Chromosome t(7;11)(p15;p15) translocation in acute myeloid leukemia coexisting with multilineage dyspoiesis and mutations in *NRAS* and *WT1*: A case report and literature review

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Abstract. The chromosomal translocation t(7;11)(p15;p15) and the resulting nucleoporin 98-homeobox A9 (*NUP98-HOXA9*) gene fusion is rare but recurrent genetic abnormity in acute myeloid leukemia (AML). The present study describes a case of AML plus maturation (-M2) with multilineage dyspoiesis in a 30-year-old male in whom a 46,XY,t(7;11)(p15;p15) karyotype was detected through chromosome analysis. Subsequent molecular and sequencing analysis demonstrated a *NUP98-HOXA9* fusion gene with a type I fusion between *NUP98* exon 12 and *HOXA9* exon 1b, and mutations in neuroblastoma V-Ras oncogene homolog and Wilms tumor 1. The patient achieved hematological complete remission (CR) following two courses of induction chemotherapy. However, the *NUP98-HOXA9* fusion gene remained detectable during the hematological CR period and following intensive consolidation chemotherapy. The disease relapsed 11 months after diagnosis, and the patient became refractory, with complications from an infection causing eventual mortality. The present case and literature review suggest that patients with AML and t(7;11) may have unique biological and clinical characteristics, and a poor prognosis.

Introduction

Acute myeloid leukemia (AML) is a biologically and clinically heterogeneous disorder, characterized by immature myeloid cell proliferation and bone marrow failure (1). The most common subtype of AML (M0-M7) is M2 under FAB classification (2,3). In total ~52% of adult patients with *de novo* AML are reported to carry at least one type of chromosomal abnormalities (e.g. translocations or deletions) (3). A number of recurrent chromosomal aberrations and gene mutations involved in hematopoietic proliferation and differentiation have been used as critical risk stratification tools, including chromosomal translocations t(8;21) and t(15;17), and internal tandem duplication of Fms-related tyrosine kinase 3 (*FLT3*) mutations (3,4). The 5-year overall survival rates for each risk group (favorable, intermediate and adverse-risk) are ~55, ~24 and ~5%, respectively (3). However, prognosis remains markedly different for each risk group (4). Therefore, there is a requirement to identify additional genetic alterations that are associated with prognosis.

The chromosomal translocation t(7;11)(p15;p15) is a rare genetic lesion in AML, which was initially reported in a patient with chronic myeloid leukemia (CML) more than 30 years ago (5). This translocation results in a fusion of the N-terminal portion of nucleoporin 98 (*NUP98*) with the homeodomain of several homeobox A (*HOXA*) genes, including *HOXA9*, *HOXA11* and *HOXA13*; the most common fusion is *HOXA9* (6-8). The association between clinical and biological characteristics from AML patients with this type of fusion remains to be fully elucidated. The present study reports the case of a male patient with AML-M2 and t(7;11) translocation resulting in a *NUP98-HOXA9* fusion gene. The patient demonstrated dyspoietic alterations, neuroblastoma V-Ras oncogene homolog (*NRAS*) and Wilms tumor 1 (*WT1*) mutations and a poor prognosis.

Case report

A 30-year-old male was admitted to Affiliated Cancer Hospital of Zhengzhou University (Zhengzhou, China) following 2 weeks of pain in each leg in August 2015. The patient presented with pale skin and sternal tenderness. Peripheral blood analysis identified a white blood cell count of 32.2×10^9/l (normal range, $4\text{-}10 \times 10^9$/l), with 44% blasts and 26% monocytes (normal range, 3-8%), a hemoglobin level of 110 g/l (normal range, 120-160 g/l) and a platelet count of 87×10^9/l (normal range, $100\text{-}300 \times 10^9$/l). A bone marrow (BM) smear demonstrated a markedly hypercellular BM,

