LETTER TO THE EDITOR

Blastoid mantle cell lymphoma with t(2;8)(p12;q24)

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The genetic hallmark of mantle cell lymphoma (MCL) is the translocation t(11;14)(q13;q32), which occurs in more than 95% of the cases. It juxtaposes the cyclin D1 encoding gene CCND1/BCL1/PRAD-1 on 11q13 and the immunoglobulin heavy chain (IGH) gene located on 14q32 [1]. It results in overexpression of the cyclin D1 protein that drives the transition from G1 to S phase of cell cycle. However, t(11;14) alone is insufficient for the malignant transformation [2]. Thus, secondary chromosomal alterations are needed for the development of MCL. Frequent findings in MCLs are deletions of parts of 11q involving the ATM gene [3], alterations in 13q involving the retinoblastoma (RB) gene, losses in 1p, alterations of 6q, and gains of 3q, 8q, and 15q regions [4].

We report the co-existence of t(2;8) and t(11;14) in a case of MCL. A 33-year-old man presented with lymphocytosis. Physical examination showed lymphadenopathy and hepatosplenomegaly. Peripheral blood counts were as follows: hemoglobin 7.7 g/dL and leukocytes 49 \times 10^9/L, with 52% of medium-sized lymphoid cells resembling lymphoblasts. Surface markers of bone marrow lymphoid cells revealed an immunophenotype consistent with mantle cell lymphoma: CD5+, CD10−, CD19+, CD23−, CD34−, CD38−, CD79a+, CD79b+, FMC7+, TdT−, and surface membrane Ig kappa + weak. The patient was submitted to six cycles of induction chemotherapy Hyper-CVAD (ciclosfosfamide, vincristine, adriamycin and dexametasone) and died 9 months after diagnosis. Cyto genetic analysis revealed the presence of a complex karyotype established as 47,XY,t(2;8)(p12;q24)[21], +7[21], del(9)(q13)[21],t(11;14)(q13;q32)[21],del(17)(p11.2)[21]/46,XY[9]/cp21 [Figure 1(A)]. Spectral karyotyping (SKY) confirmed the abnormalities previously seen by G-banding, and a minimum of 10 metaphases were analyzed [Figure 1(B)]. Fluorescence in situ hybridization analysis using a dual color immunoglobulin heavy chain IGH/CCND1 probe (LSI IGH/CCND1 XT Dual Color; Abbott Vysis, Des Plaines, IL, USA) showed a fusion hybridization signal on one normal chromosome 14, indicating that an insertion of the CCND1 gene into the 14q32/IgH locus had taken place (data not shown). For real-time PCR experiments, we used an ABI Prism 5700 Sequence Detection System (Applied Biosystems, Foster City, CA, USA) device under standard thermal cycling conditions. PCR reactions were prepared in replicates at a final volume of 20 µL, as described [6]. For quantitative analysis of the CCND1 (Cyclin D1) and MYCC genes, we used commercially available TaqMan probes and primers (Assays-on-Demand; Applied Biosystems, Foster City, CA, USA), by comparing experimental levels with standard curves obtained by serial dilutions of cDNA from the Granta-519 cell line, which was also used as the calibrator. The normalization factor was the geometric mean of the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene. Real-time PCR experiments showed overexpression of cyclin D1 and MYCC genes (data not shown).

Additional chromosomal abnormalities have been described in a reviewed series of 214 karyotypes of patients with MCL. Chromosomal aneuploidies...
included $-Y$, $-13$, $-18$, $+3$, and $+12$. Common structural abnormalities included $3q+$, $12q+$, $del(6q)$, $del(1p)$, $del(13q)$, $del(10q)$, $del(11q)$, $del(9p)$, and $del(17p)$ [7]. Lymph-node-based studies were associated with the presence of complex karyotypes and were more likely to show deletions and chromosome loss than those cases with peripheral blood disease [7,8].

