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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) through the cytogenetic analysis of leukemic blood and bone marrow. Further characterization with fluorescence *in situ* hybridization and array comparative genomic hybridization analysis revealed that this extra chromosome 9 was either a copy of normal chromosome 9 or a derivative chromosome 9. Conversely with the previously reported favorable outcome of AML patients with t(9;11)(p21.3;q23.3), in the present study, the cells with only translocation persisted, whereas the cells with an extra chromosome 9 disappeared following initial chemotherapy. With this unique case, the present study hypothesized that the extra chromosome 9 could serve a crucial role in AML disease progression and contribute to cellular sensitivity to chemotherapy.

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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 (1,6). AML with t(9;11)(p21.3;q23.3) translocation 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, $152x10^{9}$/l of platelet and $73.7x10^{9}$/l of WBC, including $28.0x10^{9}$/l (38%) of monocytes, $18.4x10^{9}$/l (25%) of segmented neutrophils $5.2x10^{9}$/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* was labeled as SpectrumGreen and 3'*KMT2A* was labeled as SpectrumOrange. The CEP 9 probe labeled with SpectrumGreen was used to hybridize to the centromeric region of chromosome 9. A total of 200 cultured leukemic blood cells including metaphases and interphases were screened. The FISH results are presented in Table SI. The results demonstrated that 8 normal cells carried two yellow fusion signals of KMT2A Break Apart probe on 11q23 region and two green CEP 9 signals on centromeric region of chromosome 9. A total of 36 cells, including 10 cells in metaphase, presented one yellow intact KMT2A signal on the normal chromosome 11, one red signal on the derivative chromosome 9 and four non-fused green signals, including three CEP 9 signals on centromeric region of chromosome 9 and one 5'KMT2A signal on derivative chromosome 11, which indicated that these 36 cells may carry an extra normal chromosome 9 in addition to t(9;11)(p21.3;q23.3) (Fig. 2A). However, 140 cells, including 20 cells in metaphase, presented two red 3'KMT2A signals on two derivative chromosome 9, one yellow signal on the normal chromosome 11 and four non-fused green signals, including three CEP 9 signals on the centromeric region of chromosome 9 and one 5'KMT2A signal on the derivative chromosome 11, suggesting that these 140 cells may carry an extra derivative chromosome 9 in addition to t(9;11)(p21.3;q23.3) translocation (Fig. 2B). Furthermore, 16 cells presented one yellow signal on the normal chromosome 11, one red signal on the derivative chromosome 9 and three green signals, including two on centromeric region of chromosome 9 and one on the derivative chromosome 11, which indicated that these cells would only have a translocation without an extra chromosome 9 (Fig. 2C).

To confirm the origin of the extra chromosome 9 and to better identify the region of the rearrangement, additional assays were performed to define minor and cryptic genomic imbalances near the translocation break points. Subsequently, aCGH was performed with genomic DNA isolated from uncultured leukemic blood specimen collected from the patient during the initial visit. The results from aCGH revealed the following unique genomic imbalance patterns: i) Gain of 119.795 Mb (3 copies) at 9p21.3-qter (chr9: 20,351,514-140,146,188); ii) gain of 19.712 Mb (2-3 copies) at 9pter-p21.3 (chr9: 638,796-20,351,121) (Fig. 3A); and iii) gain of 16.578 Mb (2-3 copies) at 11q23.3-qter (chr11: 117,867,162-134,444,816) (Fig. 3B), according to the human genome build NCBI36/hg18 (http://genome-asia.ucsc.edu/cgi-bin/hgTracks?db=hg18). These results were consistent with the FISH results. The results from aCGH and FISH collectively suggested that the extra chromosome 9 in certain metaphase cells may be the derivative chromosome 9. In addition, the derivative extra chromosome 9 was detected in some metaphase cells by GTG analysis at the initial diagnosis following one additional screening (Fig. 1B). The dosage of 9qter appeared to be lower than that of other 9q regions (Fig. 3A), which may be due to the general waving feature of the whole baseline of chromosome 9.

