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The rare translocation t(14;21)(q11;q22) detected in a Moroccan patient with T-cell acute lymphoblastic leukemia

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ABSTRACT

Cytogenetic studies of acute lymphoblastic leukemia have been at the forefront of research in the pathogenesis of cancer. The presence of recurring chromosomal abnormalities (either numeral or structural rearrangements) provides immediate clues to the genetic events leading to leukemia and many abnormalities have important prognostic significance. The rare translocation t(14,21)(q11.2;q22) has been described in pediatric T lineage ALL in only one case so far in 2000. The present study is a case report of an ALL case in which we found a t(14,21)(q11.2;q22) as a non random chromosomal abnormality among 70 analyzed pediatric ALL cases referred exclusively to BIOLAB Laboratory from the children hospital of Morocco.

1. Introduction

Acute lymphoblastic leukemia (ALL) is a clonal expansion of white blood cell precursors in the blood, bone marrow, and various extramedullary tissues. The diagnosis of acute leukemia is based on the presence of more than 20% blasts in the peripheral blood or bone marrow. According to a recent study, ALL is the commonest malignancy in children (aged 1–18 years), accounting for almost 30% of all cancers in this age group [1,2].

Cytogenetic studies on ALL have led to the identification of specific recurrent abnormalities and to their correlation with the other biologic data and have helped in understanding the mechanisms of leukemogenesis [1,2].

T cell acute lymphoblastic leukemia (T-ALL) is a malignant disease of thymocytes, accounting for 10%–15% of pediatric ALL [3,4].

Current understanding of the molecular basis of T-ALL has come largely from analysis of recurrent chromosomal translocations and intrachromosomal rearrangements [5]. These abnormalities typically juxtapose strong promoter and enhancer elements responsible for high levels of expression of T cell receptor genes next to developmentally important transcription factor genes, including HOX11, TAL1, TAL2, LYL1, BHLHB1, LMO1, and LMO2 [6].

Among these chromosomal rearrangements, the rare translocation t(14,21)(q11.2;q22) has been described in pediatric T-lineage ALL in only one case so far in 2000.

It was found in a 7-years-old Caucasian female with high white blood count with lymphoblasts positive for T-cell antigens; cerebrospinal fluid negative for malignant cells and superior mediastinal mass. The patient attained a complete remission with standard chemotherapy but relapsed and died after 4 months of therapy [6,7].

In this study, we describe the clinical and cytogenetic features of a t(14;21) ALL case that we identified during the analysis of 70 pediatric ALL cases referred exclusively to our laboratory from the children hospital of Morocco in the period of 2 years.

2. Patient and method

2.1. Patients

This is a retrospective study preformed over a period of 2 years (from October 2012 to December 2014), of 70 bone marrow samples referred to the BIOLAB laboratory by the children's hospital for an ALL suspicion. The median age of the patients is 8 y.o. (from 1 to 15 y.o) and the sex ratio is M/F = 1,08.

2.2. Diagnosis

The diagnosis of ALL was based on morphologic, cytochemical, and

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immunologic features of the cells. Immunophenotyping was performed at local centers using standard techniques by immunofluorescence and flow cytometry.

2.3. Cytogenetic analysis

Cytogenetic analysis is performed in BIOLAB laboratory where our study is carried out.

We culture the bone marrow samples of the patient with an ALL suspicion in RPMI basal medium, containing L-glutamine and fetal bovine serum, for 24 h at 37 °C in a CO_2 incubator. Then we treat them with colcemid to stop the cells in the metaphase of mitosis. After harvesting with a hypotonic solution and fixation with acetic acid / methanol, we spread and stain the chromosomes using the standard R-banding technique.

After that, we capture the mitosis using a connected camera to semi automatic software, and write the karyotype according to the International Chromosome Nomenclature (ISCN 2013) [8]. Criteria for clonality were based on guidelines as defined by the International System for Cytogenetic Nomenclature.