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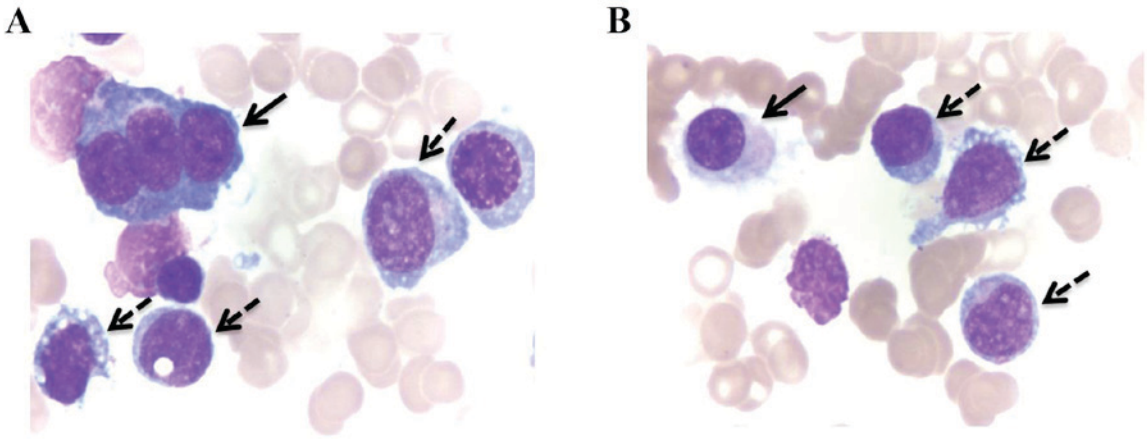

Figure 1. Representative images of increased myeloblasts with multilineage dyspoiesis in bone morrow smears. (A) Increased myeloblasts with dysplastic erythrocytopoiesis. The solid arrow indicates a multinucleated red blood cell and the dashed arrows indicate myeloblasts. (B) Increased myeloblasts with dysplastic megakaryocytopoiesis. The solid arrow indicates a micromegakaryocyte and the dashed arrows indicate myeloblasts. Wright-Giemsa staining; magnification, x1,000.

with 71% myeloblasts, and a positive result for myeloperoxidase staining, which suggested an AML-M2 subtype (2). Dyspoietic alterations, including multinucleated erythrocyte precursors and micromegakaryocytes, were identified (Fig. 1). Subsequently, immunophenotyping was performed on a multi-color flow cytometer (BD FACSCalibur; BD Biosciences, Franklin Lakes, NJ, USA) with monoclonal antibodies in 1:1 dilutions, including cluster of differentiation (CD) 34-fluorescein isothiocyanate (FITC) (catalog no. 555821), human leukocyte antigen-antigen D-related (HLA-DR)-allophycocyanin (APC) (catalog no. 340549), CD13-phycoerythrin (PE) (catalog no. 347837), cytoplasmic myeloperoxidase (cMPO)-FITC (catalog no. 340580), CD15-FITC (catalog no. 332778), CD20-APC (catalog no. 340941) cytoplasmic (c)CD3-APC (catalog no. 340440), CD5-APC (catalog no. 340583), CD11b-APC (catalog no. 340937) and CD3-APC (catalog no. 555335), all of which were purchased from BD Biosciences. Immunophenotyping was also performed with the following antibodies in 1:1 dilutions: CD33-PE (catalog no. 555450; BD Pharmingen, San Diego, CA, USA), CD117-PE (catalog no. 340529; BD Pharmingen), CD56-PE (catalog no. A07788; Beckman Coulter, Inc., Brea, CA, USA), CD7-PE (catalog no. IM1429U; Beckman Coulter, Inc.), CD19-FITC (catalog no. A07768; Beckman Coulter, Inc.), CD4-FITC (catalog no. A07750; Beckman Coulter, Inc.), CD2-FITC (catalog no. A07743; Beckman Coulter, Inc.), CD10-PE (catalog no. A07760; Beckman Coulter, Inc.), CD14-FITC (catalog no. 0645U; Beckman Coulter, Inc.) and cCD79a-PE (catalog no. IM2221; Beckman Coulter, Inc.).

Blasts were positive for CD34, HLA-DR, CD13, CD33, CD117 and cMPO antigens, and negative for CD56, CD7, CD15, CD19, CD4, CD2, CD10, CD20, CD3, CD5, CD11b, CD14, cCD79a and cCD3 antigens. These results confirmed that the blasts were committed to being myeloid precursors.

Chromosome analysis using the R-banding method identified a 46,XY,t(7;11)(p15;p15) karyotype in all 20 metaphase cells (Fig. 2). *NUP98-HOXA9* was identified via a screen of leukemia-associated fusion genes using a multi-fusion gene detection system (43 Fusion Gene Screening kit; Shanghai Yuanqi Biopharmaceutical Company, Ltd., Shanghai, China) (9). The copy of the *NUP98-HOXA9* fusion transcript was subsequently detected by reverse transcription-quantitative polymerase chain reaction (RT-qPCR) using Leukemia Related Fusion Gene Fluorescent qPCR Detection kit (Shanghai Shenyou Bio Technology Co., Ltd., Shanghai, China) with a *NUP98-HOXA9*/Abelson tyrosine-protein kinase 1 (*ABL1*) ratio of 0.71. The sequences of primers were designed as previously reported (10). PCR was performed on an ABI PRISM 7000 machine (Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, MA, USA) under the conditions as previously described (11) and quantified using the standard curve method (12). The experiment was repeated independently three times.

