ELSEVIER

Acute Promyelocytic Leukemia Relapsing into FAB-M2 Acute Myeloid Leukemia with Trisomy 8

Niki Stavroyianni, Xenophon Yataganas, Danai Abazis, Constantinos Pangalos, and John Meletis

ABSTRACT: *Acute promyelocytic leukemia was diagnosed in a 48-year-old man; the karyotype was normal, whereas reverse transcriptase polymerase chain reaction (RT-PCR) analysis identified PML/RARα chimeric transcripts of the bcr3 type. Rather unexpectedly, the patient did not respond to all-trans retinoic acid administration; he attained complete remission with conventional chemotherapy and became PML/RARα negative. Two years later, while PML/RARα negative on RT-PCR, he presented with thrombocytopenia. Bone marrow examination was compatible with myelodysplasia of the RAEB type; the karyotype was normal. Then, after 10 months, he developed overt acute myeloid leukemia with PML/RARα negative, French–American–British M2 blasts; karyotypic analysis revealed mosaicism for trisomy 8.*

INTRODUCTION

Acute promyelocytic leukemia (APL) is characterized by the t(15;17) chromosomal translocation that fuses the *PML* and *RARα* genes and creates the chimeric *PML/RARα* gene. PML/RARα chimeric transcripts are present in the leukemia cells of all patients and serve as a "clone specific" molecular marker for the diagnosis and monitoring of patients [1]. APL blasts exhibit a unique sensitivity to the differentiating action of all-*trans* retinoic acid (ATRA) [1].

We report a patient in remission after chemotherapy for APL who developed acute myeloid leukemia (AML) with PML/RARα-negative French–American–British (FAB)-M2 blasts, associated with mosaicism for trisomy 8.

CASE REPORT

A 48-year-old man with no significant previous medical history presented in April 1995 with pancytopenia. Bone marrow examination revealed invasion by blasts and promyelocytes typical of APL. The karyotype was normal; reverse transcriptase polymerase chain reaction (RT-PCR) analysis of the diagnostic bone marrow (performed as described in [2]) identified PML/RARα chimeric transcripts of the bcr3 type. The patient was initially treated with ATRA (45 mg/m^2/d PO) for 45 days to which, rather unexpectedly, he was resistant. He attained complete remission (CR) with an induction course of mitoxantrone (10 mg/m^2/d IV over days 1–3), etoposide (75 mg/m^2/d over days 1–7), and cytarabine (100 mg/m^2/d over days 1–7). After the first induction course, the patient was still PML/RARα positive. A similar second induction course was administered. The first consolidation chemotherapy course consisted of high-dose (2 g/m^2/24h) cytarabine as a 3-hour IV infusion over days 1–4. At the end of the first consolidation course, the patient was PML/RARα positive. The second consolidation chemotherapy course consisted of cytarabine $^+$(500 mg/m^2/12h)$^+$(1 g/m^2/d) as 3-hour IV infusion over days 1–6 and mitoxantrone (10 mg/m^2/d IV over days 4–6); on hematologic recovery, he was found PML/RARα negative. The treatment was completed in January 1996 with a third consolidation chemotherapy course, consisting of daunorubicin (40 mg/m^2/d over days 1–3) and cytarabine (100 mg/m^2/d in 24-hour continuous IV infusion over days 1–5).

The patient remained in CR with negative RT-PCR tests, performed at 3-month intervals, until August 1997, when he presented with thrombocytopenia. Bone marrow examination was compatible with myelodysplasia of the RAEB type (bone marrow blasts 10%); the karyotype was normal, whereas the RT-PCR analysis was again negative for PML/RARα chimeric transcripts. The patient remained in stable clinical and hematological condition for about 6 months.

Since March 1998, the patient gradually deteriorated and, finally, in June 1998, he developed AML with 80% bone marrow blasts of FAB-M2 morphology. RT-PCR for PML/RARα transcripts was negative. His karyotype was: 47,XY,+8[2]/46,XY[18].

From the First Department of Medicine, University of Athens, Laikon General Hospital, and the Diagnostic Genetic Center, Athens, Greece.

Address reprint requests to: Niki Stavroyianni, M.D., First Department of Medicine, University of Athens, 9, K. Krystalli St., 151 26 Maroussi, Greece.

Received April 16, 1999; accepted June 15, 1999.

655 Avenue of the Americas, New York, NY 10010

0165-4608/00/$–see front matter
PII S0165-4608(99)00132-6

The patient attained complete hematological and cytogenetic remission after two identical courses of etoposide (150 mg/m^2/d over days 1–5) and idarubicin (20 mg/m^2/d over days 1–3). He is currently being prepared for autologous peripheral blood stem cell transplantation.

DISCUSSION

In most APL cases, t(15;17)(q22;q12) is the only cytogenetic abnormality [1]. Conventional cytogenetics detect t(15;17) in only 70–80% of APL cases; even when metaphase cytogenetic analysis fails, as seems to have happened in our patient at diagnosis, PML/RARα fusion is always identified by fluorescence in situ hybridization (FISH) or molecular biology techniques ("cryptic rearrangements"). Occasionally, additional chromosome aberrations are observed; the commonest is trisomy 8 (+8), which has been reported to occur in as many as 25% of t(15;17)-positive APL cases [3]. Our patient had a normal karyotype at diagnosis of APL and exhibited +8 in 2/20 (10%) metaphases when he developed FAB-M2 AML. As shown recently, +8 per se is rarely a marker of cryptic PML/RARα rearrangements [4]; this was also true in our patient.

The identification of PML/RARα chimeric transcripts denotes patients who are likely to respond to ATRA. AML diagnosed as APL according to FAB criteria alone, negative for PML/RARα chimeric sequences, is not "true" APL and will be refractory to ATRA [1]. Primary resistance to ATRA, as seen in our patient, is very rare (<2%); however, the therapeutic effect of ATRA may be modulated by the pattern of expression of hematopoietic growth factors by the leukemic cells [5]. The possibility of a false positive RT-PCR test for PML/RARα transcripts leading to misdiagnosis of our patient as APL can be ruled out, because recommended measures were adopted to prevent cross-contamination of samples as well as potential pitfalls [6]. Furthermore, PML/RARα transcripts were identified in three different RT-PCR tests performed on RNA samples obtained at different phases of the disease.

Relapse of APL after successful ATRA/chemotherapy treatment with a different subtype of AML is a rare event [7–10]. In our patient, the emergence of the secondary FAB-M2 AML 3 years after the diagnosis of the primary APL makes the possibility of a clonal relation between these two entities remote but not improbable; unfortunately, trisomy 8 was not studied by FISH at diagnosis, which would have been very helpful in understanding whether the two leukemias were independent events. However, it should be noted that, recently, a case of de novo chimeric M3:M2 AML was reported [11], and a similar case has been attended by our group (Stavroyianni et al., submitted). In this scenario, a second clonal population with trisomy 8 might already have existed at disease presentation, albeit at very low numbers, thus precluding detection by conventional cytogenetic analysis. Nevertheless, it is more reasonable to speculate that the secondary leukemia may be therapy related, especially because our patient was exposed to drugs classically implicated in the pathogenesis of therapy-related (t-) AML (i.e., topoisomerase II inhibitors mitoxantrone, etoposide, and daunorubicin); furthermore, he was found to carry +8, one of the most common unbalanced chromosomal abnormalities observed in t-myelodysplasia and t-AML [12].

This work was supported by the Programme EPET II of the National Secreteriat for Research and Technology of Greece.

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