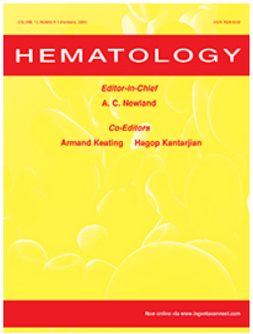

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Rapid transformation of atypical myeloproliferative disorder with consistent t(8;13) to B-cell acute lymphoblastic leukemia: A case report

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Abstract

8p11 myeloproliferative syndrome (EMS; also known as the stem cell leukemia syndrome-SCLL) is a rare atypical myeloproliferative disorder associated with chromosomal abnormalities involving the 8p11 chromosomal band. Translocations associated with this syndrome result in the fusion of the fibroblast growth factor receptor 1 (FGFR 1) gene with various partners, resulting in ligand independent FGFR activity. The most commonly observed translocation of this syndrome is t(8;13), which results in the expression of a chimeric ZNF198-FGFR1 tyrosine kinase. Disease phenotype associated with this translocation has some typical features such as poor prognosis, and transformation to mainly acute leukemia and non-Hodgkin lymphoma; commonly with a T-cell phenotype in which obtaining and maintenance of remission is difficult by conventional chemotherapy. We hereby present a case diagnosed as atypical chronic myeloproliferative disease with consistent t(8;13)(p12;q12) and transformed rapidly to pre-B-cell acute lymphoblastic leukemia which is a rare clinical presentation.

Keywords: *Atypical myeloproliferative disorders, acute lymphoblastic leukemia, t(8;13), FGFR*

Introduction

Myeloproliferative disorders are a heterogeneous group of diseases characterized by excess proliferation of cells originated from the myeloid lineage. Chronic myeloid leukemia, polycythemia vera, essential thrombocythemia and myelofibrosis are leading forms of the disorder [1]. Chronic myeloid leukemia differs with its unique chromosomal abnormality known as Philedelphia chromosome.

An atypical form of myeloproliferative disorder presented as a leukemia/lymphoma syndrome with myeloid hyperplasia that rapidly progresses to acute myeloid leukemia (AML), peripheral eosinophilia and lymphoblastic lymphoma of commonly T-cell origin has been described in recent years [2,3]. The hallmark of this syndrome is chromosomal translocations involving the fibroblast growth factor receptor 1(FGFR1) gene located on chromosome band 8p11–12. Several different translocation partners such as ZNF198, FOP, CEP110, BCR, HERV-K have been described to fuse with FGFR1 resulting in constituitive and ligand independent activity of the FGF signal transduction pathways. The most commonly observed translocation is t(8;13)(p12;q12), in which the N-terminal two-thirds portion of ZNF198 is fused to the intracellular region of FGFR1 [4,5]. Main characteristics of patients carrying this translocation can be described as an indolent course and rapid transformation to malignant hematological diseases mostly to AML and non-Hodgkin lymphoma [6–8]. We hereby present a case diagnosed as atypical chronic

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myeloproliferative disease with t(8;13)(p12;q12) and progressed to acute B-cell lymphoblastic leukemia which is refractory to treatment.

