Acute monocytic leukaemia with t(11; 12) (p15; q13) chromosomal changes: A case report and literature review

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Abstract. Acute myeloid leukaemia (AML) is a type of heterogeneous disease derived from haematopoietic stem cells. Cytogenetic characterisation is essential for diagnosis and prognosis stratification. Here, we present the case of a 43-year-old female diagnosed with leukaemia, who demonstrated a rare chromosomal change of t(11; 12) (p15; q13) along with a positive FLT3-ITD mutation. The patient had a white blood cell count of 76.41x10^9/l. Bone marrow morphology revealed that monoblasts accounted for 25.5% of cells, and premonocytes accounted for 49.0%. This patient strongly responded to idarubicin and Ara-c (cytarabine) chemotherapy, which rapidly eliminated the leukaemia cell clones. However, the proliferation rate of the leukaemia cells was high during the intermission of chemotherapy. Subsequently, following two courses of chemotherapy, full haematological remission could not be attained. AML patients with t(11; 12) (p15; q13) combined with FLT3-ITD mutations are expected to have a short life expectancy; however, early haematopoietic stem cell transplantation therapy may improve the treatment outcome for these patients.

Introduction

Cytogenetic changes are diagnostically and prognostically significant in the case of acute myeloid leukaemia (AML). However, for certain rare cytogenetic changes, including t(11; 12) (p15; q13), t(16; 21) (p11; q22) (1) and t(8; 17; 15; 21) (q22; q15; q23; q22) (2), the pathogenesis, clinical features and impact of the cytogenetic changes on the biological characteristics of the leukaemic cells of these patients remain unclear due to the low incidence of these changes. In the present study, we report the case of a leukaemia patient, recently diagnosed at the Zhongshan Hospital of Xiamen University, China, whose morphological and immunological manifestations were consistent with acute monocytic leukaemia (AML-M5b), and who demonstrated a rare chromosomal change of t(11; 12) (p15; q13) along with a positive FLT3-ITD mutation. The clinical features and therapeutic responses are presented in the case report. Written informed consent was obtained from the patient and ethical approval was obtained from the Medical Ethics Committee of Zhongshan Hospital of Xiamen University (Xiamen, China).

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Case report

Patient presentation. A 43-year-old Han Chinese female experiencing fever and cough for two days was admitted to the Zhongshan Hospital of Xiamen University. The results of her physical examination were as follows: body temperature, 37.0˚C; pulse, 82 beats/min; respiration, 21 times/min; and blood pressure, 102/60 mmHg. The patient appeared mildly anaemic; no skin mucocutaneous petechiae or ecchymoses, no scleral jaundice, no tenderness in the sternum, and no gingival hyperplasia were observed. No superficial enlarged lymph nodes were palpable, pharyngeal congestion and enlarged tonsils at degree III were observed, and no enlargement of the liver and spleen was detected. The results of the routine blood laboratory test were as follows: white blood cells (WBC), 76.41x10^9/l; neutrophils, 33.62x10^9/l; monocytes, 15.28x10^9/l; haemoglobin, 92 g/l; platelets, 296x10^9/l; and primitive cells, 27%. Bone marrow morphology revealed that the proliferation of nucleated cells was extremely active, whereas myeloid and erythroid proliferation was inhibited. Monoblasts accounted for 25.5% of cells, and premonocytes accounted for 49.0% (Fig. 1A). Peroxidase detection was positive, accompanied by periodic acid-Schiff-positive granules. The hot-saline solubility test was negative and α-naphthyl butyrate esterase was strongly positive (Fig. 1B). The immunophenotyping results were as follows: CD69, CD14(+) cells accounted for 82.1%, CD33(+) cells accounted for 68.7%, and CD34(+) cells accounted for 64.2%. The screening of the 18 AML-related fusion genes (BCR-ABL, AML1-ETO, CBFβ-MYH11, PML-RARα, MLL-AF9, AML1-MDS1, NPM-MLF1, AML1-ETO, NPM-RARα, PLZF-RARα, DEK-CAN, MLL-ELL, AML1-EAP, MLL-AF10, SET-CAN, TEL-ABL1, TLS-ERG and NPM-ALK) yielded negative results.

