



Case Report

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Isochromosome i(9)(q10): A Rare Chromosomal Aberration in B-cell Acute Lymphoblastic Leukemia

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Abstract

Cytogenetic analysis in Acute Lymphoblastic Leukemia (ALL) reveals number of non-random chromosome abnormalities which play an important role in prognostication of patients. Isochromosomes are uncommon non-random chromosome aberrations in acute lymphoblastic leukemia (ALL) and prognostic significance of the presence of isochromosome(s) remains to be well established. The incidence of i(9q) in ALL is very low. Majority of the patients are older than 10 years and the aberration occurs in combination with other chromosomal abnormalities. We present two cases of adult BALL with i(9q) as one of the cytogenetic aberration at diagnosis. Case 1 patient was given standard treatment protocol and complete remission was achieved at the end of induction phase II therapy and Case 2 was a newly diagnosed case and was planned for standard BFM 90 chemotherapy. The early remission is indicative of a favorable outcome in such cases.

Keywords

B-cell Acute Lymphoblastic Leukemia; FISH; Isochromosome

Abbreviations

B-ALL: B-cell Acute Lymphoblastic Leukemia; FISH: Fluorescent *in situ* Hybridization.

Introduction

The role of cytogenetics in determining the biologic basis of acute lymphoblastic leukemia (ALL) is widely recognized [1,2]. The non-random chromosome abnormalities recognized by cytogenetics have an important role in identifying causative mechanisms leading to ALL, determining the prognosis and in designing an appropriate therapeutic regimen [3]. Isochromosomes are uncommon structural chromosomal aberrations observed in 9% acute lymphoblastic leukemia (ALL) cases [4]. The most frequent isochromosomal changes are i(6p), i(7q), i(9q), and i(17q). Isochromosome 9q occurs in 0.6% of patients [5]. It is known to be commonly associated with late-stage disease; it has rarely been reported at diagnosis in hematological malignancies hence, the impact of isochromosome 9q on prognosis

is not well understood. Here we present two rare cases of B-ALL with i(9)(q10) referred to Tata Memorial Hospital, Mumbai and their clinical outcome.

Clinical Cases

Case 1

A twenty-eight-year old male patient with complaints of fever, weight loss, fatigue, loss of appetite and two episodes of vomiting in one month duration. On examination he had lymphadenopathy, hepatosplenomegaly, LMN facial palsy and involved CSF. His investigations revealed a white blood cell count of $18.5 \times 10^9/L$, platelet count of $23 \times 10^9/L$, and hemoglobin of 6.8 g/dL. Bone marrow was myeloperoxidase (MPO) negative and had a blast percentage of 95%. By flow cytometry, the blasts were CD34 (negative), CD19 (moderate), CD10 (moderate), CD45 (dim to negative), CD20 (variable), CD38 (moderate), CD56 (negative), CD73 (variable), CD86 (dim), CD123 (dim to negative), HLA-DR (variable) and CD304 (negative). He was diagnosed as pre-B cell precursor acute lymphoblastic leukemia (B-ALL) with facial palsy. For cytogenetic studies the bone marrow sample was cultured using 5 ml complete culture medium, incubated at 37°C without any mitogens and standard harvesting protocol was followed [6]. Fluorescence *in situ* hybridization (FISH) using commercially available disease specific dual color translocation probe LSI *BCR/ABL1* t(9;22) (Zytovision, Germany), LSI *PBX1/TCF3* t(1;19), LSI *ETV6/RUNX1* t(12;21), LSI break apart *MLL* translocation probe [Vysis Abbott Molecular, Germany] and centromeric probe CEP 4,10,17 (Zytovision, Germany) was performed according to the manufacturer's protocol. The patient was positive for t(1;19) (q23;p13), trisomy 4 and showed evidence of 3 copies of *ABL1* allele which was further confirmed as i(9)(q10) by metaphase FISH (Figures 1 and 2). Ploidy analysis revealed hyperdiploidy (chromosome no 47) in 20% cells and diploidy in 80% cells. For treatment standard BFM 90 therapy protocol was followed and at the end of induction phase II patient was in complete remission. Bone marrow was normocellular with no excess of blasts, a white blood cell count of $4.8 \times 10^9/L$, platelet count of $200 \times 10^9/L$, hemoglobin of 12.8 g/dL and cytogenetic analysis revealed all markers negative indicating cytogenetic remission as well. The patient received central nervous system chemoprophylaxis with High-dose methotrexate (HDMTX) after induction phase II.

