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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 49×10^9/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 sIg kappa + weak. The patient was submitted to six cycles of induction chemotherapy Hyper-CVAD (ciclosfosfamide, vincristin, adriamicin and dexametasone) and died 9 months after diagnosis. Cytogenetic 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

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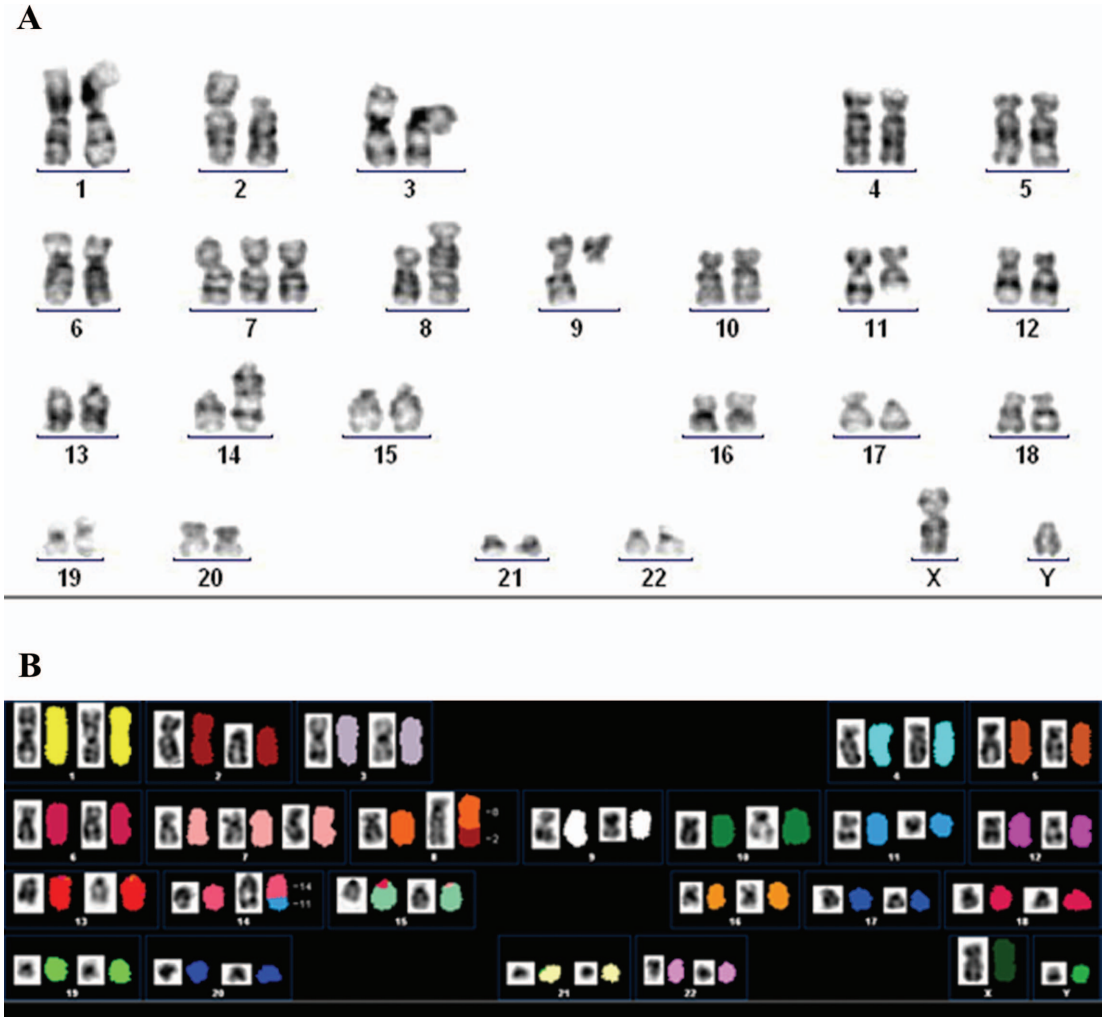

Figure 1. A: Peripheral blood samples at time of diagnosis was used for classical (G-banding) and molecular cytogenetic (SKY) analysis after 48-h of nonstimulated culture in RPMI 1640 medium with 20% fetal calf serum. The karyotypes were described according to the International System for Human Cytogenetic Nomenclature [5]. Cytogenetic analysis revealed the presence of a complex karyotype showing t(2;8)(p12;q24), +7, del(9)(q13), t(11;14)(q13;q32), and del(17)(p11.2) (G-band with trypsin – Giemsa). B: The SKY assay was performed using the SKY probe cocktail (Applied Spectral Imaging, ASI, Migdal Ha'Emek, Israel) according to the manufacturer's instructions and the analysis was carried out with the SkyView 1.6.2 software (ASI, Carlsbad, CA, USA). Image acquisition was performed using a SD200 Spectracube system (ASI) mounted on an Olympus BX60 microscope with a custom-designed optical filter (SKY-1, Chroma Technology, Brattleboro, VT, USA). SKY karyotype from MCL at time of diagnosis, showing the inverted DAPI (left) and the classified (right) profiles for each chromosome. Translocations involving chromosomes 2 and 8, 11 and 14, extra copy of chromosome 7, del(17)(p11.2) and del(9)(q13) are presented. (Please see colour online)

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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 of with peripheral blood disease [7,8].