A successful cytogenetic analysis required the detection of at least 2 or more cells with the same structural change or chromosomal gain, 3 or more cells with the same chromosomal loss, in at least 20 metaphases, to establish the chromosome formula.

The patients' karyotypes were thereafter subdivided into 3 prognosis risk groups: favorable, intermediate or unfavorable.

2.4. Interphase fluorescence in situ hybridization (FISH)

FISH was performed in a foreign laboratory. The selected probes were LSI, DNA dual color probes, ''Break-apart'' locusIgH in 14q32 (Vysis), and whole chromosome 21 painting probes. FISH was performed according to the manufacturer's instructions.

3. Results

In this study, we had a successful cell culture rate of 93% among which many relevant recurrent chromosomal abnormalities had been perceived.

13 of the studied cases belong to T-lineage ALL (19%) and 57 belong to B-lineage ALL (81%).

Among the 70 eligible cases entered on this study, we revealed chromosomal abnormalities in 41 cases (59%), of whom we identified a t(14;21) in one case (1,4% of the total and 2,4% of the abnormal karyotypes).

It was a 13 years old Moroccan male patient. The onset of symptoms goes back to two months by the gradual installation of a major weakness with cutano mucosal pallor and weight loss. All evolving in a context of apyrexia. Complete blood count showed a hemoglobin of 9.3 gydl, a white blood count of 388,000 yml, and a platelet count of 79,000 yml, with circulating lymphoblasts. A bone marrow aspirate demonstrated L2 ALL, and flow cytometry was positive for T-cell antigens: cCD3, partial sCD3, CD7, CD8, CD34, HLA-DR and TdT. The patient was treated with standard chemotherapy but relapsed and died after a year and a half of therapy

3.1. Cytogenetic analysis

After analyzing 34 mitosis, we noticed a reciprocal translocation between the long arm of a chromosome 14 in the breakpoint 14q11 and a long arm of a chromosome 21 in the breakpoint 21q22 in 22 mitoses (65%), while the karyotype was normal in 12 mitosis (35%).

Karyotype was interpreted as 46, XY,t(14;21)(q11;q22)[22]/46,XY [12] (Fig. 1)

FISH has confirmed the t(14;21) in 17 mitosis of the 20 analyzed mitosis (Fig. 2).

4. Discussion

T-cell acute lymphoblastic leukemia (T-ALL) is a malignant disease of thymocytes, relatively rare in children, accounting for 15% of newly diagnosed cases of pediatric ALL and 25% of adult ALL cases [9]. Patients with T-ALL tend to present very high circulating blast cell counts, mediastinal masses, and central nervous system involvement [10].

The biological knowledge of T-ALL has until recently been rather limited. The introduction of novel technologies has allowed an increasing number of alterations to be unraveled. The most relevant results have been obtained by using FISH (Fluorescent In Situ Hybridization), molecular biology and gene expression profiling, which have enabled five subgroups to be recognized, immature/LYL1, TAL1, HOX11, HOX11L2 and HOX [11].

4.1. Cytogenetic characterization

Current understanding of the molecular basis of T-ALL has come largely from analysis of recurrent chromosomal translocations and intrachromosomal rearrangements [12].

Initial cytogenetics studies of T-ALL cases showed nonrandom breakpoints within the following T-cell receptor (TCR) gene clusters: TCRA/D locus (14q11.2), or TCRB locus (7q34). The TCR breakpoints were present in about 30% to 35% of T-ALL cases [13]. The TRG (TCRG) locus (7p14) may be restricted to T-cell ALL in patients with ataxia telangiectasia [14,15]. They typically juxtapose enhancer elements of the TCR genes with transcription factors involved in T-cell differentiation, with deregulation of hemopoiesis, including HOX11/TLX1, TAL1/SCL, TAL2, LYL1, BHLHB1, LMO1, and LMO2 [16].

