Chronic myelogenous leukemia (CML) is characterized by the presence of the abnormal chromosome 22, which is termed the Philadelphia chromosome (Ph). The Ph is derived from a translocation between chromosomes 9 and 22, t(9;22) (q34;q11). The c-abl oncogene on the long arm of chromosome 9 fused to the bcr gene on the long arm of chromosome 22 and leads to the formation of a chimeric bcr/abl gene located on the Ph. The chimeric bcr/abl gene produces 8.5-kb bcr/abl transcript and chimeric fusion protein, p210 BCR/ABL. The p210 BCR/ABL protein plays a central role in the leukemogenesis of CML.

The case shown in the Figures was a rare Ph-negative CML case having typical clinical findings of CML. In these Ph-negative CML cases, in addition to cytogenetic analysis, molecular biological analyses such as fluorescence in situ hybridization (FISH) and spectral karyotyping (SKY) FISH are used as potential tools for diagnosis.

FISH and SKY FISH are used as an adjunct to standard G-banding karyotyping (Fig. 1) to achieve a higher sensitivity and specificity. FISH and SKY FISH provided additional cytogenetic information including the clarification of complex chromosomal rearrangements. The present SKY FISH revealed a translocation between chromosomes 2 and 9 (Fig. 2), and FISH revealed a chimeric bcr/abl gene on chromosome 22 (Fig. 3). From these findings, the present case was finally diagnosed as a Ph-negative and bcr/abl-positive CML.

**Fig. 1** Chromosomal analysis of bone marrow cells by the conventional trypsin-Giemsa banding technique. The cells were processed by a direct method. The karyotype was determined by both direct microscopic analysis and photography. Karyotyping of a metaphase cell showed 46,XX,add(2)(q33),del(3)(p21p24),del(7)(q34),add(9)(q34), but failed to detect Ph. Aberrant chromosomes are indicated by arrows.
Fig. 2  SKY FISH of the classification-colored metaphase chromosomes. Chromosomes were simultaneously hybridized with a combination of 24 labeled chromosome painting probes. Multicolor SKY revealed a translocation of the chromosome 2 material to the long arm of chromosome 9 this was not detected by G-banding analysis. Unbalanced translocation of der(9) is indicated by arrowhead. SKY failed to detect any abnormality of chromosome 22. The combination of Giemsa banding and SKY allowed us to refine the karyotype to 46, XX, add (2) (q 33), del (3) (p 21 p 21), del (7) (q 34), der 9t (2; 9) (q 33; q 34).

Fig. 3  FISH analysis of BM cells in metaphase using a Vysis LSI BCR-ABL translocation DNA probe. A yellow signal indicates by the arrow head, composed of a red signal of bcr and a green signal of abl showing bcr/abl fusion gene was detected in all 20 cells analyzed.

References