A variant Philadelphia chromosome (Ph1) positive chronic myelocytic leukemia.

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Abstract

A rare case of variant Philadelphia (Ph1) chromosome positive [46, XX, t (9; 22) (q34; q11), inv (9) (9q22; 22q13)] chronic myelocytic leukemia (CML) was described. The patient, 73 years old female, was hospitalized to our hospital because of leukocytosis. Hematological findings corresponded to those of CMLs. However, this case lacked hepatosplenomegaly. Southern blot analysis using a 3 breakpoint cluster region (bcr) probe revealed a bcr rearrangement. The patient has been in the chronic phase for sixteen months without treatment. Clinical and chromosomal changes are under observation in order to get accumulate data for a pathophysiological analysis of variant Ph1 positive CMLs.

KEYWORDS: variant Ph1 positive chronic myelocytic leukemia, bcr rearrangement

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A Variant Philadelphia Chromosome (Ph1) Positive Chronic Myelocytic Leukemia


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A rare case of variant Philadelphia (Ph1) chromosome positive [46, XX, t (9; 22) (q34; q11), inv (9) (9q22; 22q13)] chronic myelocytic leukemia (CML) was described. The patient, 73 years old female, was hospitalized to our hospital because of leukocytosis. Hematological findings corresponded to those of CMLs. However, this case lacked hepatosplenomegalaly. Southern blot analysis using a breakpoint cluster region (bcr) probe revealed a bcr rearrangement. The patient has been in the chronic phase for sixteen months without treatment. Clinical and chromosomal changes are under observation in order to get accumulate data for a pathophysiological analysis of variant Ph1 positive CMLs.

Key words: variant Ph1 positive chronic myelocytic leukemia, bcr rearrangement

The Philadelphia chromosome (Ph1), a translocation of the distal deleted segment of 22q to the distal portion of 9q, [t (9; 22) (q34; q11)], is found in most patients with chronic myelocytic leukemia (CML) (1). Among Ph1 positive CMLs, Ph1 variants such as a translocation to a chromosome other than 9 and the interchanging in three or more chromosomes including chromosome 9 were found at about 4.3 % (1). Recent advances in molecular biology revealed that in Ph1 positive CMLs the oncogene c-abl normally located on chromosome 9 band q34 is translocated to chromosome 22 band q11 in 5.8 kilobase (Kb) region named the breakpoint cluster region (bcr) (2–5). An altered c-abl protein p210 is expressed as the consequence of the molecular rearrangement in leukemic cells (6). The present paper describes a unique Ph1 variant with [46, XX, t (9; 22) (q34; q11), inv (9) (9q22; 22q13)].

The patient is a 73-year-old female who visited the hospital with leukocytosis in October 1988. Hemorrhagic tendency and hepatosplenomegalaly were not observed. Examination of peripheral blood showed a red blood cell count (RBC) of $3.71 \times 10^{12}/\mu l$, a platelet count of $18.9 \times 10^{11}/\mu l$, and white blood cell count (WBC) of $15.5 \times$
10^3/µl with 8% myelocytes, 15% metamyelocytes, 64% neutrophils, 4% basophils, 4.5% monocytes, and 18% lymphocytes. Bone marrow aspirates showed a nucleated cell count (NCC) of 64.2 x 10^3/µl with 0.2% myeloblasts, 4.0% promyelocytes, 41.6% myelocytes, 8.2% metamyelocytes, 36.0% neutrophils, 1.4% eosinophils, 1.0% basophils, 1.8% lymphocytes, 1.0% monocytes, and 4.6% erythroblasts. Neutrophil alkaline phosphatase (NAP) score was 30. The serum levels of vitamin B12 and folic acid were 1.042 µg/ml and 5.6 ng/ml, respectively. Cytogenetic analysis was performed on bone marrow cells by using G- and Q-banding techniques in October 1988, in December 1988, and in January 1990. Cells showed a modal number of 46 chromosomes and all banded metaphases showed [46, XX, t (9; 22) (q34; q11), inv (9) (9q22; 22q13)] (Figs. 1, 2 and 3). Intrachromosomal changes within the 9q+ (chro-
omosome 9 with a translocated segment derived from chromosome 22 as a result of the standard trans-
location) were recognized in this case. The paracentric inversion within 9q+ was disclosed by both of the G- and Q-banding analyses. All of the cells examined revealed this complex translocation. Southern blotting was performed on peripheral blood cells showing the rearrangement of bcr (Fig. 4) (7, 10).

Ph^1 chromosome is observed in more than 90% of cases with CML. Variant Ph^1 translocations do occur with about 4.3% of the Ph^1 positive CML cases. The present case with a unique Ph^1 variant of [t (9; 22) (q34; q11), inv (9) (9q22; 22q13)] also showed the bcr rearrangement. At this point, it would be difficult to completely explain the process of the translocation clearly in the present case. However, we could assume three steps; namely after the standard Ph^1 translocation, t (9; 22) (q34; q11), subsequent breaks occurred at 9q22 and 22q13 on the 9q+. Then, this region inverted paracentrically and was inserted into the center of the long arm of chromosome 9. More study is required to delineate this inversion in 9q+ by using the high resolution method.

Recently, the bcr rearranged by c-abl oncogene has been implicated as the pathogenesis of

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Fig. 1  Karyotype of G-banded metaphase cells obtained from bone marrow, showing 46, XX, t(9; 22) (q34; q11), inv (9) (9q22; 22q13). The arrow on #9 indicates segment 22q12 inserted into the #9. The arrow on #22 shows a Ph^1 chromosome. (performed on 26th October, 1988).
CML (5,6,8,9), because it is detected not only in standard Ph\textsuperscript{1} positive CML but also in Ph\textsuperscript{1} variants (3, 10). Previous studies from our laboratory have shown bcr rearrangement in two Ph\textsuperscript{1} variants, $[t(9;22)(q21;q11)]$ and $[(9;22;13)(q34;q11;q22)(10)]$. Ishihara et al. reported a case of CML with the same variant Ph\textsuperscript{1} as ours, although bcr rearrangement was not

**Fig. 2** Q-banded karyotype of the patient with the paracentric inversion within 9q+, inv (9) (9q22; 22q13). See Fig. 1 (performed on 14th December, 1988).

**Fig. 3** The same karyotype as in Fig. 1 and in Fig. 2 is shown by the G-banding technique (performed on 25th January, 1988).
Phase, accelerated phase, and blast crisis.

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