Case 2

A fifty-three-year old female patient presented with generalized weakness, restricted in physically strenuous activity, no organomegaly. Her investigations revealed a white blood cell count of $2.8 \times 10^9/L$, platelet count of $346 \times 10^9/L$, and hemoglobin of 9.8 g/dL. Bone marrow was myeloperoxidase (MPO) negative and had a blast percentage of 91%. By flow cytometry, the blasts were CD34 (variable), CD19 (moderate), CD10 (Mod-Bri), CD45 (dim to negative), CD20 (Mod-dim), CD38 (moderate), CD56 (negative), CD73 (Bri in subset), CD86 (Subset), CD123 (Bright), HLA-DR (Mod-Bri) and CD304 (Bright). She was diagnosed as pre-B-ALL. Cytogenetic analysis revealed duplication of long arm of chromosome 1 i.e. 1q25.2 along with i(9)(q10) (Figure 3). BFM 90 therapy was planned.

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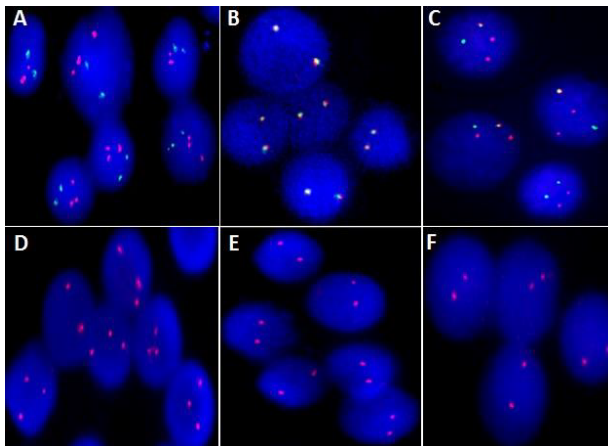


Figure 1: (A) *BCR/ABL1* dual color fusion probe shows 2 normal *BCR* allele and 3copies of *ABL1* allele (2 Green and 3 Red signal); (B) Dual color *MLL* break apart probe on interphase cells shows normal *MLL* allele (2 Yellow signal); (C) *TCF3/PBX1* dual fusion probe shows *TCF3/PBX1* fusion (2 Yellow signals), 1 *TCF3* allele and 1 *PBX1* allele (1 Green and 1 Red signal) (D) CEP 4 probe shows trisomy 4 (3 Red signals); (E) CEP 10 probe shows 2 normal chromosome 10 (2 Red signals); (F) CEP 17 probe shows 2 normal chromosome 17 (2 Red signals).

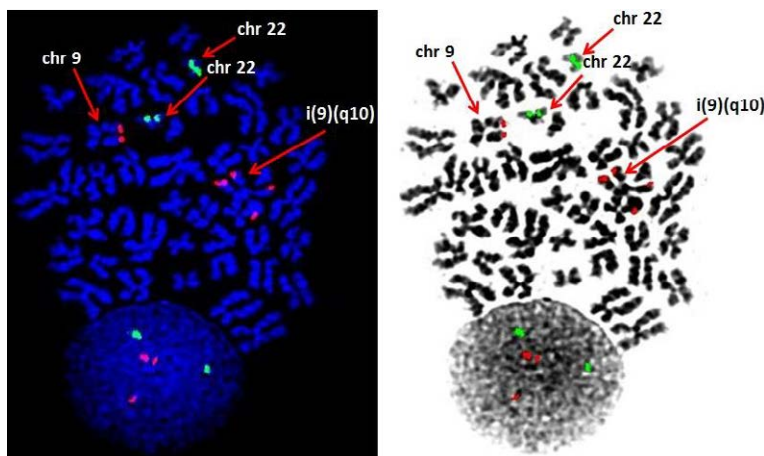


Figure 2: Metaphase FISH using *BCR/ABL1* dual color fusion probe.

