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

Takeuchi, Mai ; Katayama, Yoshio ; Okamura, Atsuo ; Yamamoto, Katsuya ; Shimoyama, Manabu ; Matsui, Toshimitsu

(Citation)
Cancer Genetics and Cytogenetics,179(1):85-87

(Issue Date)
2007-11

(Resource Type)
journal article

(Version)
Accepted Manuscript

(URL)
https://hdl.handle.net/20.500.14094/90000767

Cancer Genet Cytogenet
Letter to the editor

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

Mai Takeuchi, Yoshio Katayama, Atsuo Okamura, Katsuya Yamamoto, Manabu Shimoyama, Toshimitsu Matsui

Hematology/Oncology, Department of Medicine, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

* Correspondence to:
Yoshio Katayama, MD, PhD
Hematology/Oncology, Department of Medicine,
Kobe University Graduate School of Medicine
7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan
Tel: +81-78-382-5885
Fax: +81-78-382-5899
Email: katayama@med.kobe-u.ac.jp

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 24×10^9/L) with increased basophils (2.9×10^9/L), anemia (Hb 9.1g/dl) with iron deficiency, and high platelet count (730×10^9/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 hematoligic 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

1. El-Zimaity MM, Kantarjian H, Talpaz M, O'Brien S, Giles F, Garcia-Manero G, Verstovsek S, Thomas D, Ferrajoli A, Hayes K, Nebiyou Bekele B, Zhou X, Rios MB, Glassman AB, Cortes JE. Results of imatinib mesylate therapy in chronic myelogenous leukaemia with variant Philadelphia chromosome. Br J Haematol 2004; 125:187-95.
2. Emig M, Saussele S, Wittor H, Weisser A, Reiter A, Willer A, Berger U, Hehlmann R, Cross NC, Hochhaus A. Accurate and rapid analysis of residual disease in patients with CML using specific fluorescent hybridization probes for real time quantitative RT-PCR. Leukemia 1999; 13:1825-32.
3. Bartram CR, Anger B, Carbonell F, Kleihauer E. Involvement of chromosome 9 in variant Ph1 translocation. Leuk Res 1985; 9:1133-7.
4. Guillaume B, Ameye G, Libouton JM, Dierlamm J, Vaerman JL, Straetmans N, Ferrant A, Verellen-Dumoulin C, Michaux L. Chronic myeloid leukemia with a rare variant Philadelphia translocation: t(9;22;21)(q34;q11;q22). Cancer Genet Cytogenet 2000; 116:166-9.
5. Mancini M, Nanni M, Cedrone M, De Cuia MR, Rondinelli MB, Malagnino F, Alimena G. Application of fluorescence in situ hybridization in defining a complex t(9;21;22) Ph formation. Haematologica 1994; 79:536-9.
6. Vallcorba I, Garcia-Sagredo JM, San Roman C, Ferro MT, Gonzalez A, Cabello P, Villegas A. Translocation (9;22;21) in a chronic myeloid leukemia fluorescence in situ hybridization definition. Cancer Genet Cytogenet 1998; 104:72-3.
7. Zhang J, Meltzer P, Jenkins R, Guan XY, Trent J. Application of chromosome microdissection probes for elucidation of BCR-ABL fusion and variant Philadelphia chromosome translocations in chronic myelogenous leukemia. Blood 1993; 81:3365-71.
8. Johansson B, Fioretos T, Mitelman F. Cytogenetic and molecular genetic evolution of chronic myeloid leukemia. Acta Haematol 2002; 107:76-94.
9. Jeandidier E, Dastugue N, Mugneret F, Lafage-Pochitaloff M, Mozziconacci MJ, Herens C, Michaux L, Verellen-Dumoulin C, Talmant P, Cornillet-Lefebvre P, Luquet I, Charrin C, Barin C, Collonge-Rame MA, Perot C, Van den Akker J, Gregoire MJ, Jonveaux P, Baranger L, Eclache-Saudreau V, Pages MP, Cabrol C, Terre C, Berger R. Abnormalities of the long arm of chromosome 21 in 107 patients with hematopoietic disorders: a collaborative retrospective study of the Groupe Francais de Cytogenetique Hematologique. Cancer Genet Cytogenet 2006; 166:1-11.
10. dos Santos Aguiar S, de Jesus Girotto Zambaldi L, dos Santos AM, Pinto W, Jr., Brandalise SR. Comparative genomic hybridization analysis of abnormalities in chromosome 21 in childhood osteosarcoma. Cancer Genet Cytogenet 2007; 175:35-40.

11. Shen JJ, Williams BJ, Zipursky A, Doyle J, Sherman SL, Jacobs PA, Shugar AL, Soukup SW, Hassold TJ. Cytogenetic and molecular studies of Down syndrome individuals with leukemia. Am J Hum Genet 1995; 56:915-25.

12. Bera TK, Zimonjic DB, Popescu NC, Sathyanarayana BK, Kumar V, Lee B, Pastan I. POTE, a highly homologous gene family located on numerous chromosomes and expressed in prostate, ovary, testis, placenta, and prostate cancer. Proc Natl Acad Sci U S A 2002; 99:16975-80.

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