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Short Communication

Homing Receptor $\alpha4\beta7$ Integrin Expression Predicts Digestive Tract Involvement in Mantle Cell Lymphoma

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Appropriate staging and evaluation of residual disease is critical to improving the treatment of patients with lymphoma. The specific expression of homing receptors may determine the preferential dissemination pattern of tumoral cells. We investigated the expression of the mucosal homing receptor $\alpha4\beta7$ on tumoral cells from peripheral lymph node in patients with newly diagnosed mantle cell lymphoma (MCL) to check whether it is associated with gastrointestinal involvement. Expression of the $\alpha4\beta1$ integrin and the peripheral lymph node addressin CD62L were also examined. Thirteen MCL patients presenting with peripheral lymphadenopathy were studied. Expression of the mucosal homing receptor integrin $\alpha4\beta7$ by peripheral lymph node lymphoma cells was found to be frequent (5/13) and associated with gastrointestinal involvement (5/7). In contrast, lymphoma cells from patients without gastrointestinal involvement did not express $\alpha4\beta7$ (6/6) ($P = 0.03$). These data suggest that $\alpha4\beta7$ integrin is expressed by a subset of MCLs and that its expression may predict digestive tract involvement in MCL, furnishing a basis for recognizing two distinct clinical and phenotypic forms, ie, "digestive homing (or digestive primitive)" *versus* "peripheral" MCL. Further studies on more patients will be needed to understand the impact of biological differences on the prognosis of these two clinical forms. ***(Am J Pathol 1998, 153:1701–1705)***

Recent studies focused mainly on T-lymphocytes have led to the concept that finely tuned mechanisms involving adhesion molecules regulate leukocyte migration and organ targeting in the human body.[1–3] Discrete subpopulations of leukocytes appear to be able to migrate specifically to certain tissues due to the restricted expression of receptor-ligand pairs.[2,4]

The $\alpha4\beta7$/MAdCAM-1 pair is one of the best characterized receptor-ligand pairs shown to play a role in the control of leukocyte circulation. Integrin $\alpha4\beta7$ (LPAM-1) mediates murine and human B and T memory lymphocyte migration into the intestinal mucosa by binding to MAdCAM-1, a vascular recognition molecule selectively expressed on digestive tract lamina propria, Peyer's patch endothelium, and the spleen. [5–9] Indeed, in mice with targeted disruption of the $\beta7$ ($\beta7-/-$) or the $\alpha4$ integrin, the formation of the gut-associated lymphoid tissue (GALT) is severely impaired, whereas $\beta7-/-$ mice exhibit otherwise normal immune system development and function.[10,11] Human MAdCAM-1 was recently cloned and MAdCAM-1 mRNA and protein were found to be expressed mainly in the small bowel and to a lesser extent in the colon and spleen.[8,9] $\alpha4$ integrin may also be expressed on leukocytes as a heterodimeric integrin with the $\beta1$ integrin chain (CD18). $\alpha4\beta1$ is a ligand for VCAM-1 (CD106) and is involved in adhesion to cytokine-activated endothelial cells, germinal centers within lymph nodes,[12,13] and bone marrow stromal cells.[14]

We previously proposed that expression of $\alpha4\beta7$ on peripheral tumoral cells was associated with digestive tract involvement in Langerhans cell histiocytosis, a clonal proliferative disease of dendritic cell origin.[15] Mantle-cell lymphoma (MCL) is a recently reappraised entity among B-cell non-Hodgkin's lymphoma, on the basis of

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Table 1. Clinical and Biological Data of 13 Patients with MCL

