

# A Variant t(14;17) in Acute Promyelocytic Leukemia

## Positive Response to Retinoic Acid Treatment

J. C. Cigudosa, M. J. Calasanz, M. D. Odero, J. Marín, E. Bengoechea, and A. Gullón

**ABSTRACT:** We present a case of acute promyelocytic leukemia (APL) carrying an atypical translocation involving chromosomes 14 and 17. This translocation could be considered a variant of the APL-specific t(15;17). Positive response to retinoic acid treatment suggests molecular rearrangement of retinoic acid receptor  $\alpha$ .

### INTRODUCTION

The most recurrent chromosomal rearrangement found in acute promyelocytic leukemia (APL) is t(15;17)(q22;q21). Since this specificity was established [1], several reports have described simple variant and complex translocations in APL [2–7]. Molecular studies of the t(15;17) have shown that the retinoic acid receptor  $\alpha$  (RAR $\alpha$ ) gene located on chromosome 17 is rearranged and recombined in a novel gene, named PML, on chromosome 15. It generates the PML/RAR $\alpha$  fusion gene, which is then transcribed into PML/RAR $\alpha$  fusion mRNA (reviewed in [8]). These findings were made closely after the observations of the striking efficacy of all-trans-retinoic acid in the treatment of a patient with APL [8] and they illustrate advancements in cancer research that may cause immediate changes in the treatment of the disease.

We here report a case of APL showing a variant translocation involving, at the cytogenetic level, chromosomes 14 and 17. In the absence of molecular studies, the patient's response to retinoic acid treatment suggests the rearrangement of the RAR $\alpha$  gene, in the same way as it occurs in a common APL with the t(15;17).

### MATERIALS AND METHODS

#### Case Report

A 26-year-old man was admitted in August 1993 with ecchy-

mosis affecting both arms. His complete blood count showed a white blood cell count of  $5.4 \times 10^9/L$  with 41% blasts, a hemoglobin of 13.1 g/dL, and a platelet count of  $14 \times 10^9/L$ . He also presented a disseminated intravascular coagulation profile. The bone marrow aspirate was compatible with a diagnosis of ANLL of the M3 FAB subtype. Immunologic markers were CD13 96% and CD33 93%.

After 1 month of conventional chemotherapy (farnitastine and cytarabine), hematologic remission was not achieved by 9/27/93 and treatment with retinoic acid (50 mg every 12 hours) was started. Two weeks later, the white blood cell count rose to  $14.9 \times 10^9/L$  and treatment with retinoic acid and chemotherapy (cytarabine, M-AMSA, and thyoguanine) was followed. After 38 days of retinoic acid treatment and 21 days of chemotherapy he entered complete remission. Finally, he received a consolidation chemotherapy cycle with the same drugs mentioned above. The patient then left the hospital and underwent a bone marrow transplantation program.

#### Cytogenetic Results

Bone marrow cells were short-term cultured (24–48 hours) and analyzed by standard cytogenetic methods, which include Trypsin-Giemsa banding.

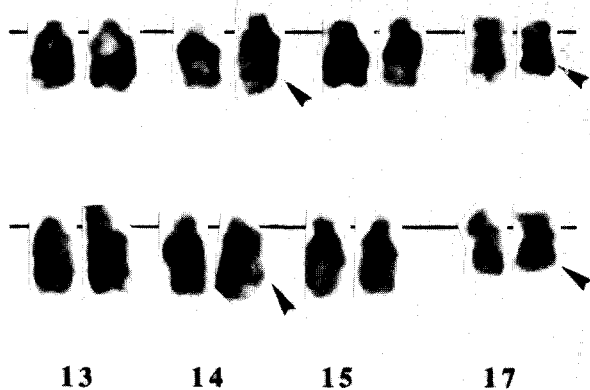
Chromosome analysis failed at diagnosis. It was performed again after 1 month of conventional chemotherapy and we were only able to roughly analyze five cells. A karyotype with a t(15;17)(q22;q21) translocation was proposed. However, the metaphase spreads were not of adequate quality and we could not be sure of this diagnosis.

A new culture was established with a sample that corresponded to day 30 after RA-treatment and day 14 after chemotherapy. Thirty-four cells were analyzed; 14 cells showed a reciprocal translocation that was interpreted as t(14;17)(q22;q21). The remaining cells were normal. A composite karyotype is shown in Figure 1.

From the Department of Genetics (M. J. C., M. D. O., A. G.), University of Navarra, Pamplona; Service of Cytogenetics (J. C. C.), Faculty of Medicine, University of La Laguna, Canary Islands and the Service of Hematology (J. M., E. B.), Hospital N. Sra. de Aránzazu, San Sebastián, Spain.

Address reprint requests to: Dr. M. J. Calasanz, Dpto. de Genética, Universidad de Navarra, Apdo. 273, 31080 Pamplona, Navarra, Spain.

Received June 13, 1994; accepted August 31, 1994.



**Figure 1** A partial karyotype from two bone marrow metaphases showing t(14;17) (q22;q21). Normal chromosomes 13 and 15 also are shown. Arrows indicate abnormal chromosomes.

The next analysis was performed at day 38 after RA-treatment and day 22 after chemotherapy. All 35 observed cells were normal.

## DISCUSSION

To our knowledge, only a single case of APL with a t(14;17) has been reported [9]. As the authors suggest, this rearrangement may represent a variant of t(15;17) in the same way as variant translocations have been described for t(9;22) in chronic myeloid leukemia. Thus, our case represents a recurrent variant translocation that involves, cytogenetically, only chromosomes 14 and 17.

Prior to the molecular studies and looking to the variant translocations in APL, there was a scientific controversy about which was the most essential chromosomal segment involved in the pathogenesis of this disease. It seemed that, because of the higher number of reported cases with anomalies of 17q, the changes affecting the long arm of chromosome 17 were more important [10] than those affecting the long arm of chromosome 15. Our case would have supported this hypothesis, however, since the understanding of the molecular events is associated with the t(15;17), it is obvious that both changes are equally essential.

Moreover, Ogawa et al. [6] described a case of APL showing a complex translocation and demonstrated molecular rearrangements leading to the PML/RAR $\alpha$  fusion gene similar to those described for the common t(15;17) [8]. As these

authors propose, it is likely that this molecular rearrangement occurs in other variant and complex translocations seen in APL.

In the absence of molecular analysis, the clinical response to treatment with retinoic acid, as seen in our case, would represent an indirect evidence of a rearrangement of the RAR $\alpha$  gene. Conventional chemotherapy was unsuccessful, and only when treatment with retinoic acid was started, alone or combined with other drugs, was complete remission achieved. This evidence justifies the role of the RAR $\alpha$  gene rearrangement in the disease but, unfortunately, tells nothing about whether the rearrangement also involves the PML gene. It has been proposed that the genetic events in APL with variant translocations could resemble those occurring in CML, which always involve BCR and ABL rearrangements [8, 10]. However, more molecular studies are needed to documentate such a hypothesis.

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