The leukaemia gene mutation screening results revealed that the CEBPA gene, WT1 gene exon 7, exon 9, DNMT3A R882, KIT gene, IDH1 gene exons, IDH2 exon 4, RUNX1

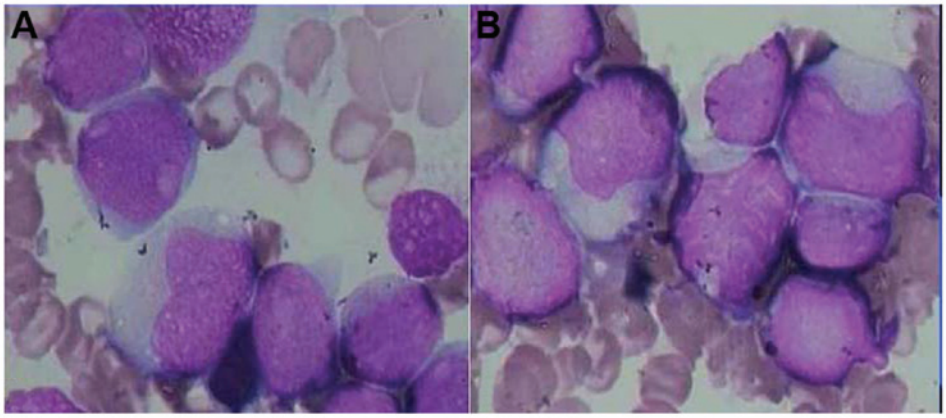

Figure 1. Image of bone marrow aspirate smear from patient. (A) The proliferation of nucleated cells was extremely active; monoblasts accounted for 25.5% of cells, and premonocytes accounted for 49.0%. (B) α-naphthyl butyrate esterase was strongly positive.

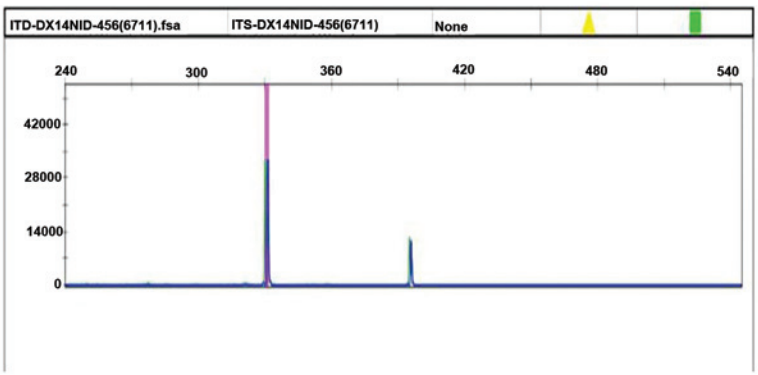

Figure 2. An FLT3-ITD gene mutation was detected (exon 14, 15).

gene, FLT3-TKD (D835) gene and NPM1 gene were negative. An FLT3-ITD gene mutation was detected (exon 14, 15) (Fig. 2). The karyotype was 46, XX, t(11; 12) (p15; q13) (4) (the chromosome image is not available due to malfunction of the image acquisition instrument). In accordance with the combined morphologic, immunologic, cytogenetic and molecular biologic classification, the patient was diagnosed with AML-M5b.

Treatment process. Following the initial diagnosis, the patient received chemotherapy, using an idarubicin and Ara-c (cytarabine) (IA) regimen. After one week of chemotherapy, the proliferation of the bone marrow cells was at a low level, with primitive cells accounting for 1.5%. After two weeks, bone marrow cell proliferation became active, with primitive cells accounting for 35%. Subsequently, the patient received another IA chemotherapy treatment course. After one week, the proliferation of the bone marrow cells was at an extremely low level, with primitive cells accounting for 3%, and after 2 weeks, bone marrow cell proliferation became active, with primitive cells accounting for 40%. No remission was observed.

