Case Report

Rearrangement of PDGFRβ gene in a patient with Ph-negative chronic myeloid leukemia t(5;12)(q33;p13) in imatinib mesylate treatment-free remission: a case report

Jing Zheng¹, Jincheng Huang³, Yao Xiao¹, Xueqin Wu¹, Kai Wang², Chun Feng¹, Kaibo Gao¹

Departments of ¹Hematology, ²Rheumatology and Clinical Immunology, The First People’s Hospital of Yichang, China Three Gorges University, Yichang, Hubei, China; ³Department of Respiratory Medicine, The First Affiliated Hospital of Xiamen University, Xiamen, Fujian, China

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Abstract: Chronic myeloid leukemia (CML) is a hematologic malignancy, in which more than 95% of CML patients are discovered with the Philadelphia chromosome (Ph) or BCR-ABL rearrangement. Those patients mainly suffer from CML, associating with lack of tyrosine kinase activity and BCR-ABL fusion gene. Here, we reported a patient with Ph-negative CML t(5;12)(q33;p13), accompanying with a rare genetic fusion between the TEL and PDGFRβ genes. We identified a novel TEL-PDGFRβ rearrangement, joining TEL (exon 12) to PDGFRβ (exon 5), resulting in overexpression of PDGFRβ. A promising result was achieved, in which TEL-PDGFRβ fusion gene could not be effectively detected during imatinib treatment, demonstrating complete molecular biologic remission. Thus, multiple tyrosine kinase inhibitors are associated with Ph-negative CML t(5;12)(q33;p13) with TEL-PDGFRβ rearrangement.

Keywords: Chronic myeloid leukemia (CML), myeloproliferative neoplasia (MPN), platelet-derived growth factor receptor (PDGFR), imatinib

Introduction

Chronic myeloid leukemia (CML), also known as chronic myelogenous leukemia, is a cancer of the white blood cells. It is a form of leukemia characterized by the increased and unregulated growth of myeloid cells in the bone marrow and the accumulation of these cells in the blood. It accounts for approximately 15% of newly diagnosed cases of leukemia in adults [1].

In addition, more than 95% of CML patients have t(9;22)(q34.1;q11.2) or Philadelphia (Ph) chromosome, which results in the BCR-ABL1 fusion gene (Ph+ BCR+ CML) [2]. Another 5% of CML patients have the BCR-ABL1 fusion gene, while t(9;22)(q34;q12) is undetectable by conventional cytogenetic analysis (Ph+ BCR+ CML). Three clinically important variants are the p190, p210, and p230 isoforms; p190 is generally associated with acute lymphoblastic leukemia (ALL), while p210 is generally associated with chronic myeloid leukemia but can also be associated with ALL. The BCR-ABL oncogene is generated by the Ph translocation, fusing the BCR gene to the ABL gene. The BCR-ABL fusion protein has elevated ABL tyrosine kinase activity that is critical for transformation of hematopoietic cells. CML cells transformed by BCR-ABL show reduced growth factor requirements and apoptosis, as well as enhanced viability and altered adhesion. Here, we reported a patient with Ph-negative CML who showed an infrequent t(5;12)(q33;p13) chromosome translocation, accompanied with rearrangement of platelet-derived growth factor receptor beta (PDGFRβ) gene.

Case presentation

In March 31, 2016, a 42-year-old man was admitted to our hospital for examination with abdominal distension. The hematologic exami-
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The number of white blood cells (WBC) was increased to 60 $\times$ 10$^9$/L, accompanied by the number of red blood cells (RBC) that was 3.25 $\times$ 10$^{12}$/L, in addition to the content of hemoglobin (HGB) equal to 113 g/l, platelets (PLT) was 54 $\times$ 10$^9$/L, and percentage of neutrophil granulocytes, eosinophil granulocytes, and basophil granulocytes was 78.2%, 3.7%, 2.2%, respectively. Color Doppler flow imaging revealed that splenomegaly which spleen size and spleen pachy-diameter were 14 and 4.2 cm, respectively.

A peripheral blood smear resulted as follows: neutrophil granulocyte (54%), leukomonocyte (13%), monocyte (1%), eosinophil granulocyte (4%), promyelocyte (2%), myelocyte (15%), late promyelocyte (11%), and late erythroblast (3%).

Cytomorphological bone marrow examination showed active hyperplasia in the myelocyte, with granulocyte (79%), myeloblast (3%), promyelocyte (5%), neutrophil myelocyte (27%), late promyelocyte (33%), eosinophil myelocyte (2%), eosinophil late promyelocyte (2%), basophil myelocyte (3%), basophil late promyelocyte (4%), nucleated erythrocyte (10%), leukomonocyte (8%), and monocyte (3%) cells.

Flow cytometry analysis of the bone marrow revealed the following results: leukomonocyte (6.5%), granulocyte (87%), monocyte (3.2%), dim expression of CD45 (0.2%), and negative expression of CD45 (3.1%). The dim expression of CD45 was led to myeloid blasts which could express positive expressions of CD34 and CD117 (Figure 1).

