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ELSEVIER

Dicentric (17;18) in a Case of Atypical B-Cell Chronic Lymphocytic Leukemia

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ABSTRACT: *We report a new dic(17;18)(p11.2;p11.2) in a 61-year-old male patient diagnosed with atypical B-cell chronic lymphocytic leukemia. The dic(17;18)(p11.2;p11.2) was detected in 90%, 10%, and 100% of metaphases in the peripheral blood, bone marrow, and lymph node, respectively. Fluorescence in situ hybridization studies with chromosome 17 and 18 centromeric probes revealed the presence of two normal centromeres of both chromosomes 17 and 18. The centromere of one chromosome 17 was found together with the centromere of one chromosome 18, confirming the dicentric nature of the rearrangement. In addition, with the use of a 17p13.1 region probe, monosomy of the 17p13 region, where the Tp53 gene is located, was observed.*

INTRODUCTION

Atypical B-cell chronic lymphocytic leukemia (aCLL) is a cytologically differentiated form of B-cell chronic lymphocytic leukemia (B-CLL) first described by the French–American–British group [1]. It is morphologically defined as a pathological accumulation of small B lymphocytes. When more than 10% of the lymphocytes are larger or are prolymphocytes, the diagnosis of mixed cell type should be considered. aCLL is defined as a variant that presents with >10% but <55% large lymphocytes, prolymphocytes, or centrocytes, and prolymphocytic leukemia is defined as a variant that presents >55% prolymphocytes [1]. The most common cytogenetic abnormality associated with aCLL is trisomy 12 [2–11]. Other chromosomal abnormalities involve 4q, 6q15–q23, 11q23, t(11;14)(q13;q32), 13q14, t(14;19)(q32;q13), 17p, and 17q [8–14]. Cytogenetic abnormalities related to poor prognosis in patients with B-CLL are 11q23 deletions, trisomy 12, and abnormalities of 17p [9, 15–22].

Thus, we wish to report a new case of aCLL refractory to treatment in which dic(17;18)(q10;q10) is the sole cytogenetic abnormality.

CASE REPORT

A 59-year-old man was diagnosed with B-CLL clinical stage A in 1996. The patient was initially treated with Leukeran. Two years later, the patient was referred to our institution for evaluation of his disease. Peripheral blood cell examination showed: hemoglobin, 8.8 g/dL; white blood cells, 15.6×10^9/L with 93.4% lymphocytes; and platelets 20×10^9/L. A peripheral-blood lymphogram revealed 20% mature lymphocytes, 2% large lymphocytes and lymphocytes with nucleoli, 46% centrocytes, 2% bilobulated forms, and 24% lymphocytes with small nucleoli with some villous prolongations. A biochemistry profile revealed serum lactate dehydrogenase, 521 U/L (reference range 150–450 U/L), and β-2-microglobulin, 4.1 mg/L (reference range 0.6–2.4 mg/L). Immunophenotyping of peripheral blood cells gave the following results: CD5+, CD19+, CD23+, CD25−, CD11c−, and weak Smlg+. A bone-marrow aspirate showed lymphoid infiltration of 90% (32% mature lymphocytes, 43% large lymphocytes, and 15% centrocytes). Bone-marrow and laterocervical lymph-node biopsies revealed an interstitial infiltration by B-CLL lymphocytes. Lymphadenopathies and splenomegaly were present. Atypical B-CLL clinical stage C (IV) diagnosis was established. The patient presented a cutaneous infiltration of the same lymphocyte population

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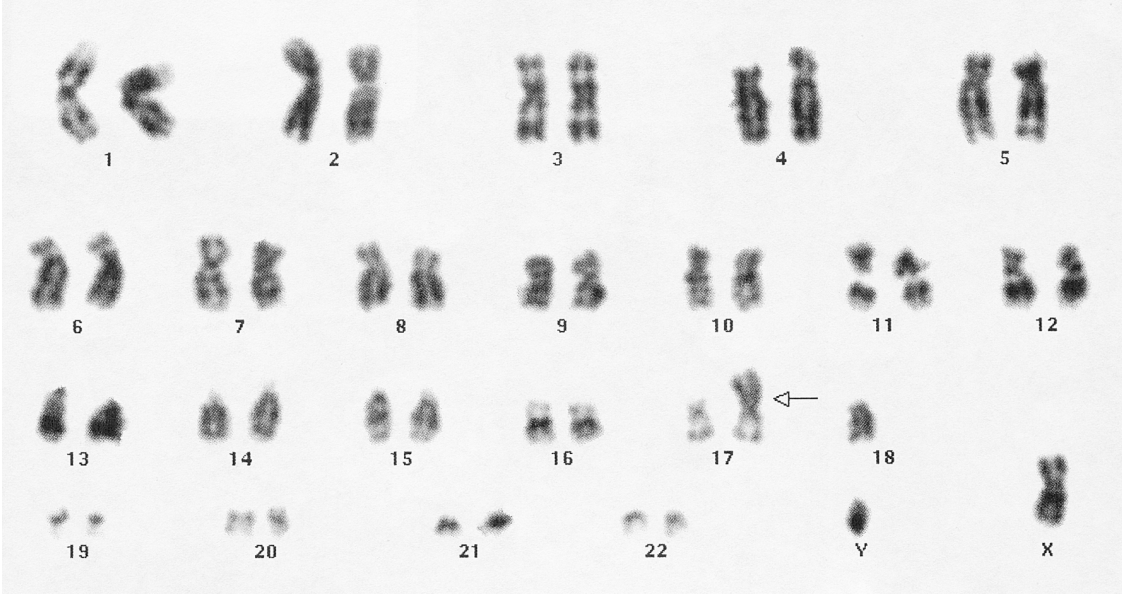

