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Case Report

Case of Chronic Lymphocytic Leukemia with Unusual Chromosome Aberrations

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Abstract

Chronic lymphocytic leukemia is one of the most common leukemias in the western world and consists of many chromosome aberrations. We report the case of a 74-year-old male patient with chronic lymphocytic leukemia with complex variant translocations t(8;22)(q24;q11) and der(8)t(6;8)(p21;p21) identified by chromosome banding analysis and confirmed by fluorescence in situ hybridization analysis of interphase cells. Because of the rarity of these changes, possible molecular mechanisms associated with this karyotype are discussed.
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Key words: Chronic lymphocytic leukemia; Chromosome aberration; t(8;22); t(6;8)

1. Introduction

Chronic lymphocytic leukemia (CLL) is characterized by clonal proliferation and accumulation of neoplastic B-lymphocytes. Conventional chromosome banding analysis shows that CLL harbors chromosome aberrations in approximately 40% to 50% of cases [1]. Trisomy 12 is the most frequent chromosome abnormality in most studies, followed by structural aberrations of the long arm of chromosomes 13 and 14 [1-3]. With fluorescence in situ hybridization (FISH) analysis, the incidence of abnormalities has increased to 80%, deletion 13q becoming the most common, followed by 11q deletion, and trisomy 12 [1,4]. Many chromosomes are involved in the aberrations in CLL; however, complex variant translocations, including t(8;22)(q24;q11) and der(8)t(6;8)(p21;p21), have been rare in previous reports. We report a case of CLL with these unusual chromosome abnormalities.

2. Case Report

A 74-year-old male patient had been well except for ischemic heart disease. For 1 week in March 2002 he suffered from a progressively productive cough with yellowish sputum. Marked leukocytosis was found, and the patient was transferred to our hospital for further management. Physical examination revealed hepatosplenomegaly with bilateral inguinal lymphadenopathy. Chest x-ray and plain abdominal films showed pneumonia over the right lower lung field and splenomegaly. The peripheral blood examination showed hemoglobin, 8.9 g/dL; platelets, 126.0×10^9/L; and white blood cell count, 339.2×10^9/L, with myelocytes, 0.5%; band forms, 1.0%; segments, 2.5%; monocytes, 1%; eosinophils, 0.5%; lymphocytes, 94%; and atypical lymphocytes, 0.5%. Smudge cells also were clearly found (Figure 1). Because of marked leukocytosis with severe dyspnea, emergency leukophoresis was performed. A sudden onset of pulseless ventricular tachycardia occurred 1 day later, and cardiopulmonary resuscitation was performed. The patient was transferred to an intensive care unit for further care after resuscitation. Bone marrow examination was performed in the intensive care unit and showed infiltration by lymphocytes (78.6%). Results of immunophenotyping of the marrow cells were positive for CD19, CD20, and Ia but negative for POX, SBB, CD7, CD10, CD11b, and CD33. CLL (stage III by Rai classification) was diagnosed, but no further treatment was given owing to the patient's poor general condition. He died of pneumonia 10 days after the diagnosis was made.

3. Material and Methods

Cytogenetic studies were performed on direct bone marrow preparations and on 24-hour culture with phytohemagglutinin stimulation by the ethidium bromide technique.

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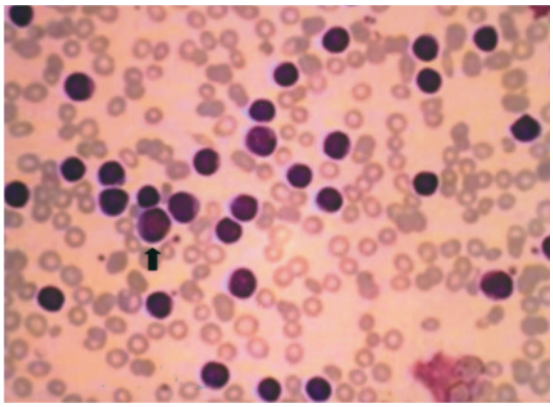

Figure 1. The peripheral blood smear showed a predominance of mature lymphocytes with some atypical lymphocytes (arrow).

The karyotype was described according to the International System for Human Cytogenetic Nomenclature. The chromosomes were stained by modified G-banding technique. The same specimen was used for FISH analysis 6 months later with a commercially available whole-chromosome painting probe for chromosome 8 (LSI probe; Vysis, Downers Grove, IL, USA).

4. Results

Analysis of a total of 15 metaphases revealed a reciprocal translocation between chromosomes 8 and 22 with breakpoints at 8q24 and 22q11. The other chromosome 8 was a derivative containing extra material with a break at 6p21 translocated to 8p21 (Figure 2). FISH analysis was performed on interphase cells with whole-chromosome painting probe for chromosome 8. The results showed one whole chromosome 8 with 2 separated small chromosome 8 materials (Figure 3). These findings were comparable with reciprocal translocation t(8;22).

5. Discussion

CLL is a predominantly B-cell neoplasm, and it is seen more frequently in the western world. Although the short interval from diagnosis to death, lymphocytosis (more than 10×10^9/L) with monoclonal lymphocytes in peripheral blood, and bone marrow infiltration by lymphocytes with monoclonal B-cells confirmed by immunophenotyping made the diagnosis CLL in this case, the complex variant translocations, including t(8;22)(q24;q11) and der(8)t(6;8)(p21;p21), were unusual abnormalities and may have important implications.