Case report

A 58-year-old female patient presented with weakness and fatigue. No organomegaly was detected and laboratory analysis showed leukocytosis with prominent myelocytes and metamyelocytes, eosinophilia, anemia and normal platelet count. Leukocyte alkaline phosphatase score was found to be 2%. Bone marrow aspirate showed myeloid hyperplasia resembling chronic myelogeneous leukemia in the chronic phase. Bone marrow biopsy of the patient initially diagnosed as atypical myeloproliferative disease with dysplasia and aspiration samples were sent to the Cytogenetics and Molecular Biology Laboratories of the Medical Biology and Genetics Department, Dokuz Eylul University. Chromosome analysis was performed at presentation and after a 24 h short-term culture period. Harvesting, G-band staining of the metaphase chromosome and their karyotypic analysis were performed by conventional methods as previously described [9]. Cytogenetical analysis of bone marrow showed t(8;13) (p12;q12) in 2 of 16 metaphases (Figure 1). Bone marrow specimens were negative for the Philadelphia chromosome both by conventional cytogenetics and fluorescence *in situ* hybridization; also RT-PCR was negative for the BCR-ABL transcript. The patient was diagnosed as atypical chronic myeloproliferative disease with t(8;13)(p12;q12). Supportive treatment with erythrocyte suspension was started and hydroxiurea was given to control the leukocyte count. Patient was hospitalized due to pallor, weakness and presence of blastic cells in peripheral blood smear at third months after first complaints with the diagnosis of acute lymphoblastic leukemia. Immunophenotypical analyses have confirmed pre-B-cell ALL. Bone marrow biopsy revealed existence of lymphoblastic cells with CD10, CD19, CD79a and TdT positivity (Figure 2). Hoelzer's protocol (prednisone 60 mg/m^2 D1–28, vincristine 1.5 mg/m^2 D1,8,15,22, daunorubucin 25 mg/m^2 D1,8,15,22, L-asparaginase 5000 u/m^2 D1–14 as phase I in 4 weeks and cyclophosphamide 650 mg/m^2 D29,43,57, cytosine arabinoside 75 mg/m^2

