product from the patient's leukemic cells. Sequences adjacent to the junction are shown and exon 14 of *NUP98* and exon 7 of *DDX10* are indicated (type II fusion). The arrow indicates the junction points of the 2 genes.

sequence analysis revealed an in-frame fusion between *NUP98* nucleotide 1907 (exon 14) and *DDX10* nucleotide 914 (exon 7), which presented as a type II fusion (Fig. 1). After the patient received induction chemotherapy, follow-up BM examination and cytogenetic analyses showed no residual leukemic cells with the 46,XY karyotype [20]. The patient tolerated a 4-month follow-up period of consolidation chemotherapy quite well.

Among the 29 *NUP98* fusion partners and their fusion transcripts, the *NUP98-DDX10* rearrangement, which encodes proteins that contain a coiled-coil domain that is thought to function in the oligomerization of proteins, has been reported to increase the proliferation and self-renewal of primary human CD34+ cells and disrupt their erythroid and myeloid differentiation [9, 10]. Among the 16 reported *NUP98-DDX10*-positive cases including the present case, 8 were children and 8 were adults. Nine of them were *de novo* (7 AML, 1 MDS, 1 accelerated phase of CML) and 6 were therapy-related cases (3 AML, 2 MDS, and 1 chronic myelomonocytic leukemia) [1-7]. For the remaining 1 case, the information whether the case was therapy-related or not was not available [8]. Male predominance was observed (12/16 cases). Although the prognostic implications of the *NUP 98/DDX10* rearrangement have not been clearly identified, nucleoporin-associated malignancies tend to occur at a younger age and have a poor outcome [2-4, 6-8]. The majority of reported cases showed evidence of monocytic differentiation: AML-M4 and AML-M5, according the French–American–British classification, and chronic myelomonocytic leukemia (CMML) [1-3, 5-7]. Although this patient's leukemic cells were not morphologically monocytic, flow cytometry showed that they were positive for monocytic markers (CD64 and CD11c). Cytogenetically, the reported *NUP98-DDX10* fusions were derived from diverse rearrangements of chromosome 11 [i.e., inv(11) (14 cases), insertion (1 case), or reciprocal translocation (1 case)]. Among the 3 *NUP98-DDX10* fusion isoforms derived from alternative splicing, all reported childhood AML patients had type II isoforms. Although alternative splicing mechanisms have been suggested to play different roles in leukemogenesis involving other *NUP98* fusions, the mechanism and impact of nonrandom breakpoint localization within *NUP98* fused with *DDX10* are yet to be clarified [6, 7]. Considering its possible cryptic nature, identifying the *NUP98-DDX10* rearrangement could contribute to expanding its use as a marker for minimal residual disease and future therapeutic approaches [6].

Here, we describe a *de novo* childhood AML patient with *NUP98-DDX10* rearrangement (type II fusion) and inv(11)(p15q22) as the sole karyotypic abnormality, comparable to previous studies. Due to its possible association with adverse clinical outcomes, further studies are required to explore the implications of this karyotypic abnormality.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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