Clinical and Biological Data									Immunophenotype									Molecular Biology	
No.	Sex/ Age	Stage	DIG macro	DIG micro	SM	CS	BM	LDH	CD20	CD3	CD5	CD10	CD23	α4β7	CD62L	α4	β1	t(11;14)*	CCND1 RNA†
1	F/69	IV	NS	GI	+	+	+	N	+	−	+	−	−	+	−	nd	nd	+	nd
2	M/46	IV	P	GI	+	−	+	N	+	−	+	−	−	+	−	+	+	nd	nd
3	F/73	IV	NS	G	+	+	+	2N	+	−	+	−	−	−	−	+	+	+	+
4	M/64	IV	P	GI	+	−	+	2N	+	−	+	−	nd	+	−	+	+	−	+
5	M/76	IV	P	GI	+	+	+	3N	+	−	+	−	nd	+	−	+	+	−	+
6	F/56	IV	P	GI	+	+	+	2N	+	−	+	−	−	+	−	+	+	+	nd
7	M/52	IV	NS	GI	+	+	+	1,5N	+	−	+	−	−	−	−	+	+	−	+
8	M/51	IV	NS	0	−	−	+	N	+	−	+	−	−	−	−	+	+	+	+
9	M/66	IV	NS	0	+	+	+	2N	+	−	+	−	−	−	−	+	+	−	+
10	M/60	IV	NS	0	+	+	+	2N	+	−	+	−	−	−	−	+	+	+	nd
11	F/64	II	NS	0	−	−	−	N	+	−	+	−	−	−	−	+	+	+	−
12	M/54	III	NS	0	−	−	−	N	+	−	+	−	−	−	nd	nd	nd	nd	nd
13	F/54	IV	NS	0	−	+	+	N	+	−	+	−	−	−	+	+	+	−	nd

Patients were staged according to the Ann Arbor system. NS, normal or nonspecific lesion; P, features of lymphomatous polyposis (abnormal thick folds in stomach and/or polyps in small bowel); G, gastric; GI, gastrointestinal; 0, no digestive tract involvement; SM, splenomegaly; CS, circulating lymphoma cells; BM, bone marrow involvement; LDH, lactate dehydrogenase; nd, not done.

*Detection of the t(11;14) by karyotype and/or polymerase chain reaction.

†Slot-blot detection of cyclin D1 mRNA.

its clinical course and morphological, immunophenotypic, cytogenetic, and molecular features.[16] Although no prospective study is available, digestive tract involvement appears to be more frequent in MCL at diagnosis compared to other peripheral lymphomas; it was diagnosed at presentation in 11.5% to 15% of MCL patients.[17] In the present study, we investigated whether the "homing model" may be of clinical relevance in MCL digestive tract involvement and whether the α4β7 adhesion molecule may, if it is expressed on peripheral tumoral cells, help to predict the existence of gastrointestinal (GI) tract involvement.

Materials and Methods

MCL Patients

Thirteen consecutive patients with nodal peripheral MCL for whom material from frozen lymph node biopsy was available and who underwent digestive tract endoscopic examination and biopsies were studied.

Histology and Immunohistochemistry

Deparaffinized lymph node sections were stained with hematoxylin-eosin-safran, Giemsa stain, and silver stain. Immunohistochemistry was performed on deparaffinized formalin-fixed sections with an avidin-biotin-peroxidase protocol[18] revealed by 3–3′ diaminobenzidine as chromogen (Vectasin ABC Kit, Vector, CA), using antibodies against CD20 (clone L26, IgG2a, Dako, Glostrup, Denmark), and CD3 (clone PS1, IgG2a, Immunotech, Marseille, France). Immunohistochemistry was then performed on frozen lymph node biopsies using 5-micrometer-thick cryostat sections with the same avidin-biotin-peroxidase protocol revealed by 3–3′ diaminobenzidine as chromogen. Antibodies used on frozen sections were CD22 (clone To15, IgG2b, Dako), CD3 (clone PSI, IgG2a, Immunotech), CD5 (clone L17F12, IgG2a, Becton Dickinson, Mountain View, CA), CD10 (clone ALB1, IgG1, Immunotech), CD23 (clone MHM6, IgG1, Dako), CD62L (L-selectin, clone DREG-56, IgG1, R&D Systems, Minneapolis, MN), anti-α4β7 (clone Act-1, IgG1, kindly provided by Dr. A.I. Lazarovits, Robarts Research Institute, University of Western Ontario, London, Ontario, Canada), CD49d (VLA4, α4 integrin chain, clone 44H6, IgG1, T-Cell Diagnostics, Woburn, MA), and CD29 (β1 integrin chain, clone K20, IgG2a, Immunotech). Cases were considered positive for α4β7 staining when most tumoral cells stained positive (>70%). The topography of α4β7 positivity was compared to B-cell antigen staining to distinguish between T cells and tumoral B-cell nodules. When only minor populations showed positive α4β7 staining, this positivity was shown to correspond to T cells' areas.