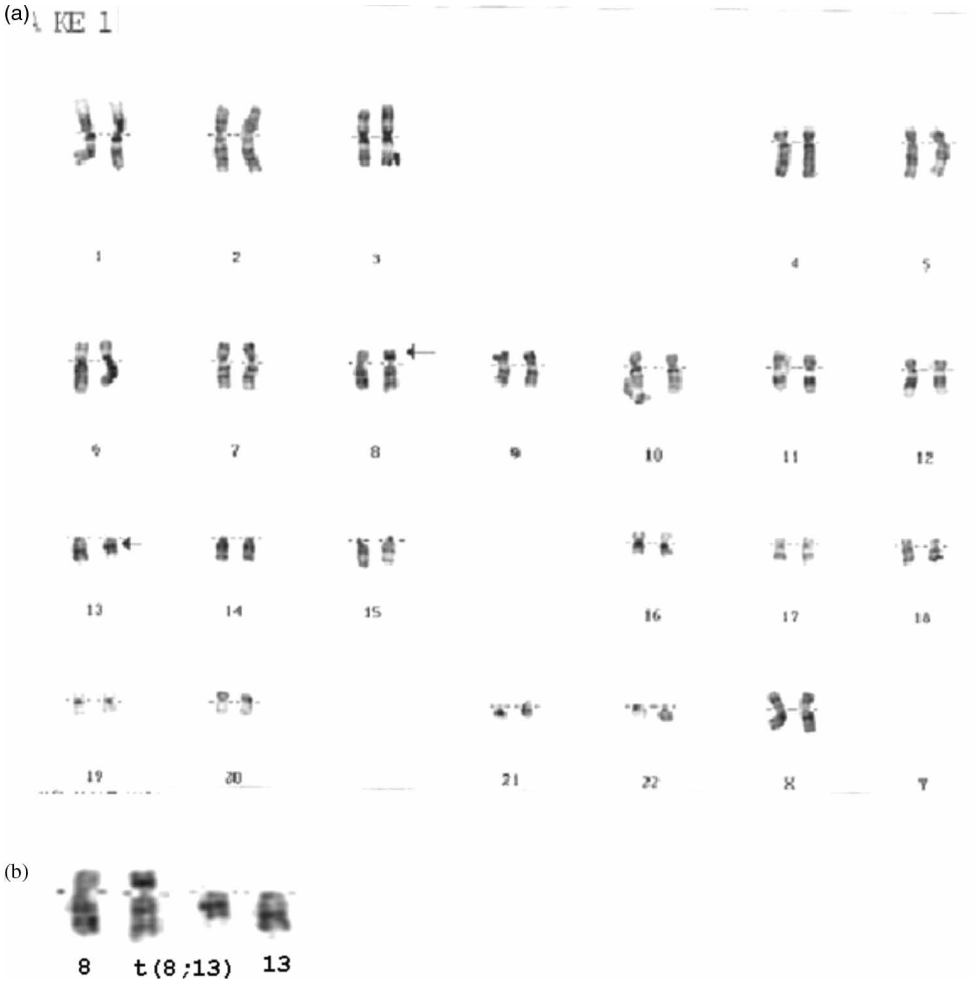

Figure 1. Karyotype analysis of the patient showing normal chromosomes 8 and 13 along with t(8;13)(p12;q12) (G-banding) (A) and t(8;13) as extracted from karyotype (B).

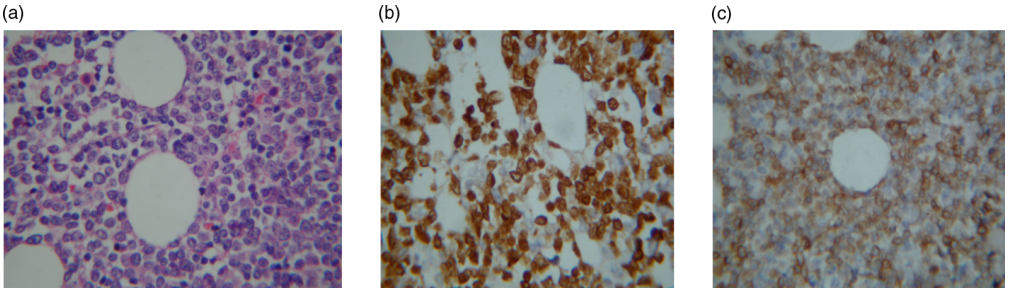

Figure 2. (A) Diffuse infiltration of lymphoblasts in the bone marrow biopsy (HδE). (B) Nuclear TdT positivity of the lymphoblasts. (C) Cytoplasmic CD79a positivity of the lymphoblasts.

D31–34,38–41,45–48,52–55, 6-mercaptopurine 60 mg/m^2 D29–57, methotrexate IT 10 mg/m^2 D31,38,45,52 as phase 2 and 2400 cGy cranial radiotherapy) was given and after first cycle, remission was obtained. Cytogenetic analysis on bone marrow cells revealed a normal 46,XX karyotype. Since she had no matched sibling donor for allogeneic bone marrow transplantation, autologous peripheral stem cell transplantation was planned as consolidation treatment. Mobilization of stem cells for autologous peripheral blood stem cell (APBSC) transplantation was performed with high dose methotrexate. 8.87×10^6/kg CD34 positive cells were harvested. Cytogenetical analyses of collected autologous cells were found to be normal without any sign of cytogenetical anomalies including t(8;13)(p12;q12) in all metaphases analyzed. After the conditioning regimen collected cells were infused to the patient. Neutrophil engrafment was obtained at day 11 and the patient was discharged in healthy condition after remission status was confirmed by bone marrow analyses. The patient was followed by monthly regular outpatient visits. On the third month of transplantation she presented with weakness, fatigue and pallor. After physical and laboratory examination she was diagnosed as relapsed acute lymphoblastic leukemia with same immunohistochemical features and Ida-FLAG regimen was applied with the previously established doses [10]. Cytogenetical analysis of bone marrow during relaps revealed complex chromosomal abnormalities including the t(8;13)(p12;q12) in all 20 metaphases examined with the addition of clonal add [12] (q24) and trisomy 14 (Figure 3). High dose chemotherapy was started but the patient died because of neutropenic fever, sepsis and multiorgan failure.

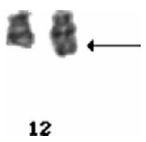

Figure 3. Partial karyotype showing normal chromosome 12 and der(12)t(?;12)(?;q24). der(12)t(?;12)(?;q24) along with trisomy 14 was observed in addition to t(8;13)(p12;q12) as a result of clonal evolution during progression of disease.

