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Case Report

A Novel Case of Sole Constitutional Nonhomologous Robertsonian Translocation rob(14;15) (q10:q10) in B-Cell Acute Lymphoblastic Leukemia

Running Title: A novel case of sole Robertsonian translocation rob (14; 15)

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Abstract:

Robertsonian translocation is one of the major chromosomal rearrangements with an incidence rate of 0.1% of the general population. The current study presents a novel case of 18 years old male with complaint of high-grade fever was admitted at The Gujarat Cancer & Research Institute, Ahmedabad, India for treatment. Molecular cytogenetic study revealed sole constitutional nonhomologous Robertsonian translocation rob (14; 15) (q10:q10) in a B-cell Acute Lymphoblastic Leukemia. The constitutional translocation might be associated with a degree of genetic instability within the probability of somatic cytogenetic changes leading to hematopoietic disorders and neoplasia. Thus, present case report therefore support the hypothesis of increased susceptibility of rob (14; 15) carriers to leukemia. However prognostic significance of constitutional cytogenetic abnormalities in Acute Lymphoblastic Leukemia has remained a matter of debate.

Keywords: cytogenetic; translocation; chromosome

Introduction:

Robertsonian translocation is structural chromosomal abnormality that results from the fusion of two acrocentric chromosomes. They are formed when the long arms of two acrocentric chromosomes are translocated, ultimately forming a single chromosome [1]. The Robertsonian translocation is also referred to as a "centric fusion" type of translocation, and is a fusion of the entire long arms of two acrocentric chromosomes (chromosomes 13, 14, and 15 of the D group, and chromosomes 21 and 22 of the G group) after breakage at the centromeres [2]. During meiosis, these rearrangements form trivalent, the segregation of which may result in nullisomic or disomic gametes for one of the chromosomes involved in the rearrangement, and consequently, a zygote with trisomy or monosomy for one of the chromosomes involved [3]. The clinical relevance of Robertsonian translocation is with the increased risk of spontaneous abortion, infertility, and chromosomally unbalanced offspring [2].

Although Robertsonian translocations are one of the most common constitutional chromosomal changes, in humans, an individual with "balanced" Robertsonian translocation have an estimated incidence rate [1]. They are rarely encountered in human cancers. In the present study, we report a case of B cell Acute Lymphoblastic leukaemia (B cell ALL) which harboured the Robertsonian translocation on cytogenetic analysis of bone marrow cells and review published literature on this rare event in leukemia. We have reviewed the literature of this rare event in leukemia and found that the prognostic significance of constitutional cytogenetic abnormalities in ALL has remained a matter of debate.

Case Report:

An 18 years old male with high grade fever was registered at The Gujarat Cancer & Research Institute, Ahmedabad, India. The hematological reports revealed: haemoglobin levels 9.1 gm/dL, white blood cell count 3,590/µL and platelet count 37,000/µL. The investigations from bone marrow aspiration showed marked proliferation of tumor blast cell population. Blast cells were small having course chromatin, occasional 1–2 prominent nucleoli and scant to moderate amount of cytoplasm. Other hematopoietic elements were suppressed. Sudan Black-B and Periodic acid Schiff (PAS) staining was negative, M: E ratio was altered, and megakaryocytes were not seen. Diagnosis based on morphological findings was Acute Leukemia and suggested for immunophenotyping. In immunophenotyping blasts mainly expressed lymphoid markers; cCD79a

and CD19 along with CD34. Final diagnosis based on immunophenotyping was B cell ALL. The patient was treated with standard protocol BFM-90 for ALL, which was uneventful, and a complete haematological remission was attained.

This study was approved by the Institutional Scientific Review Board and Ethics Committee. Prior consent obtained from the patient.

Cytogenetic study at diagnosis was performed in direct bone marrow preparations and after short-term overnight cultures using standard cytogenetic protocol. Subsequently at diagnosis and after achieved complete remission, the patient's constitutional karyotype was examined in Phytohaemagglutinin-M (PHA-M) stimulated culture of lymphocytes from peripheral blood. Mitogen-stimulated blood culture was set for 72 hours. Metaphase chromosomes were banded by GTG-banding technique [4]. Detail of the karyotypes were reported according to the International System for Human Cytogenomic Nomenclature 2016 [5].

FISH was performed on metaphase cells following the manufacturer's guidelines (Abbott Molecular, Inc., Des Plaines, IL, USA). Locus Specific Identifier (LSI) probes for *BCR/ABL* DCDF (dual color dual fusion) probe was used to rule out the possibility of translocation between chromosome 9 and chromosome 22. Whole chromosome painting for chromosome 14 (WCP 14) with Spectrum Orange (SO) and WCP 15 with Spectrum Green (SG) were used to reveal the Robertsonian translocation.

The analysis of both conventional cytogenetics and FISH was carried out using Zeiss AxioImager.Z2 fluorescence microscope (Carl Zeiss, Germany) equipped with Metafer and CCD camera (MetaSystems, Germany).

