t(4;11) translocation in hyperdiploid de novo adult acute myeloid leukemia: A case report

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**Abstract**

**BACKGROUND**

MLL gene rearrangement is a common genetic abnormality of acute myeloid leukemia (AML), which predicts poor prognosis and is important in clinical diagnosis. MLL rearrangement involves many chromosomes, among which, t(4;11) translocation is rare in AML. The present case was t(4;11) AML, accompanied by a hyperdiploid karyotype. Such cases have not been reported previously.

**CASE SUMMARY**

An adult male with self-reported symptoms of fatigue, febrility and hyperleukocytosis was diagnosed with AML by morphology and confirmed by immunophenotype analysis. Uncommonly, chromosomal and fluorescence in situ hybridization (FISH) analysis showed a hyperdiploid karyotype with t(4;11) translocation and MLL rearrangement, and a negative MLL–AF4 fusion gene result. The patient died of respiratory and circulatory failure 5 days after diagnosis.

**CONCLUSION**

t(4;11) AML with hyperdiploid karyotype has not been reported. In this case, t(4;11) was only detected by karyotype analysis and FISH, suggesting their importance in MLL rearrangement detection.

**Key Words:** Acute myeloid leukemia; MLL gene rearrangement; Translocation t(4; 11); Hyperdiploid; FISH; Case report
Core Tip: t(4;11) translocation is a rare karyotypic abnormality in acute myeloid leukemia (AML). We report for the first time an AML patient with t(4;11) and hyperdiploid karyotype abnormality only detected by karyotype analysis and fluorescence in situ hybridization. This highlights their importance in the diagnosis and prognosis of leukemia. We also describe the phenotype and gene mutation profile of his leukemia cells.

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INTRODUCTION

The MLL gene (also known as KMT2A, mapping at chromosome 11q23) was first identified and reported in 1991, and its rearrangement is a common genetic change in hematopoietic malignancies, such as acute leukemia (AL) and myelodysplastic syndrome[1,2]. The MLL rearrangement (MLL-r) occurs in 2.8%–3.5% of acute myeloid leukemia (AML) cases, indicating poor prognosis[3,4]. Conventional karyotype analysis and molecular genetic technology, fluorescence in situ hybridization (FISH) and reverse-transcription polymerase chain reaction (RT-PCR) are the primary methods to detect MLL-r, used individually or in combination in previous studies[3-10]. Other methods, such as Southern blotting and cDNA panhandle PCR have been used in the exploratory study of MLL-r AL[11-13], and 94 translocation partner genes (TPGs) have been characterized so far[14], indicating the cytogenetic heterogeneity of MLL-r AL. Considering this characteristic, current retrospective research preferred to divide MLL-r into different subgroups based on TPGs[4,15]. The most common MLL-r subgroup is MLL–AF4 [also known as KMT2A–AFF1, or t(4;11)(q21;q23)], which is formed by translocation between MLL and AF4 genes (located on chromosome 4q21), and occurs almost entirely in acute lymphoblastic leukemia (ALL) [16]. By contrast, t(4;11) AML only accounts for 0.8%–1.2% of MLL-r+ AML[9,13,14,16,17]. Limited by the sample size, t(4;11) AML has not been analyzed as a single subgroup, and its characteristics, pathogenesis and therapeutic options have not been established. More information needs to be accumulated about t(4;11) AML.

We here report a case of uncommon t(4;11) AML, review the literature and summarize the diagnostic features of MLL-r AML.

CASE PRESENTATION

Chief complaints
A 52-year-old man was admitted to Shengjing Hospital of China Medical University with complaints of fatigue for 1 mo, febrility for 2 wk and increased leukocytes for 3 d.

History of present illness
The patient exhibited signs of fatigue 1 mo ago and did not receive treatment. After 2 wk, he developed febrility with the highest temperature of 38.0°C, and improved after taking unknown ingredients of traditional Chinese medicine. The patient had no other symptoms or bleeding episodes.

