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Original Article

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[1] 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-

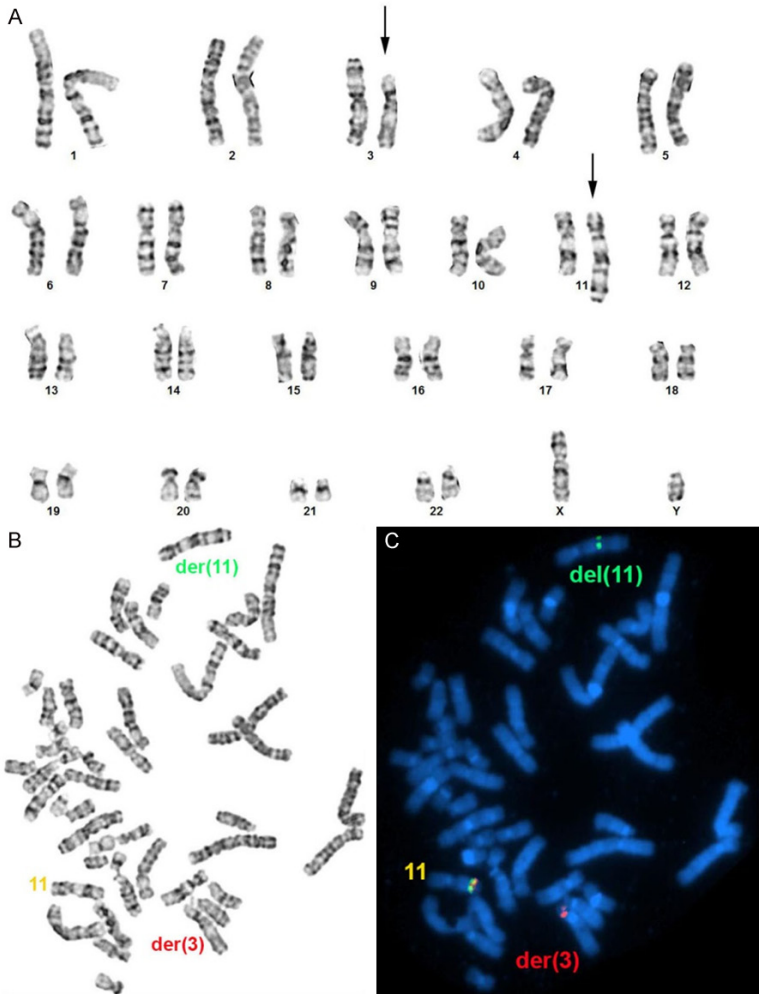

Figure 1. Karyotype and FISH analysis with *MLL* dual-color, break-apart probe. A: Karyotype 46,XY,t(3;11)(p13;q23); B, C: FISH map-back on a G-banded metaphase. One intact *MLL* signal (yellow) on normal chromosome 11, one split *MLL* signal with red signal on abnormal chromosome 3 and green signal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

rangement was confined to hematopoietic cells including myeloid cells and erythrocytes, but not in CLL cells (**Figure 2A**, **2B**). Morphologically, the BM showed ~60% CLL infiltrate, 0% blasts and no dysplastic features. Complete blood cell count (CBC) showed a white blood cell count (WBC) of 11.3 × 10^9/L with 48% lymphocytes, hemoglobin 12.6 g/dL and platelet count 279 × 10^9/L.

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 ibrutinibin 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.

The exact reason accounting for this "silent" clone is not very clear. It is noteworthy that the *MLL* FISH probe covers the entire *MLL* gene (~90 kb) and extends to the centromeric as well as telemetric side >200 kb away from

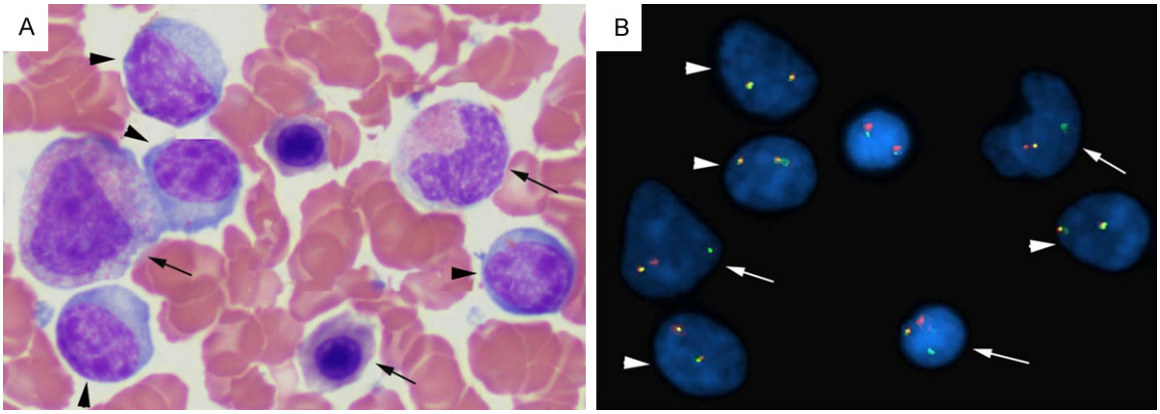

Figure 2. Combined morphologic-FISH analysis with *MLL* probe. A: Giemsa stained bone marrow aspirate smear; B: FISH map-back Giemsa stained slide. Split signals were seen in myelocyte, metamyelocytes, and one erythrocyte, not in lymphocytes (CLL cells). Arrow: cells with *MLL* rearrangement; arrow head: lymphocytes (CLL cells).