To date, four types of fusion transcripts have been reported, which appear to result from alternative splicing of *NUP98* and *HOXA9* and each fusion is in-frame (10). In this case, detection of the *NUP98-HOXA9* breakpoint was performed by RT-PCR and sequencing as previously described (10). Analysis demonstrated a type I fusion transcript, which means that the breakpoint of *NUP98-HOXA9* is between *NUP98* exon 12 and *HOXA9* exon 1b (10) (Fig. 3). Subsequently, 1 point mutation in *NRAS* and 2 point mutations in *WT1* were detected using the next generation sequencing (NGS)-based multigene mutational screening system on an Ion-Torrent Personal Genome machine (Thermo Fisher Scientific, Inc.) (13). The gene screening profile and results are summarized in Table I.

Following diagnosis, the patient was treated with induction chemotherapy for 7 days using a combination of daunorubicin (80 mg/day for 3 days) and cytosine arabinoside (Ara-c; 200 mg/day for 7 days). After 3 weeks, the patient demonstrated hematological complete remission (CR), with 1.6% myeloblasts in the BM smear. The repeat RT-qPCR revealed a decrease in the *NUP98-HOXA9*/*ABL1* ratio to 0.0076. Subsequently, the patient underwent 4 courses of consolidation chemotherapy with a high-dose Ara-c (HD-Ara-c) regimen (1.5 g/m^2 q12 h on days 1, 3 and 5) at the same time as seeking an HLA-matched sibling or unrelated donor for allogenic-hematopoietic stem cell transplantation (HSCT). During this period, repeated BM and fusion examinations were performed 4 times. Hematological CR was observed in the 4 tests, however, the *NUP98-HOXA9*/*ABL1* ratio remained detectable, with a lowest level of 0.0023.

Table I. Leukemia-associated fusion genes and mutation-screened genes.

Fusion and mutation gene screening profile
Fusion genes for screening
AML1-ETO, AML1-MDS1/EV11, AML1-MTG16, BCR-ABL, CBFβ-MYH11, DEK-CAN, E2A-HLF, E2A-PBX1, ETV6-PDGFRA, FIP1L1-PDGFRA, MLL-AF4, MLL-AF9, NPM-MLF, PML-RARα, PLZF-RARα, SET-CAN, SIL-TAL1, STAT5b-RARα, TEL-ABL, TEL-JAK2, TEL-PDGFRβ, TLS-ERG, MLL-(AF6, AF10, AF17, AF1q, AF1p, AFX, ELL, ENL, SEPT6), NUP98-(HOXA13, HOXA11, HOXA9[a], HOXC11, HOXD13, PMX1), (NPM, FIP1L1, PRKAR1A, NUMA1)-RARα
Genes for mutational detection
AKT3, ASXL1, ATRX, BCOR, CBL, CCND1, CDKN2A, CEBPA, CREBBP, CSF1R, CSF3R, DNMT3A, EP300, ETV6, EZH2, FLT3, GATA2, IDH1, IDH2, IKZF1, JAK3, KIT, KRAS, MLH1, MPL, NOTCH1, NOTCH2, NPM1, NRAS[b], PHF6, PTPN11, RAD21, RUNX1, SETBP1, SRSF2, STAG2, STAT3, TET2, TP53, U2AF1, WT1[c], ZRSR2

[a]*NUP98-HOXA9*-positive; [b]*NRAS* point mutation (exon 2, c.38G>A, p.Gly13Asp); [c]*WT1* point mutations (exon 7, c.1109G>C, p.Arg370Pro; exon 7, c.1144_1145insTCGG, p.Ala382fs). *NUP98*, nucleoporin 98; *HOXA13*, homeobox A9; *NRAS*, neuroblastoma rat sarcoma viral oncogene homolog; WT1, Wilms tumor 1.