History of past illness
The patient had high blood pressure (160/110 mmHg), and had been taking oral amlodipine (10 mg, qd) and betaproc (100 mg, bid).

Personal and family history
The patient denied any medical history, and declared no exposure to chemotherapeutic agents or radioactive elements. No special family history was noted.

Physical examination
Physical examination showed a pale appearance and sternal tenderness. No enlarged lymph nodes or hepatosplenomegaly was noted.

Laboratory examinations
Complete blood count revealed hyperleukocytosis, anemia and thrombocytopenia [white blood cells
(WBC) 227.8 × 10⁹/L; neutrophils (N) 25.1 × 10⁹/L; lymphocytes (L) 16.2 × 10⁹/L; monocytes (M) 18.9 × 10⁹/L; red blood cells (RBC) 1.92 × 10¹²/L; hemoglobin (HGB) 54g/L; platelets (PLT) 27 × 10¹²/L. (reference range: WBC 3.5-9.5 × 10⁹/L; N 1.9-7.2 × 10⁹/L; L 1.1-2.7 × 10¹²/L; M 0.3-0.8 × 10¹²/L; RBC 4.3-5.8 × 10¹²/L; HGB 130-172g/L; PLT 135-350 × 10⁹/L). Creatinine was 199.6 mmol/L (reference range: 59-104 mmol/L) and D-dimer 9196 mg/L (reference range: 0-252 mg/L).

**Imaging examinations**

No imaging examination.

**Further diagnostic work-up**

Bone marrow (BM) examination revealed 74.4% of typical premonocytes and 7.6% myelocytes (Figure 1A), and peroxidase staining was weak positive (Figure 1B). Flow cytometry detected 91.87% malignant myeloid cells in BM expressing CD33+, CD9+, CD38+, CD15+, CD64+, CMPO+, BCL2+, HLADR+, CD13+, and CD14+ (Figure 1C). Cytogenetic test revealed a hyperdiploid karyotype with addition of chromosomes 6, 8, 9, 14, 16, 17, 18, 22 and t(4;11)(q21;q23) balanced translocation on R-banded metaphases (Figure 1D), suggesting MLL rearrangement, which was confirmed by an MLL break-apart FISH probe with 1RIG1Y signal and atypical 2RIG1Y signal (Figure 1E). However, molecular biological analysis showed that none of the common TPGs involved in MLL-r AML (MLL-AF4/AF6/AF9/AF10/ELL/ENL/SETP6/AF17/AF1q/AF1p/AFX) was positive by RT-PCR. Next-generation sequencing found mutations of ASXL1 (exon12: c. 2083C>T), and U2AF1 (exon2: c. 101C>T) and a TET2 mutation (exon3: c. 652G>A) of undetermined significance.

**FINAL DIAGNOSIS**

Based on the information above, this case was diagnosed as MLL-r AML with poor prognosis.

**TREATMENT**

After diagnosis was established, the patient began to receive cytoreductive drugs (homoharringtonine and hydroxyurea, 2 mg and 3 g per day, respectively).

**OUTCOME AND FOLLOW-UP**

The patient died of respiratory and circulatory failure 5 d after the diagnosis.

**DISCUSSION**

MLL rearrangement is a common category of genetic abnormalities accounting for 2.8%–3.5% of AML cases, and indicating poor prognosis[3,4]. Among the multiple MLL-r AML subtypes distinguished by TPGs, MLL-AF4, also known as t(4;11)(q21;q23), is rare, especially in adult patients. According to previous reports, t(4;11) only accounts for 0.8%-1.2% of MLL-r AML[9,13,14,17] and 0.05% of all AML [10]. Existing reports on t(4;11) AML differ in age and pathological pattern, covering pediatric, secondary AML and acute megakaryoblastic leukemia[18-20], yet there are no reports of adult de novo AML with t(4;11).