Classical chromosome analysis with a mitogen-stimulated and non-stimulated culture detected an abnormal male chromosome complement. The karyotype results showed 45, XY,rob(14;15)(q10;q10)[20]. It showed the presence of derivative chromosome composed of long arm of chromosome 14 and long arm of chromosome 15 in all analyzed metaphase plates. It revealed presence of total 45 chromosomes [Figure 1].

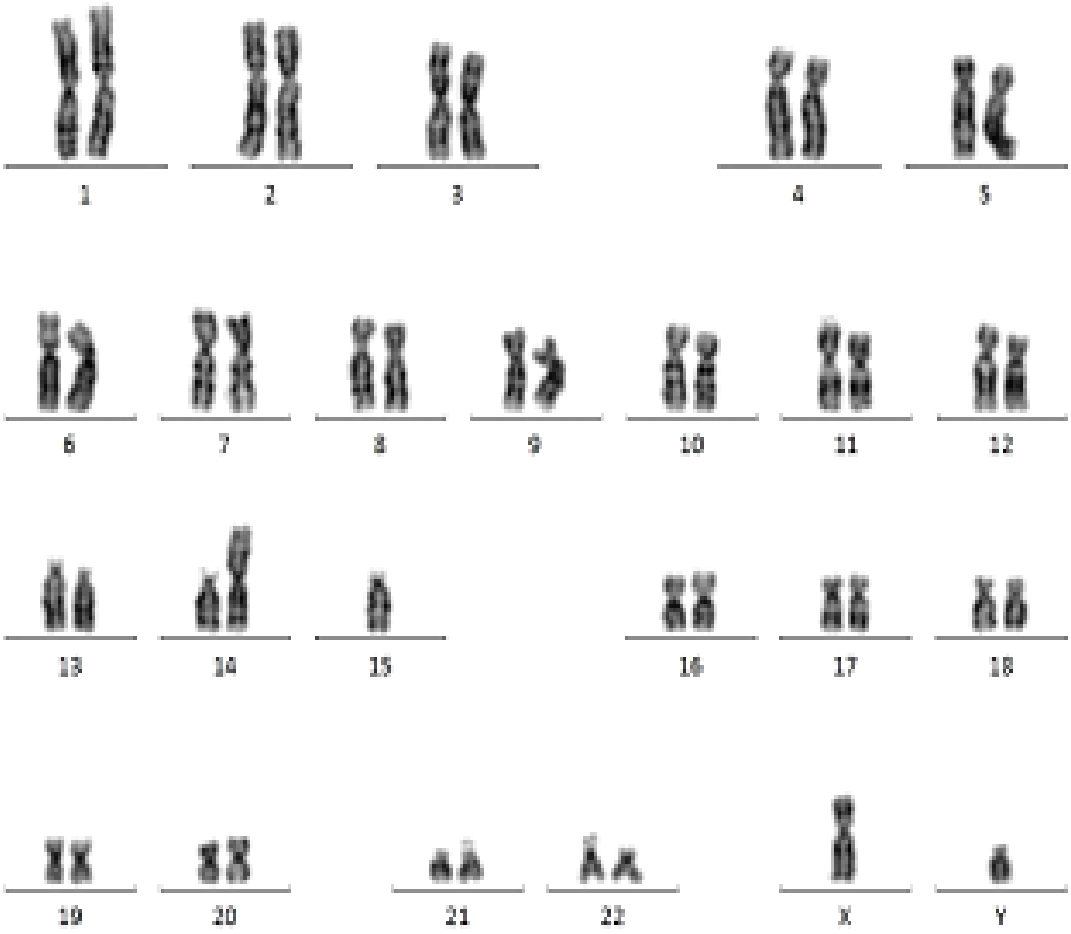

Figure 1: *Giemsa-banded karyotype shows rob (14; 15) (q10; q10)*

The metaphases and interphases FISH results of LSI *BCR-ABL* DCDF probe showed two orange, two green signals which indicated the absence of *BCR-ABL* fusion gene [Figure 2a].

The metaphase FISH results for WCP 14 with SO and WCP 15 with SG revealed a derivative chromosome composed of centric fusion between chromosome 14 and 15. WCP FISH results confirmed presence of Robertsonian translocation between chromosome 14 and 15. [Figure 2b].

