

Adhesion molecule profiles of B-cell non-Hodgkin's lymphomas in the leukemic phase

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Abstract

We evaluated the expression of 10 adhesion molecules on peripheral blood tumor cells of 17 patients with chronic lymphocytic leukemia, 17 with mantle-cell lymphoma, and 13 with nodal or splenic marginal B-cell lymphoma, all in the leukemic phase and before the beginning of any therapy. The diagnosis of B-cell non-Hodgkin's lymphomas was based on cytological, histological, immunophenotypic, and molecular biology methods. The mean fluorescence intensity of the adhesion molecules in tumor cells was measured by flow cytometry of CD19-positive cells and differed amongst the types of lymphomas. Comparison of chronic lymphocytic leukemia and mantle-cell lymphoma showed that the former presented a higher expression of CD11c and CD49c, and a lower expression of CD11b and CD49d adhesion molecules. Comparison of chronic lymphocytic leukemia and marginal B-cell lymphoma showed that the former presented a higher expression of CD49c and a lower expression of CD11a, CD11b, CD18, CD49d, CD29, and CD54. Finally, comparison of mantle-cell lymphoma and marginal B-cell lymphoma showed that marginal B-cell lymphoma had a higher expression of CD11a, CD11c, CD18, CD29, and CD54. Thus, the CD49c/CD49d pair consistently demonstrated a distinct pattern of expression in chronic lymphocytic leukemia compared with mantle-cell lymphoma and marginal B-cell lymphoma, which could be helpful for the differential diagnosis. Moreover, the distinct profiles of adhesion molecules in these diseases may be responsible for their different capacities to invade the blood stream.

Key words

- Non-Hodgkin's lymphoma
- Adhesion molecules
- Flow cytometry
- CD49c/CD49d

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Introduction

B-cell non-Hodgkin's lymphomas (B-NHL) are a heterogeneous group of neoplastic diseases whose tumor cells are the malignant counterparts of normal B-lymphocytes (1). Although in most cases B-NHL arise from the lymph node (2), they can also display a leukemic phase characterized by the

presence of lymphoma cells in peripheral blood. The frequency of patients in the leukemic phase is different among the subtypes of B-NHL: in chronic lymphocytic leukemia, by definition, the involvement of peripheral blood is present in all patients (3); in mantle-cell lymphoma, the leukemic phase is present in 26-44% of cases (4,5), but has also been reported to be present in 77% of

cases in other series (6), and in nodal and splenic marginal B-cell lymphoma, it has been reported to be present in 11 and 57% of cases, respectively (7). These differences in the clinical behavior of B-NHL are most likely related to differential expression of various adhesion molecules on the membrane of tumor cells (4).

Adhesion molecules are a group of ligands and receptors involved in several biological processes, particularly cell migration (8). Given that some B-NHL subtypes are considered to be the malignant counterparts of distinctive steps in normal B-cell development, it is reasonable to infer that the malignant lymphoid cells use the same mechanisms of lymphocyte migration as normal B-cells to disseminate from their primary sites. In fact, a number of *in vitro* (9) and preclinical experiments (10,11), as well as clinical observations (12-14) give support to this hypothesis.

Here we studied the expression of 10 adhesion molecules in tumor cells from the peripheral blood of patients with leukemic B-NHL (chronic lymphocytic leukemia, mantle-cell lymphoma, nodal or splenic marginal B-cell lymphoma) to determine how the down-regulation of specific adhesion markers inherently associated with malignant transformation contributes to the biogenesis of the leukemic phase observed in some B-NHL subtypes.

Patients, Material and Methods

Patients

We studied the peripheral blood of 47 patients with a diagnosis of B-NHL in the leukemic phase: 17 with chronic lymphocytic leukemia, 17 with mantle-cell lymphoma, and 13 with nodal or splenic marginal B-cell lymphoma. Some clinical and laboratory features of the patients are shown in Table 1. We defined the leukemic phase of B-NHL by the presence of a minimum of

3000 abnormal lymphoid cells/ μL associated with immunoglobulin light chain restriction. The flow cytometry studies were performed before the beginning of treatment. The research protocol was approved by the Ethics Committee of the University Hospital, School of Medicine of Ribeirão Preto, and written informed consent was obtained from all patients.

The diagnosis of B-NHL was based on cytological, histological, immunophenotypic, and molecular biology methods. All cases of chronic lymphocytic leukemia had a score of 4 or 5 in the Matutes scoring system (15,16), while mantle-cell lymphoma and marginal B-cell lymphoma had a score of 0 to 3. In addition, except for one patient, who showed *CYCLIN D1* positivity only by immunohistochemistry, all cases of mantle-cell lymphoma showed evidence of *CYCLIN D1* overexpression as measured by real-time polymerase chain reaction (data not shown).

