Acute promyelocytic leukemia with a novel variant (15;17) rearrangement

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Dear Sir,

Acute promyelocytic leukemia (APL) is characterized by the translocation of chromosomal (15;17)(q22;q21) involving the fusion of the promyelocytic leukemia (PML) and RARA genes, resulting in a PML/RARA fusion gene on derivative chromosome 15 and reciprocal RARA/PML fusion gene on derivative chromosome 17 [1]. Variant rearrangements have been reported in 5% to 10% of APL patients [2]. We report a case of APL associated with a novel variant translocation.

The patient is a 67-year-old male presented with epistaxis. He was found to have pancytopenia and rare abnormally

hypergranular, bilobed, immature cells consistent with leukemic promyelocytes on peripheral blood smear. No definite Auer rods were seen. Additional laboratory tests show a prolonged prothrombin time (PT) and elevated D-dimer. Bone marrow aspirate smear showed replacement by the same type of cells noted on the peripheral blood smear. Flow cytometric analysis of the marrow aspirate indicated the presence of a large-sized, immature, hypergranular myeloid population. This population brightly expressed CD33, CD13, CD117, and MPO, dimly expressed CD64, and was negative for CD34, HLA-DR, and CD11b.

Cytogenetic G-banded analysis of 20 metaphase cells from bone marrow revealed a karyotype of 46,XY, del (17)(q12q21.1), ins(15;17)(q22;q21.2q25.3)[18]/46,XY[2] (Figs. 1 and 2).

FISH analysis using the dual-color, dual-fusion PML (15q22-red)/RARA (17q21-green) probe showed a variant abnormal pattern (Fig. 2). Typical APL patients have 1R (red):1G (green):2F (fusion) signals, indicating the presence of two fusion genes. In our case, this typical abnormal pattern (Fig. 3A) was seen in only 1.5% of the cells. On the other hand, 85% of the cells had 2R:1G:1F (Fig. 3B). PML gene remained on the der (15), and PML/RARA was inserted into or translocated to the der (15) (Fig. 2).

This indicated an absence of the RARA/PML fusion gene on the derivative (der) chromosome 17 and the insertion or translocation of the PML/RARA fusion gene to the der (15). The remainder of the nuclei (3.5%) demonstrated a normal signal pattern (2R:2G) (data not shown). Metaphase FISH on ten cells using the TelVysion 17q probe showed that the subtelomeric region of the long arm of chromosome 17 was present on both 17 homologs (data not shown).

Reverse transcription polymerase chain reaction performed on the RNA extracted from peripheral blood is positive for PML–RARA transcripts.

This case was presented at the 2011 annual meeting of the College of American Pathology in Grapevine (Dallas/Ft. Worth), Texas.

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Fig. 1 G-banded karyotypes demonstrating the abnormal variant rearrangement. *Arrows* indicate the derivative chromosomes 15 and 17

1 Fusion, 2 Red, 1 Green

Red – PML (15q21) Green – RARA (17q22) Yellow (fusion) – PML/RARA

Fig. 2 Metaphase FISH using the dual-color–dual-fusion PML(15q22 red) RARA (17q21 green) probe. *Arrows* indicate the der(15) chromosome. The right (DAPI) and left (reverse DAPI) metaphases

demonstrated the variant abnormal signal pattern with PML remaining on the der(15) chromosome and PML/RARA either inserted into or translocated to the der(15) chromosome

A. Typical Abnormal Signal Pattern

B. Variant Abnormal Signal Pattern

Fig. 3 Interphase FISH using the dual-color–dual-fusion PML(15q22 red) RARA (17q21 green) probe. **(A)** Interphase nuclei demonstrating the typical abnormal signal pattern (1R:1G:2F). **(B)** Interphase nuclei demonstrating the variant abnormal signal pattern (2R:1G:1F)

The patient showed morphologic evidence of residual disease 30 days post induction therapy, but cytogenetic studies were negative. Bone marrow biopsy on day 41 post induction therapy indicated morphologic, cytogenetic, and molecular remission. The patient was discharged after completion of consolidation therapy and remains in complete remission.

The formation of a variant PML/RARA fusion gene may result from a number of possible mechanisms. Some are characterized by a two-step process in which the typical translocation occurred first and then a second event caused a disruption of the RARA–PML fusion gene on the derivative chromosome 17. Alternatively, an insertion of 17q into 15q could have occurred in which case a reciprocal fusion gene would not form. Such cases are usually cryptic and require molecular techniques for detection. Finally, more complex mechanisms have been described such as three-way translocations involving chromosomes 15, 17, and another chromosome [3]. We speculate that the variant rearrangement resulted from a two-step event, as hinted by the presence of the typical t(15;17) (q22;21) in 1.5% of nuclei (Fig. 3A).

In conclusion, we identified a variant rearrangement not previously reported in APL. The neoplastic promyelocytes showed a paucity of Auer rods, which is unusual for APL. It is not clear whether the novel cytogenetic findings are

related to the slower than usual response to ATRA induction therapy. Approximately 5% to 10% of all APL patients have variant rearrangements that show a variable response to ATRA [2].

Conflict of interest The authors declare that they have no conflict of interest.

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