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CASE REPORT

A Novel Variant Translocation t(8;16;21)(q22;q24;q22) in Acute Myeloid Leukemia Expressing both Myeloid and Lymphoid Markers

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ABBREVIATIONS:
AML = acute myeloid leukemia
BCR-ABL = breakpoint cluster region - Abelson murine leukemia viral oncogene homolog 1 *(*fusion gene)
CBFB = core binding factor subunit beta
EGIL = European Group of Immunological Markers for Leukemias
FISH = fluorescence *in situ* hybridization
FLT3 = Fms-like tyrosine kinase 3
GVHD = graft-versus-host disease
MLL= mixed-lineage leukemia
MRD = minimal residual disease
NPM1 = nucleophosmin 1
PCR = polymerase chain reaction
WHO = World Health Organization

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ABSTRACT

We present a novel, rare but recurrent, variant three-way translocation of t(8;21), t(8;16;21)(q22;q24;q22), resulting in *RUNX1-RUNX1T1* fusion gene in a patient with acute myeloid leukemia expressing both myeloid and lymphoid markers. Our patient was considered as a high risk patient based on his single blast population with immunophenotypic evidence of simultaneous myeloid and B-lymphoid differentiation, the unknown implications of t(8;16;21) and the presence of minimal residual disease shortly after the last chemotherapy cycle. However, he had an excellent outcome after allogeneic stem cell transplantation and he is well and fully functional 4 years post diagnosis. This case could be advisable for prognostic and therapeutic purposes.

INTRODUCTION

Translocation t(8;21) found in ~5% of acute myeloid leukemia (AML) cases occurs predominantly in young patients with AML-M2 and is generally associated with a favorable outcome. Complex cytogenetic variants of this translocation, most of which are three-way translocations, involving regions 8q22, 21q22 and a third chromosome, are observed in approximately 3% of all t(8;21) cases in AML. However, the clinical and pathological features of such cases are less characterized compared to the standard translocation and their clinical significance remains controversial.[1-4] According to the World Health Organization (WHO) 2008, AML cases with t(8;21) may express B-cell markers (CD19 or to a lesser extent, CD7).[5,6] These cases were previously diagnosed as biphenotypic acute leukemia according to the European Group of Immunological Markers for Leukemias (EGIL) scoring system when a score over 2 points was reached for the myeloid as well as 1 for the lymphoid lineage and were associated with a poor outcome.[7-9]

Herewith, we present a case of AML expressing both myeloid and B-lymphoid antigens with a novel variant translocation t(8;16;21)(q22;q24;q22), resulting in *RUNX1-RUNX1T1* fusion gene which could be advisable for prognostic and therapeutic purposes.

CASE REPORT

On January 24, 2011, a 36-year old male was admitted to the hospital with weakness, fatigue and cytopenia. A full blood count showed a white blood cell count of 17,900/mm^3, hematocrit of 16.9%, platelet count of 16,000/mm^3, and mean corpuscular volume of 106 fL. Peripheral blood smear revealed 35% blasts and mild dysplastic features. Bone marrow aspirate showed 43% blasts, positive for myeloperoxidase by cytochemistry. Flow cytometric analysis disclosed a single blast population with evidence of simultaneous myeloid and B- lymphoid differentiation (CD34+, CD13+, CD33+, CD19+, CD38+, CD117+, weak TdT and HLA-DR expression). Cytogenetic analysis of bone marrow cells showed 2 abnormal clones with karyotypic evolution. The first clone was characterized by a three-way translocation between chromosomal regions 8q22, 16q24 and 21q22 (Fig. 1), while the evolutionary clone showed additionally loss of chromosome Y. The karyotype was described as: 46,XY,t(8;16;21)(q22;q24;q22)[16]/45,X,-Y,t(8;16;21)(q22;q24;q22)[4]. Interphase and metaphase fluorescence *in situ* hybridization (FISH) analysis using Vysis LSI *RUNX1/RUNX1T1* Dual Color Dual Fusion Probes (Abbott Laboratories, Abbott Park, Illinois, USA), showed that 87% of cells had 2 fusion signals, one on the derivative chromosome 8 and the other on the derivative chromosome 21 (Fig. 2). Metaphase FISH, using the core binding factor subunit beta (CBFB) breaking apart probe showed that the *CBFB* gene was intact on the der(16), indicating that the breakpoint was distal to 16q22. Molecular diagnosis by polymerase chain reaction (PCR) for *RUNX1-RUNX1T1* fusion gene was not performed at the time of diagnosis or during the follow up of the patient. The diagnostic bone marrow sample was negative for "breakpoint cluster region" - Abelson murine leukemia viral oncogene homolog 1 *(BCR-ABL)* fusion gene and negative for Fms-like tyrosine kinase 3 (*FLT3)*, nucleophosmin (*NPM1)* and mixed-lineage leukemia (*MLL)* mutations by PCR.