Figure 1 Peripheral blood karyotype showing 45,XY,dic(17;18)(p11.2;p11.2). Arrow indicates the abnormal chromosome.

detected in lymph nodes, bone marrow, and peripheral blood. He was treated with two courses of 2-CDA and three courses of CHOP without achieving a response. At present, he is receiving palliative treatment because of the refractory nature of the disease.

CYTOGENETIC AND FLUORESCENCE IN SITU HYBRIDIZATION

Cytogenetic analyses of several tissues were performed. A 72-hour peripheral-blood TPA-stimulated culture showed the presence of a 45,XY,dic(17;18)(q10;q10) karyotype in 18/20 metaphases. A 24-hour bone-marrow TPA-stimulated culture and a 72-hour lymph-node TPA-stimulated culture also showed a 45,XY,dic(17;18)(q10;q10) karyotype in 1/10 and in 2/2 metaphases, respectively. A peripheral-blood PHA-stimulated culture was performed to establish the constitutional karyotype and showed 46,XY(17)/45,XY,dic(17;18)(q10;q10)(3). A 45,XY,dic(17;18)(q10;q10) karyotype was seen in all cultures (Fig. 1; Table 1). Karyotypes were described according to the ISCN 1995 nomenclature [23]. Fluorescence in situ hybridization (FISH) analysis was performed by using two centromeric probes (SpectrumOrange-labeled chromosome 17-specific alpha-satellite DNA probe and SpectrumGreen-labeled chromosome 18-specific alpha-satellite DNA probe) and a SpectrumOrange-labeled 17p13.1 DNA probe (p53 locus) (Vysis) on TPA-cultured peripheral blood cells. FISH revealed the presence of two normal centromeres for chromosomes 17 and 18, with one centromere of each chromosome fused, confirming the dicentric nature of the rearrangement. A monosomy of 17p13.1 region was found. A minimum of 200 nuclei per case were scored.

Conventional cytogenetics and FISH results revealed the karyotype to be: 45,XY,der(17;18)(q10;q10).ishdic(17;18)(p11.2;p11.2)(D17Z1+;D18Z1+).

DISCUSSION

Structural abnormalities of chromosome 17 detected by conventional cytogenetics have been observed in 4% of cases of CLL [24]. However, a higher incidence may be detected by FISH [25]. In a recent study, Callet-Bauchu et al. reported a series of 14 B-CLL/small lymphocytic lymphoma patients with involvement of 17p, 4 of them showing a dic(17;18) [26]. Patients were characterized by resistance to chemotherapy and poor clinical outcome. Lack of response to chemotherapy appears to include several therapeutic agents, such as alkylating agents, anthracyclin, and purine analogs. In our case, the patient received different drugs and was refractory to all of them. In lymphoid neoplasms, a strong correlation between p53 alteration

Table 1 Cytogenetic results in patient with atypical B-CLL

Tissue	Mitogen	Karyotype
Peripheral blood	PHA	46,XY[17]/45,XY,dic(17;18)(p11.2;p11.2)[3]
Peripheral blood	TPA	45,XY,dic(17;18)(p11.2;p11.2)[18]/46,XY[2]
Bone marrow	TPA	46,XY[9]/45,XY,dic(17;18)(p11.2;p11.2)[1]
Lymph node	TPA	45,XY,dic(17;18)(p11.2;p11.2)[2]

and advanced clinical stage, resistance to chemotherapy and short survival has been previously reported [24]. In a study by Döhner et al., multivariate analysis revealed that deletion of the p53 gene was the strongest prognostic factor for survival in B-cell leukemias [25]. The present case showed a dic(17;18)(q10;q10) karyotype as a single anomaly, which resulted in loss of the short arm of chromosome 17, where the p53 gene is located. Deletion of 17p as a sole abnormality could explain the aggressive clinical course of the disease.

This report presents a new case of a recurrent cytogenetic abnormality in B-CLL patients involving a deletion of 17p13 as a dic(17;18)(q10;q10) and confirms the association with disease progression and lack of response to chemotherapy.

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