CASE REPORT

A chronic myeloid leukemia-like syndrome case with del (12) (p12) in a Li-Fraumeni syndrome family

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Summary

Li-Fraumeni syndrome is a familial cancer syndrome characterized by different tumors and hereditary p53 mutations. Here, a chronic myeloid leukemia-like syndrome case in a Li-Fraumeni syndrome family with del (12) (p12) cytogenetic abnormality was presented. A hereditary p53 mutation (pro309ser) supported the Li-Fraumeni syndrome diagnosis in this family. This syndrome was characterized by the clonal myeloproliferative accumulation in bone marrow and peripheral blood with negative bcr/abl gene rearrangement finding. The etiology of this rare syndrome is still unclear. This is the only chronic myeloid leukemia-like syndrome case reported in a Li-Fraumeni syndrome family. Del (12)(p12) was observed in leukemias except chronic myeloid leukemia-like syndrome. The deletion in chromosome 12p12 with hereditary p53 mutation should have a critical role in chronic myeloid leukemia-like syndrome etiology in our case.

Keywords

Li-Fraumeni syndrome, Philadelphia chromosome, bcr/abl translocation, chronic myeloid leukemia-like syndrome, p53

Introduction

Li-Fraumeni syndrome is a hereditary cancer syndrome characterized by various tumors in childhood and adult time periods (Garber et al., 1991). Finding a hereditary p53 mutation supports the diagnosis (Malkin et al., 1990).

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder resulting from oncogenic transformation of a bone marrow stem cell with a karyotypic hallmark named as Philadelphia (Ph) chromosome because of bcr/abl gene rearrangement (Deisseroth et al., 1993; Heim & Mitelman, 1995). Patients with a chronic myeloid leukemia-like picture but lacking both Ph chromosome and bcr rearrangement have been described as chronic myeloid leukemia-like syndrome (CML-like syndrome).

Such patients appear to have a distinct clinical course characterized by increasing leukocytosis, organomegaly, extramedullary infiltrates and bone marrow failure. The etiology of CML-like syndrome is still unclear (Kurzrock et al., 2001).

Here, a CML-like syndrome case with clonal del (12) (p12) cytogenetic abnormality was presented in a Li-Fraumeni syndrome family (a hereditary p53 pro309ser mutation carrier). These two genetic abnormalities observed in our case may have an important role in CML-like syndrome progression.

Case report

A 45-year-old man came to our notice with dyspnea and fatigue symptoms and a high leukocyte count ($367 \times 10^9/l$). The family history revealed different tumors in an autosomal dominant inheritance pattern (Figure 1). Splenomegaly and pallor was observed in physical examination. The peripheral blood and bone marrow...
analyses revealed myeloid hyperplasia (the myeloblast ratio: 18.5%; Figure 2). No Ph chromosome as a result of bcr/abl gene rearrangement was observed. Cytogenetic and molecular genetic analyses revealed del (12) (p12) and hereditary p53 pro309ser point mutation (Figures 3 and 4). As a result of these findings, the patient had CML-like syndrome diagnosis as a Li-Fraumeni syndrome family member. Following chemotherapy, allogenic bone marrow transplantation was applied (from one of his siblings/III-11). Eighteen months later, the patient died because of progression of the leukemia.

Materials and methods

Cytogenetic and FISH analyses

The cytogenetic analyses of bone marrow cells were studied after 1 h and 24 h of incubation. Methotrexate synchronization (high resolution) was also applied. Chromosomal preparations were GTG banded (Yunis, 1981). Metaphases were karyotyped according to the ISCN (Mitelman, 1995). Vyses LSI Bcr/abl ES Dual Color Translocation probe (VYSIS-3219102) was used for FISH analyses using the manufacturer’s recommendations.

P53 gene mutation analyses

The DNA was isolated using standard procedures (Sambrook, Fritsch & Maniatis, 1998). The hereditary p53 mutation was analyzed in exons 5 to 9 by using protocols.
described by Guran and Tali (1999). LOH in the p53 gene was analyzed by using the protocol of Barel et al. (1998). Two polymorphic loci in the p53 gene [restriction fragment length polymorphism (RFLP)-exon 4 and RFLP-intron 6] were used in LOH analyses.

**RNA preparation and RT-PCR**

The total RNA from bone marrow was isolated by using QiampRNA blood mini kit (Qiagen, Valencia, CA, USA), according to the manufacturer’s recommendations. Reverse transcription was carried out with Omniscript-RT, following the manufacturer’s protocol, with random hexamers primers. Following reverse transcription, 2 µl (1/10) of each RT reaction was used for PCR using QIAGEN Taq DNA Polymerase and gene-specific primers, designed to span translocation regions as previously described (von Dongen et al., 1999).

**Results**

The cytogenetic analyses of the patient revealed 46, XY [4], 46, XY del (12) (p12) [8], 46, XY, −15, del (7 q?), der (15) t (q15: ?) + mar [1] (Figure 3). t (9; 22) (q34: q11) (bcr/abl), t (8; 21) (q22; q22) (AML-1/MGT8), t (12;21) (p13; q22) (TEL/AML), t (15; 17) (q22; q21) (PML/RARA) and inv (16) (p13; q22) (CBFB/MHY 11) were negative in RT-PCR analyses. No bcr/abl gene rearrangement finding was observed in FISH analyses. The DNA samples revealed a hereditary p53 pro309ser point mutation in this family (Figure 4). No LOH of the p53 gene was observed in DNA samples.

**Discussion**

The Li-Fraumeni syndrome was characterized by multiple malignant tumors (in childhood and adulthood) and hereditary p53 gene mutations (Guran, Tunca & Imirzalioglu, 1999). Several tumors were observed in this family in an autosomal dominant inheritance pattern with the hereditary p53 pro309ser mutation (Figure 1). P53 codon 309 mutations had been reported frequently in different tumors (Levine, MomAnd & Finlay, 1991).

The Ph negative CML is a very rare clinical entity (Cortes et al., 1995). Poor prognosis had been reported in these cases (Martiat, Michaux & Rodhain, 1991). Despite intensive chemotherapy and bone marrow transplantation, the patient died in a short time period. The genetic basis of CML-like syndrome is not well understood. Some chromosomal abnormalities (such as +18, +21, breakpoints at 5q33 and 8p11) were reported in the literature (Mcdonald et al., 1995), but their significance is still

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**Figure 3.** The karyotype (a) represents 46, XY, del (12) (p12), and partial karyotype (b) represents del (12) (p12).

**Figure 4.** The single strand conformational polymorphism and sequence results of p53 gene represent pro309ser mutation (N, normal; P, patient).
unclear. Here we observed a del (12) (p12) clonal cytogenetic abnormality. This cytogenetic abnormality was frequently reported in myelodysplastic syndrome, acute myeloid leukemia and acute lymphoblastic leukemia (L1 subtype with B or T cell lineage) (de Souza Fernandez et al., 2000; Adeyinka & Dewald, 2003). Our case was the only example in CML-like syndrome with del (12) (p12) cytogenetic finding. The chromosome and gene alterations reported in our case should have an important role in disease progression in CML-like syndrome.

References