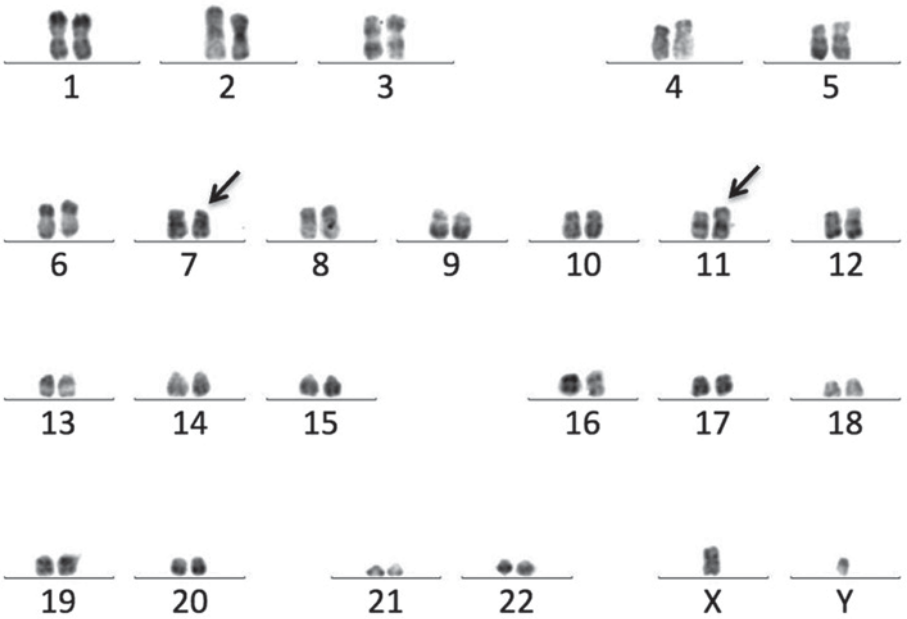

Figure 2. t(7;11)(p15;p15) karyotype from the patient with acute myeloid leukaemia. The arrows indicate translocations in chromosomes 7 and 11.

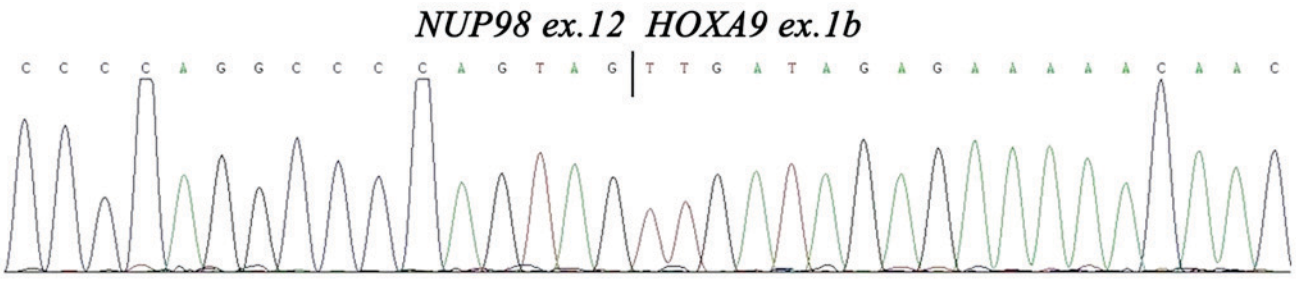

Figure 3. Sequence analysis of the type I *NUP98-HOXA9* fusion transcript. The vertical line indicates the joining point between the two genes. *NUP98*, nucleoporin 98; *HOXA9*, homeobox A9; ex., exon; c, cytosine; a, adenine; g, guanine; t, thymine.

Due to the failure to find an HLA-matched donor, it was suggested that the patient should receive autogenic-HSCT. However, following treatment with a further course of HD-Ara-c chemotherapy (1.5 g/m^2 q12 h on days 1, 3 and 5) as a hematopoietic stem cell mobilization method, the disease reoccurred 11 months after the original diagnosis (June 2016).

A BM smear indicated 46% myeloblasts, with the presence of micromegakaryocytes. The *NUP98-HOXA9/ABL1* ratio was markedly increased to 0.079. Cytogenetic analysis and NGS demonstrated the same 46,XY,t(7;11)(p15;p15) karyotype and *NRAS* and *WT1* mutations as the diagnostic tests, which indicates that there was no genetic evolution of the tumor. The disease became refractory, and the patient contracted severe pneumonia and respiratory failure, which caused mortality 1 month after recurrence.