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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References

[1] Meyer C, Hofmann J, Burmeister T, Gröger D, Park TS, Emerenciano M, Pombo de Oliveira M, Renneville A, Villarese P, Macintyre E, Cavé H, Clappier E, Mass-Malo K, Zuna J, Trka J, De Braekeleer E, De Braekeleer M, Oh SH, Tsaur G, Fechina L, van der Velden VH, van Dongen JJ, Delabesse E, Binato R, Silva ML, Kustanovich A, Aleinikova O, Harris MH, Lund-Aho T, Juvonen V, Heidenreich O, Vormoor J, Choi WW, Jarosova M, Kolenova A, Bueno C, Menendez P, Wehner S, Eckert C, Talmant P, Tondeur S, Lippert E, Launay E, Henry C, Ballerini P, Lapillone H, Callanan MB, Cayuela JM, Herbaux C, Cazzaniga G, Kakadiya PM, Bohlander S, Ahlmann M, Choi JR, Gameiro P, Lee DS, Krauter J, Cornillet-Lefebvre P, Te Kronnie G, Schäfer BW, Kubetzko S, Alonso CN, zur Stadt U, Sutton R, Venn NC, Izraeli S, Trakhtenbrot L, Madsen HO, Archer P, Hancock J, Cerveira N, Teixeira MR, Lo Nigro L, Möricke A, Stanulla M, Schrappe M, Sedék L, Szczepański T, Zwaan CM, Coenen EA, van den Heuvel-Eibrink MM, Strehl S, Dworzak M, Panzer-Grümayer R, Dingermann T, Klingebiel T, Marschalek R. The MLL recombinome of acute leukemias in 2013. Leukemia 2013; 27: 2165-76.

[2] Meyer C, Schneider B, Jakob S, Strehl S, Attarbaschi A, Schnittger S, Schoch C, Jansen MW, van Dongen JJ, den Boer ML, Pieters R, Ennas MG, Angelucci E, Koehl U, Greil J, Griesinger F, Zur Stadt U, Eckert C, Szczepański T, Niggli FK, Schäfer BW, Kempski H, Brady HJ, Zuna J, Trka J, Nigro LL, Biondi A, Delabesse E, Macintyre E, Stanulla M, Schrappe M, Haas OA, Burmeister T, Dingermann T, Klingebiel T, Marschalek R. The MLL recombinome of acute leukemias. Leukemia 2006; 20: 777-84.

[3] Marschalek R. Mechanisms of leukemogenesis by MLL fusion proteins. Br J Haematol 2011; 152: 141-54.
[4] Zeisig BB, Schreiner S, Garcia-Cuellar MP, Slany RK. Transcriptional activation is a key function encoded by MLL fusion partners. Leukemia 2003; 17: 359-65.
[5] Secker-Walker LM, Moorman AV, Bain BJ, Mehta AB. Secondary acute leukemia and myelodysplastic syndrome with 11q23 abnormalities. EU Concerted Action 11q23 Workshop. Leukemia 1998; 12: 840-4.
[6] Super HJ, McCabe NR, Thirman MJ, Larson RA, Le Beau MM, Pedersen-Bjergaard J, Philip P, Diaz MO, Rowley JD. Rearrangements of the MLL gene in therapy-related acute myeloid leukemia in patients previously treated with agents targeting DNA-topoisomerase II. Blood 1993; 82: 3705-11.
[7] Tang G, Zuo Z, Thomas DA, Lin P, Liu D, Hu Y, Kantarjian HM, Bueso-Ramos C, Medeiros LJ, Wang SA. Precursor B-acute lymphoblastic leukemia occurring in patients with a history of prior malignancies: is it therapy-related? Haematologica 2012; 97: 919-25.
[8] Hess JL, Yu BD, Li B, Hanson R, Korsmeyer SJ. Defects in yolk sac hematopoiesis in Mll-null embryos. Blood 1997; 90: 1799-806.
[9] Buechele C, Breese EH, Schneidawind D, Lin CH, Jeong J, Duque-Afonso J, Wong SH, Smith KS, Negrin RS, Porteus M, Cleary ML. MLL leukemia induction by genome editing of human CD34+ hematopoietic cells. Blood 2015; 126: 1683-94.
[10] Tang G, Wang SA, Lu V, Lee HC, Qazilbash MH, Wang XI, Yin CC, Orlowski R, Wang Y, Patel A, Medeiros LJ, Lu G. Clinically silent clonal cytogenetic abnormalities arising in patients treated for lymphoid neoplasms. Leuk Res 2014; 38: 896-900.