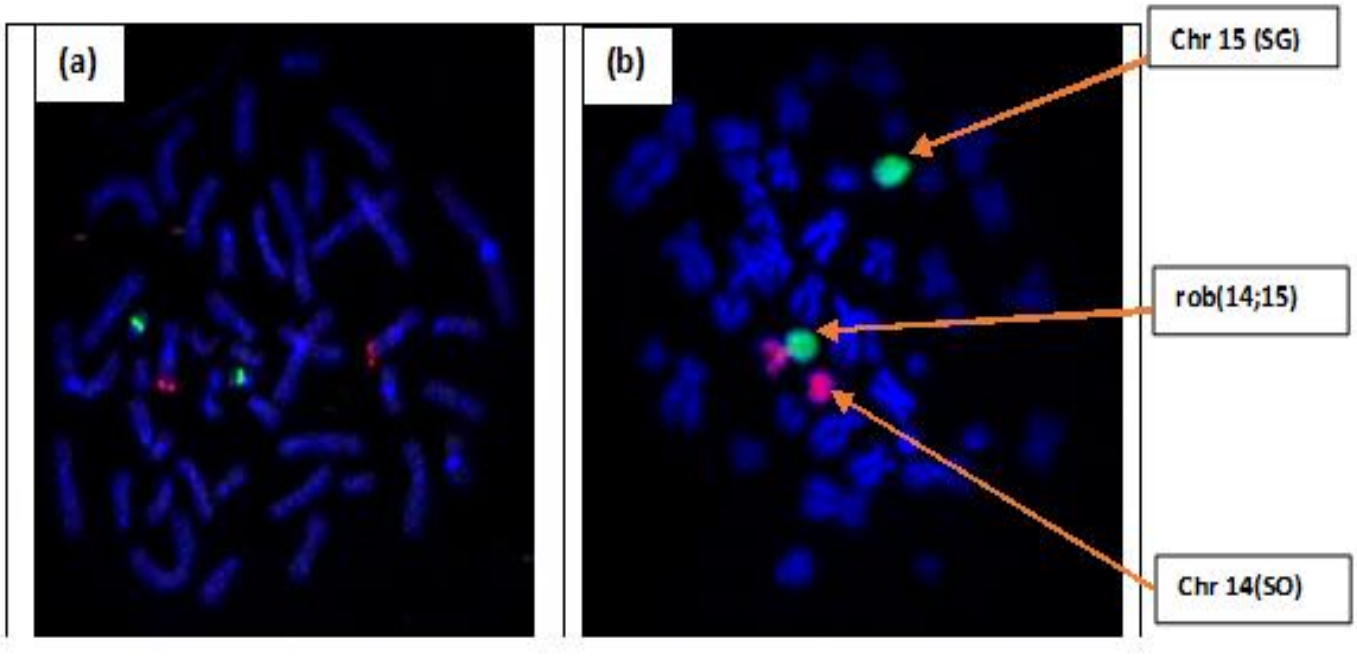

Figure 2: (a) *Metaphase fluorescent in situ hybridization showing locus specific identifier (LSI) BCR-ABL probe results.* **(b)** *Results of whole chromosome paint probes. Spectrum Orange for chromosome 14 and Spectrum Green for chromosome 15.*

Discussion:

In review of the literature, few cases of Robertsonian translocations are reported previously making it a rare phenomenon in leukemia. However such case involving rob (14; 15) as sole cytogenetic abnormality in ALL has been not reported previously. Usually 20% of adult ALL and 2-5% of children ALL found *BCR-ABL* positive [6]. To ruled out the possibility FISH for *BCR-ABL* was performed in the present case study. It was confirmed *BCR-ABL* negative B cell ALL. The rob (14; 15) occurs as a sole cytogenetics abnormality in our patient. Thus, the present study is reported as a novel case [7].

The reason for the Robertsonian translocations in leukaemia remains undefined but may suggest that chromosomal recombination leading to Robertsonian translocations probably observed more frequently in meiosis than in mitosis [8]. A predisposition to hematological malignancies in carriers of balanced Robertsonian translocations has been suggested [9]; reported evidence for this and for premalignant conditions is, however, derived from case reports [10]. Carriers of rob (15; 21) have been assessed to be at much higher risk of a rare form of ALL with intrachromosomal amplification (iAMP) of chromosome 21 [11]. However, it is not clear about breakpoints involvement in balanced Robertsonian translocations could affect predisposition to malignant condition. Various mechanisms underlying the stated relationship have been proposed. The constitutional translocation might be associated with genetic instability within the possibility of somatic cytogenetic changes and it may lead to hematopoietic disorders [12]. The present study therefore supports the hypothesis of increased susceptibility of rob (14; 15) carriers to leukemia.

In the present case, ALL occurred might be the cause of the genetic instability of his Robertsonian t (14; 15). However, reports of patients with a balanced t (14; 15) are rare, and to the best of our knowledge there are very few reports in literature of such carriers suffering from hematological disorders. A study from Germany found a patient with Ph-Positive CML patient with a Constitutional Robertsonian Translocation t (14; 15) [13]. From the present case study and literature [13, 14] it has been hypothesised that constitutional chromosomal abnormalities are related with some degree of genetic instability, which may then result in further predisposition to preleukemia and leukemic condition. Nevertheless, to the best of our knowledge rob (14; 15) (q10; q10) in B-cell ALL as observed in our patient has unusual recurrence [7]. To evaluate risks in individuals with balanced Robertsonian translocations, one needs a detail cohort study in which large numbers of carriers are followed over a long period of time for predisposition to malignant condition or cancer risk.

In conclusion, our study suggests that patients diagnosed with balanced Robertsonian translocations might be at increased risk of leukemia. These findings might be related to genetic factors as well as factors correlated with reasons for referral for cytogenetic test.

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