The translocation t(2;8)(p13;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

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Table I. Cases of mantle cell lymphoma (MCL) with 8q24 abnormalities described in the literature.[a]

Author and reference	No. of cases	Classical cytogenetics
Leroux et al. [1]*	1	46,XX,**t(2;8)(p11;q24)**,t(11;14)(q13;q32),dup(10)(q22q26),t(16;?)(p13;?),t(21;?)(p11;?)/idem,t(4;?)(q35;?),del(3)(p21)/idem,t(4;?)(p16;?)
Tirier et al. [10]*	1	45,XY,**t(2;8)(p12;q24)**,−10,dic(10;15)(p10;p13),del(11),t(11;14)(q13;q32),del(11)(q14q22),−15[20]/45,idem,del(6)(q?15q?24)[7]/46,XY[6]
Kaneko et al. [11]	1	47,XY,−8,+18,del(1)(p31−p35),t(11;14)(q13;q32),+**der(8)t(8;?)(q24;?)**
Bloomfield et al. [12]	1	50,XX,+3,+7,+12,+18,dup(1)(q11q32),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(1;3)(q21;q25)(29%)/50,XX,+3,+12,+18,t(1;9),t(8;14),t(11;14),+der(7)t(7;?)(q36;?)(4%)
Au et al. [13]	4	43−44,X,−Y,add(3)(p11),**t(8;9)(q24;q13)**,der(11),t(11;14)(q13;q32),der(14)(14pter→14q32::?::9qter),−15,der(17),t(3;17)(q13;p11) 42−45,XY,add(2)(p25),del(6)(p21),del(6)(q15),der(8),**ins(8;14)(q24;q24q32)**,del(9)(p22),t(11;14)(q13;q32),del(12)(q15),−14,−15,add(16)(q24)[cp8]/46,XX[8] 64−65,XX,−X,−2,add(2)(p23),add(3)(p12)×2,−4,+6,+8,**add(8)(q24)×2**,+9,del(10)(q24),add(10)(q24),+11,t(11;14)(q13;q32),+12,−13×3,+14,−15,der(15),t(5;15)(p11;p11)×2,−16×3,+17,add(18)(q23),?idic(18)(q23),+dic(19)t(19;?)(p13;?),−20×3,−21,−22,+7mar[cp7]/46,XX[7] 45,XY,**dic(8;9)(q24;p24)**,−9,t(11;14)(q13;q32)[13]/46,XY[13]
Vaishampayan et al. [14]	2	44,X,−Y,add(6)(p25),**t(8;14)(q24;q32)**,del(9)(q12),t(11;14)(q13;q32),−12,der(19)t(1;19)(q21;p13) 42,X,−Y,add(6)(q27),**dup(8)(q24q13)**,t(11;14)(q13;q32),dup(12)(q13q15),der(14)t(14;19)(p11;q11),add(15)(p11),−15,−17,−19
Hao et al. [15]*	5	46−48,XX,**add(8)(q24)**,add(9)(q34),t(11;14)(q13;q32),−13,add(13)(q22),del(17)(p11.2),+0−2mar[cp28] 46,XY,del(7)(q22),**add(8)(q24)**,t(11;14)(q13;q32)[4] 42−44,−X,Y,add(3)(q29),−5,**add(8)(q24)**,add(9)(q34),add(10)(q26)t(11;14)(q13;q32),add(11)(p15),−13,add(13)(p13),−17,−18,add(22)(q13),del(22)(q11),+2−6mar[cp13] 45,X,−X,del(1)(p13p22),−2,der(8),**t(2;8)(q13;q24)**,del(9)(p12),t(11;14),(q13;q32),t(12;18)(q13;q23),−13,add(15)(p15),add(21)(p13),+2mar[9] 46,X,del(X)(q26),**t(8;14)(q24;q32)**,t(11;14)(q13;q32),add(13)(q32)add(15)(q24),del(17)(p11p13),add(18)(p11)[14]

[a]Refs. with asterisks are three cases of MCL with t(2;8).

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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 o *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.

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