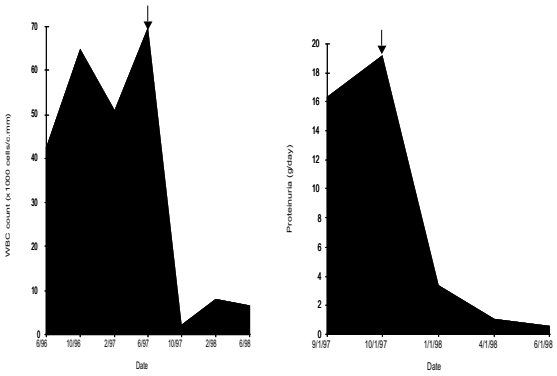

Figure 1. The response of white blood cell count (left) and proteinuria (right) after initiation of fludarabine therapy (arrows) in October 1997.

(NAD) and apoptotic cell death. In dividing lymphocytes these agents inhibit the ribonucleotide reductase that ultimately leads to inhibition of DNA synthesis.[5] As a result of its cytotoxic activity, fludarabine induces a profound lymphocytopenia. A marked decrease in CD4 lymphocytes occurs that may persist for several years, while affecting other mononuclear cell populations (CD5), which recover more rapidly.[6] Although this case and a previous case[6] showed that fludarabine may be considered as a reasonable and efficacious alternative to traditional alkylator-based therapy in patients with severe membranous glomerulopathy coexistent with CLL, general conclusions can not be definitely made, and further clinical evaluation is required to define the role of this drug in the treatment of CLL-associated NS.

Majdi M. Abdel-Raheem, Mohamad G. Jamil, Anil Potti, Gerald G. Gross

Department of Internal Medicine, University of North Dakota School of Medicine, Fargo, ND, USA

Key words

Fludarabine, CLL, nephrotic syndrome.

Correspondence

Majdi M. Abdel-Raheem M.D., Department of Internal Medicine, University of North Dakota School of Medicine,1919 N Elm Street, Fargo, ND 58102. Phone: international +701-234-5934. Fax: international +701-234-7230 – E-mail: majdiabdelraheem@meritcare.com

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8q24 translocations in blastic transformation of mantle cell lymphoma

We report four cases of blastic transformation of mantle cell lymphoma (MCL), cytogenetically characterized by 8q24 karyotypic abnormalities in addition to t(11;14), suggestive of *c-myc* deregulation. Three patients developed blastic disease in lymph nodes, peripheral blood and bone marrow, after one to seven years, and died after 1 to 3 months. One patient presented with blastic MCL and died after 15 months. We propose that *c-myc* activation may be another cell cycle deregulation event leading to aggressive transformation in MCL.

Sir,

Mantle cell lymphoma (MCL) is characterized by relentless disease progression.[1] Blastic presentations are associated with poor survival.[2] Blastic histology is also recognized on serial biopsies.[3] We report four cases of blastic transformation of MCL, characterized by 8q24 karyotypic abnormalities.

Case #1. A 58-year old man with stage IIIA MCL reached a complete remission (CR) with oral chlorambucil. Two years later, he presented with progressive lymphadenopathy, jaundice, and circulating blasts, and died despite combination chemotherapy.

Case #2. A 45-year old man with stage IA MCL reached remission with VACOP-BP chemotherapy and radiotherapy (RT). Seven years later he presented with rapid lymph node enlargement and abundant large circulating blasts. He died after one month's treatment with chlorambucil.

Case #3. A 67-year old woman presented with a jaw mass and chest X-ray opacity. Fine-needle aspirate cytology diagnosed metastatic small

Table 1. Cytogenetic findings and molecular analysis of the four cases.