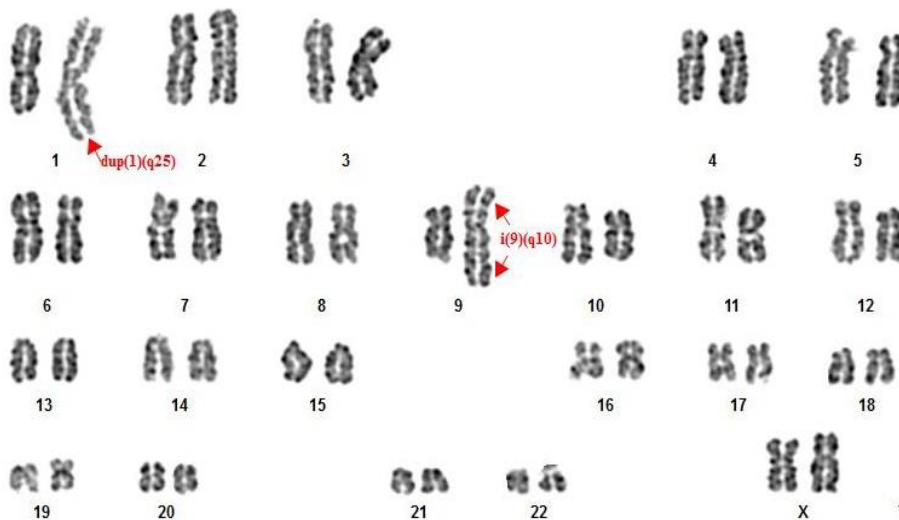


Figure 3: G-banded karyotype of the patient- 46, XX, dup(1)(q25.2),i(9)(q10).

Discussion

Nonrandom chromosomal aberrations have important prognostic significance in acute lymphoblastic leukemia (ALL). Among the nonrandom chromosomal aberrations isochromosome have been observed in 9% of ALL patients. The occurrence of i(9)(q10) in newly diagnosed ALL is uncommon (0.6%–1%) and its clinical characteristics have little understanding. It has been reported that i(9)(q10) is usually associated with the late-stage disease, more likely to be in patients older than 10 years and to have a pre-B immunophenotype [5]. It is found associated with other non-random chromosomal abnormalities including t(1;19)(q23;p13) (involving the *PBX* and *E2A* genes), t(9;22)(q34;q11) (involving fusion of the *BCR* and *ABL* genes) and few cases of Down syndrome [5,7]. Central nervous system (CNS) leukemia and presence of mediastinal mass has been reported in few cases. In studies evaluating the characteristic features of isochromosome i(9)(q10) with presence of nonrandom abnormalities majority of cases had a favorable outcome i.e. they were in remission at 3+ to 86+ months but it is not clear whether the isochromosome represented a primary or secondary chromosomal change. The i(9)(q10) can be well recognized by loss of 9p and gain of 9q that could contribute to development or proliferation of leukemic blasts in these cases [8]. The deletion of the interferon- α or β 1 gene, localized to the 9p22 region, and the overexpression of the *ABL* proto-oncogene, localized at 9q34, have each been suggested as playing a role in the malignant proliferation of leukemia [9].

Conclusion

Cytogenetic studies proved to be an efficient technique in detecting the prevalence of rare, high prognostic significant structural

and non-random chromosomal abnormalities in leukemia cells. In addition to the unusual presentation of disease, remission was achieved by induction therapy, supporting the literature that i(9)(q10) has a favorable outcome in B-ALL. It was not clear whether the isochromosome represented a primary or secondary chromosomal change, thus continued understanding of the relationship between cytogenetic abnormalities and clinical outcome will lead to improved risk stratification and better disease management.

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