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Acute myeloblastic leukemia with minimal myeloid differentiation featuring a three-way translocation t(8;13;14)

We describe the case of a young girl with minimally differentiated acute myeloblastic leukemia (AML-M0) featuring a complex chromosomal abnormality. Fluorescence *in situ* hybridization (FISH) showed a three-way translocation t(8;13;14). To our knowledge, this is the first case of AML-M0 with this chromosomal translocation to be reported in literature.

AML-M0 is an infrequent subtype of AML with minimal myeloid differentiation, frequently associated with poor prognosis.[1-3]

An 18-year old girl was admitted to our hospital in November 1998 because of weakness, diplopia, dizziness, and fever. The diagnosis of AML-M0 was made according to FAB criteria.[4] Conventional cytogenetic analysis of bone marrow and peripheral blood suggested a 46, XX, t(8;14) (q24;q11). A co-hybridization experiment using WCP #8 and WCP #14[5] as probes revealed the involvement of chromosomes 8 and 14 in a complex translocation (Figure 1a). The der(8) was not the product of a reciprocal t(8;14) translocation, as its distal part did not belong to chromosome #14. der(14) was involved in a t(8;14): its telomeric region was lit up by WCP #8, while the chromosome #14 telomeric region was translocated to a marker chromosome resembling a deleted D-group chromosome (Figure 1a). FISH experiments using WCP #15 excluded the involvement of this chromosome in the rearrangement (data not shown). A co-hybridization experiment using WCP #8 and WCP #13 showed that chromosome #13 was split and translocated to chromosome #8 on der(8) (Figure 1b). The breakpoint on 13 was very close to the centromere so that der(13) appeared as a short acrocentric chromosome (Figure 1b). A further co-hybridization experiment performed using WCP #14 and a pool of YACs spanning the 13q12-13 region showed that the telomeres of der(13) belonged to chromosome #14 and that the breakpoint on chromosome 13 was located inside the 13q12-13q13 region (data not shown). This complex rearrangement was ish t(8;13;14) (q24;q12;q32) (wcp8$^+$, wcp13$^+$; wcp13$^+$, wcp14+; wcp14+, wcp8+).

Computed tomography cranial examination showed localization in the dural meninges with involvement of the subarachnoid space. The patient was treated with high-dose Ara-C 3 g/m^2 x 2 for 4 days and mitoxantrone 10 mg/m^2 for 3 days; on the 28th day bone marrow evaluation showed persistence of blast cells (79%). We started 2nd line therapy including vincristine 2 mg, idarubicin 12 mg/m^2 and methotrexate 2 g/m^2. The patient achieved hematologic complete remission (CR) and resolution of the cranial involvement, demonstrated by magnetic resonance imaging and cerebrospinal fluid examination. The chromosomal rearrangements were not detected during the CR phase, thus excluding the possibility that they were constitutional.

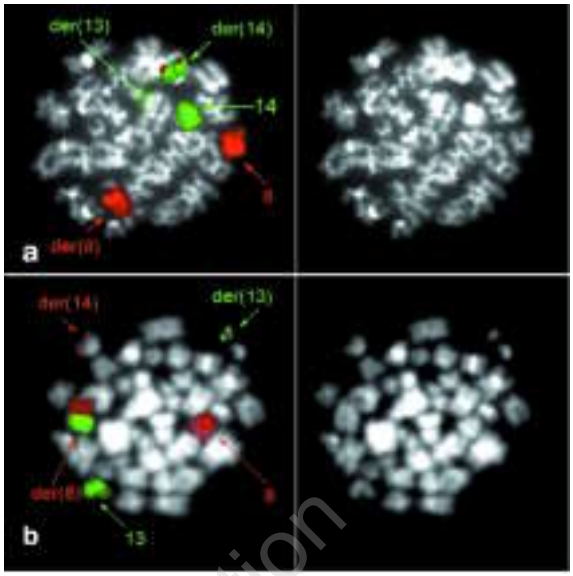

Figure 1: (a) WCP #200 (chromosome #8, red) was co-hybridized with WCP #198 (chromosome #14, green) on a metaphase from the patient's bone marrow; (b) Co-hybridization experiment using WCP #200 (chromosome #8, red) and WCP #138 (chromosome #13, green). For details see text.

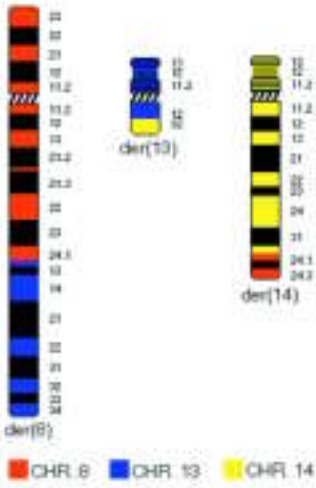

Figure 2. Diagram of the complex rearrangements described in Figure 1.

The patient received two cycles as consolidation therapy (methotrexate, idarubicin) but we observed hematologic relapse after three months of CR; FISH analysis showed the same chromosomal abnormality. Reinduction therapy was started with the FLANG regimen. The girl died of resistant disease in December 1999.

Several groups have reported a higher incidence of abnormal/complex karyotypes in AML-M0, particularly deletion -7/7q and/or -5/5q and trisomy 8, 4 and 13, which are all frequently associated with poor prognosis.[1,6] To our knowledge, this t(8;13;14) is the first described in the literature.[7] In this three-way translocation between chromosomes 8, 13 and 14 we also analyzed whether the regions of chromosomes 8 and 14 involved were the same as those found in the t(8;14) reciprocal translocation commonly associated with ALL L3.[8,9] Our data showed that C-MYC was not involved in the rearrangement (data not shown). Larger studies are needed to clarify which chromosome abnormalities contribute to the poor prognosis of this disease.

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Key words

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Monitoring of minimal residual disease and mixed chimerism in a case of high-risk TEL/AML1-positive acute lymphocytic leukemia

We report the case of a child with acute lymphocytic leukemia with a combination of positive (TEL/AML1 positivity, age, low level minimal residual disease before bone marrow transplantation) and negative (poor prednisone response, high leukocytosis) prognostic features. We used molecular-genetic techniques and flow cytometry for the follow-up of minimal residual disease.

Sir,

Children with TEL/AML1-positive acute lymphocytic leukemia (ALL) generally have an excellent prognosis. This fusion gene, resulting from t(12;21), is usually found in children aged 2-5 years, with non-hyperdiploid DNA content and low leukocyte count at presentation[1] and very low expression of CD66c.[2] Nevertheless, rare cases have been described in the literature of TEL/AML1 together with a WBC higher than $50x10^9$/L or age over 10 years at diagnosis.[3] It has been documented that relapses do occur in children with TEL/AML1-positive ALL, although their frequency is still discussed.[4,5] Minimal residual disease (MRD) monitoring is a valuable predictor of prognosis throughout conventional chemotherapy as well as before and after bone marrow transplantation (BMT).[6] We combined molecular-genetic techniques and flow cytometry for MRD monitoring in a 4-year old child with TEL/AML1-positive ALL with initial hyperleukocytosis and involvement of the central nervous system. Leukemic blasts were classified as $CD10^+$ with aberrant expression of CD33 on 15% of blasts. Other myeloid markers were negative.[2]