

A Novel Cytogenetic Variant Translocation in Acute Myeloid Leukemia

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Abstract

Background: Acute myeloid leukemia (AML) is a heterogeneous group of malignant neoplasm of hematopoietic disorders characterized by an abnormal proliferation of myeloid precursors. Variant forms of classic translocation t(8;21) are uncommon, and either third or fourth chromosomes accounts for approximately 3-4% in acute myeloid leukemia. **Case Report:** We report a rare case of a 16-year old male having t(8;19;21) (q22;q13;q22) associated with loss of sex chromosome. To the best of our knowledge, only few cases are described with variants of t(8;21) in AML and we first time report the involvement of 19q13 breakpoint region in AML. **Conclusion:** Translocation t(8;19;21) (q22;q13;q22) is a novel, rare but recurrent variant translocation of t(8;21). Due to the rarity of this translocation future accumulation of similar cases needed to evaluate clinical as well as prognostic and biological features.

Keywords: Chromosomes, Cytogenetics, Karyotyping, Neoplasms, Sex Chromosome, Translocation.

Introduction

Acute myeloid leukemia (AML) is a heterogeneous group of malignant neoplasm of hematopoietic disorders characterized by an abnormal proliferation of myeloid precursors [1]. Conventional cytogenetic analysis can be used for identification recurrent chromosomal abnormality and thereby it serves as one of the most important diagnostic and prognostic markers in AML patients. Variants of t(8;21) involving chromosome 8,21 and other chromosomes account for approximately 3-4% in AML associated t(8;21) [2,3].

The translocation t(8;21)(q22;q22) is recurrent chromosomal aberrations typically found in AML and is closely associated with French American British (FAB) classification M2 subtype and less frequently in M1 or M4 subtype [4]. In addition, the complex cytogenetic variants of this translocation are the three-way translocations involving regions of 8q22, 21q22

and third chromosome [5]. Molecularly, the t(8;21) leads to fusion of AML1 (RUNX1) gene located at 21q22 to ETO(RUNX1T1) gene located at 8q22, generating a chimeric AML1/ETO fusion gene on derivative chromosome 8 (der8) [2]. However, Grimwade *et al.* [6] suggested that the patients positive for this chimeric fusion are known to have a favorable prognosis. In addition, the formation of AML1/ETO chimeric fusion gene are frequently accompanied by additional chromosomal changes such as loss of sex chromosome and del(9) (q22) [7]. The frequency is approximately 10-15% of all such cases [8].

Moreover, the variants in some cases present as hidden translocation, in such cases it is difficult to identify the t(8;21) by conventional cytogenetic analysis [4]. Here, we describe a case of three-way complex translocation t t(8;19;21) (q22;q13;q22) associated with additional chromosomal abnormalities including loss of Y chromosome.

Case Report

A 16 years old male with no significant past medical history was referred for cytogenetic analysis. His complete blood counts showed a hemoglobin level 4.4 g/dL, a platelet count of 97000/ μ L and white blood cell count of 8400/ μ L with 37.0% neutrophils, 18.0% lymphocyte, and 45% blasts. The initial results of the karyotype of this patient were 45, X,-Y,t(8;19;21)(q22;q13;q22) in all metaphases analyzed.

Conventional cytogenetic technique was performed on 24 hours unstimulated short term culture of bone marrow cells. The cells were grown in culture medium Marrowmax (GIBCO) supplemented with 20% of FBS (fetal bovine serum). The colcemid was added for 30 minutes followed by KCL (75mM) at room temperature for 27 minutes and Carnoys fixative was used to fix the cells for four times. Slides were stained with GTG banding technique [9]. GTG banded metaphase from each culture was analyzed and karyotyped by using automatic IKAROS karyotyping software. In general, twenty metaphases from each specimen were analyzed as per the International System for Human Cytogenetic Nomenclature (ISCN) [10].

A dual colour FISH assay using Abbott Molecular Vysis Locus-specific identifier Eto and AML1 specific probes was performed on bone marrow cells. The ETO (RUNX1T1) was directly labeled with spectrum orange and RUNX1 (AML1) with spectrum green. The slides were hybridized overnight and subsequently analyzed. Microscopic evaluation of metaphases chromosome revealed a reciprocal translocation between 8q22,19q13 and 21q22. Cytogenetic analysis of BM cells revealed an abnormal karyotype with a novel complex translocation involving chromosome 8,21,19 with the loss of Y chromosome, resulting in the karyotype 45, X,-Y,t(8;19;21)(q22;q13;q22) in all metaphases analyzed [Fig.1].

