CASE REPORT

Asclepius

Acute Promyelocytic Leukemia Presenting Unusual Case with Additional Cytogenetic Abnormality

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ABSTRACT

Acute promyelocytic leukemia (APML) is cytogenetically characterized by t(15;17) (q22;q21), which results in the fusion of *PML* gene at 15q22 with the retinoic acid α-receptor (RARα) gene at 17q21. The current study presents the case of a 50-year-old female with rare cytogenetic abnormality. The patient carrying the typical *PML/RARα* fusion in addition inv(11) (p15q13) revealed by whole chromosome painting fluorescent *in situ* hybridization. We propose that the study of additional cytogenetic abnormality in APML would contribute to the clinical decisions for selection between all-trans retinoic acid and cytotoxic agents. It would be of interest to correlate additional cytogenetic abnormalities other than *PML-RARα* with disease grade and prognosis of the patients.

Key words: Acute promyelocytic leukemia, Chromosome, Cytogenetic, Fluorescent *in situ* hybridization, Leukemia

MANUSCRIPT

Acute promyelocytic leukemia (APML) consisting 5% to 8% of the patients of acute myeloid leukemia (AML). APML is one of the best explained and understood hematopoietic malignancies. Unlike other forms of AML, APML is unique in that it can cause coagulopathy and death if not readily diagnosed. Morphologically classified as AML-M3 by the French-American-British classification, APML is typically characterized by neoplastic proliferation of cells in the bone marrow with a promyelocytic phenotype and the balanced reciprocal translocation t(15;17) (q24.1;q21.2), leading to the fusion of PML and retinoic acid receptor-α (RARα) genes.[1] PMLRARA gene is supposed to play a key role in the pathophysiological process of APML,[2] and patients with the fusion gene could benefit from treatment with all-trans retinoic acid (ATRA). Although the specific factors that lead to myeloid leukemogenesis remain unknown, a number of chromosomal abnormalities have been described in association with AML at the time of diagnosis or relapse, with the incidence ranging from 29% to 43% in previous reports. Although t(15;17) is considered to be a favorable cytogenetic feature, the prognostic significance of additional cytogenetic abnormalities in APML has remained a matter of debate.[3]

CLINICAL PRESENTATION

The current study presents a 50-year-old female with APML who was registered at our institute due to high-grade fever. The peripheral blood examination showed hemoglobin levels of 6.7 g/dl, platelet count was 7000/μl, and a white blood cell count of 39,800/μl with 91% blasts. Bone marrow aspiration showed hypercellular marrow showing proliferation of blasts. The blasts were medium to large in size with high N:C ratio, moderate amount of cytoplasm, fine nuclear chromatin, and 1–2 prominent nucleoli. Some of the blasts were binucleated. Buttock cells were seen. At places, the blasts show cytoplasmic blebbing. Myeloid and erythroid series cells are suppressed. Sudan Black B was strong positive and periodic acid–Schiff was block negative. M:E ratio-altered megakaryocytes not seen. Final diagnosis based on morphological findings was Acute promyelocytic leukemia (APL), M3 variant was determined.

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The patient received standard chemotherapy of daunorubicin combined with ATRA, for AML. The patient expired after 7 days of diagnosis during the induction period.

MATERIALS AND METHODS

Chromosome preparation

A G-banded chromosome study was performed using standard cytogenetic protocol. Unstimulated culture of bone marrow aspirate was set up in RPMI-1640 medium supplemented with 20% newborn calf serum, L-glutamine, and antibiotics (penicillin and streptomycin). The cells were cultured in incubator at 37°C followed by overnight incubation in the presence of colcemid (10 µl/8 ml of culture). The cultures were exposed to hypotonic solution (0.075 mol/L KCL) and fixed with methanol: acetic acid (3:1). The slides were prepared by air dry method and stained with Giemsa banding.[4] 20 metaphases were analyzed and karyotypes were described according to the International System for Human Cytogenetic Nomenclature 2016.[5]

FISH assay

FISH was performed on metaphase cells following the manufacturer's guidelines (Abbott Molecular, Inc., Des Plaines, IL, USA). LSI PML-RARα Probe used to confirm translocation between chromosome 15 and chromosome 17. Whole chromosome painting for chromosome 11 (WCP 11) with spectrum orange (SO) and centromeric enumeration probe for chromosome 11 (CEP 11) with spectrum green (SG) were used to reveal the derivative chromosome 11 karyotype results.

The analysis of both conventional cytogenetics and FISH was carried out using BX-61 Olympus fluorescence microscope (Olympus, Japan) equipped with CCD camera.