Discussion

In 1998, Wong *et al* (3) reported the first case of AML that developed following radiotherapy for breast cancer, demonstrating a karyotype of t(11; 12) (p15; q13), following administration of a dose-adjusted daunorubicin and Ara-c (cytarabin) (DA) regimen chemotherapy. Complete remission (CR) was achieved and re-examination revealed that the chromosomes exhibited a normal karyotype. In 2002, Taketani (4) *et al* reported a case of primary AML-M1 with t(11; 12) (p15; q13). CR was observed one month after the administration of the ANLL-91 regimen. This patient received haematopoietic stem cell transplantation 9 months later and succumbed due to a relapse after six months of sustained remission. Taketani *et al* identified an NUP98-HOXC11 gene fusion caused by the t(11; 12) translocation for the first time. In 2003, La Starza *et al* (5) also reported a case of primary AML-M2 with t(11; 12) (p15; q13) chromosome translocation, and confirmed the formation of the NUP98-HOXC13 fusion gene (6). Subsequently, a number of cases of such chromosomal abnormalities in leukaemia were reported, including AML-M2a, M2, M4 and M5b (6-8). To date, four cases of positive NUP98-HOXC13 and NUP98-HOXC11 fusion genes have been reported (3,6-8). In 2009, La Starza *et al* (9) again identified a case of AML-M2 with t(11; 12) (p15; q13). However, the fluorescence *in situ* hybridisation method failed to detect the NUP98-HOXC13 and NUP98-HOXC11 fusion genes.

In 2011, Such *et al* (10) published a study on a 35-year-old male diagnosed with acute promyelocytic leukaemia (APL) in accordance with the French-American-British (FAB)

criteria, but lacking the PML-RARα fusion gene. The patient's karyotype was also t(11; 12) (p15; q13), which formed the NUP98-RARr fusion gene. In this fusion gene, the NUP98 breakpoint was located on exon 12, and the RARr breakpoint was located on exon 4. There was a complete absence of HOXC11, HOXC13 and PML-RARα fusion genes. This patient had a WBC count of $12x10^9$/l and achieved CR after receiving the standard DA chemotherapy without tretinoin treatment. Later on, the patient underwent autologous stem cell transplantation and remained in CR at the 8-month follow-up point. In 2013, Gong *et al* (11) also reported two cases of APL with karyotype t(11; 12) (p15; q13). Neither of the patients underwent tests to detect HOXC11 and HOXC13 fusion genes, and the tretinoin and arsenic trioxide therapies were ineffective. One of the patients had a WBC count of $14.6x10^9$/l at the time of diagnosis. No remission was achieved following the DA chemotherapy and subsequent myeloablative chemotherapy, and the patient succumbed to infection. The patient had a WBC count of $3.7x10^9$/l and positive FLT3-TKD; CR was achieved following high-dose asparaginase (HDA) chemotherapy. Subsequently, the patient remained in CR following two courses of consolidation chemotherapy.

A study by Gu *et al* (7) revealed that the NUP98 gene on chromosome 11p15 encodes the protein associated with a nuclear pore complex, which regulates the nucleocytoplasmic transport of proteins and mRNA. Mouse bone marrow transplantation experiments revealed that the NUP98 fusion protein causes leukaemia, and that the translocation of the NUP98-HOXA9 fusion protein of the bone marrow cells causes AML in mice. The NUP98-HOXC11 fusion protein is not involved in HOXC11 transcriptional regulation, but promotes the expression of the upstream reporter gene as a reverse activator. In addition, t(11; 12) (p15; q13) unbalanced translocation may lead to a loss of significant tumour suppressor genes on the telomere of chromosome 11p, which may also be one of the key mechanisms that lead to leukaemia.

AML patients with t(11; 12) (p15; q13) undergo primary or secondary clonal changes, which may return to normal following treatment. La Starza *et al* (5) reported a new t(1; 21) (p32; q22) karyotype that occurred in a patient with relapsed AML. Masuya *et al* (12) published a study on a 55-year-old female patient with therapy-related myelodysplastic syndrome who had normal karyotype chromosomes at diagnosis, but demonstrated t(1; 2) (p36; p21) and secondary t(11; 12) (p15; q13) when the relapse occurred. This patient survived for more than 6 years. In the cases of secondary AML reported by Wong *et al* (3) and APL reported by Gong *et al* (11), the chromosomes returned to the normal state following DA chemotherapy.

