Complex karyotype in one patient with small cell variant of T-prolymphocytic leukemia. Analysis by G-banding and comparative genomic hybridization

We report the genetic changes in a case of small cell variant of T-prolymphocytic leukemia. The use of comparative genomic hybridization allowed the characterization of otherwise hidden genetic abnormalities such as a high level amplification on 8q24, the chromosomal site of the c-MYC oncogene, gain on 15q and deletions of 11p and 13q.

The small cell variant of T-prolymphocytic leukemia (T-PLL) is a rare disorder representing around 20% of cases.[1] The case described here showed the clinical and immunologic features characteristic of T-PLL, including co-expression of CD4 and CD8, a phenotype frequent in the small cell variant of T-PLL.[1,2] While T-PLL is morphologically heterogeneous, the disease is characterized by recurrent chromosome abnormalities, chiefly inv(14) or t(14;14)(q11;q32) and trisomy 8q, thus supporting the hypothesis that all the morphologic T-PLL variants constitute a unique entity.[1-6]

A 41-year old female was seen for evaluation of lymphocytosis. Physical examination revealed splenomegaly and lymphadenopathy. Peripheral blood counts showed a white blood count of 104×10^9/L with 91% small prolymphocytes, Hb 8.6 g/dL and platelets 131×10^9/L. Bone marrow showed increased cellularity with a marked infiltration by small lymphocytes. Immunophenotyping in circulating lymphocytes demonstrated a $CD3^+$, $CD7^+$, $CD38^+$, $CD4^+$, $CD8^+$ phenotype. A diagnosis of T-PLL was made (small cell variant), and the patient was treated with 3 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) with no response, but progression. The patient did not respond to fludarabine (1 cycle) and 2'-deoxycoformycin (2 injections), and died with widespread disease (organomegaly, rising counts, pleural effusion) six months after diagnosis. Karyotype analysis at diagnosis failed. G-banding analysis post-treatment showed a complex hypodiploid karyotype with breakpoints at 14q and 7q:

44~45,XX,t(1;20)(q13;q13)[4],-4[6],del(6)(q24)[3],del(7)(q32)[3], add(8)(p11)[4],+add(8)(p11)[4],+der(14)t(14;14)(q11;q32)[6], -16[6],-20[6],mar1[4],mar2[3][cp6]

The following chromosomal imbalances were identified using comparative genomic hybridization (CGH): loss of chromosomal material on 4q11-q24, 4q32-q35, 6q24-q27, 7q36, 11p11-p12 and 13q13-q34; and gains on 8q24, 14q11-q32 and 15q23-q26 (Figure 1). A high amplification on 8q24 was detected.

Chromosome translocations in T-PLL frequently involve the T-cell receptor (*TCR*) genes, with the TCRα/δ locus on chromosome 14q11 affected in 80% of cases.[1] In this disorder, rearrangements of 14q11 usually occur in association with trisomy 8q, detected in the CGH analysis of our patient. Both similarities and discrepancies were found when conventional and CGH karyotypes were compared. CGH detected losses on chromosomes 6q and 7q that corresponded with the 6q and 7q deletions found in the G-banded karyotype, respectively. The CGH loss of 4q, and not of the whole chromosome could be due to the presence of chromosome 4 material in one of the markers. In the same way, the gain on 14q11-q32 that was observed in the CGH profile could reflect the presence of material from 14q included in the marker chromosome. On the other hand, by CGH we were able to demonstrate two gains that were not detected by conventional cytogenetics. A gain of 15q23-26 and, more significantly, a high level amplification signal on band 8q24, the chromosomal site of the c-MYC oncogene. Overexpression of

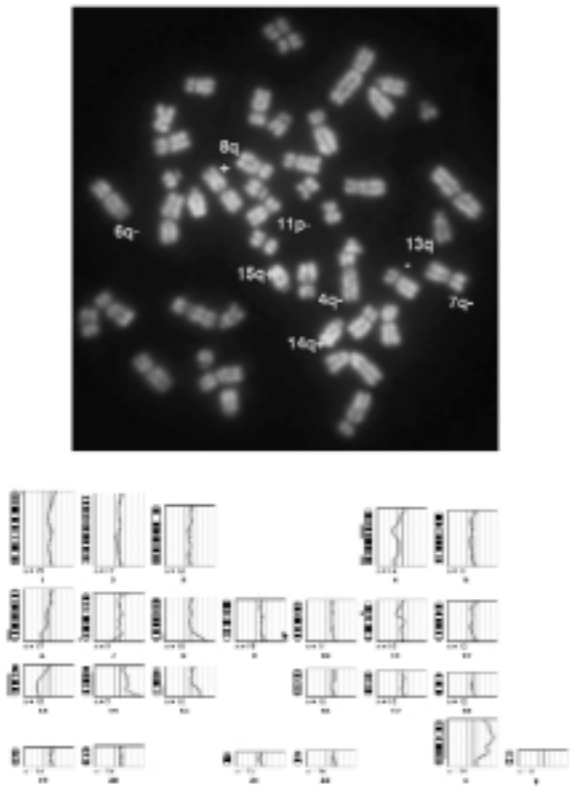

Figure 1. Metaphase (top) and CGH ideogram showing the corresponding ratio profiles (bottom) observed in a case of T-PLL.

the c-MYC oncogene, as a result of trisomy for 8q has been reported and could have a role in the pathogenesis of T-PLL,[7,8] The usual mechanism for the 8q gain is the i(8)(q10). In our case, the presence of the 8q24 amplification was only detected by CGH. The material added to the add(8)(p11), that is duplicated, might include 8q material. Because of the the poor quality of the G-banding, it was difficult to identify the material added and there was no material left for FISH analysis. So far, abnormalities of the 8q24 breakpoint have not been described in T-PLL. Espinet *el al*.[9] by using cross-species color banding (RxFISH) detected translocations involving 4q, 8q and 15q in 4 T-PLL patients with complex karyotypes.[9] Deletion of 11p11-12 and 13q13-q34 were only shown in our case after CGH analysis. The deletion del(13)(q14) has been recently documented by FISH in a group of patients with T-PLL.[10] This abnormality is very common among B-cell malignancies. Its prognostic impact is variable in the various diseases suggesting different deleted regions in 13q. At present, there are no data as to whether del(13q) has a prognostic impact in T-PLL. Monosomies of chromosomes 16 and 20 were only detected by conventional cytogenetics, probably reflecting the fact that these monosomies were clonal but not present in all analyzed cells. In conclusion, T-PLL is a rare disorder with specific chromosomal-genetic aberrations. The cytogenetic abnormalities present in our case are known to be associated either specifically with T-cell leukemias, such as rearrangements of 14q11, or less specifically such as deletions

6q, 7q, and 13q. The use of a DNA-based technique such as CGH, additionally allowed the characterization of otherwise hidden genetic abnormalities such as the high level amplification on 8q24, the gain on 15q23-26 and the deletion of 11p and 13q. A more systematic use of CGH in T-PLL may help to estimate the chromosome changes in this disease more accurately.

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Key words: CGH, T-PLL small cell, 8q24.

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