Translocation (15;17)(q22;q21) not associated with acute promyelocytic leukemia and negative for PML/RARα rearrangement

We describe the cytogenetic abnormality of t(15;17)(q22;q21) in a case of acute myeloid leukemia without evidence of *PML/RARα* rearrangement on molecular analysis. Due to its important therapeutic implications, this report reinforces the need for molecular characterization of t(15;17) in acute leukemia with features not typical of acute promyelocytic leukemia.

Sir,

A 44-year old Chinese man presented with a two-week history of bone pain and myalgia. Complete blood counts showed: hemoglobin (Hb) 6.3 g/dL, white cell count (WBC) 1.1×10^9/L (blasts 21%), and platelet count (Plt) 159×10^9/L. The clotting profile was normal. Bone marrow aspiration revealed a morphologic diagnosis of acute myeloid leukemia-M2 (Figure 1A). Cytochemically, the blast cells were negative for myeloperoxidase and showed a low level of Sudan black B positivity (10%). Immunophenotyping showed multilineage antigen expression (CD13, CD33, CD7 and surface CD22) in addition to CD34 and HLA-DR. Cytogenetic studies performed on synchronized and non-synchronized short term cultures of bone marrow cells supplemented by direct harvest[1] showed: 46,XY, t(15;17) (q22;q21)[3]/46,XY[5] (Figure 2).

All-*trans* retinoic acid was started empirically at the dose of 45 mg/m^2/day in view of the t(15;17) (q22;q21), but was discontinued after two weeks when molecular studies showed no evidence of the *PML/RARα* rearrangement. A complete remission was attained by induction chemotherapy followed by two courses of consolidation. The patient relapsed one year later and died of the disease.

Southern blot hybridization of RARα gene configuration was performed with a 5.5 kb RARα probe (covering intron 2 to exon 4) on BglII and HindIII DNA digests.[2] No rearrangement of the RARα gene could be defined in our patient (data not shown). Similarly, no PML/RARα fusion transcript could be detected at diagnosis by polymerase chain reaction as described.[3]

Fluorescence *in situ* hybridization, performed on interphase nuclei using a PML/RARα dual color translocation probe (Vysis, Downers Grove, IL, USA), showed two separate PML and RARα signals (Figure 1B) in 300 interphase nuclei and all metaphases analyzed. No PML/RARα fusion signal was identified.

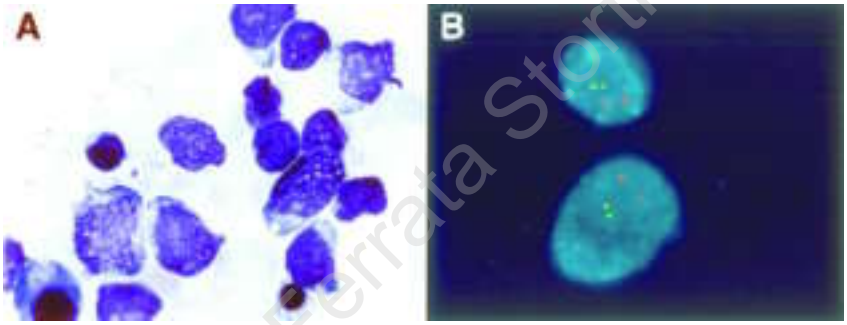

Figure 1. A. Bone marrow aspirate showing blast cells with round nucleus, open chromatin, multiple small nucleoli and abundant pale basophilic cytoplasm containing azurophilic granules. Granulocytic maturation is evident, but hypergranular abnormal promyelocytes are not found. Wright Giemsa ×1,000. B) FISH on interphase nuclei counterstained with DAPI, showing two orange (PML) and two green (RARα) signals. No PML/RARα fusion signal (which should appear yellow) is found. Original magnification ×1,000.

