

LETTER

Therapy-related acute myeloid leukemia with t(9;11)(p12;q23) in a patient treated for acute promyelocytic leukemia

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Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML), characterized by a striking response to differentiating therapy with all-*trans* retinoic acid (ATRA).^{1,2} In the recent years, the inclusion of this agent in front-line treatment has considerably improved the outcome of the disease, such that the majority of patients receiving combined chemotherapy and ATRA regimens are reported to become long-term survivors;^{3,4} however, in about 30% of cases relapse still occurs.^{3,4} In most cases, relapse occurring in APL develops from the original promyelocytic clone.⁴ However, in APL patients with sustained CR, different authors have described the occurrence of therapy-related myelodysplastic syndrome (t-MDS) or t-AML, characterized by morphologic, immunophenotypic and chromosomal abnormalities unrelated to the initial clone.^{5,6} Most of these reports referred to t-AML patients with abnormalities of chromosomes 5 or 7, in whom a dysplastic phase did frequently precede the onset of leukemia, while involvement of chromosome 11-band q23, a typical finding of secondary AML associated with exposure to topoisomerase II inhibitors,⁷ has never been reported.

In this study we describe a patient who, in hematologic and molecular CR from classical APL, developed t-AML with t(9;11)(p12;q23). Of interest, a MLL germline genomic configuration was detected by Southern blot analysis from the leukemic blasts at the onset of t-AML. A 27-year-old woman was diagnosed on August 1999 as having hypergranular APL. Neither clinical nor laboratory evidence of disseminated intravascular coagulation (DIC) was present at diagnosis. The bone marrow aspirate was hypercellular and showed 95% hypergranular promyelocytes with frequent Auer rods; immunophenotyping analysis of bone marrow cells, performed as previously described,⁸ revealed a classic antigenic pattern of APL (CD13+, CD33+, CD117+, HLA-DR-). Chromosomal analysis of bone marrow was performed by RHG banding using direct methods and unstimulated short-term (24 and 48 h) cultures and showed 46 XX, t(15;17) in 20 out of 20 metaphases analyzed; molecular analysis, performed by polymerase chain reaction (RT-PCR), revealed the presence of PML/RAR- α fusion gene (bcr 1-2 type).

The patient received induction treatment according to AIDA GIMEMA protocol,⁹ with achievement of CR. Then, three consolidation courses were administered, according to the protocol. The molecular analysis was performed 1 month after the last consolidation course

and revealed no evidence of PML/RAR- α fusion gene. Hence, according to the therapeutic program, the patient started maintenance therapy with methotrexate, 6-mercaptopurine and ATRA. The bone marrow analysis on December 2001 confirmed complete hematological and molecular remission.

On January 2002, while on maintenance therapy, the patient was admitted to our institution because of cough, asthenia and fever. Blood count showed leukocytosis (WBC $120 \times 10^9/l$ with 100% myelo-monocytoid blast cells) and thrombocytopenia (PLT $14 \times 10^9/l$). Bone marrow examination showed 98% large and vacuolated myelo-monocytoid blasts; Auer rods were absent. According to FAB classification, a diagnosis of M4-AML was made. Immunophenotyping studies revealed positivity for CD13, CD33, CD14, CD56, CD11c, CD11b and HLA-DR antigens. Cytogenetic examination demonstrated 46 XX,t(9;11)(p22;q23) in 24 out of 24 metaphases analyzed (Figure 1). At molecular analysis, there was no evidence of PML/RAR- α fusion gene. Of interest, germline genomic configuration of MLL gene was detected by Southern blot analysis from the leukemic blasts at the onset of secondary AML.

The patient developed acute respiratory failure; chest X-ray showed massive lobar pneumonia. Cyto-reductive therapy with hydrossiurea (3 gr/ die), wide broad-spectrum antibiotics and oxygen therapy were started, but death occurred few days after diagnosis from acute respiratory distress syndrome.

