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Chronic myeloid leukemia with a rare variant BCR-ABL translocation: t(9;22;21)(q34;q11.2;q11.2)

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The diagnosis of chronic myeloid leukemia (CML) is anticipated by the morphological manifestations on blood and bone marrow smears, followed by the confirmation of the translocation t(9;22)(q34;q11) by banded karyotyping or the BCR-ABL fusion gene by fluorescence in situ hybridization (FISH) or reverse-transcriptase polymerase chain reaction (RT-PCR). Philadelphia chromosome can be recognized clearly by an abnormal size and banding pattern at chromosome 22 together with abnormality in chromosome 9 by Giemsa (G)-banding analysis. It is well known that translocations different from the standard t(9;22)(q34;q11) occurs in approximately 5-10% of all CML cases [1]. The vast majority of these consist of three-way translocation involving an additional chromosomal abnormality other than 9 and 22. Even in these cases, the involvement of chromosome 22 is usually evident by G-banding analysis. We report here a case of CML seemingly with t(9;21)(q34;q11) with no apparent abnormality in chromosome 22 by G-banding analysis. This was a pitfall of a banding method, and we proved that this case had a t(9;22;21)(q34;q11;q11) by spectral karyotyping (SKY) FISH.

A 40-year-old Japanese female was referred to our hospital on April 2007 because of an occasional blood test displaying a moderate leukocytosis (WBC $24 \times 10^9/L$) with increased basophils ($2.9 \times 10^9/L$), anemia (Hb 9.1g/dl) with iron deficiency, and high platelet count ($730 \times 10^9/L$) in the absence of any relevant symptom. No spleen and liver enlargements were evident. The WBC differential, bone marrow aspirate, NAP score were consistent with a chronic phase of CML. The diagnosis was confirmed because a major BCR-ABL fusion transcript was amplified by RT-PCR. Direct nucleotide sequencing revealed that this fragment consisted of exon b2 of the BCR gene and exon a2, a3, and a4 of the ABL gene [2]. The BCR-ABL fusion was also confirmed by dual color FISH in metaphase nuclei. This patient was treated with imatinib (400mg/day) followed by a complete hematologic response within a month.

Surprisingly, conventional G-banding method showed that this patient had 46, XX, t(9;21)(q34;q11) with intact chromosome 22 (Figure 1A). Since conventional FISH and RT-PCR had revealed the presence of the BCR-ABL fusion gene, it was unclear where the Philadelphia chromosome was. To address this issue, we performed SKY FISH. As shown in Figure 1B, hybridization with painting probes revealed the three-way translocation involving chromosomes 9, 22 and 21. It appears that the omission of Philadelphia chromosome by G-banding method was due to the translocation of almost whole long-arm of chromosome 22 to 21 at the break point of 21q11 resulted in composition of chimera chromosome mimicking intact 22 (Figure 1C). Thus, we defined the karyotype of this patient as 46, XX, t(9;22;21)(q34;q11.2;q11.2).
In the literatures, several CML cases with t(9;22;21) have been reported [1,3-7]. The vast majority of these display t(9;22;21)(q34;q11;q22). Because in these cases the breakpoint of chromosome 21 is located at peripheral site q22, aberrant chromosome 21 cannot mimic normal chromosome 22 as observed in our case. To our knowledge, only one case of t(9;22;21) CML with the breakpoint 21q11 has been described in detail [6]. Even in this case, Philadelphia chromosome and aberrant chromosome 21 were apparently observed by G-banding method. Therefore, our case is the first description about CML with three-way translocation in which the sight of Philadelphia chromosome was lost by classical karyotyping.

All chromosomes have been described as participating in variant rearrangements in CML, however, there is a marked breakpoint clustering to some chromosome bands [8]. According to the review by Johansson et al., a major breakpoint in chromosome 21 is q22, and the q11 is very rare [8]. The translocation with 21q22 is also popular in other hematologic malignancies, whereas 21q11 was reported only in a few cases such as myelodysplastic syndrome (MDS), chronic lymphocytic leukemia (CLL), and acute myelogenous leukemia (AML) [9]. Proximal chromosome 21 including 21q11 has been recognized to be frequently involved in childhood osteosarcoma [10], leukemia in Down syndrome [11], and prostate cancer [12]. This suggests the localization of responsible genes for tumorigenesis in this region such as the POTE gene family in prostate cancer [12]. Although CML with variant chromosomal abnormalities has a similar prognosis to that of cases with typical t(9;22)(q34;q11) [1], the accumulation of patients involving 21q11 may be needed to conclude that it is also the case.
References


Figure legends

Figure 1
(A) Bone marrow karyotype showing t(9; 21)(q34;q11) (red arrows).
(B) Spectral karyotyping-fluorescence in situ hybridization (SKY-FISH) analysis.
(C) Refined karyotype according to the result of SKY-FISH. Red box indicates the chimera chromosome 21 which mimicked intact chromosome 22. Dotted arrows show three way translocation t(9;22;21)(q34;q11;q11).
Figure 1

(A)

(B)

(C)