In the period of 2 years, we came across several relevant chromosomal abnormalities that involve some of these genes while performing cytogenetic analysis on 70 pediatric ALL Moroccan patients, among which 13 cases were a type T-ALL (19%). In this study, we display the cytogenetic characteristics of a rare translocation t(14,21)(q11.2;q22) and compare our findings with a similar case reported in the literature.

The t(14,21)(q11.2;q22) results from a reciprocal translocation between chromosomes 14 and 21, respectively at q11 and q22, resulting in the production of a fusion gene, designated BHLHB1 (for basic domain, helix–loop–helix protein, class B), located on21q22. This BHLHB1 gene is shown to be activated in leukemic cells that had undergone a t(14;21)(q11.2;q22) translocation [17].

4.2. Treatment and outcome

Historically, a diagnosis of T-ALL portended a worse prognosis than other forms of ALL in children [18]. However, the outcome for childhood T-ALL has improved in recent decades, with the advent of high-dose, multi-agent chemotherapy regimens which have become the backbone of pediatric ALL therapy, resulting in long-term event free survival (EFS) rates of 70–75% for T-ALL [19]. In spite of the progress made, 20–25% of children with T-ALL experience relapse, most of whom cannot be salvaged with standard therapies [20].

The historically unfavorable outcome of patients with T-ALL has recently improved through the use of highly effective treatment protocols. T-ALL is now treated the same way as high-risk B-progenitor ALL [21,15]. With appropriately intensive therapy, children with T-ALL have an outcome similar to that of children with B-precursor ALL, i.e., the estimated 5-year event-free survival (EFS) is 75%–80% [22]. Nevertheless, patients with T-ALL remain at increased risk for remission induction failure, early relapse, and isolated CNS relapse. In a recent study of adolescents with ALL, no significant difference in outcome of T-ALL was found on the basis of age; older patients did as well as younger ones [23].