The results from follow-up cytogenetic studies reported the karyotypes 46,XX,t(9;11)(p22;q23)[3]/46,XX[17] (Fig. 1C) and 46,XX,t(9;11)(p22;q23)[2]/46,XX[18] (Fig. 1D) for the bone marrow samples collected on the 17th and the 45th day of AML induction therapy, respectively. The results from FISH analyses presented one yellow signal, one red signal and three non-fused green signals, which confirmed the cytogenetics results (Fig. S1) that the cells with only t(9;11) persisted, whereas the cells with the extra chromosome 9 disappeared following induction therapy. The patient did not get complete remission (CR) and succumbed to the disease in March 2012.

Discussion

The present study reported the case of a patient with AML positive for t(9;11)(p21.3;q23.3) translocation. Trisomy chromosome 9, either a normal or a derivative chromosome 9, was detected in the initial sample. This extra chromosome 9 was hypothesized to be secondary to the primary chromosomal change t(9;11), since some of the extra chromosome 9 were abnormal chromosome 9 derived from t(9;11) (p21.3;q23.3). The results from the follow-up cytogenetic studies indicated that only the balanced translocation t(9;11), rather than the extra chromosome

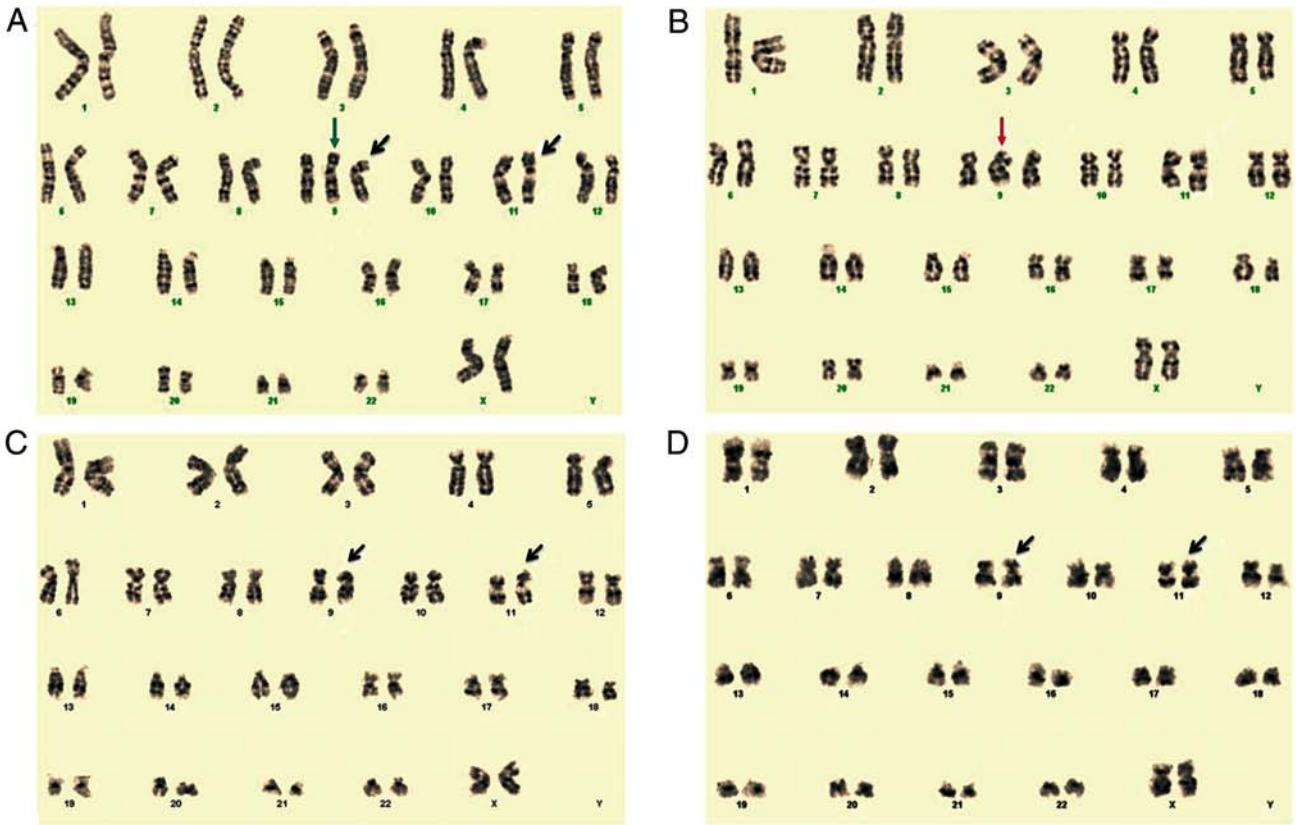

Figure 1. G-banded karyotype results of the patient. (A) Karyotype result of one cell from the leukemic blood at initial diagnosis. Cytogenetically recognizable translocation between chromosome 9 and 11 at 9p22 and 11q23, is indicated by black arrows. An extra normal chromosome 9 is indicated by a green