Molecular Analysis

Cytogenetic and molecular studies of the t (11;14) translocation and of the cyclin D1 mRNA could be performed as previously described[19,20] in 11 of 13 cases.

Statistical Analysis

Fisher's exact test, two-tailed, for small samples was used.[21]

Results

Digestive Tract Involvement in MCL

MCL was diagnosed on lymph node biopsies according to histological and immunophenotypical criteria[16,19] (Table 1). To further confirm the diagnosis, cytogenetic and molecular studies were informative in 10 of 13 cases

(Table 1). Patients were staged according to the Ann Arbor classification on the basis of physical examination, routine laboratory tests, chest X-ray and/or CT scan, abdominal ultrasound and/or CT scan, and bone marrow trephine biopsy.

Because of the frequency of GI involvement in MCL, upper and lower digestive tract endoscopic examination was done in the absence of prominent digestive symptoms in all 13 cases, 11 at diagnosis and 2 at relapse. Seven patients displayed histological features of GI involvement by lymphoma cells (six at diagnosis, one at relapse); six patients did not (five at diagnosis, one at relapse).

Characteristics of Digestive Tract Involvement

Digestive tract involvement was not associated with specific digestive clinical symptoms. In the seven patients with histologically proven digestive tract involvement, one patient had diarrhea (patient 2), three had a history of abdominal pain (patients 1, 4, and 5), and three patients had no symptoms. Endoscopy revealed features of lymphomatous polyposis consisting of abnormal thick folds in the stomach and/or polyps in the small bowel in four cases (patients 2, 4, 5, and 6), and either a normal aspect or nonspecific lesions (ie, gastritis) in three cases (patients 1, 3, and 7). Histological examination revealed multifocal involvement in six out of the seven positive cases (Table 1).

$\alpha4\beta7$ Expression on Peripheral Lymph Node Lymphoma Cells Is Associated with GI Tract Involvement in Patients with Mantle Cell Lymphoma

$\alpha4\beta7$ heterodimeric integrin expression on peripheral lymph node lymphoma cells at diagnosis was absent in all patients (6/6) without GI tract involvement. In contrast, expression of $\alpha4\beta7$ on peripheral lymphoma cells was detected in five of the seven patients with histologically proven digestive involvement ($P = 0.03$) (Figure 1, Tables 1 and 2). Patients 3 and 7, who displayed microscopic digestive tract involvement without $\alpha4\beta7$ positivity of tumoral cells from peripheral lymph node, did not present macroscopic GI involvement at endoscopy. Lymphoma cells infiltrating the GI tract expressed $\alpha4\beta7$ in 3/3 tested patients with $\alpha4\beta7$ positivity of tumoral cells from peripheral lymph node, whereas in patient 7, tumoral cells from the GI tract were not recognized by the anti-$\alpha4\beta7$ antibody. Thus, in this patient tumoral cells from both the GI tract and the peripheral lymph node did not express $\alpha4\beta7$.

In contrast, peripheral tumoral cells from all tested patients (11/11) co-expressed $\alpha4$ and $\beta1$ integrin chains. Lymphoma cells in almost all MCL patients (11/12) did not express the lymph node homing receptor CD62L.

Interestingly, splenomegaly was present in all cases with digestive involvement, but in only two of six cases without digestive involvement ($P = 0.04$) (Table 2). However, when comparing $\alpha4\beta7$-positive patients to $\alpha4\beta7$-negative patients, the correlation with splenomegaly was not statistically significant (5/5 *vs.* 4/8).