Case	Sex	Age	Specimen	Cytogenetics	VJ PCR	SA bcl-1	SA cMyc
1	M	58	BM	43-44,X,-Y,add(3)(p11),t(8;9)(q24;q13), der(11)t(11;14)(q13;q32), der(14)(14pter-->14q32::?::9q13-->9qter), 15, der(17)t(3;17)(q13;p11)	clonal	rearranged	germline
2	M	45	BM	42-45,XY,add(2)(p25), del(6)(p21),del6(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]	clonal	germline	germline
3	F	67	FNA	64-65,XX,-X,-2,add(2)(p23),add(3)(p12)x2,-4,-4,+6,+8, add(8)(q24)x2, +9,del(10)(q24), +add(10)(q24), +11,t(11;14)(q13;q24),+12,-13x3,+14,-15, der(15)t(5;15)(p11;p11)x2, -16x3,+17,add(18)(q23),?idic(18)(q23), +dic(19)t(19;?)(p13;?), -20x3,-21,-22,+7mar[cp7] / 46,XX[7]	clonal	Not done	Not done
4	M	56	LN	45,XY,dic(8;9)(q24;p24) ,-9, t(11;14)(q13;q32)[13] / 46,XY [13]	clonal	Not done	Not done

M: male; F: female; BM: bone marrow aspirate; FNA: fine needle aspirate; LN: lymph node; PCR: polymerase chain reaction; SA: Southern analysis (c-myc:exon 3 probe form ATCC; bcl-1: MTC 2.1 kb Sst I probe from Dr. A. Bakhshi, Bethesda, MD, USA).

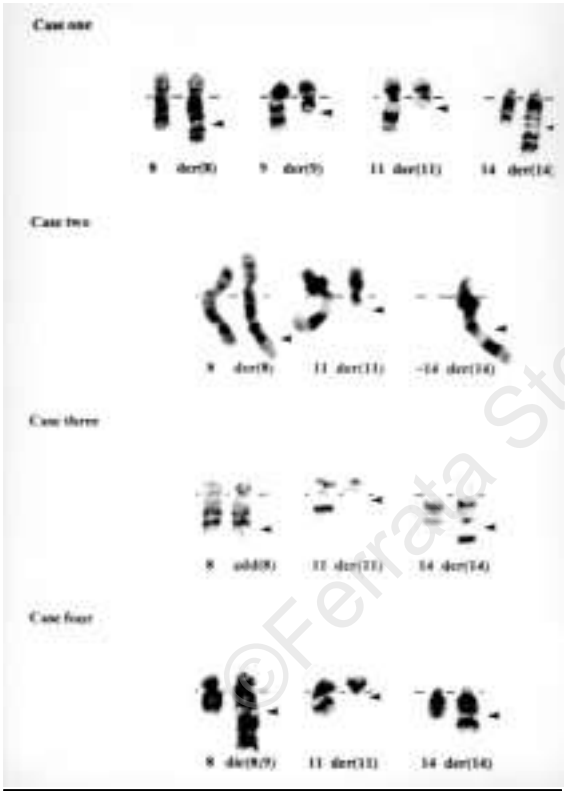

Figure 1. Partial karyotypes showing t(11;14) and der(8)(q24) in the four cases. Arrows indicate translocation breakpoints. See Table 1 for full karyotypic description.

cell carcinoma, and she was treated with cisplatinum and etoposide. Cytogenetic results raised the suspicion of MCL, which was supported by clonal VJ-PCR analysis (Table 1). She died of cerebral recurrence 15 months after presentation.

Case #4. A 56-year old man presented with stage IVB MCL involving the marrow. A CR was achieved with VACOP-BP chemotherapy and RT. Eight months later, disease relapsed with cord compression and circulating blasts, and he died after three months.

All four cases showed t(11;14)(q13;q32) with additional complex changes (Table 1 and Figure 1). The number of additional changes varied from 4 to 40, with cell-to-cell heterogeneity. Classical t(8;14) or t(8;22) were not seen. Case two, with an insertion ins(8;14)(q24;q24q32) may represent a t(8;14) variant. One case showed near-triploidy. Residual normal cells were found in all cases. Sufficient DNA was available for Southern analysis in two cases, but *c-myc* rearrangement could not be demonstrated.