The development of t-MDS/AML is a well-known devastating complication occurring after treatment for curable hematologic malignancies, such as Hodgkin's disease, non-Hodgkin's lymphoma and childhood acute lymphoblastic leukemia.¹⁰ More recently, cases of t-MDS/AML have been reported in patients with prolonged CR or cured from APL.^{5,6} In a recent review focusing on t-AML and t-MDS after APL treatment, most common cytogenetic abnormalities consisted of deletion of the long arm or loss of the whole chromosome 5 and/or 7 and, less frequently, complex karyotypes or balanced translocation involving chromosome band 21q22.⁶ In the series by Latagliata *et al*,⁵ cytogenetic characterization revealed numeric abnormalities of chromosome 5 and 7 in two cases, normal karyotype in one patient and one case of balanced t(10;11)(p14;q21). Of interest, in this patient, the involvement of the MLL gene was ruled out by Southern blot analysis. The case here described is unique in that a balanced t(9;11)(p22;q23) was detected 18 months in clinical and molecular CR from classical APL. It is well known that a strict association exists

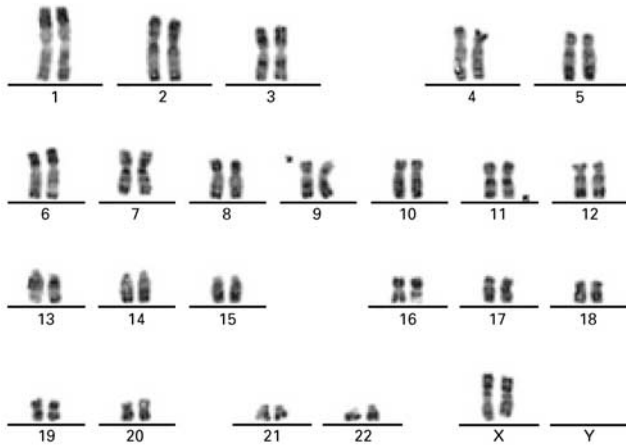


Figure 1 Patient's karyotype at diagnosis of t-AML showing t(9;11)(p22;q23).

between cytogenetic abnormalities involving the 11q23 cytogenetic band, such as t(9;11), t(11;19), t(11;14), and development of t-AML.⁷ As in our patient, these cases are usually associated with short interval time from previous chemotherapy with DNA topoisomerase II inhibitors, absence of myelodysplastic phase, hyperleukocytosis and young age. However, while in most of these cases the MLL gene at q23 band is consistently altered, in our patient a MLL genomic configuration was detected by Southern blot analysis, suggesting that in the 11q23 cytogenetic band, genes other than MLL may be involved in leukemogenesis. In this regard, it is worthy of note that at least two other genes, identified within this cytogenetic region, have been found to be altered in blood malignancy, that is, the p54/RCK gene in B-cell non-Hodgkin's lymphoma and the PLZF gene in APL with t(11;17)(q23;q21).¹¹ More recently, a novel RING finger gene located on 11q23 band, RNF26 gene, was cloned and found to be upregulated in different cancer human cell lines including HL-60 promyelocytic cell line.¹² Whatever the gene(s) involved, in our patient

the short latency time from APL to t-AML diagnosis (18 months), the lack of previous MDS features and the chromosome band 11q23 involvement suggest a leukemogenic role of topoisomerase II inhibitors, such as anthracyclines, mitoxantrone and epipodophyllotoxins, used during induction and consolidation treatment. As to other drugs, while there is no argument for a leukemogenic potential of ATRA, we cannot definitively exclude that low-dose methotrexate and 6-mercaptopurine, administered during maintenance therapy, may have contributed to the onset of t-AML in this patient. Enhanced risk of developing t/MDS/AML has been clearly demonstrated for both these drugs, when used after other cytotoxic agents, such as etoposide.¹³

In conclusion, if the prognosis for APL patients is markedly improved since the introduction of ATRA, the association with chemotherapy is still essential to obtain sustained molecular remission and cure.¹⁻⁴ However, the occurrence of t-AML/MDS in potentially cured patients is an emerging problem, which raises the question of tailoring treatment intensity, in order to spare unnecessary toxicity. The introduction of new protocols based on prognostic score systems to stratify the patients at diagnosis, a careful molecular monitoring of PML/RAR α fusion gene, and the use of biologic agents, proven as effective in APL, may consistently contribute to reduce the risk of secondary AML in APL patients in the years to come.^{14,15}

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