Cancer Genetics 209 (2016) 166–170

Cancer Genetics

A der(11)t(4;11)(q21;p15) in a T-ALL/LBL patient

Sandra Colli [a], Lilian Furforo [b], Eduardo Rojo Pisarello [c], Marcela Maidana [c], Carlos Martín [d], Javier Bordone [c], Irma Slavutsky [a,*]

[a] *Laboratorio de Genética de Neoplasias Linfoides, Instituto de Medicina Experimental, CONICET-Academia Nacional de Medicina, Buenos Aires, Argentina;* [b] *Centro Nacional de Genética Médica, Buenos Aires, Argentina;* [c] *Hospital de Alta Complejidad "Presidente Juan Domingo Perón", Formosa, Argentina;* [d] *Consultorio de Hematopatología, La Plata, Argentina*

Translocation t(4;11)(q21;p15) is a rare recurrent change associated to T-cell acute leukemia. In most cases, this alteration appears as the only abnormality or as part of a simple karyotype. In this report, we present the first case of T acute lymphoblastic leukemia/lymphoma (T-ALL/LBL) with the unbalanced translocation der(11)t(4;11)(q21;p15) as part of a very complex karyotype with multiple chromosome abnormalities, most of them not previously described in the literature. FISH (fluorescence in situ hybridization) and spectral karyotype (HiSKY) analysis confirmed the presence of complex alterations. The patient, a 16-year-old male, showed poor response to treatment and short survival (11 months). A detailed review of previously reported cases with t(4;11)(q21;p15) is also provided. The description of this type of alterations may contribute to the identification of new molecular mechanism associated to neoplastic development.

Keywords T-cell acute leukemia/lymphoma, cytogenetics, FISH, spectral karyotype

Introduction

T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma (T-ALL/LBL) is a neoplasm committed to the T-cell lineage that can be observed involving bone marrow (BM) and peripheral blood (T-acute lymphoblastic leukemia, T-ALL) or presenting with primary involvement of thymus, nodal or extranodal sites (T-lymphoblastic lymphoma, T-LBL) (1). By convention, the term lymphoma is used when the process is confined to a mass lesion with no or minimal evidence of peripheral blood and BM involvement. If the patient presents with a mass lesion and lymphoblasts in the BM, the distinction between leukemia and lymphoma is arbitrary. T-ALL comprises about 15% of childhood ALL while T-LBL correspond to about 85–90% of all lymphoblastic lymphomas; both are most frequent in male adolescents. The annual incidence is 1.6/100,000 individuals in the general population (1). In Argentina, data of the Onco-Hematology Argentine Registry (2) show an incidence of 3.0/100,000 in children under 15 years.

Cytogenetic studies in this pathology have demonstrated an abnormal karyotype in about 50% of patients (3). Thirty five percent of cases show translocations involving T cell receptors and different genes (4,5). These translocations usually result in oncogenes becoming juxtaposed to the promoter and enhancer elements of *TCR* genes, leading to their aberrant expression and the development of T-ALL/LBL. Alternatively, aberrant expression of one or more transcription factors is a critical component of the molecular pathogenesis of T-ALL/LBL (5). On the contrary, the presence of arecurrent reciprocal translocation without involvement of at least one *TCR* encoding gene is a rare event in this pathology. The translocation t(4;11)(q21;p15) is a very uncommon rearrangement described in 1985 (6) that, at the molecular level, induces the fusion of the *RAP1GDS1* (RAP1, GTP-GDP dissociation stimulator 1) gene located at band 4q21, with the *NUP98* (nucleoporin 98 kDa) gene mapped at 11p15 (7,8), leading to a new chimeric transcript encoding a protein with dominant oncogenic properties: *NUP98-RAP1GDS1* (7). In most cases, this alteration appears as the only abnormality or as part of a simple karyotype (9). The literature shows only two cases with complex karyotype (three or more alterations) (10,11) and only one case with a complex translocation (12). In this study, we present the first case of T-ALL/LBL with an unbalanced translocation der(11)t(4;11)(q21;p15) as part of a very complex karyotype

Received September 21, 2015; received in revised form December 2, 2015; accepted January 6, 2016.

* Corresponding author.
E-mail address: islavutsky@hematologia.anm.edu.ar

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http://dx.doi.org/10.1016/j.cancergen.2016.01.001

with multiple chromosome abnormalities, most of them not previously described in the literature.

Case report

A 16-year-old male was referred to the Hospital of High Complexity "Presidente Juan Domingo Perón", Formosa, Argentina, in November 2013 with cervical and inguinal lymphadenopathies and splenomegaly. Hematological data showed: white blood cells count 20×10^9/L (28% neutrophils, 62% lymphocytes, 4% monocytes, 6% eosinophils), hemoglobin 15.4 g/dL, hematocrit 44% and platelet count 138×10^9/L. Lactate dehydrogenase was raised to 448 IU/L (normal range 240–480 IU/L). The patient had a normal liver and kidney function and, negative serology for hepatitis B and C. The histopathological study of the lymph node showed complete replacement for a lymphoid population with diffuse pattern, composed of medium sized blasts with scant cytoplasm, condensed nuclear chromatin and indistinct nucleoli. Immunohistochemical analysis showed co-expression of CD1a, Tdt, CD34 and CD10, and moderate reactivity of CD3 (Figure 1a). The Ki67 antigen disclosed 80% of proliferating cells. The BM aspirate showed 90% lymphocytes with diffuse pattern, with typical T-ALL/LBL morphology. Flow cytometry showed proliferation of T-cell precursors, which accounted for 76.21% of cell population. The patient started chemotherapy according to the protocol of the Argentine Group of Acute Leukemia Treatment (GATLA) (13). A complete hematological remission was achieved. Four months after consolidation, the patient showed hematological relapse and died three months later.