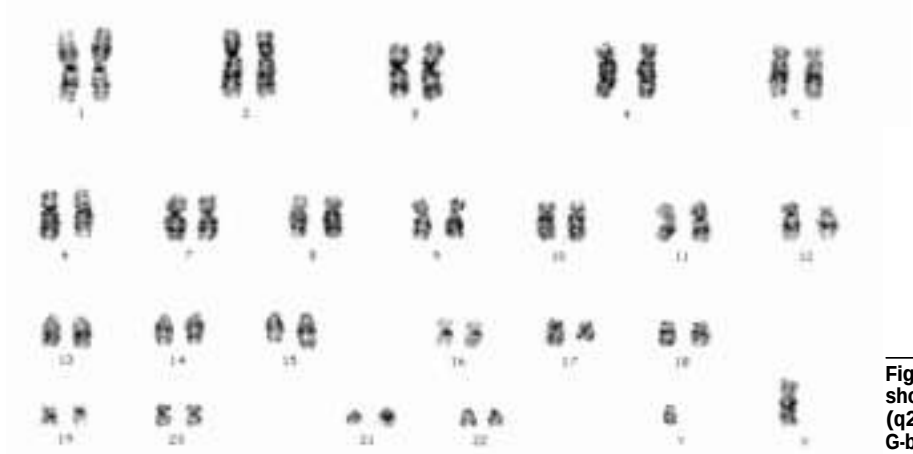

**Figure 2. Complete karyotype showing 46,XY, t(15;17) (q22;q21).
G-banding with trypsin/Giemsa.**

Although translocation (15;17) and PML/RARα fusion are regarded as highly specific for acute promyelocytic leukemia (APL), they have been reported in rare cases of acute leukemias that were neither morphologically or immunophenotypically consistent with APL.[4-8] However, these cases showed therapeutic response to ATRA despite non-APL features. These observations showed that morphologic, cytogenetic and molecular features must all be considered for an accurate diagnosis of APL. Our case highlights the importance of this combined approach. While the t(15;17)(q22;q21) translocation seen in this patient was indistinguishable from that in APL, the clinical and hematologic features were not compatible with a diagnosis of APL. Detailed molecular analysis showed no evidence of PML/RARα rearrangement, which confirmed that the translocation breakpoints in this patient did not involve the PML and RARα gene. In fact a similar case of AML with t(15;17)(q24.3;q21.1) not associated with APL has previously been reported,[9] in which detailed molecular analysis did not reveal any involvement of PML and RARα genes. Interestingly, both cases showed AML-M2 morphology and expression of stem cell antigen CD34. In addition to CD34, the present case showed multi-lineage antigen expression, suggesting the involvement of an early hematopoietic progenitor cell.

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Key words

Acute promyelocytic leukemia, PML/RARα rearrangement, t(15;17).

Acknowledgments

The authors thank Ms. A. Pang for technical assistance. The RARα probe was a kind gift from Professor Z.Y. Wang of the Shanghai Institute of Hematology, China.

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Lung toxicity following fludarabine, cytosine arabinoside and mitoxantrone (FLAN) treatment for acute leukemia

The clinical profile of pulmonary drug toxicity of fludarabine phosphate associated with other drugs, particularly cytarabine (ARA-c), is not well defined. We describe the pulmonary complications observed in two patients treated with these drugs.

Sir,

we present brief case reports of 2 patients treated with FLAN.

Case #1. A 31-year old man was diagnosed as having acute myeloid leukemia M2 in October 1998. A partial remission was obtained with a course of ICE and a second course of FLAN (fludarabine 60 mg/daily for 5 days; ARA-c 4,000 mg/daily for 5 days and mitoxantrone 12 mg/daily for 3 days was given. Seven days after therapy discontinuation, during severe neutropenia, the patient developed fever and dyspnea (pO_2 39 mmHg). The chest roentgenogram showed patchy alveolar shadows in the left hemi-thorax. A high resolution computed tomography (HRCT) showed bilateral pulmonary ground glass opacities (Figure 1). Empirical intravenous antibiotic therapy was administered, with 0.8-1 mg/kg prednisolone. Blood cultures were positive for *Staphylococcus simulans*. The cytospin preparations of bronchoalveolar lavage (BAL) fluid showed a pattern of alveolar hemorrhage. After 6 days clinical symptoms and blood gas abnormalities had resolved (pO_2 93.6). Transbronchial lung biopsies performed 20 days after the first BAL, showed a patchy interstitial mononuclear cell inflammation and intralveolar loose fibrotic buds. BAL fluid analysis showed: 540,000 cells/mm^3, macrophages with vacuolated cytoplasm 67%, neutrophils 1%, lymphocytes 32%. Flow cytometric analysis of lymphocytes showed: $CD3^+$ cells 95%, $CD4^+$ cells 24%, $CD8^+$ cells 47%, CD20 0%, CD 3/$CD25^+$ 2%, $CD3^+DR^+$ 66%, CD4 /CD8 ratio< 0.5%. Virus cultures and tests for acid-fast bacilli were negative.