An extra chromosome 9 derived from either a normal chromosome 9 or a derivative chromosome 9 in a patient with acute myeloid leukemia positive for t(9;11)(p21.3;q23.3): A case report

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Abstract. Translocation (9;11)(p21.3;q23.3) is one of the most common lysine methyltransferase 2A (KMT2A)-rearrangements in de novo and therapy-related acute myeloid leukemia (AML). Numerous in vitro and in vivo studies have demonstrated that the KMT2A/MLLT3 super elongation complex subunit (MLLT3) fusion gene on the derivative chromosome 11 serves a crucial role in leukemogenesis. Trisomy 9 as a secondary chromosome change in patients with t(9;11) is relatively rare. The present study reported a unique case of AML with a chromosome 9 trisomy secondary to t(9;11)(p21.3;q23.3). Using routine G-banded cytogenetics, fluorescence in situ hybridization and array comparative genomic hybridization analysis revealed that the extra chromosome 9 could serve a crucial role in AML disease progression and contribute to cellular sensitivity to chemotherapy.

Introduction

Chromosomal rearrangements of the lysine methyltransferase 2A (KMT2A) gene (former MLL) at 11q23 have been reported in ~10% of patients with acute leukemias (1). Analysis of the KMT2A recombinome of acute leukemias has identified 135 totally different KMT2A rearrangements, and 94 related translocation partner genes have now been identified at the molecular level (2-5). The MLLT3 super elongation complex subunit (MLLT3) gene (former AF9) at 9p21.3 is one of the most common translocation partner genes in acute myeloid leukemia (AML). In the 2016 World Health Organization (WHO) classification, AML was divided into four main categories as follows: i) AML with recurrent genetic aberrations; ii) AML with myelodysplasia-related features; iii) therapy-related myeloid neoplasms; and iv) AML not otherwise specified (2-5). The MLLT3 super elongation complex subunit (MLLT3) gene (former AF9) at 9p21.3 is one of the most common translocation partner genes in acute myeloid leukemia (AML). In the 2016 World Health Organization (WHO) classification, AML was divided into four main categories as follows: i) AML with recurrent genetic aberrations; ii) AML with myelodysplasia-related features; iii) therapy-related myeloid neoplasms; and iv) AML not otherwise specified (1,6). AML with t(9;11)(p21.3;q23.3) can be de novo AML according to the WHO heading of ‘AML with recurrent genetic abnormalities’ and therapy-related AML (t-AML; mostly caused by DNA topoisomerase II inhibitors) that were separately categorized into ‘therapy-related myeloid neoplasms’ (1,7). KMT2A/MLLT3 (former MLL/AF9) fusion gene resulting from t(9;11)(p21.3;q23.3) serves a crucial role in malignant clone proliferation of bone marrow stem cell and leukemogenesis according to in vitro and in vivo studies (8-10). Furthermore, secondary chromosome abnormalities to t(9;11) are very common, especially trisomy 8 or a partial duplication of 8q due to unbalanced rearrangements (11). However, trisomy 9 as a secondary chromosome change in patients with t(9;11) is quite rare. The present study reported a unique case of AML with an extra chromosome 9 secondary to t(9;11)(p21.3;q23.3). Using routine G-banded cytogenetics, fluorescence in situ hybridization (FISH) and array comparative...
genomic hybridization (aCGH) analysis, the results demonstrated that the extra chromosome 9 was the copy of either a normal chromosome 9 or a derivative chromosome 9.

**Case report**

In May 2011, a 37-year-old female complaining of lower back pain was found to have elevated white blood cell (WBC) with peripheral blasts. The complete blood cell count of the patient comprised 4.29x10^12/l of red blood cell, 124 g/l of hemoglobin, 52x10^12/l of platelet and 73.7x10^12/l of WBC, including 28.0x10^12/l (38%) of monocytes, 18.4x10^12/l (25%) of segmented neutrophils, 5.2x10^12/l (7%) of lymphocytes and 30% of peripheral blasts. The immunophenotype of peripheral blood blasts was positive for the cell surface markers Human Leukocyte Antigen-DR isotype, CD45, CD64, CD13, CD14 and CD15. The peripheral blood smear presented numerous blasts and immature monocyte-like cells.