The patient was commenced on antileukemic induction chemotherapy [idarubicin+cytarabine (3+10, 12 mg/M2 D1-D3 +100 mg/M2 bid D1-D10) and dexamethasone 24 mg iv D1-D5] and achieved complete remission 28 days later. Four additional courses of consolidation multiagent chemotherapy were administered until June 11th of the same year in order to ensure continuing and deep complete remission. Following a treatment gap of several weeks, in September 2011, he was reevaluated and found to be in morphological remission but a small number of biphenotypic blasts (≤1%) was detected by flow cytometry. The patient's leukemic characteristics and his disease evolution and behavior classified him as a high risk-acute leukemia case in complete remission 1 (CR1), minimal residual disease (MRD)-positive and therefore eligible for allogeneic stem cell transplantation. He received an allogeneic graft from an unrelated 43-year-old male donor, who was histocompatible in 9/10 antigens. The patient's Karnofsky performance status at transplant was 100%. Conditioning therapy consisted of busulfan/cyclophosphamide - alemtuzumab (BuCy-Campath) while graft-versus-host disease (GVHD) prophylaxis included cyclosporine and alemtuzumab monoclonal antibody. He received a total amount of 4.2x10^6/kg CD34(+) cells from his donor and engraftment was successful for the white blood cell count on day 11 and for platelets on day

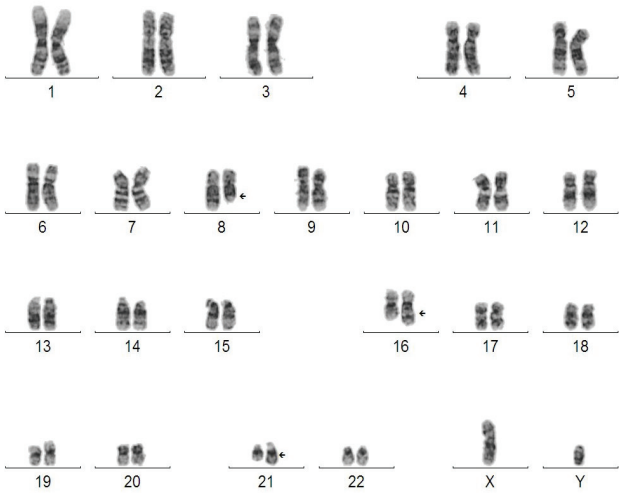

FIGURE 1. G- banded bone marrow karyotype showing 46,XY,t(8;16;21)(q22;q24;q22).

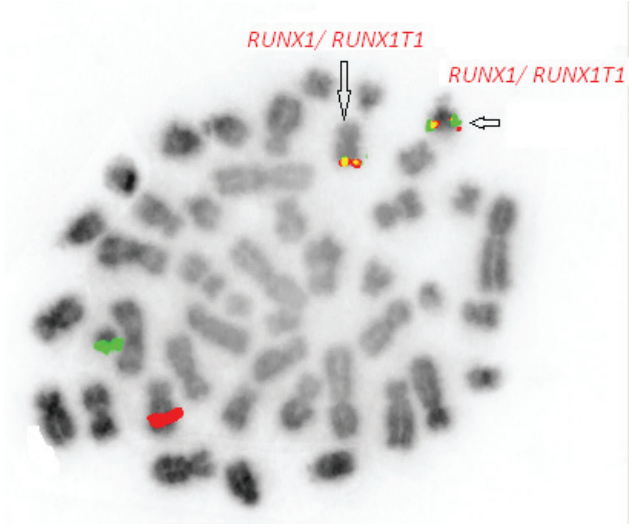

FIGURE 2. FISH using LSI *RUNX1-RUNX1T1* dual-color dual fusion probe showing one red signal corresponding to *RUNX1T1* gene on the normal chromosome 8, one green signal corresponding to *RUNX1* gene on the normal chromosome 21 and two yellow fusion signals (*RUNX1-RUNX1T1*) located on der(8) and der(21). FISH = fluorescence *in situ* hybridization.

13. On day 176 post transplantation a new bone marrow biopsy, flow cytometry and cytogenetic analysis, confirmed that our patient was in continuous morphological, immunophenotypic and cytogenetic remission. The patient remains well and in full activities until now, 4 years post diagnosis.

DISCUSSION

Variant forms of the classic translocation t(8;21) are uncommon in acute myeloid leukemia (AML) patients and their prognostic significance is still controversial. This could be partly attributed to the third implicated chromosome and its breakpoints involved in the translocation. These breakpoints in a variant three-way translocation may disturb the normal function of hematopoietic cells and subsequently be crucial for the clinical course of the disease. Band 16q24, involved in our case, is a very important chromosomal region not only because it carries tumor suppressor genes but because it is also implicated in the translocation t(16;21)(q24;q22), which is a recurrent translocation in AML with poor prognosis.[10] A systematic review of the literature revealed that t(8;16;21) has been reported only once in a patient with AML-M2, confirming that this is a rare but recurrent aberration in AML.[11] Unfortunately, the clinical course and outcome of that patient is not available and the prognostic significance of t(8;16;21)(q22;q24;q22) is currently unknown.

Our patient was diagnosed with AML carrying a novel variant translocation of t(8;21), according to WHO 2008 classification. He was considered as a high risk patient on the basis of his single blast population with immunophenotypic evidence of simultaneous myeloid and B-lymphoid differentiation, the unknown implications of t(8;16;21) and the presence of minimal residual disease shortly after the last chemotherapy cycle. On those grounds and due to the availability of a matched unrelated donor it was decided to receive an allogeneic graft whilst in first complete remission. So far, 4 years post diagnosis he remains in good condition and carries a normal life.

In conclusion, t(8;16;21)(q22;q24;q22) is a novel, rare but recurrent variant translocation of t(8;21), resulting in *RUNX1-RUNX1T1* fusion gene . In this case, t(8;16;21) was found in an AML patient with a single blast population showing simultaneous expression of myeloid and B- lymphoid markers negative for *FLT3*, *NPM1* and *MLL* mutations. Patients with this translocation may have a favorable outcome after allogeneic stem cell transplantation.

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