arrow. (B) Karyotype result of a different cell from the leukemic blood at initial diagnosis. Extra chromosome 9 carries a light band (red arrow) on the distal part of its p arm, which suggests that this extra chromosome 9 is a derivative chromosome 9. (C and D) Karyotype results of the bone marrow from the 17th day and 45th day of the induction therapy shows that the extra chromosome 9 disappeared and that only t(9;11) remained. Black arrows indicate the derivative chromosome 9 and 11.

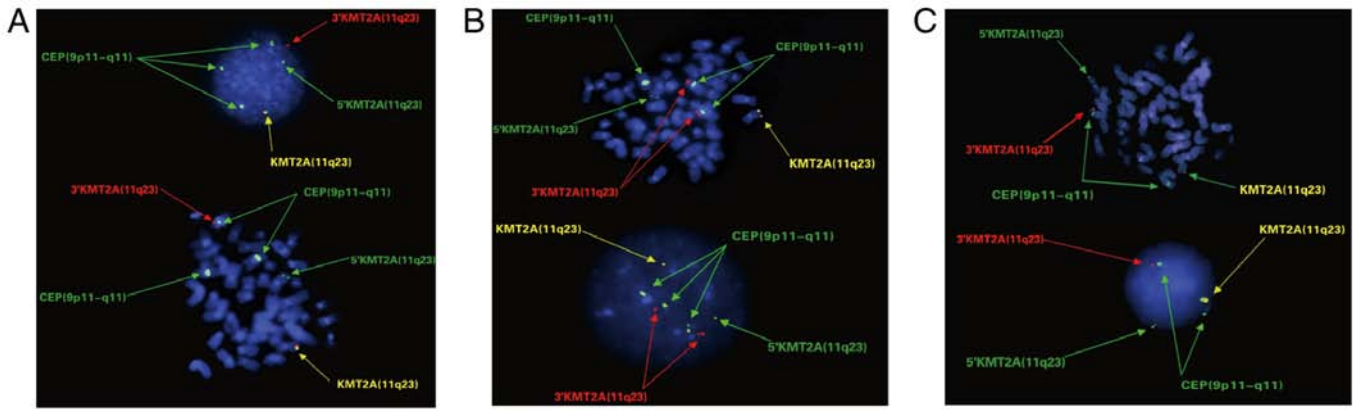

Figure 2. Fluorescence in situ hybridization results of initial sample with co-hybridization of LSI KMT2A probe and CEP 9 probe. (A) There were two normal chromosome 9 with prominent green CEP 9 signals, one derivative chromosome 9 with a red signal of 3'KMT2A on its short arm and a green CEP 9 signal, one normal chromosome 11 (yellow), and one derivative chromosome 11 with a small green signal of 5'KMT2A on its long arm. (B) There were two derivative chromosome 9 with a small red signal of 3'KMT2A on short arms and one normal chromosome 9 without red signals. Prominent green CEP 9 signals present in the centromeric region of all three chromosome 9. (C) Cells with typical t(9;11) without trisomy 9: One normal chromosome 9 with only one green CEP 9 signal, one normal chromosome 11 with a yellow intact KMT2A signal, one derivative chromosome 9 with a red 3'KMT2A signal and a green CEP 9 signal and one derivative chromosome 11 with only one small green signal of 5'KMT2A. CEP, centromere enumeration probe; KMT2A, lysine methyltransferase 2A.