The translocation $t(2;8)(p12;q24)$, and its variants $[t(8;14)(q24;q32)$ and $t(8;22)(q24;q11)]$, are associated with the majority of the aggressive high grade Burkitt’s lymphoma and also is present in mature B-cell or Burkitt’s type acute lymphoblastic leukemia (ALL L3). They represent less than 5% of all ALLs, including those in children and adults [9]. The juxtaposition of the MYCC gene, at $8q24$ to the immunoglobulin light chain locus ($IGK$), at $2p13$ results in overexpression of MYCC and uncontrolled cell proliferation [9].

Fifteen cases of mantle cell lymphoma with the $t(11;14)$ and abnormalities involving $8q24$ have been previously described and are listed in Table I [1,10–15]. However, only three cases presented the variant Burkitt’s $t(2;8)(p12;q24)$. Our patient is the
Table I. Cases of mantle cell lymphoma (MCL) with 8q24 abnormalities described in the literature.

<table>
<thead>
<tr>
<th>Author and reference</th>
<th>No. of cases</th>
<th>Classical cytogenetics</th>
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<tbody>
<tr>
<td>Leroux et al. [1]*</td>
<td>1</td>
<td>46,XX,t(2;8)(p11;q24),t(11;14)(q13;q32),dup(10)(p22q26),t(16;?)p(13;?)/i.dem,t(4;?)p(35;?),del(3)(p21)/i.dem,t(4;?)p(16;?)</td>
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<tr>
<td>Tirier et al. [10]*</td>
<td>1</td>
<td>45,XY,t(2;8)(p12;q24),t(11;14)(q13;q32),del(11)(q14q22),−15[20]/45,i.dem,del(6)(q15p24)</td>
</tr>
<tr>
<td>Kaneko et al. [11]</td>
<td>1</td>
<td>47,XY,−8,+18,del(1)(p31–p35),t(11;14)(q13;q32),+der(5)(s2?)(q24p?)</td>
</tr>
<tr>
<td>Bloomfield et al. [12]</td>
<td>1</td>
<td>50,XX,+7,+12,+19,del(1)(q13q32),t(1;9)(q23;p22),t(8;14)(q24;q32),t(11;14)(q13;q32)(59%),+50,XX,+7,+12,+18,t(1;19),t(8;14),t(11;14),+der(3)(t;13)(q21q21)(29%),50,XX,+7,+12,+18,t(1;19),t(8;14),t(11;14),+der(7)(t;7)(q36q24)(4%)</td>
</tr>
<tr>
<td>Au et al. [13]</td>
<td>4</td>
<td>43–44,XY−Y,add(3)(p11),t(8;9)(q24q13),der(11),t(11;14)(q13q32),der(14)(14pter→14q24::s::t9qter),−15,der(17),t(3;17)(q13p11)</td>
</tr>
<tr>
<td>Hao et al. [15]*</td>
<td>5</td>
<td>46−48,XX,add(8)(q24p20),add(9)(q34),t(11;14)(q13q32),−13,add(13)(q22),del(17)(p11.2),+0−2mar(2p28)</td>
</tr>
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*Refs. with asterisks are three cases of MCL with t(2;8).
youngest case reported and represents the first case studied by a combination of classical cytogenetic and spectral karyotype analysis.

In transgenic mouse model, it has been demonstrated that cyclin D1 overexpression is not enough to cause lymphoma. Other genetic changes, such as mutation of MYCC, RAS gene, and loss of TP53 have been implicated in the establishment of lymphoma phenotype [2]. This may suggest that t(11;14) is an initial event; other genetic alterations are required for the development or progression of MCL.

The CCND1/IGH fusion followed by disruption of MYCC and loss of TP53 may act together and permit the development of MCL. These findings could explain the patient’s rapid clinical course. Identifying these genetic alterations will play a very important role in providing information for the confirmation of clinical diagnosis, as well as the classification, treatment, and prognosis of patients with MCL.

References