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A case of atypical myelodysplastic syndrome with a novel reciprocal translocation t(1;12)(q21;p13)

Reciprocal translocations as unique primary karyotypic anomalies are not frequently found in myelodysplastic syndromes. We report a case of refractory anemia with excess blasts in transformation (RAEB-t) with total absence of erythroid precursors in bone marrow. Cytogenetic study revealed that all 25 spontaneous metaphases analyzed carried a novel reciprocal translocation t(1;12)(q21;p13) as sole abnormality without detectable TEL (ETV6) gene involvement.

Sir,

A 64-year old man was admitted to hospital because of asthenia and fatigue with minor exercise of sudden onset. There was no evidence of exposure to toxic agents and no fever or bleeding were noted. Physical examination showed pallor, without hepato-splenomegaly or lymph node enlargement. The complete blood count was: leukocytes $53 \times 10^9/L$ (differential: 30% neutrophils, 60% myelocytes and metamyelocytes cells and 10% myeloid blasts); hemoglobin: 5.9 g/dL and platelets $57 \times 10^9/L$. Dysplastic signs were evident in myelocytes and metamyelocytes with intense hypogranular cytoplasm. Bone marrow aspiration showed hypercellularity, scarce micromegakaryocytes, 75% of markedly hypogranular myeloid cells, 22% of blast cells of myeloid appearance with-

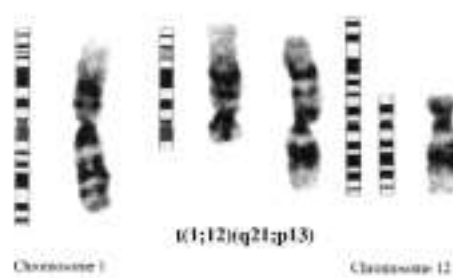


Figure 1. Partial karyotype showing t(1;12)(q21;p13) detected in all studied metaphases. G-banding with trypsin/Giemsa.

out Auer rods, and 3% of lymphoid cells. Strikingly there was a total absence of erythroid cells. Cytochemical staining of blast cells was positive only for peroxidase and naphthol-AS-D-acetate esterase. Immunophenotypic markers of blast cells were positive for CD13, CD33 and HLA-DR. Conventional cytogenetic analysis of bone marrow showed a unique clonal abnormality with a reciprocal translocation t(1;12)(q21;p13) in all 25 metaphases (Figure 1). DNA and RNA were extracted from bone marrow cells at diagnosis. Southern blot with a specific probe for TEL gene after enzyme digestion with *Bam*HI, *Hind*III and *Eco*RI, did not demonstrate that this gene was involved in the translocation. No *bcr-abl* fusion products were detected using a nested RT-PCR approach. A diagnosis of refractory anemia with blast excess in transformation was established on the basis of the morphologic picture.

Cytogenetic abnormalities can occur in the marrow cells of patients with *de novo* MDS in approximately 40-60% of cases. Detected by conventional methods, they involve mostly chromosomes 5, 7, 8, 11, 12 and 20, and have been proved to be an independent prognostic factor.^{1,2} Abnormalities of 12p13 in hematologic malignancies result in at least three different molecular changes: deletion of KIP1, amplification of CCND2 and rearrangement of the ETS-like gene TEL.³ The first description and cloning of TEL gene was carried out in a case of CMML bearing a t(5;12) and the gene has subsequently been identified as a hot spot frequently found in childhood ALL, especially in t(12;21). In MDS, translocations of 12p13 involving the TEL gene, with chromosomes 5, 10 and 3, have been reported previously;^{4,5} all cases displayed atypical signs such as eosinophilia or monocytosis, all carrying a dismal prognosis. Our case of MDS presented with symptoms of acute leukemia, marked normocytic anemia, thrombocytopenia and immature leukocytosis, without eosinophilia or monocytosis but with a striking total absence of erythroid medullary precursors. Despite the involvement of the breakpoint of the TEL gene in our case, and despite using a specific probe for the TEL gene, we were not able to demonstrate the presence of the TEL rearrangement, although we cannot rule it out definitively. On the other hand, the breakpoint

at 1q21 is a common feature of B-cell malignancies including acute lymphoblastic leukemias (ALL) and non-Hodgkin's lymphomas. Recently, a novel gene (BCL9), was cloned from a t(1;14)(q21;q23) in a cell line CEMO-1 derived from a pre-B ALL.⁶ Whether or not this novel gene is rearranged with the TEL gene in this translocation requires further elucidation. The limits between MDS and myeloproliferative syndromes as well as truly acute non-lymphoblastic leukemias with myelodysplasia seem to be indistinct⁷ and new entities could be defined provided that non-random chromosomal abnormalities can be demonstrated in these patients.

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Cytogenetic and molecular studies of variant Ph' translocations

We describe the cytogenetic and molecular studies of three simple variant Ph'-translocations: t(11;22)(p15;q11), t(13;22)(p11;q11) and t(20;22)(q12;q11), representing only 1% of our chronic myeloid leukemia cases. Breakpoints 13p11 and 20q12 have not previously been reported. All cases showed *bcr/abl* rearrangement, indicating the participation of chromosome 9 in spite of the normal cytogenetic appearance.

Sir,

The Ph' chromosome is present in hematopoietic cells from about 95% of patients with chronic myeloid leukemia (CML). Variant forms of the t(9;22) have been found in a low percentage of cases (5-10%). Two variant forms have been recognized: simple (the segment lost from 22q is translocated into a chromosome other than 9) and complex (three or more chromosomes are involved).¹ In spite of the normal cytogenetic appearance of chromosome 9 in simple variants, some papers reported detection of the *bcr/abl* rearrangement by polymerase chain reaction (PCR)² or *in situ* hybridization techniques.³

We present the cytogenetic and molecular studies of three patients with simple variant translocations, two of whom with points not previously described. These findings are uncommon events in our population, representing only 1% (3/300) of all cytogenetically analyzed CML patients.

The three patients had a diagnosis of CML and two of them were in accelerated phase treated with hydroxyurea. One patient in chronic phase received high dose interferon (5MU/m/d) and achieved a hematologic complete response. None of them reached cytogenetic remission. After a period of 2 to 5 years all of them evolved to blast crisis and died after the failure of AML treatment.

The cytogenetic analysis was performed on bone marrow cultures of 24-48 hrs without mitogen and the karyotype was analyzed by G-banding.⁴ For molecular study total RNA was extracted from peripheral blood and processed by RT (reverse transcriptase)-PCR.⁵ Cytogenetic, molecular and clinical studies are summarized in Table 1.

The chromosome bands involved in our simple variant Ph' translocations were: 11p15, 13p11 and 20q12 (Figure 1a). The band 11p15 has been reported on several occasions⁶ indicating a frequent site in both types of variant forms in CML. Bands 13p11 and 20q12, to our knowledge, have not been documented in variant Ph' translocations, although nearby bands such as 13p13⁷ and 20q13⁸ have been reported.

The three translocations showed the involvement of chromosome 22 and a chromosome other than 9. Molecular analysis detected the *bcr/abl* rearrangement in the three cases (Figure 1b).

The literature contains controversies about the significance of the Ph' variant translocations in the clinical course. Potter *et al.*⁹ found a shorter chronic