RESULTS

Conventional cytogenetics

Classical chromosome analysis detected an abnormal female chromosome complement. The karyotype results showed 46,XX,der(11),t(15;17)(q22;q21)[20]. It shows the presence of t(15;17) with derivative chromosome 11 in all analyzed metaphase plates [Figure 1].

FISH

The metaphases and interphases FISH results of LSI PML-RARα Probe showed one orange, one green, and two fusion signals indicated the presence of PML-RARα fusion gene. The metaphase FISH results WCP 11 with SO and CEP 11 with SG revealed inversion of chromosome 11 and confirmed. The revised karyotype was 46,XX,inv(11)(p15q13),t(15;17)(q22;q21)[20]. [Figure 2].

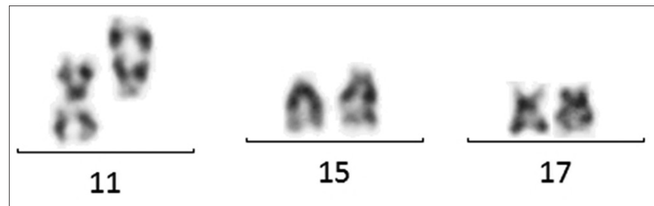

Figure 1: Giemsa-banded partial karyotype shows t(15;17) with derivative chromosome 11

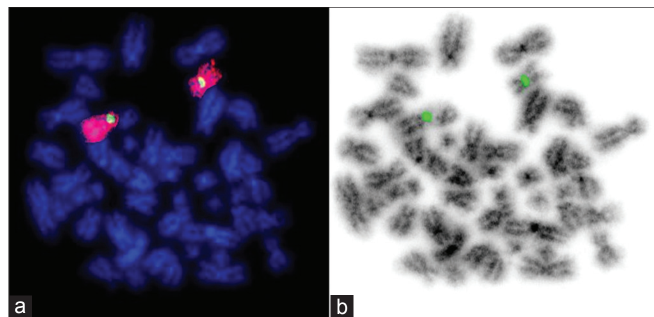

Figure 2: (a) Whole chromosome painting FISH for chromosome 11 (spectrum orange) and centromeric enumeration probe for chromosome 11 (CEP 11) (spectrum green [SG]), (b) invert DAPI (4',6-diamidino-2-phenylindole) image with CEP 11 (SG) shows inversion of chromosome 11

DISCUSSION

The concept of clonal expansion in hematological oncogenesis is conceivable due to that phenotypic or genetic feature occurs first.[8] According to this logic, the clone with PML-RARα is original in the present case, and thereafter, it obtained additional chromosomal abnormalities such as inv (11). The concomitant appearance of PML-RARα and some of the recurring chromosomal abnormalities that characterize APL are rare.

The majority of patients with APL manifest t(15;17)(q22;q21) translocation. This alteration results in disruption of PML and RARα genes on chromosomes 15q and 17q, respectively, and subsequently, the fusion protein PML-RARα is expressed.[6] Both PML and RARα have a role in normal hematopoiesis, with PML having both growth suppressor and proapoptotic activity and RARα functioning as a transcription factor that mediates the effect of retinoic acid, which is necessary for normal myeloid maturation, at specific response elements.

In APML, the function of PML- RARα fusion protein is believed to impair the normal growth suppressor and proapoptotic activity of PML and may prevent differentiation of myeloid cells by repressing the target genes of retinoic acid, thus resulting in constitutive proliferation and inhibition of terminal differentiation.[7] The current understanding is that PML-RARα fusion gene encoding a chimeric protein is required, but it is not sufficient for leukemogenesis.[9] The molecular pathogenesis supports the hypothesis that

PML-RARα rearrangement is one of the favorable molecular markers.[10]

In this study, we analyzed patient with APML with inv(11)(p15q13) and translocation between chromosome 15 and 17. PRAD1 gene is found on chromosome band 11q13 and encodes cyclin D1. Cyclin D1 plays an important role in control of the cell cycle, and overexpression of PRAD1/cyclin D1 may be involved in disease progression in this case. In the present case, patient expired within 7 days of diagnosis during induction period of treatment, so it is assumed that acute PML with inv(11)(p15q13) might have poor prognosis compared to acute PML without inv(11)(p15q13). We consider that potential leukemogenesis could be predictable in APL patients throughout their lives, most probably underlying the genetic instability of hematopoietic stem cells. Our reported case and review of rare cases cited herewith[11-15] indicate that a further aggregation of APL cases with additional chromosomal abnormalities is needed for the determination of the clinical importance, best possible treatment, and level of chromosomal risk based on the differences in genetic prognosis.

CONCLUSION

Overall, there is minimal information regarding the prognosis of APL patients with other chromosomal abnormalities. However, the present study indicates that APL patients with additional chromosomal abnormalities should be considered as a separate entity.

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