The patient had been diagnosed with bilateral, poorly differentiated and infiltrating ductal breast carcinoma in 2008. Subsequently, she underwent neoadjuvant chemotherapy with adriamycin (topoisomerase II inhibitor), cytoxan and cytosar-U. The patient also received radiation and a lumpectomy that detected 0/13 nodes positive for malignancy. Next, she received adjuvant Taxol on a weekly basis for 12 weeks along with breast radiation and anticancer endocrine therapy with tamoxifen, which was continued until the present study. The clinical diagnosis of AML was made in 2011. Following diagnosis, the patient received standard cytarabine and daunorubicin induction therapy.

Cytogenetic analysis was performed using G-banding by trypsin using Giemsa (GTG) as a stain technique on 72-h cultures of leukemic blood collected during the patient’s initial clinical visit for low back pain. The results from the initial G-banding analysis revealed that the patient’s karyotype was 47,XX,+9,t(9;11)(p21.3;q23.3) [17]/46,XX [3] (Fig. 1A). Karyotypes were described according to the International System for Human Cytogenetic Nomenclature (ISCN 2016) (12).

To confirm t(9;11)(p21.3;q23.3) translocation and the presence of the extra chromosome 9, FISH analyses were performed with the combination of the KMT2A Break Apart probe (Vysis/Abbott, Inc.) and the centromere enumeration probe (CEP) 9 probe (Vysis/Abbott, Inc.). The KMT2A Break Apart probe was mapped to 11q23, 5'KMT2A signals on two derivative chromosome 9, one yellow signal on the normal chromosome 11 and three green signals, including two on centromeric region of chromosome 9 and one red signal on the derivative chromosome 11. The present study reported the case of a patient with AML positive for t(9;11)(p21.3;q23.3) translocation.

The clinical diagnosis of AML was made in 2011. Following diagnosis, the patient received standard cytarabine and daunorubicin induction therapy. The patient did not get complete remission (CR) and succumbed to the disease in March 2012.
9, persisted in the samples following induction therapy, which suggested that, in this particular case, chemotherapy may exert selection pressure against secondary chromosomal changes, but not against the primary cytogenetic abnormality.

\[ t(9;11)(p21.3;q23.3) \] translocation is one of the most common KMT2A-rearrangements in AML which can cause \( KMT2A/MLLT3 \) fusion \((8,13,14)\). \( t(9;11) \) positive AML can occur primarily as a de novo neoplasm or as a result of
previous therapy, for example, t-AML, typically caused by topoisomerase II inhibitors (15-17). It has been suggested that the topoisomerase II cleavage site and the DNase I hypersensitive site can colocalize in the break cluster regions of MLLT3 and KMT2A (16,18,19). Furthermore, an in vivo experiment reported the cleavage site of VP-16 (a topoisomerase II-like inhibitor) localized in the break cluster regions of KMT2A in a patient with AML (20). The majority of t-AML cases appeared in patients who had advanced-stage breast cancer and who had been treated with topoisomerase II inhibitors such as adriamycin, VP-16 and mitoxantrone. In addition, the latency period following primary therapy with this type of inhibitors can vary from 24 to 48 months (15-17). The patient from the present study suffered from breast carcinoma and received chemotherapy, including the topoisomerase II inhibitor adriamycin, and radiation straight after the diagnosis. After three years, the patient was diagnosed with AML. According to the 2016 WHO classification of myeloid neoplasms (1), this patient probably suffered from t-AML.