Thus, the t(11; 12) (p15; q13) chromosomal abnormality is a rare recurrent genetic event in AML, and may occur in primary AML or in chemotherapy-related secondary AML. Various subtypes of AML with t(11; 12) (p15; q13) have been reported, with the exception of M6 and M7. To date, 13 AML patients with t(11; 12) (p15; q13) between the ages of 2 and 59 years have been reported. Males account for 40% and females for 60% of patients. Among these patients, the WBC count was generally in the range $3.5\text{-}25x10^9$/l, with the exception of one patient, in whom it reached $211x10^9$/l. Taken together, the t(11; 12) (p15; q13) chromosomal abnormality exhibits strong heterogeneity, and the translocation may involve different genes or may have different breakpoints even when the same genes are involved. However, the pathogenic mechanism and the prognosis remain unclear.

AML with t(11; 12) (p15; q13) combined with FLT3-ITD mutations has also been reported (8,13). These patients succumbed in the early stages following treatment, indicating poor prognosis (13). However, the prognosis of the FLT3-TKD mutation is relatively superior. In the APL patient with FLT3-TKD mutations reported by Gong *et al* (11), CR was achieved following one course of HDA remission induction. This patient's chromosomes returned to normal and the FLT3-TKD was observed to be negative. The patient remained in CR following two subsequent courses of consolidation treatment.

In the patient reported in the present study, one of the molecular biological characteristics of leukaemia was the combination of the FLT3-ITD mutation and a negative NPM1 gene. The FLT3-ITD mutation-positive AML cases often have a poor outcome, and demonstrate a poor response to chemotherapy, leading to a low remission rate and high early mortality (14-16). The positive expression rate of the NPM1 gene is 20-50% in newly diagnosed AML patients, and AML patients expressing the NPM1 gene have a relatively superior prognosis (17). The clinical efficacy (including CR, event-free survival and overall survival rate) of the AML patients with FLT3-ITD mutations and positive NPM1 gene expression is superior to that of patients with only positive FLT3-ITD mutations (18-20). Most of the literature suggests that clinical features of FLT3-ITD mutation-positive patients include a high number of peripheral blood leukocytes and a high percentage of leukaemia cells in the bone marrow (16,21). At the time of diagnosis, the WBC count of our patient was $76.41x10^9$/l, and the monoblasts and premonocytes accounted for 75% of bone marrow cells. This result was consistent with the previous reports in literature. However, this patient did not exhibit any symptoms of leukaemia infiltration. Unlike the patients with FLT3-ITD mutations who succumbed during the early stages, this patient responded positively to the IA chemotherapy, which quickly eliminated the leukaemia cell clones. However, the proliferation rate of the leukaemia cells was high during the intermission of chemotherapy. Four weeks after chemotherapy, the proportion of immature bone marrow cells was 38%, which remained unchanged after another course of IA chemotherapy. Subsequently, two courses of chemotherapy could still not achieve a complete haematological remission, as indicated by the fact that the proportion of bone marrow immature cells remaining were only 40% of the expected total. It was speculated that the patient's rapid proliferation of leukaemia cells may be related to the FLT3-ITD gene mutation. Under normal circumstances, the juxtamembrane region and the 'activation loop' of tyrosine kinase receptors exhibit a self-inhibiting function to maintain an inactive conformation of the kinase. An FLT3-ITD mutation leads to the continuous activation of the tyrosine kinases, thus causing a spontaneous and non-dependent excessive proliferation of cells.

Currently, studies on the immunology and cytogenetic features of FLT3-ITD mutation-positive AML are scarce (22,23). Among the 14 cases of AML with t(11; 12) (p15; q13) reported, including the present case, 21% (3 cases)

demonstrated an FLT3-ITD mutation. Further cases need to be studied to determine whether a correlation exists between the FLT3-ITD mutation and t(11; 12) (p15; q13).

In conclusion, AML patients with t(11; 12) (p15; q13) combined with FLT3-ITD mutations are expected to have a short life expectancy; however, an early haematopoietic stem cell transplantation therapy may improve the treatment outcome for these patients (10,24).

Acknowledgements

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