Case Report:
Acute Promyelocytic Leukemia with +der(17)t(15;17)
Detected by Fluorescence In Situ Hybridization (FISH)

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Abstract. We describe an unusual case of acute promyelocytic leukemia with +der(17)t(15;17) as the additional cytogenetic abnormality and with t(15;17) defined by fluorescence in situ hybridization (FISH) using a PML/RARA dual color, dual fusion translocation probe. By performing a step-by-step, complementary approach to evaluate unusual chromosomal abnormalities, we detected RARA/PML fusion on a marker chromosome similar to chromosome 17. (received 20 December 2004; accepted 31 January 2005)

Keywords: acute promyelocytic leukemia, PML/RARA, RARA/PML, fluorescence in situ hybridization

Introduction

Translocation (15;17)(q22;q21) and PML/RARA gene fusion are present in the great majority of patients with acute promyelocytic leukemia (APL) [1]. The use of all-trans retinoic acid (ATRA) has made APL one of the most curable leukemias [2]. Fluorescence in situ hybridization (FISH) combined with conventional cytogenetic analysis is performed in the clinical laboratory to detect PML/RARA fusion genes. Special formulations of FISH are sometimes used to detect an unusual translocation involving chromosome 15 and chromosome 17 [3,4]. In this article, we report a case of APL with +der(17)t(15;17) as the additional cytogenetic abnormality and with t(15;17) defined by FISH using a PML/RARA dual color, dual fusion translocation probe.

Case Report

A 37-yr-old man was referred to our hospital because of a bleeding tendency and fever for 7 days following the extraction of a tooth. The results of his laboratory tests were: hemoglobin 8.7 g/dl, platelets 62 x 10⁹/L, and leukocyte count 7.2 x 10⁹/L with 80% promyelocytes.

Abnormal coagulation studies included 63% PT, prolonged aPTT (43 sec, control 31 sec), high D-dimer (>2000 µg/ml), and FDP (71.7 µg/ml). Bone marrow aspiration and biopsy revealed a hypercellular marrow (100% cellularity). Most of the marrow nucleated elements were abnormal promyelocytes and many of them had Auer rods. Faggot cells were frequently found.

Classical cytogenetic analysis performed on the bone marrow aspirate showed 10 metaphase cells with 46,XY,t(15;17)(q22;q21) and 1 normal metaphase. Nine metaphase cells with a chromosome count of 50 were found, plus an additional chromosome 8, 18, 21, and a marker with bands similar to those of chromosome 17, but slightly shorter than normal chromosome 17 (Fig. 1).
Fig. 1. G-banded karyotype showing 50,XY,+t(15;17)(q22;q21),+der(17)t(15;17)(q22;q21),+18,+21.

Fig. 2. Metaphase FISH analysis using PML/RARA dual color, dual fusion probe. Arrows indicate fusion of RARA/PML on 2 chromosomes 17.
As the majority of chromosomes were short in this case, it was difficult to confirm the marker chromosome as chromosome 17 or der(17)t(15;17). Initially, we performed FISH using the LSI PML/RARA dual color translocation probe (Vysis, USA) showing single fusion on der(15)t(15;17). If the marker chromosome were a normal chromosome 17, there would be 2 green signals on the interphase cells and 1 green signal on the marker chromosome. The result showed 1 orange, 1 green, and 1 fusion (PML/RARA) signal. The marker chromosome did not have a RARA-green signal.

After FISH using a LSI PML/RARA dual color, dual fusion translocation probe (Vysis), we detected 1 orange, 1 green, and 3 fusion signals on interphase nuclei. The metaphase cell revealed a fusion signal on the marker chromosome (Fig. 2). FISH using Iso 17q (MPO/p53) probe (Qbiogene, USA) revealed three p53 (17p13) signals and 2 MPO (17q23) signals on the same metaphase. Therefore, the marker chromosome was established as der(17)t(15;17)(q22;q21) and the karyotype as 46,XY,t(15;17)(q22;q21)[10]/50, idem, +8, +der(17)t(15;17)(q22;q21), +18,+21[9]/46,XY[1].

The patient received induction therapy with oral ATRA (45 mg/m²/day) and idarubicin (12 mg/m² on days 1, 3, 5, and 7). A complete hematological remission was obtained and 3 monthly consolidation courses were administrated according to a previously recommended protocol [5]. Molecular assessment of the response by RT-PCR showed conversion to PCR-negative.

Discussion

Chromosomal rearrangements in addition to t(15;17) have been reported in 25 to 40% of APL, with a large predominance of trisomy 8, followed by chromosome 17 [especially ider(17)], chromosome 9 [particularly del(9q)], and chromosome 7 [mainly del(7q)] abnormalities [6]. A survey result of 1 organ showed 28.6% having chromosomal changes in addition to t(15;17), and only 1 case with simultaneous presence of both trisomy 8 and trisomy 21 [7]. Our case showed t(15;17) with trisomy 8, 18, 21 and additional der(17)t(15;17). The der(17)t(15;17) was not detected by FISH using the dual color translocation probe that detects only a PML/RARA fusion gene. The result was confirmed by FISH using an LSI PML/RARA dual color, dual fusion translocation probe. This FISH strategy produces 2 fusion signals, 1 for PML/RARA fusion at 15q22 and 1 for RARA/PML fusion at 17q21 and is known to be highly sensitive to detect PML/RARA fusion and all alternate translocations involving RARA.

Interphase FISH is an effective technique for molecular diagnosis and follow-up of APL patients. It can be performed first for patients with a possible diagnosis of APL prior to conventional cytogenetic study [8]. A FISH study of metaphase cells is needed to clarify the causes of extra fusion signals in a single cell such as ider(17) [9].

In this case, we performed a careful, step-by-step, complementary approach to evaluate unusual chromosomal abnormalities in the APL case and we could detect RARA/PML fusion on a marker chromosome similar to chromosome 17. In many APL studies of the additional chromosome aberrations, presence of a marker chromosome was frequently found. We expect to detect more extra PML/RARA and/or RARA/PML genes on that marker chromosome.

The PML/RARA fusion protein is associated with APL characteristics and sensitivity to ATRA [10]. The exact role of RARA/PML in the pathogenesis is unclear. It is known that RARA/PML alone is sufficient for a cytological APL phenotype, but does not confer sensitivity to ATRA.

Although additional chromosomal abnormalities as a whole do not influence the prognosis of patients, an isochromosome for the long arm of the derivative chromosome 17 is probably associated with poor outcome. The chromosome aberration results in 2 RARA/PML fusion genes, as well as deletion of the whole short (p) arm of chromosome 17 [11].

In our case, deletion of p53 was not detected. The patient achieved hematological and molecular complete remission by the treatment schedule for APL [5]. More studies are necessary to determine the clinical significance of an extra RARA/PML gene.
References