Flow cytometry

All samples were analyzed with a FACScan flow cytometer (Becton Dickinson, San Jose, CA, USA) equipped with an argon ion laser with a wavelength of 488 nm, by collecting 10,000 events per tube. The Cell Quest software (Becton Dickinson) was used for data acquisition and analysis. Only CD19-positive cells were gated for analysis (Figure 1A), and the expression of adhesion molecules was measured by the mean fluorescent intensity (MFI) obtained from histogram graphs on a linear scale (Figure 1B). Since the setting of an arbitrary cut-off value led to no meaningful conclusions, we preferred to use the MFI as the variable to estimate the intensity of expression of the adhesion molecules. The final MFI value was obtained by subtracting the "MFI of non-specific isotypes" from the "MFI of the relevant antigen".

Mononuclear cells were isolated from peripheral blood samples by Fycoll Hypaque

density gradient centrifugation (1.077 g/mL; Becton Dickinson). The flow cytometry panel consisted of monoclonal antibodies against the following adhesion molecules (with the respective clones in parentheses): CD11a, α_L integrin (HI111); CD11b, α_M integrin (ICRF44); CD11c, α_X integrin (B-ly6); CD18, β_2 integrin (6.7); CD29, β_1 integrin (MAR4); CD44, H-CAM (G44-26); CD49c, α_3 integrin, VLA-3 (C3II.1); CD49d, α_4 integrin, VLA-4 (9F10); CD54, ICAM-1 (HA58); CD62L, L-selectin (Dreg-56). All monoclonal antibodies were conjugated with fluorescein isothiocyanate, phycoerythrin, or perydin chlorophyll protein and all were purchased from Becton Dickinson. To exclude T lymphocytes and monocytes from analysis, CD19 was added to all tubes: tube 1, CD18 x CD11a x CD19; tube 2, CD11b x CD19; tube 3, CD11c x CD19; tube 4, CD44 x CD29 x CD19; tube 5, CD62 x CD54 x CD19; tube 6, CD49c x CD19; tube 7, CD49d x CD19.

Statistical analysis

Comparison of the expression of adhesion molecules between the three groups was performed by the Kruskal-Wallis test using GraphPad Prism and Statistical Analysis System (SAS) softwares, with the level of significance set at $P < 0.05$. When a P value of 0.05 or less was found in the Kruskal-Wallis test, the Dunn post-test was applied to analyze pairs of groups.

Results

The expression of the adhesion molecules of malignant lymphoid cells was measured by flow cytometry in CD19-positive cells. The MFI of the adhesion molecules CD11a, CD11b, CD11c, CD18, CD49c, CD49d, CD29, and CD54 was different in the three groups, as shown in Table 2. The Dunn post-test was applied when the P value was 0.05 or less. The results of pair comparisons are

Table 1. Clinical and laboratory features of the patients according to diagnosis.

	CLL	MCL	MZL
Sex (M/F)	11/6	14/3	10/3
Age (years)	62 (45-78)	67 (34-81)	66 (28-95)
Lymphadenomegaly	9/17 (53%)	11/17 (65%)	4/13 (31%)
Splenomegaly	8/17 (47%)	14/17 (82%)	13/13 (100%)
Lymphocytes ($\times 10^9/L$)	42.7 (6.0-122.4)	62.4 (6.7-256.0)	18.7 (3.6-67.6)

Data are reported as median (range) or number (percent). CLL = chronic lymphocytic leukemia; MCL = mantle-cell lymphoma; MZL = marginal B-cell lymphoma.

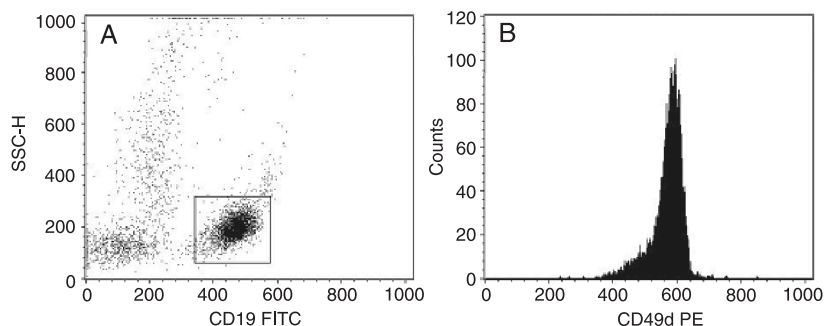


Figure 1. Flow cytometry graphs. A, A gate strategy graph: only both CD19-positive and low side scatter-SSC (internal cellular granularity) cells were selected for analysis (square). B, A histogram graph: a single-parameter histogram in linear scale shows the expression of the adhesion molecule CD49d.