Methods

Cytogenetic analysis

Cytogenetic study was performed on BM cells cultured in RPMI 1640 medium supplemented with 20% fetal calf serum (Gibco) during 24 h at 37 °C. G-banding technique was used. Chromosome abnormalities were described according to the International System for Human Cytogenetic Nomenclature (ISCN) (14).

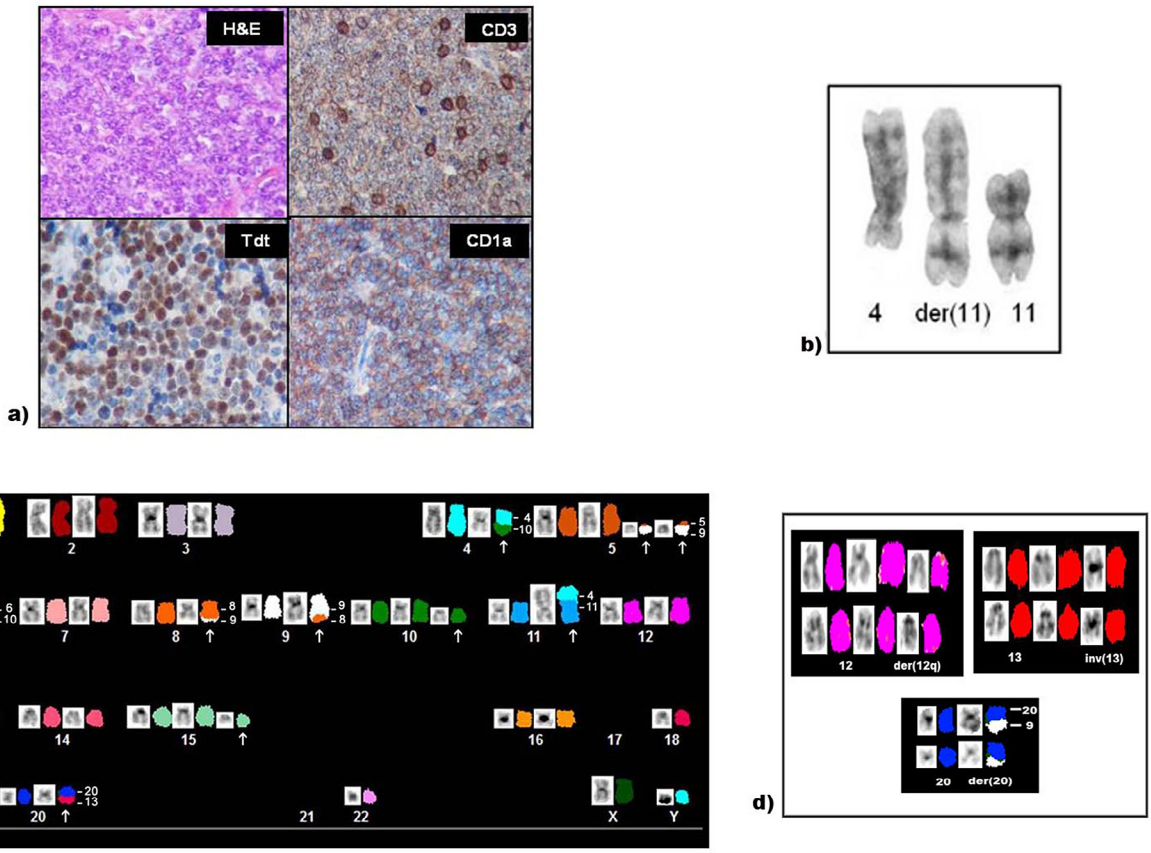

Figure 1 (a) Lymph node biopsy stained with Hematoxylin & Eosin showing complete replacement by lymphoblastic lymphoma, and immunohistochemical technique showing: moderate reactivity of CD3; Tdt expression; CD1a expression (400x); (b) G-banding partial karyotype showing normal chromosomes 4 and 11 and der(11)t(4,11)(q21;p15); (c) Spectral karyotype of the patient showing chromosome alterations: der(4)t(4;10)(q12;q?22), der(5)t(5;9)(?;?)x2, der(6)t(6;10)(q13;?), t(8;9) (q24;q34), der(10)del(10)(p11)del(10)(q24), der(11)t(4;11)(q21;p15), del(15)(q15), der(20)t(13;20) (?;q11) (arrows), as well as losses of chromosomes 17, 18, 21 and 22.The presence of a normal chromosome 9 in this cell is nonclonal; (d) G-banding and Spectral partial karyotypes showing: normal chromosomes 12 and del(12)(q11q13), normal chromosomes 13 and inv(13)(p11q14) and normal chromosome 20 and der(20)t(9;20)(?;q13).