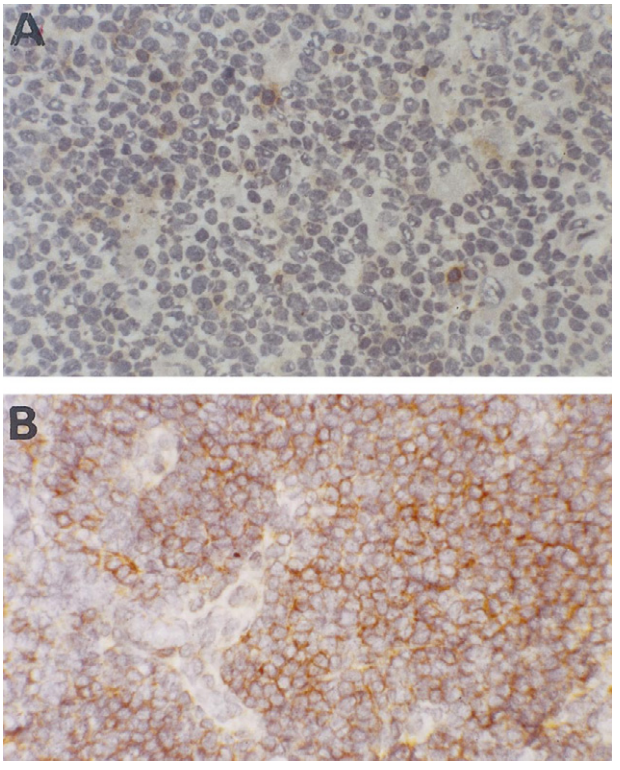

Figure 1. A: Peripheral lymph node in MCL patient without digestive tract involvement. Lymphoma cells are not stained with the anti-$\alpha4\beta7$ ACT-1 antibody, although scattered infiltrating lymphocytes express $\alpha4\beta7$ (brown peroxidase staining). B: In contrast, in a case with digestive tract involvement, peripheral lymph node lymphoma cells are positive for $\alpha4\beta7$. Endothelial cells are negative.

Discussion

The present study shows evidence that a large proportion of peripheral nodal B-cell MCLs express the mucosal homing receptor $\alpha4\beta7$ and are associated with multifocal lymphomatous involvement of the GI tract. In contrast, MCL without digestive tract involvement did not express $\alpha4\beta7$. $\alpha4\beta7$ integrin expression may thus represent a specific marker of GI tract involvement in MCL. Moreover, splenomegaly appears to be more frequent in $\alpha4\beta7$-

Table 2. Characteristics of Patients with (GI+) or Without (GI−) Digestive Tract Involvement

	GI+	GI−	*P**
sex (M/F)	3/4	2/4	ns
age at diagnosis (mean, years)	65	58,2	ns
splenomegaly	7/7	2/6	0.04
bone marrow involvement	7/7	4/6	ns
stage (II/III/IV)	0/0/7	1/1/4	ns
LDH > N	5/7	2/6	ns
circulating lymphoma cells	5/7	3/6	ns
nodal lymphoma cells $\alpha4\beta7+$	5/7	0/6	0.03

*Fisher exact's test (two-tailed).
ns, not significant.

positive MCL. These data on lymphoma cells are consistent with the physiological pattern of expression of $\alpha4\beta7$ ligand MAdCAM-1 at the mRNA and protein levels in the human bowel and spleen.[8,9]

However, not all patients with digestive tract involvement were found to express $\alpha4\beta7$ in our study. Two patients displayed microscopic digestive tract involvement without $\alpha4\beta7$ positivity of tumoral cells in the peripheral lymph node. Both patients had circulating lymphoma cells, as did three of the five patients with $\alpha4\beta7$-positive lymph node. Both patients also displayed unremarkable macroscopic features at endoscopy, in contrast to four of the five $\alpha4\beta7$-positive patients. Interestingly, in one of these two patients (patient 7) $\alpha4\beta7$ immunostaining could be performed on digestive tract tumoral cells and was negative. Thus, in these two cases digestive tract involvement may be due to a nonspecific leukemic spreading, as suggested by the lack of macroscopic lesions and the negativity of the $\alpha4\beta7$ staining of digestive tract tumoral cells, or to an unknown adhesion molecule. Alternatively, we cannot exclude the possibility that the $\alpha4\beta7$ antigen might be present but not recognized by the ACT-1 antibody in these two patients.