With the conventional chromosome banding method, the most frequent abnormalities involved in CLL were trisomy 12, 13q14, 11q, 6q, 17p, and translocations involving 14q32 [1-3]. A t(8;22) translocation has previously been described in only 1 case of CLL [5]. Those authors described a CLL patient who had 3 separate clones, all harboring a t(8;22) with or without other cytogenetic abnormalities. Because of the abnormalities consistent with t(8;22) in different clones,

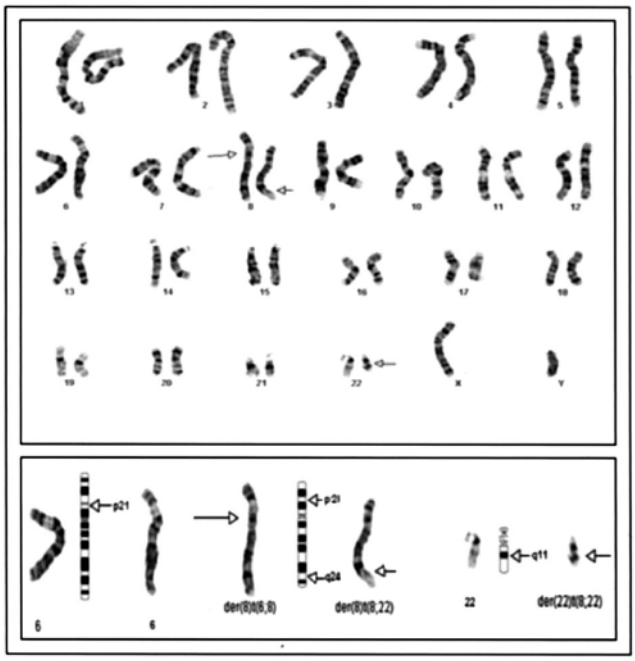

Figure 2. Karyotype of modified G-band technique showed 46XY,t(8;22)(q24;q11),der(8)t(6;8)(p21;p21) (top). Partial karyotype showed the complex chromosome abnormalities (bottom).

the authors suggested the presence of t(8;22) in their patient may have been associated with B-cell CLL and other abnormalities, including trisomy 7 and del(11)(q14), and may have been a secondary change. Our patient, however, had only 1 clonal change found at chromosome analysis, and the data demonstrated t(8;22) and der(8)t(6;8) in all metaphases. Therefore the possible molecular mechanisms of these 2 translocations in the leukemogenesis of CLL need further investigation.

The t(8;22) translocation is a variant of t(8;14) and accounts for approximately 5% of cases of Burkitt lym-

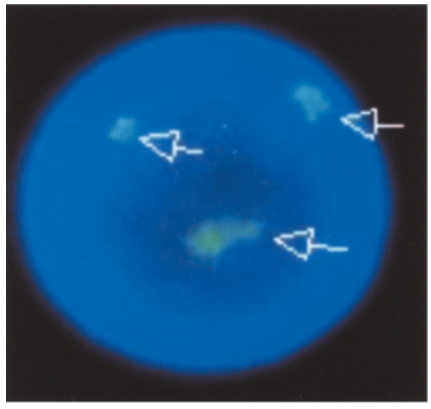

Figure 3. Interphase cell hybridized by chromosome 8 painting probe has 1 whole chromosome 8 and 2 separate pieces (arrows), findings comparable with t(8;22).

phoma [6]. These translocations are associated with c-*myc* rearrangement, and dysfunction of c-*myc* may also be found in other B-cell lymphocytic neoplasms. A few investigators have demonstrated amplification of c-*myc* in cases of CLL. Using FISH analysis, Dohner et al [4] found amplification of 8q24 in 5% of cases (16 of 325 cases). Bentz et al [7] reported 2 cases of overexpression of chromosome material of 8q by comparative genomic hybridization with 1 case of proven amplification of c-myc by FISH probe. Wang et al [8] found amplification in 1 case of CLL. The findings in our case, although the patient harbored a rare karyotypic change of t(8;22) in CLL, may also imply the possible role of c-myc in the leukemogenesis of CLL. The translocation involving *c-myc* in our case may also account for the atypically rapid progression observed.

Chromosome 6 abnormalities, as previously described in cases of CLL, most commonly involve the 6q region [1,6,7]. However, Philip et al described a roughly equal number of 6p and 6q abnormalities in 193 cases of CLL [9]. They also suggested an advanced clinical stage, diffuse pattern of bone marrow infiltration, and poor prognosis in CLL patients with aberrations of chromosome 6. Other studies have shown the important role of gene involvement over the chromosome 8p11-p12 area in T-prolymphocytic leukemia [10]. Some candidate genes, including the fibroblast growth factor receptor 1 gene and the MOZ gene, which are associated with myeloproliferative disease and lymphoma [11,12], have been found with abnormalities over the chromosome 8p11 area [10]. The finding of der(8)t(6;8)(p21;p21) in our patient may be a rare one in CLL. Whether this translocation would fuse any candidate genes to form an oncotranscript or whether this change was only a secondary abnormality in transformation of CLL needs further investigation.

Genomic aberrations also harbor important independent predictors in CLL patients. With the chromosome 17q deletion, 11q deletion, and abnormal 14, patients have had shorter median survival times [7,13]. Patients with a normal karyotype or single cytogenetic abnormality also have longer survival periods than patients with complex karyotypic changes [7,13]. It was not surprising that our patient with multiple cytogenetic abnormalities, including 1 involving c-myc, did poorly.

In summary, we report a case of CLL with rare coexisting t(8;22)(q24;q11) and der(8)t(6;8)(p21;p21) cytogenetic abnormalities. Study of more cases of these alterations is warranted for more gains in our understanding of the molecular biology of CLL.

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