CLINICAL CASE

Philadelphia variant, t(5;9;22)(q13;q34;q11), in a case with chronic myeloid leukemia

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Summary

In this paper we report on a case of chronic myeloid leukemia (CML) with a Philadelphia variant involving chromosome 5 as a second change of the standard Philadelphia chromosome (Ph). Molecular analysis found a fusion gene BCR-ABL with participation of exons b3 and a2, respectively (b3a2). The molecular variant of the fusion gene BCR/ABL or the rare involvement of chromosome 5 could possibly explain the mild course of the disease.

Key words: chemotherapy, chronic myeloid leukaemia, Philadelphia variant translocation

Introduction

Chromosome translocation t(9;22)(q34;q11), or the so-called Philadelphia chromosome (Ph), is a typical cytogenetic marker of CML, found in about 95% of the cases and well known as a diagnostic and prognostic sign [1]. In 5-10% of CML cases other chromosome(s), additionally to t(9;22)(q34;q11), have been involved [2,3]. The resulting translocation is known as Philadelphia variant. In all cases the translocation results in a fusion gene, M(major)-BCL/ABL with transcripts b3a2 and/or b2a2 and synthesis of the p210BCL/ABL oncoprotein [4]. In acute leukemias the same translocation results in an alternative gene, m(minor)-BCL/ABL with a transcript e1a2 and p190BCL/ABL protein [1].

There are about 600 cases reported in the literature with different kinds of Ph chromosome variants [4]. Some of them reveal no differences in clinical and hematological features or prognosis in comparison with standard Ph chromosome cases [5]. On the other hand, some authors describe Ph variants with specific features [6] which are most likely to be explained by additional molecular changes as a result of involvement of other chromosomes rather than by only the fusion gene BCR/ABL. Herein we report on a CML case with a Ph chromosome variant, t(5;9;22)(q13;q34;q11), as a second genome change. The disease showed a mild clinical course, possibly due to the molecular variant of the fusion gene BCR/ABL or the rare involvement of chromosome 5.

Case presentation

Clinical data

A 42-year-old male presented with classical features of CML e.g. splenomegaly, leucocyte count $9\times10^3$/ml with a left shift, lack of granulocyte alkaline phosphatase and standard Ph. The patient was treated with busulfan, 6 mg per day for 35 days. After the achievement of complete hematological remission, the patient continued on maintenance chemotherapy with a decreased dosage of busulfan (4-6 mg per week) [7]. Two years after the initial diagnosis hydrea, 0.5-1.0 g
per day and after 20 months alpha-interferon 3MU 3 times a week were administered. The mild course of the disease and the normalization of the hematological data were the reason for single-therapy with interferon 4 years after the initial diagnosis.

**Cytogenetics**

Routine chromosome analysis was carried out 3 times in the course of the disease on G-banded (GTG) metaphases of cultured and noncultured bone marrow cells. The first analysis, performed at the initial diagnosis, found standard Ph chromosome [46,XY,t(9;22)(q34;q11)]. The following 2 chromosome analyses, 6 and 7 years afterwards, revealed karyotype 46,XY,t(5;9;22)(q13;q34;q11) in all studied cells (20 and 11, respectively; Figure 1).

**Molecular analysis**

Reverse transcriptase - polymerase chain reaction (RT-PCR) was performed on cDNA synthesised of peripheral blood RNA, extracted 7 years after the initial diagnosis, at the time of the variant Ph finding. Primers used were as proposed by the European program BIOMED 1 [8]. Transcripts b3a2 interpreted as M-BCR/ABL fusion gene with strong expression comparable with those of the control cell line K562 were found.

**Discussion**

So far there are 9 cases with variants Ph chromosome t(5;9;22)(q13;q34;q11) described in the literature [4]. The case presented here expresses this aberration as a second change in the course of the disease, and, thus, it supports the hypothesis that these anomalies may occur not only as a result of many simultaneous chromosome breaks but also as a result of 2 or more genomic events appearing consecutively after the previously existing standard Ph chromosome [2]. Clinically, the case demonstrated a mild disease course, e.g. 8 years of uninterrupted and still ongoing hematological remission out of 9 years of follow-up. Chromosome aberration, t(5;9;22)(q13;q34;q11) in 100% of the analysed cells, as well as molecular alteration including strong expression of fusion transcripts of M-BCR/ABL gene persist during the whole period of this hematological remission, just opposite to the usual finding of reestablishment of the normal karyotype and molecular changes [9]. The mild pattern of the disease course could hardly be explained by the common molecular marker but rather by the rare involvement of chromosome 5 in the translocation and by some molecular changes, a possible result of the latter.

Two protein coding genes have been mapped on 5q13 so far, RAS-GAP (RAS p21 GTPase activating protein) and Ras-GRF2 (Ras protein-specific guanine nucleotide-releasing factor 2) [10]. RAS cascade is one of the main targets of BCR/ABL oncoprotein which acts as its activator, leading to proliferation in the absence of growth factors as well as blocking apoptosis [11,12]. It is suggested that some molecular defects of the involved cascade factors could partially block the transforming potency of BCR/ABL oncoprotein [13]. In our case one could speculate that 5q13 breakpoint affected one of these genes leading to suppression of CML pathogenic mechanisms. Thus, the disease displayed a mild course and very good response to the treatment administered, regardless the strong expression of the fusion gene BCR/ABL.

Our case, a rare Ph variant involving chromosome 5, supports the hypothesis that not only standard molecular alterations of CML (a fusion gene BCR/ABL), but also second molecular changes which appear in the course of the disease may play a role in the clinical course and prognosis of the disease.

**References**


**Figure 1.** Partial karyotype of G-banded metaphases of the CML patient showing t(5;9;22)(q13;q34;q11).