Discussion

Chronic myeloproliferative disorders are classified as the grey zone of hematopoietic neoplasms. They have been characterized with the proliferation of myeloid precursors in the bone marrow. Each chronic myeloproliferative disorder is identified by a characteristic expansion of a subset of myeloid cell lineages. Nonspecific myeloproliferative disorders show phenotypic features that overlap with classic chronic myeloproliferative disorders, but are sufficiently dissimilar to be diagnosed as distinct clinicopathologic entities. However, atypical chronic myeloproliferative diseases have more aggressive clinical course and tend to rapidly transform to acute form of either leukemia or lymphoma.

An atypical chronic myeloproliferative disorder that is associated with T-cell leukemia/lymphoma and peripheral blood eosinophilia is firstly described by Abruzzo et al. [11]. The atypical myeloproliferative disorder characterized by an initial myeloproliferative phase with eosinophilia, without basophilia has been transformed to high incidence of T- or B-cell non-Hodgkin's lymphoma or acute leukemia, especially myeloid leukemia within 1–2 years of diagnosis [12]. Several phenotypically related cases have been described until now [2,6,13,14]. All cases described to date involve chromosomal translocations where one of the breakpoints localized to 8p11–12. Different groups identified that the breakpoint on 8p11 disrupt the FGRF1 gene resulting in fusion transcripts with various translocation partners. The breakpoint in the FGFR1 gene is localized at the carboxyl end, retaining the intercellular region containing its two tyrosine kinase domains. Thus, the resulting chimeric proteins cause unregulated, ligand independent activation of FGF signaling pathway. The most commonly observed translocation is t(8;13)(p11–12;q12), in which the N-terminal two-thirds portion of ZNF198 (also called RAMP or FIM) is fused to the intracellular region of FGFR1. The translocation results in a chimeric protein with aberrant tyrosine kinase activity. The hybrid oncogenic protein is composed of the FIM and FGFR1, resulting in constitutive activation of FGFR1 signal transduction pathways and malignant transformation [15–20]. The translocation t(8;13)(p12;q12) could be found in cells of both myeloid and

lymphoid lineages as the disease originates from a hematopoietic stem cell.

It is usually observed as a single anomaly; although duplication of the der(13), +8, +21 has been observed during disease progression [15,16]. In our case, we described t(8;13)(p12;q12), and multiple chromosomal abnormalities including t(8;13)(p12;q12), add [12](q24), +14, inc.[cp20] on assessment after she relapsed.

Although it has been reported that the transformation of atypical myeloproliferative syndromes to T-cell leukemia and/or lymphoma have been more frequent than the transformation to B-cell lymphoid malignancies, we have hereby reported a case with multiple and complex cytogenetical abnormalities transformed to B-cell lymphoblastic leukemia. The exact mechanisms underlying for transformation to acute hematological malignancies remain to be clarified. As detected in our patient, additional newly occurred chromosomal abnormalities could explain this phenomenon.

There are approximately 20 cases reported to date and hence not enough data to establish appropriate treatment, and therapy after transformation remains to be clarified. The progressive disease appears to be non-curable by conventional chemotherapy. In our patient, we have performed APBSC transplantation to consolidate induction regimen by using the cells proven t(8;13) negative by cytogenetical analysis. But the relapse of the disease after a short-term of therapy revealed that high dose chemotherapy supported with APBSC could not eliminate all the cells with t(8;13). On the other hand, an experimental therapeutic approach in which the administration of a tyrosine kinase inhibitor successfully stabilizing a patient for 6 months has been reported to date [21], allogeneic bone marrow transplantation seems to be the only curative therapeutic option [12,17]. Since it has rapid progressive nature, aggressive treatment options including allo BMT should be considered even in earlier stages of the disease. Definition of ZNF198-FGFR1 signaling pathways in leukomogenic process would contribute to develop new targets for the treatment of the disease. Inhibition of these pathways is going to be target for further laboratory and clinical studies. Furthermore, it is still needed to have large series to understand the possible pathogenesis of transformation of the disease to acute forms. Also, the pathogenetic pathways of transformation either B- or T-cell lymphomas should be elucidated.

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