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

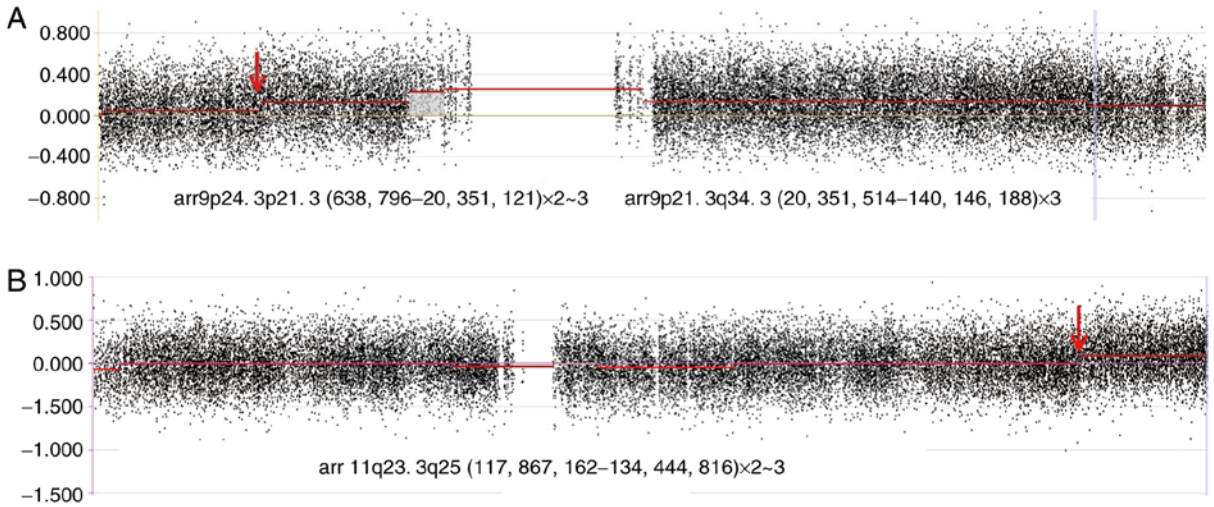

Figure 3. Results from array comparative genomic hybridization. The red arrows indicate the breakpoints of chromosomes 9 and 11 at 9p21.3 and 11q23.3, respectively. (A) Gain 119.795Mb (3 copies) at 9p21.3-q34.3 (hg18. Chr9:20,351,514-140,146,188) and gain 19.712 Mb (2-3 copies) at p24.3-p21.3 (hg18. Chr9:638,796-20,351,121). The gain ratio of the latter is smaller than that of the former. (B) Gain 16.578 Mb (2-3 copies) at 11q23.3-q25 (hg18. Chr11:117,867,162-134,444,816).

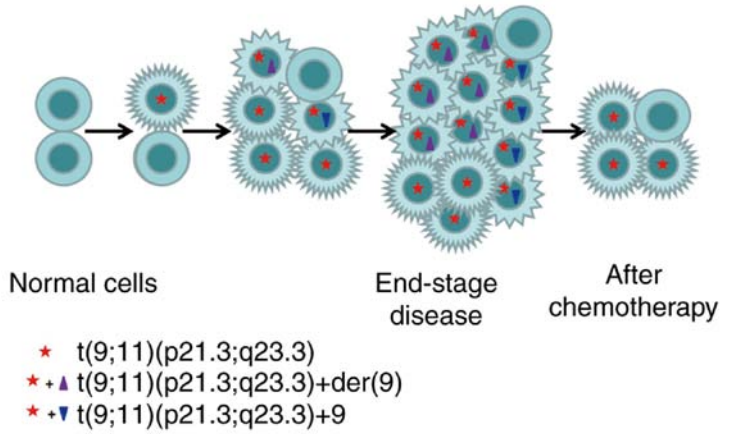

Figure 4. Hypothesis for clonal evolution. t(9;11)(p21.3;q23.3) occurred as the primary chromosomal rearrangement in the initial clone. Trisomy 9 (either an extra normal chromosome 9 or a derivative chromosome 9) occurred subsequently as the secondary chromosomal abnormality during the clonal evolution. Cells with these chromosomal abnormalities populated along with the disease progression. During the chemotherapy, normal cells and cells with the primary translocation could survive, but the cells with extra chromosome 9 were removed, which indicated the sensitivity of cells with extra chromosome 9 to the chemotherapy reagents.