Discussion

The role of *NUP98-HOXA9* in leukemogenesis has been repeatedly demonstrated in the past two decades. The transforming potential for the development of leukemia may require other cooperative factors (10). Using transgenic mouse models, breakpoint cluster region (*BCR*)/*ABL* was observed to interact with *NUP98-HOXA9* and promote AML development in CML progression (14). Using retroviral insertional mutagenesis, myeloid ecotropic viral integration site 1 homolog (*Meis1*), dynein axonemal light chain 4, Fc fragment of IgG receptor IIb, Fc receptor-like and Con1 glycoprotein were identified as co-factors that associate with *NUP98-HOXA9* in myeloid leukemogenesis (15). The most frequent of these associations was with *Meis1*, and the interaction between *Meis1* and *NUP98-HOXA9* reduces the latency of AML development (16). Furthermore, microarray analysis of human CD34-positive hematopoietic cells also identified oncogenes that may potentially associate with the *NUP98-HOXA9*, including the homeobox transcription factors, *FLT3*, c-kit proto-oncogene and *WT1* (17). The following four gene mutations, *FLT3*-internal duplications, *NRAS*, Kirsten rat sarcoma viral oncogene homolog (*KRAS*) and *WT1* have been identified with the *NUP98-HOXA9* in a total of 7 patients with AML and t(7;11) (10,18). *KRAS* and *WT1* mutations demonstrated a significantly association with the *NUP98-HOXA9* fusion gene (10). In the present study, a novel gene mutation group of *NRAS* and *WT1* mutations was found to coexist with *NUP98-HOXA9* at the initial diagnosis and at the relapse. As *RAS* and *WT1* mutations are key components of the proliferative drive of AML (19,20), taken together with previous studies, the present study indicates these gene alterations may cooperate with *NUP98-HOXA9* in promoting the development and relapse of leukemia.

Previous studies have established that patients with AML and t(7;11) have distinct epidemic and clinical characteristics. A literature review was performed using the PubMed database to search for the keywords 't(7;11)', 'acute myeloid leukemia' (www.ncbi.nlm.nih.gov/pubmed/?term=t(7%3B11)+AND+acute+myeloid+leukemia). Patient characteristics including gender, age (years) and French-American-British (FAB) classification subtypes (2) were recorded. To date, only 57 adult patients (7,10,18,21-34) were recorded with *de novo* AML in the literature. The majority of the case studies (98.2%, 56/57) originated in Japan or China. The incidence rate of t(7;11) on *de novo* adult patients with AML was low at 0.68-2.23% (10,18,27,28,30). For these 57 patients, the median onset age was 36 years (range, 31-38 years) and 63.1% (36/57) were female. A total of 54 patients had FAB classification subtypes and 68.5% (37/54) of these patients has an M2-subtype (7,10,18,21-34). These characteristics of being predominantly younger, being female and having an M2-subtype were statistically proven in a large sample study by Chou *et al* (10) by comparing 11 patients carrying t(7;11) translocations with another 482 adult patients with AML. The case identified by the present study was also of a patient of a young age and with an M2 subtype, which is concordant with these previous studies.

In the present study, marked concomitant abnormal myelopoiesis, including dysplastic erythrocytopoiesis and megakaryocytopoiesis, were established from a *de novo* bone morrow smear. Similarly, previous studies have identified t(7;11) in AML patients to be associated with myelodysplasia (MDS) or myeloid maturation (10,21,27,30,31). A transgenic murine model with the *NUP98-HOXA9* fusion gene also acquired myeloproliferative disorder and subsequently developed AML (35). Although it is primarily observed in AML, t(7;11) has also been identified in patients with MDS (36), CML (5,37) and juvenile myelomonocytic leukemia (8). Therefore, the present study is concordant with the hypothesis that t(7;11) may affect multipotent myeloid stem and progenitor cells.

Patients with AML that have t(7;11) exhibit aggressive clinical progression and a poor prognosis. Using multivariate analysis, Chou *et al* established that this translocation was an independent factor for predicting a decrease in overall, relapse-free and disease-free survival rates (10). The patient presented in the present study achieved a CR following 2 courses of induction chemotherapy, but relapsed and became refractory after a short duration, with 12 months of overall survival. Via the monitoring of *NUP98-HOXA9* transcript copies, fusion protein signals were consistently detected throughout treatment courses and after a hematological CR was achieved. This suggested that residual leukemia cells were not eradicated. This is concordant with the majority of cases reported by Chou *et al* (10), indicating that this fusion gene may promote survival signals and may be a useful prognostic marker for monitoring minimal residual disease.

The present study and literature review demonstrated that patients with AML and t(7;11) translocation are rare, and may have distinct genetic, molecular and clinical characteristics. *NRAS* and *WT1* gene mutations are able to coexist with *NUP98-HOXA9* in a number of patients, indicating that there may be an association between *NUP98-HOXA9* and leukemogenesis. Patients with AML and t(7;11) are predominantly from Asia, typically young, female and have a FAB M2-subtype, and may present with concomitant BM dyspoiesis. These patients exhibit an aggressive clinical course and have a poor prognosis. Further studies are required with regard to this distinct entity.

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