The present case was a newly diagnosed adult case of hyperdiploid AML with t(4;11), and MLL rearrangement was revealed by karyotype and FISH analysis. Confusingly, RT-PCR failed to detect MLL-AF4 fusion gene. We speculate that the MLL gene in this case amplified partially and/or rearranged with at least two TPGs simultaneously, forming an atypical 2RIG1Y positive signal of MLL break-apart probe. Therefore, it was not possible to perform PCR. Due to the sudden death of the patient, deeper verification was not available. Karyotype analysis and molecular genetic methods, including FISH and RT-PCR, are the primary techniques used to detect MLL-r[5,6,11,21]. In clinical practice, however, only a few of the most common fusion genes were included in the RT-PCR panel, which restricts the range of RT-PCR[7,13]. This case demonstrates that combined use of karyotype analysis and FISH may be beneficial for discovery of more MLL-r AMLs[5].

Considering the limited number of cases of t(4;11) AML, we compared the clinical and laboratory features with data of MLL-r AML patients. This case was diagnosed with AML by morphology, the blasts expressed CD33, which matched the majority of MLL-r AML cases reported in the literature[3,9]. MLL-r AML also has common features in karyotype analysis. Vetro showed that additional cytogenetic abnormalities (ACAs) are common in MLL-r AML and 75% of cases have one or two ACAs[22].
Figure 1 Bone marrow examination at diagnosis. A: Bone marrow (BM) smear showed large and irregular cells, with rich and dusty blue cytoplasm and a few azurophilic granules; chromatin was rough and loose, light purple red, and nucleoli were not clear; B: Peroxidase staining was weak positive; C: Flow cytometry showed that 91.87% myeloid cells in BM were malignant clones, expressing CD33+, CD9+, CD38+, CD15+, CD64+, cMPO+, BCL2+, HLA-DR+/-, CD13+/-, and CD14+/-; D: R-banded cytogenetic test showed a hyperdiploid karyotype with addition of chromosomes 6, 8, 9, 14, 16, 17, 18 and 22 and t(4;11)(q21;q23) balanced translocation; E: Fluorescence in situ hybridization showed MLL break-apart probe (Y), 1R1G1Y signal and 2R1G1Y atypical signal.

However, our case showed eight ACAs besides t(4;11), leading to a hyperdiploid karyotype with chromosome number of 54. To the best of our knowledge, there has only been one adult case of hyperdiploid karyotype with t(4;11) reported in B-ALL[23], and none has been reported in AML. Another characteristic of this case was the mutations of ASXL1 and U2AF1 genes, while most statistical data show that AML with MLL-r is commonly accompanied by mutations of RAS pathway-related genes, such as KRAS and NRAS[7,10,15,22,24]. In terms of prognosis, several studies have shown that all MLL-r AML should be classified into the poor prognosis group regardless of TPGs[3,4,13], and the WBC count at diagnosis, achieving complete remission after the first course of treatment, and transplantation are independent risk factors in multivariate analysis[7,8,9,25]. The effects of immunotherapy and inhibitors targeting MLL-r acute leukemia need to be further explored[16,26-29]. We could not observe any therapeutic effects because the patient died soon after diagnosis.

CONCLUSION

t(4;11) AML is a rare subgroup of MLL-r AML, and combination with hyperdiploid karyotype has rarely been reported. In this case, t(4;11) was only detected by conventional karyotype analysis and FISH, suggesting the importance of these tests in detection of MLL-r patients. Special genetic
information of this case is provided in our report. More data need to be collected for more in-depth studies on t(4;11) AML.

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FOOTNOTES

Author contributions: Zhang MY contributed to the writing of the manuscript; Zhao Y was involved in drafting and revising the manuscript; Zhang JH reviewed the manuscript and gave inputs; All authors have read the manuscript and approved the submitted version.

Informed consent statement: Informed consent was given by his relatives for publishing this report.

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