Numerous secondary chromosome abnormalities have been reported to be associated with t(9;11)(p21.3;q23.3), including trisomy 8 and modifications to chromosome 11 in the form of self-insertion or deletion (11,21). To the best of our knowledge, trisomy 9 as a cytogenetic abnormality secondary to t(9;11) in AML has rarely been reported and studied (22). The patient from the present study was positive for t(9;11)(p21.3;q23.3) translocation with an extra chromosome 9. In addition, the origin of this extra chromosome 9 appeared to be either a normal or an abnormal chromosome 9. According to the FISH results, this patient presented the four following cell clones: i) Normal cells; ii) cells with t(9;11)(p21.3;q23.3) translocation; iii) cells with t(9;11)(p21.3;q23.3) and a normal chromosome 9; and iv) cells with...
t(9;11)(p21.3;q23.3) and a derivative chromosome 9. The results from aCGH confirmed that the extra chromosome 9 could either be the normal chromosome 9 or the derivative chromosome 9. The karyotype for the initial sample based on the proportion determined by the FISH result should therefore be 47,XX,t(9;11)(p21.3;q23.3)[2]/47,XX,+9,t(9;11)(p21.3;q23.3)[3]/47,XX,t(9;11)(p21.3;q23.3)+der(9)t(9;11)[14]/46,XX[1].

Previous studies demonstrated that patients with t(9;11) have a favorable outcome compared with patients with other abnormalities involving 11q23 (23,24), whereas some other studies suggested that t(9;11) translocation could indicate an intermediate risk (25,26). The present study did not confirm the reported prognostically favorable outcome of patients with AML and t(9;11) (p21.3;q23.3). In addition, previous studies demonstrated that there are few intrinsic differences between de novo AML and t-AML with t(9;11)(p21.3;q23.3) translocation, and that t-AML presents minor worse prognosis compared with patients with de novo t(9;11)(p21.3;q23.3) positive AML, which could be due to prior therapy setting or additional karyotypic changes (17,27). Other studies reported that over-representation of 3′KMT2A could serve a crucial role in leukemia progression (28). Subsequently, most leukemia cells from the present case gained an extra copy of the terminal portion of chromosome 11, from band q23 to its distal end, including the 3′ end of KMT2A. In addition, one previous study proposed three stages of abnormal clone evolution: i) Appearance of balanced rearrangement; ii) trisomy; and iii) loss of chromosomal material (29). The appearance of an unbalanced genome could provide an advantage in proliferative activity and may be associated with the poor outcome of chemotherapy (29). Based on these studies, the chromosome 9 trisomy in the present study may be derived from chromosome segregation errors with the presence of the translocation. The gain of the Janus kinase 2 gene and other genes on chromosome 9 may contribute to a proliferation advantage to the cells with trisomy 9 (30). In the present study, because cells with an extra chromosome 9 disappeared following chemotherapy, cells with the extra chromosome 9 or partial trisomy 9 were likely to be sensitive to the chemotherapy (Fig. 4). To the best of our knowledge, the present study was the first to report a case of trisomy 9 as a secondary chromosome abnormality to t(9;11)(p21.3;q23.3) with the observation of clonal evolution during disease progression and AML treatments. The results from the present study suggested a likely progression course of chromosomal constitution (Fig. 5).

In conclusion, this study investigated, to the best of our knowledge, for the first time the case of t(9;11) with secondary trisomy 9 derived from either the normal chromosome 9 or a derivative chromosome 9 in a patient with AML. The extra chromosome 9 may be a consequence of AML progression and may contribute to cell sensitivity to subsequent induction therapy. To better explain the phenomenon of an extra chromosome 9, further studies are required, especially on 9p21-9q34 genes, which may help clarify the pathogenic mechanism of the extra chromosomal region in the progression of AML.
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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MG performed experiments, contributed to the analysis of the data and drafted the manuscript. HP performed cell culture, contributed to the interpretation of the data and prepared figures and tables. YMk performed karyotype and contributed to the interpretation of the data. JW performed fluorescence in situ hybridization and contributed to the interpretation of the data. XW performed array comparative genomic hybridization and contributed to the interpretation of the data. The study was approved by the Institutional Medical Ethics Review board of the First Hospital of Jilin University in 2016.

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The data are available from the corresponding author on reasonable request. The present study was supported by the grant from the National Natural Science Foundation of China (Grant. No. 81700205).

Ethics approval and consent to participate

The study was approved by the Institutional Medical Ethics Review Board of the First Hospital of Jilin University in compliance with the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of the present study.

Patient consent for publication

Written informed consent was obtained from the patient for publication of the present study.

Competing interests

The authors declare that they have no competing interests.

References


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