While the present study was in progress, others reported that T-cell leukemia/lymphoma dissemination to the digestive tract may also be related to $\alpha4\beta7$ expression detected at the peripheral level.[22] Together with our previous work on Langerhans cell histiocytosis,[15] these data strongly suggest that GI tract involvement is associated with $\alpha4\beta7$ expression in T-cell, B-cell, and dendritic cell neoplasms.

Although data on the molecular basis of normal B-cell homing are scarce, we may hypothesize that expression of the mucosal receptor $\alpha4\beta7$ on a subset of MCL might be instrumental in their dissemination to the digestive tract. MCL cells have been proposed to originate from follicle mantle cells,[16] which represent naive B cells. Human naive T and B cells are usually $\alpha4\beta7$-negative.[23] $\alpha4\beta7$-positive MCL may thus represent the neoplastic counterpart of follicle mantle cells originating from digestive tract-associated lymphoid tissue, having thus acquired $\alpha4\beta7$,[24] whereas $\alpha4\beta7$-negative MCL may originate from the peripheral lymph node's follicle mantle cells.

In agreement with this hypothesis, a primary GI lymphoma known as multiple lymphomatous polyposis (MLP), which represents about 8% of the primary GI lymphomas,[25] was recently shown to share morphological, immunophenotypic, cytogenetic, and molecular characteristics with MCL.[26,27] GI tumoral cells from MLP were shown to express $\alpha4\beta7$.[28,29] However, these studies did not investigate the correlation between $\alpha4\beta7$ expression by peripheral tumoral cells and digestive tract involvement in presenting peripheral MCL. The two clinical entities, MLP and MCL, clearly overlap. Recent studies showed that 29% to 42% of lymphomas diagnosed as MLP are associated at diagnosis with enlarged peripheral lymph nodes.[27,30] Therefore, MCL appears to be a heterogeneous disease with two distinct clinical and phenotypic forms, ie, $\alpha4\beta7$-positive "digestive homing," which may originate from the mucosal associated lymphoid tissue and be identical to MLP, and $\alpha4\beta7$-negative peripheral MCL, usually without preferential tropism for the digestive tract.

The homing of lymphocytes to peripheral lymph nodes is thought to depend on L-selectin (CD62L, peripheral lymph node homing receptor)[31] which binds to peripheral vascular addressin consisting of sialylated glycoproteins.[32] Surprisingly, although lymph nodes were involved, CD62L was not expressed by either $\alpha4\beta7$-positive or $\alpha4\beta7$-negative MCL nodal tumoral cells in this study, in contrast to small lymphocytic lymphoma (unpublished data), suggesting that L-selectin is not responsible for lymph node involvement in MCL. However, all tested MCL expressed both $\alpha4$ and $\beta1$ integrins. The $\alpha4\beta1$ integrin is involved in adhesion to cytokine-activated endothelial cells, to germinal centers within lymph nodes,[12,13] and marrow stromal cells[14] and may play a role in lymph node and bone marrow involvement in MCL.

GI tract involvement has not been identified so far as an adverse prognostic factor in MCL.[33] However, GI tract involvement was not systematically explored in patients with MCL until the present work, so a definitive conclusion cannot be drawn, and no prospective study is available. More advanced disease in MCL patients with digestive tract involvement might reflect the late discovery (ie, when peripheral lymph nodes are involved) of the primary intestinal disease known as MLP. Alternatively, it might result from more aggressive behavior of $\alpha4\beta7$-positive lymphoma cells, because it was recently suggested that $\alpha4\beta7$-positive lymphoblastic lymphomas share an aggressive clinical course.[34]

The present study shows that $\alpha4\beta7$ expression is strongly associated with and may predict GI tract involvement in MCL. This finding may support the recognition of two distinct clinical and phenotypic forms of MCL, ie, "digestive homing" *vs.* "peripheral," and help to identify patients for whom GI tract endoscopic examination is suitable. Further studies addressing the prognostic significance of $\alpha4\beta7$ expression should be considered. Moreover, therapeutic strategies currently under development should include exploration of the digestive tract to ensure the quality of response to therapy.

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