Bone marrow biopsy pathology revealed active hyperplasia in marrow karyotype (90%) that was consistent with CML, requiring diagnosis by testing BCR/ABL fusion gene (Figure 2).

Bone marrow chromosome karyotyping was undertaken to diagnosis the disease, and to explore ectopic chromosomal sequences with 46, XY, t(5;12)(q33;p13) in the 10 assessed cells (Figure 3).

In addition, fluorescence in situ hybridization (FISH) analysis was carried out to identify of BCR/ABL, JAK2/V617F, FGFR1, FIP1L1/PDGFRα, and PDGFRβ by a dual color LSI/CEP probe (Abbott Laboratories, IL, USA). As a result, rearrangement of PDGFRβ gene was achieved, and BCR/ABL, JAK2/V617F, FGFR1, and FIP1L1/PDGFRα were negatively expressed in 90.5% of the 200 metaphase or interphase cells in the FISH analysis. The fluorescent green

Figure 1. Flow cytometry analysis displayed 0.2% CD45 dim expression cells that were shown to be myeloid blasts which could express positive CD34 and CD117.

Figure 2. Bone marrow biopsy pathology revealed CML.
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dots denote (5q33) 3'PDGFRβ, and red dots represent 5'PDGFRβ (Figure 4).

The patient received subsequent treatment with imatinib mesylate (400 mg/day) from April 26, 2016. A complete cytogenetic response was obtained after 6 and 12 months; moreover, the number of WBCs decreased to absolutely normal conditions, and the shape of spleen was reduced.

Discussion

We here reported a patient with Ph-negative CML t(5;12)(q33;p13), associating with a rare genetic fusion between the TEL and PDGFRβ genes. In this study, we identified a novel TEL-PDGFRβ rearrangement, joining TEL exon 12 to PDGFRβ exon 5, resulting in overexpression of PDGFRβ.

Chromosome translocations 5 and 12 are rare types, locating at 5q33 and 12p13 segments. This translocation mainly occurs in a chromic myeloproliferative disorder (MPD), that it is difficult to accurately classify. It can be a new subtype of myelodysplastic syndrome (MDS)/(MPD), that is often diagnosed as CMML or Atypical CML, accompanied by eosinophilia and monocytosis. Meanwhile, the disease can be converted to acute leukemia [3].

Some patients who had MDS or MPD with t(5;12)(q33;p13) were discovered to have chromosome translocation with PDGFRβ gene of 5q33, as well as TEL gene of 12p13, resulting from the fusion of ETV6-PDGFRβ. ETV6-PDGFRβ fusion gene plays a significant role in the pathogenesis of the diseases. The corresponding breakpoint cluster region of the fusion gene mainly originates from ETV6 (exon 4) and PDGFRβ (exon 11) [4, 5]. In addition, there were rare abnormalities which fused ETV6 gene (exon 4) to PDGFRβ gene (exon 10), and ETV6 gene (exon 7) to PDGFRβ gene (exon 10 or 12) [6].

Tyrosine kinase inhibitors are efficient against ABL, c-Kit, and PDGFR genes [7]. Also, TEL-PDGFRβ fusion gene has been implicated in the pathogenesis of MPD. MDS/MPD patients involved in the translocation of the PDGFRβ gene are very sensitive to tyrosine kinase inhibitors (e.g., imatinib), and the majority of patients can achieve complete cytogenetic remission.
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(CCR), in particular, the CCR percentage of patients with simple t(5;12)(q33;p13) (ETV6-PDGFRβ fusion) reaches 100%. Simultaneously, it can also maintain long-term CCR or complete hematologic remission (CHR) for some patients with blast crisis or accelerated phase or complicated karyotype. Furthermore, 71% and 82% of patients with abnormal 5q33 ectopic karyotypes achieved CHR and CCR, in which the rates of CHR and CCR in patients in chronic phase were 100% and 91%, respectively [8, 9].

It has been reported that 3 cases with myeloproliferative neoplasms with t(5;12)(q33;p13) achieved CCR with imatinib mesylate [10].

A part of CML patients with 5q33 translocation mainly associate with complex chromosomal abnormalities, which may progress to an accelerated phase or blast crisis.

Conclusion

Two rare chromosome translocations 5 and 12 were reported in this study. The patient with long-term oral imatinib mesylate is still in molecular biologic remission and CCR after a long follow-up. Therefore, it is important to optimize cytogenetic and molecular biological examination for patients with Ph-negative CML, especially when gene mutations, such as ABL, KIT, and PDGFR are detected, and also tyrosine kinase inhibitors (e.g., imatinib, Nilotinib, dasatinib) are very effective for patients with those mutations. Multiple tyrosine kinase inhibitors are associated with Ph-negative CML t(5;12) (q33;p13) with TEL-PDGFRβ rearrangement.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Kaibo Gao, Department of Hematology, The First People’s Hospital of Yichang, China Three Gorges University, Yichang 443000, Hubei, China. Tel: +86-13997742655; E-mail: 2263512712@qq.com

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