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

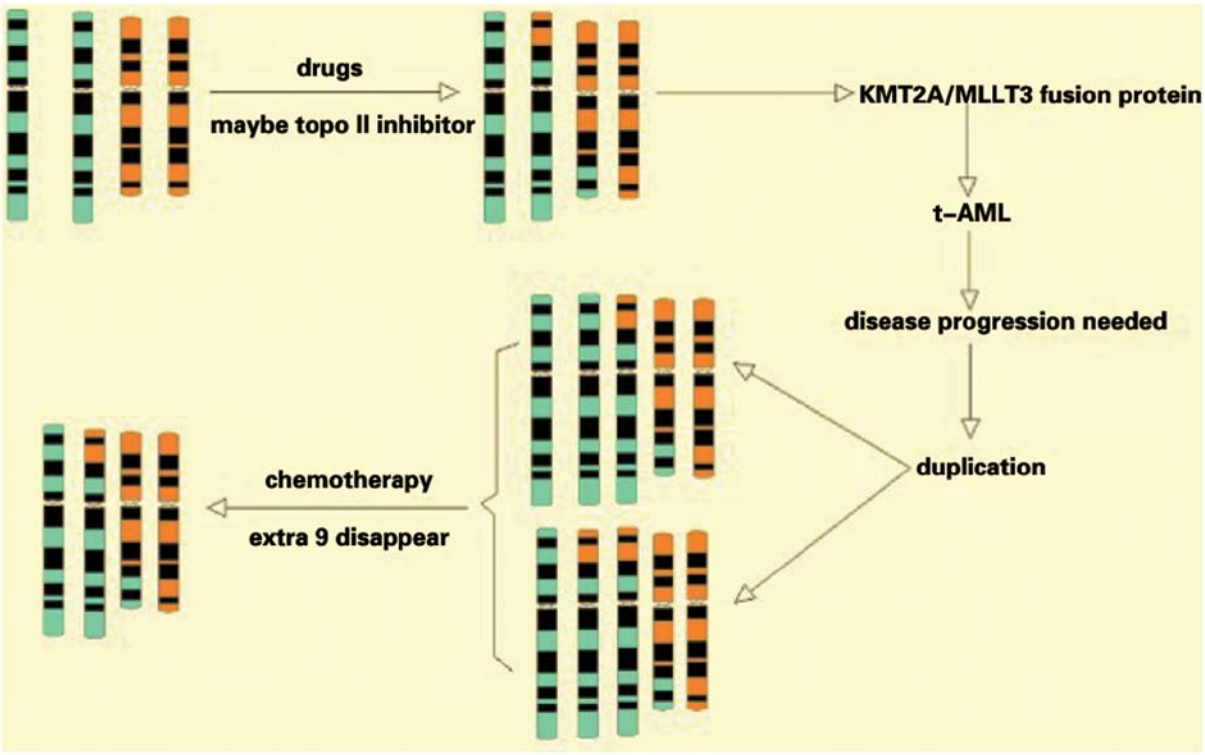

Figure 5. Progression ideograph of chromosomal constitution in the patient. t(9;11)(p21.3;q23.3) occurred during the treatment of the initial breast carcinoma, probably because of the topo II inhibitor applied in the treatment. This translocation results in formation of the *KMT2A/MLLT3* fusion gene. Thus, this patient likely had t-AML. Trisomy 9 with either an extra normal chromosome 9 or a derivative chromosome 9 occurred along the disease progression, likely contributed by errors happening during chromosome duplication or segregation. Cells with t(9;11), but not with trisomy 9, survived through chemotherapy. KMT2A, lysine methyltransferase 2A; MLLT3, MLLT3 super elongation complex subunit; t-AML, therapy-related acute myeloid leukemia.

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)(p21.3-q23.3) have a favorable outcome compared with patients with other abnormalities involving 11q23 (23,24), whereas some other studies suggested that t(9;11)(p21.3;q23.3) 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. XL 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. JL participated in the data analysis and helped with the drafting of the manuscript. MW collected and interpreted the clinical information. FM designed the study, analyzed data and helped with the interpretation of the clinical information. SL designed the study, analyzed data and revised the manuscript. All of the authors read and approved the manuscript.

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.

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