FISH analysis results showed that the cells had one orange signal corresponding to RUNX1T1(ETO) gene on chromosome 8, one

green corresponding to RUNX1(AML1) gene on chromosome 21 and two yellow, orange, green fusion RUNX1T1/RUNX1 signals located on der(8) and der(21) [Fig.2].

Discussion

Complex cytogenetic variants of the classic translocation are uncommon in AML and it can exist in a small percentage of AML patients [5]. However, the t(8;21)(q22;q22) which creates AML1/ETO fusion gene is a distinct type of transcript generally associated with favorable prognosis in the AMLM2 patient [1].

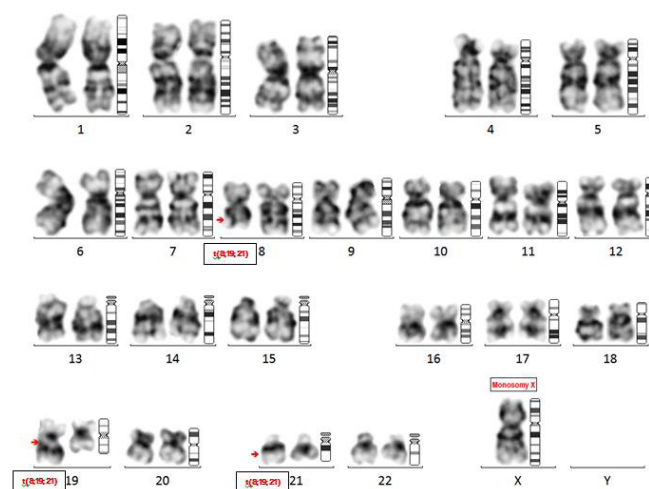


Fig 1: G-banded karyotype showing 45, X,-Y,t(8;19;21)(q22;q13;q22).

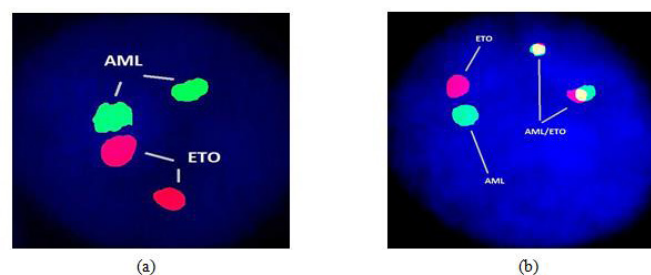


Fig 2: FISH analysis of bone marrow cells using LSI AML1/ETO dual colour dual fusion probe showed (a) Negative image of AML1/ETO-two normal orange (ETO), two normal green (AML1) signals, (b) Positive image of AML1/ETO- one normal orange (ETO), one normal green (AML1) signals on normal chromosome 8 and 21, two orange and green showing yellow fusion signals on der8 and der21 chromosomes.

Brahmbutt *et al.* [11], suggested that the variants of t(9;22) were observed in 5% cases of CML. Whereas, in AML variants of translocation t(8;21) were observed in 3-4% of cases involving chromosome 1,2,4,5,6,7,8,10,12,13,15,17,18,19 or 20 [12,13]. But the prognosis of this variants is contraversial [14]. However, Liu *et al.* [15], suggested that the there was no obvious differences between complex and typical t(8;21) with regards to remission rate and disease-free survival whereas, Gong *et al.* [16], suggested that the additional chromosome involved in the translocation could change the biological characteristic of the leukemic cells. Although the involvement of chromosome 19 with t(8;21) has been reported previously [7], the case reported here differs from previous reports in certain respects [17]. Interestingly this study reported by the Park *et al.* [7], suggested that the only two cases of three-way variants of t(8;21) involving chromosome 19 have been reported in AML as complex translocation which contains 8q22, 19p13, 21q22 region. They have also suggested that 19q13 breakpoint region was not reported previously but in the present study 19q13 breakpoint region in AML was found.

Furthermore, Farra *et al.* [2] pointed out that the t(8;21) are reportedly associated with additional chromosomal abnormalities such as sex chromosome loss, trisomy 8 and structural aberrations involving 9q. The determination of the significance of variants is important because to assess the prognosis in terms of therapy outcome.

Conclusion

In conclusion, our study indicated that the conventional cytogenetic investigation is important for the rapid and precise diagnosis of t(8;21). Translocation t(8;19;21)(q22;q13;q22) is a novel, rare but recurrent variant translocation of t(8;21). Due to the rarity of this translocation, future studies dealing with t(8;21) variants are needed to evaluate clinical as well as prognostic and biological features and its significance.

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