Acquired 11q23/MLL rearrangement of unknown clinical significance

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Abstract: Newly emerged 11q23/MLL rearrangements in patients with a prior history of cytotoxic therapies are almost always associated with therapy-related hematological malignancies. Here we report a patient who had received various chemotherapies for his chronic lymphocytic leukemia (CLL). An abnormal clone of t(3;11)(p13;q23) was detected in 7 out of 20 metaphases in the bone marrow (BM) in the 15th year of disease. MLL rearrangement was detected in myeloid and erythroid cells, not in CLL cells by combined morphologic and fluorescence in situ hybridization. BM showed no evidence of myelodysplasia or increased blasts. Patient had been closely followed for 3 years, the abnormal clone was persistently detected but the patient had normal blood counts and normal BM examinations. This is the first case to show MLL rearrangement of unknown clinical significance in the setting of post cytotoxic chemotherapy.

Keywords: MLL rearrangement, therapy-related hematological malignancy, unknown clinical significance

Introduction

Rearrangements of MLL (also known as KMT-2A), located at chromosome 11q23, are often associated with acute myeloid leukemia (AML), B lymphoblastic leukemia (B-ALL), mixed phenotype acute leukemia, and less frequently with myelodysplastic syndromes (MDS) [1]. The translocation partners for 11q23 are diverse, with over 70 MLL partner genes identified [1-3]. t(9;11)/MLL-AF9, t(4;11)/MLL-AF4, t(11;19)/MLL-ENL, t(11;19)/MLL-ELL, t(6;11)/MLL-AF6, t(10;11)/MLL-AF10, are the most common translocations and partner genes, representing >80% of all MLL rearrangements [4].

Newly emerged 11q23/MLL rearrangements in patients with prior cytotoxic therapies, especially with DNA topoisomerase II inhibitors, are highly associated with therapy-related AML [5, 6], and less commonly with MDS or B-ALL [7]. Here we present a patient who had a long standing history of chronic lymphocytic leukemia (CLL) and received multiple chemotherapies, MLL rearrangement was detected during the course of disease but no evidence of secondary AML or MDS developed after a 3-year close follow-up.

Case presentation

The patient was a 57-year old man who had CLL for 18 years. He was initially treated with chlorambucil, followed by fludarabine plus cyclophosphamide, and achieved complete remission. Ten years later, the patient experienced CLL relapse and received various treatment regimens, including FCR (rituximab, fludarabine and cyclophosphamide), lenalidomide, and ofatumumab plus rituximab, for which, he only achieved partial responses.

The patient had 3 conventional cytogenetic studies performed in the first 11 years of disease which all demonstrated a normal male diploid karyotype 46,XY[20]. Fluorescence in situ hybridization (FISH) analysis using a CLL panel detected a deletion in D13S319 locus/13q14. In the 15th year of disease, cytogenetic analysis of the bone marrow (BM) showed 46,XY,t(3;11)(p13;q23)[7]/46,XY[13] (Figure 1A). FISH analysis with MLL dual-color, break-apart probe (Abbott Molecular/Vysis, Des Plaines, IL) on a previous G-banded metaphase confirmed t(3;11) and MLL rearrangement (Figure 1B, 1C) in 32% of cells. Combined morphologic-FISH analysis showed that MLL rear-
MLL rearrangement of unknown clinical significance

The patient was followed closely in the next 3 years. FISH analysis using a CLL panel showed deletions in ATM and TP53 in addition to D13S319/13q14, consistent with cytogenetic clonal evolution. He started treatment with ibrutinib in the 16th year of disease and achieved excellent response. Since the detection of MLL rearrangement, the patient had additional 6 BM examinations and 3 cytogenetic studies. The abnormal clone of t(3:11)(p13;q23) was persistently detected, involving 5 to 12 of 20 metaphases. All 6 BMs showed minimal involvement by CLL but no evidence of MDS or AML. CBC was performed every 1 to 3 months and all showed normal counts, with WBC ranging from 7.2 to 10.4 × 10^9/L, hemoglobin 14.3-15.8 g/dL, and platelet count 227-368 × 10^9/L.

Discussion

MLL (KMT2A) is important for normal embryonic development and hematopoiesis [8]. Acquired 11q23 translocation without MLL rearrangement could be observed in some patients as of unknown significance [9]. In contrary, 11q23/MLL rearrangements are almost always associated with acute leukemia/MDS, particularly frequent in therapy-related myeloid neoplasms [10]. We reviewed all the cases with 11q23/MLL rearrangements in the past 11 years (2005-2015) at our institution. A total of 262 patients showed 11q23/MLL rearrangements, and 261 of them had acute leukemia/MDS, including 36 therapy-related. This was the only patient who showed MLL rearrangement but did not show any evidence of acute leukemia or MDS. We further confirmed that 11q23/MLL rearrangement was presented in hematopoietic cells and not in the CLL cells and then showed this to be a persistent not a transient abnormality.

Figure 1. Karyotype and FISH analysis with MLL dual-color, break-apart probe. A: Karyotype 46,XY,t(3;11)(p13;q23); B, C: FISH map-back on a G-banded metaphase. One intact MLL signal (yellow) on normal chromosome 11, one split MLL signal with red signal on abnormal chromosome 3 and green signal on abnormal chromosome 11.
**MLL rearrangement of unknown clinical significance**

*MLL* gene. If the breakpoint occurs outside of, but close to the *MLL* gene, *MLL* could appear to be rearranged (false positive) but might not form a chimeric fusion product. It is known that leukemogenesis requires the formation of an “efficient” chimeric fusion protein through a precise break and fusion. Up to now, 3p13 as a partner locus for 11q23 has not been reported and no candidate partner gene at 3p13 locus has been identified. It is likely that this balanced translocation may not generate a fusion protein to initiate leukemogenesis.

In conclusion, although the development of 11q23/*MLL* rearrangements in patients with a prior history of cytotoxic therapies always raises the concerns of therapy-related myeloid neoplasms, it could be emerged without clinical significance as seen in this case. The correlation with morphologic and clinic findings is very important in the interpretation of any BM cytogenetic findings.

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**Disclosure of conflict of interest**

None.

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MLL rearrangement of unknown clinical significance