Survival in MCL ranges from one month to eight years,[1] and blastic morphology heralds a dismal prognosis.[1,4] By morphology, we reported an incidence of 6% blastic MCL at presentation, and 22% blastic transformation over a median of 34 months.[1] A clonal link between the two stages of the disease has been demonstrated.[5,6] Except for tetraploidy, no specific cytogenetic change is associated with blastic MCL.[2] Disruption of cell-cycle regulatory genes are, however, often found.[7] Among 46 consecutive MCL karyotypes analyzed at our institution, all four cases with 8q24 aberration were blastic MCL. This suggested c-myc deregulation as an additional event in MCL progression. In a mouse model with cyclin D1 overexpression, *c-myc* rearrangement is needed for lymphomagenesis.[8] There have been seven reports of MCL cases with 8q24 aberrations, including two cases with t(2;8) and one with t(8;14).[9] Short survival, rapid proliferation and leukemic involvement were uniform features. The frequent involvement of non-immunoglobulin gene partners may be due to the involvement of the IgH loci in t(11;14) and VJ recombination. Variant 8q24 breakpoints are undetectable by Southern analy-

sis. Biologically, abrogation of multiple cell cycle control pathways provides growth advantage in MCL cell lines.[10] Hence, curative attempts for MCL must be deployed early, before secondary events accumulate.

Wing Y. Au, Douglas E. Horsman,* David S. Viswanatha,* Joseph M. Connors,° Richard J. Klasa,° Randy D. Gascoyne**

Departments of Pathology and Laboratory Medicine and Medical Oncology,° British Columbia Cancer Agency, Vancouver, BC, Canada*

Key words

Mantle cell lymphoma, 8q24 translocations.

Correspondence

Wing Y. Au, M.D., Division of Hematology, University Department of Medicine, Queen Mary Hospital, University of Hong Kong. Phone: international +852-28554597-Fax: international + 852-29741165-Email: auwing@hotmail.com

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Comparative analysis of immunophenotypic methods for the assessment of minimal residual disease in hairy cell leukemia

Hairy cell leukemia patients in complete remission may have minimal residual disease (MRD). We performed flow cytometry (FCM) and immunohistochemistry (IHC) to detect MRD in 15 patients. FCM and IHC detected MRD+ in 64% and 46 % of the patients, respectively. MRD+ did not predict relapse.

Sir,

In hairy cell leukemia (HCL), minimal residual disease (MRD) is detected by immunohistochemistry (IHC) in 13% to 50% of cases in complete remission (CR).[1-4] It is worthy of note that flow cytometry (FCM) is barely used for this purpose.[5,6] The clinical meaning of MRD remains unclear; some researchers have associated it with relapse,[1] while others have not.[3] Until this controversy is clarified, we consider it important to establish the best technique to assess MRD. For this reason we comparatively analyzed MRD by FCM and IHC in 15 patients in CR after 2-chlorodeoxyadenosine (n=12) and α-interferon (n=3) treatments, and the correlation of MRD with relapse. CR was documented in all cases according to Spiers' criteria.[7] Median follow-up: 26 months (6 to 96).

IHC assessment: paraffin-embedded bone marrow (BM) biopsies analyzed by routine techniques (hematoxylin-eosin, Giemsa and reticulin staining) showed no HCL. Residual tricoleukocytes were identified using anti-CD20 (L-26) and

Table 1. MDR status by FCM and IHC of 11 patients.

Pt.	Therapy	CR	Follow-up (mos)	Flow cytometry PB	Flow cytometry BM	IHC (BM)	Cell. (%)	FG
1	2CDA	YES	14	–	ND	–	45	I
2	2CDA	YES	15	pos. 2/5%	ND	pos. 5% mix	50	I
3	IFN	YES	41	pos. 2%	pos. 0.34-2%	pos.5% mix	50	I
4	2CDA	YES	96	–	ND	–	40	I
5	2CDA	YES	51	pos. 2%	pos. 2.9%	pos. <5% mix	40	I
6	2CDA	YES	32	pos. 1%	ND	–	40	I
7	2CDA	YES	35	pos. 0.4%	pos. 1%	–	45	I
8	2CDA	YES	26	pos. 2%	pos. 2%	pos. 6/10% mix	60	I
9	2CDA	YES	6	–	–	–	60	II
10	2CDA	YES	6	–	pos. 0.50%	–	40	II
11	2CDA	YES	6	–	pos. 0.12%	–	35	0

FG: fibrosis grade; ND: not done. CR: complete remission. PB: peripheral blood. BM: bone marrow. IHC: immunohistochemistry. Fibrosis grade 0: absent; I: thin reticulin fibers; II: gross reticulin fibers. 2CDA: 2-chlorodeoxyadenosine. IFN: interferon.