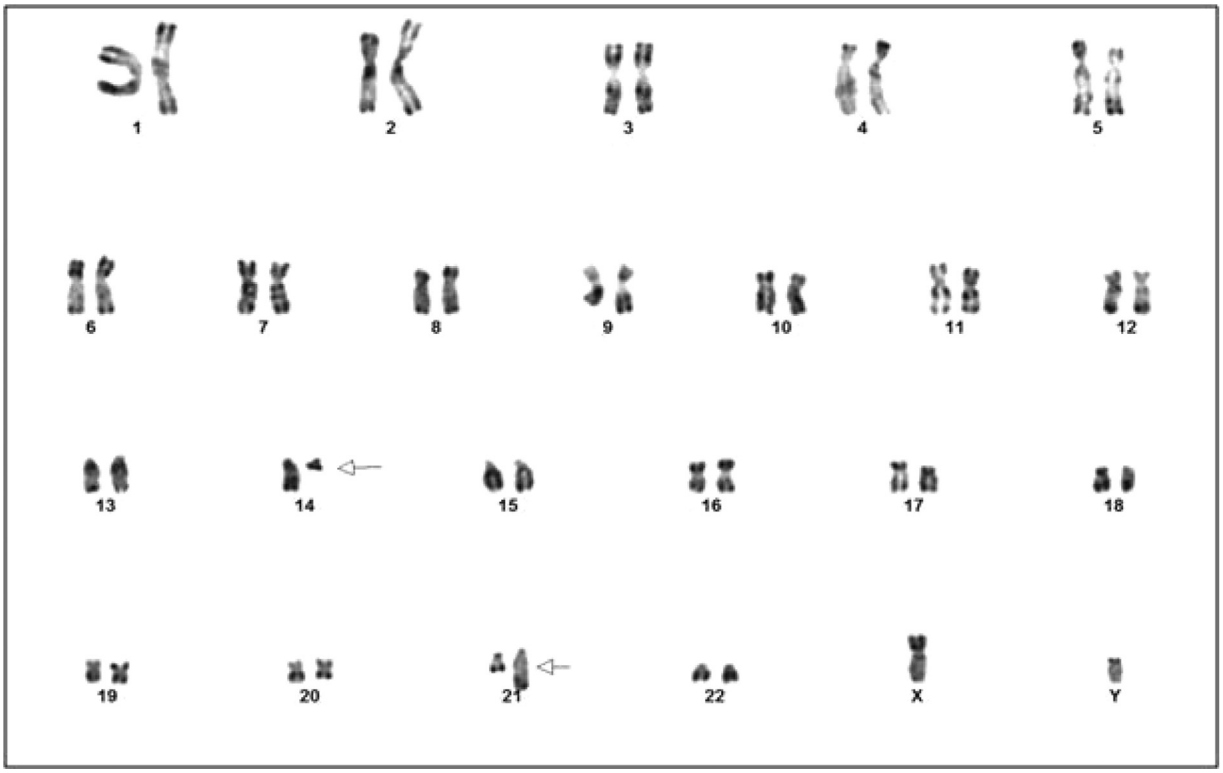

Fig. 1. Karyotype image from a cultured marrow sample of a patient with T-ALL showing the t(14;21)(q11;q22).

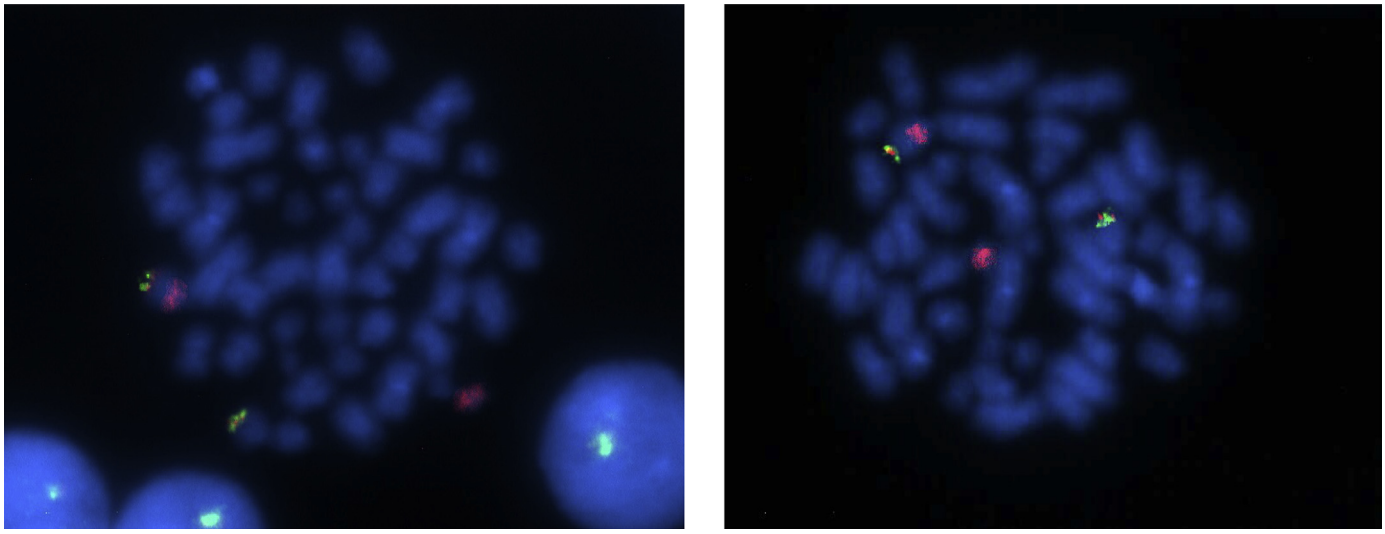

Fig. 2. Abnormal signal patterns in FISH analysis.

5. Conclusion

Cytogenetic analysis in ALL plays an important role in the classification and prognosis of the patients. This study was the second of its kind to publish the finding of a very rare recurring translocation t (14;21)(q11.2;q22) related to pediatric ALL cases. This chromosomal abnormality is associated with T-cell phenotype and with high-risk features.

Extensive research will allow a molecular profile of T-ALL to be defined.

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