Table 2. Adhesion molecule on lymphoma cells according to diagnosis.

	CLL (N = 17)	MCL (N = 17)	MZL (N = 13)
CD11a	167.9 (20.7-376.9)	257.9 (90.2-363.5)	401.6 (203-519.4)
CD11b	0 (0-53.2)	21.7 (0-274.1)	42.7 (0-409.3)
CD11c	46.3 (0-222.7)	0 (0-43.5)	143.6 (0-425.2)
CD18	105.9 (15.5-264.4)	150.1 (52.2-244.7)	275.2 (194-415.9)
CD49c	75.5 (0-274.8)	0 (0-87.2)	0 (0-151.3)
CD49d	97.9 (0-369.8)	248.0 (135.9-430.4)	362.1 (196.3-443.7)
CD29	117.6 (11.7-335.6)	116.6 (2.8-310)	236.0 (75.3-353.3)
CD44	311.4 (175.3-422.8)	316.4 (228.4-431.7)	285.0 (84.1-383.7)
CD54	223.4 (117.7-308)	238.1 (134.5-413.2)	317.2 (191.3-470.1)
CD62	4.2 (0-98.4)	10.2 (0-108.6)	12.1 (0-302.7)

Data are reported as median and range (in parentheses) of the mean fluorescent intensity (MFI). The MFI represents the mean fluorescence of all events (lymphoma cells) in the histogram graphs. CLL = chronic lymphocytic leukemia; MCL = mantle-cell lymphoma; MZL = marginal B-cell lymphoma. The Kruskal-Wallis test gave $P < 0.05$ for all markers except CD44 and CD62, indicating that there was at least one significant difference between most of the markers for the three cell types.

shown in Table 3.

Comparison of chronic lymphocytic leukemia and mantle-cell lymphoma showed that chronic lymphocytic leukemia presented a higher expression of CD11c and CD49c, and a lower expression of CD11b and CD49d. Comparison of chronic lymphocytic leukemia and marginal B-cell lymphoma showed that the former presented a higher expression of CD49c and a lower expression of CD11a, CD11b, CD18, CD49d, CD29, and CD54. Finally, comparison of mantle-cell lymphoma and marginal B-cell lymphoma showed that the latter had a higher expression of CD11a, CD11c, CD18, CD29, and CD54.

Discussion

We analyzed the expression of 10 adhesion molecules in the peripheral blood of 47 patients with a diagnosis of B-NHL. We expected that the higher frequency of blood invasion by tumor cells in chronic lymphocytic leukemia, when compared with the other B-NHL, could be explained by specific profiles of adhesion molecule expression.

Our finding of the lower expression of

CD11a and CD49d in chronic lymphocytic leukemia suggests that these adhesion molecules are probably responsible for the different compartment the disease infiltrates compared to its related entity, the small lymphocytic lymphoma (17,18). Actually, since the structure of normal lymphoid follicles in lymph nodes depends on the appropriate association between B lymphocytes and dendritic follicular cells through the interaction of CD11a and ICAM-1 (an intercellular adhesion molecule), and of CD49d and VCAM-1 (a vascular cell adhesion molecule), respectively (19), the lower expression of CD11a and CD49d on tumor cells of chronic lymphocytic leukemia could facilitate their detachment from the lymph node, while the expression of these adhesion molecules is preserved in small lymphocytic lymphoma (17,18). In fact, the down-regulation of CD11a and CD49d in chronic lymphocytic leukemia could also explain the peripheral blood invasion by these malignant cells, as compared with the occasional infiltration observed in mantle-cell lymphoma and marginal B-cell lymphoma.

Our findings of a greater expression of CD49c and a lower expression of CD49d in chronic lymphocytic leukemia as compared with the other B-NHL have been previously observed (20,21). The combination of strong expression of CD49c and weak expression of CD49d is the hallmark of chronic lymphocytic leukemia and can be used in the differentiation between this disease and the other B-NHL in the leukemic phase. In fact, it has been shown that imbalance in CD49c/CD49d expression in chronic lymphocytic leukemia also contributes to the peripheral blood invasion (22). Moreover, a recent study has demonstrated prognostic relevance for the combination of high CD49c and low CD49d expression in chronic lymphocytic leukemia (23).

CD29 is the common β 1 chain of α subunits of integrins α 3/CD49c and α 4/CD49d (8). Since the CD29 and α subunits are

Table 3. Pairwise comparison of B-cell non-Hodgkin's lymphomas for surface antigens by the Dunn post-test.

	CLL x MCL	CLL x MZL	MCL x MZL
CD11a	NS	S	S
CD11b	S	S	NS
CD11c	S	NS	S
CD18	NS	S	S
CD49c	S	S	NS
CD49d	S	S	NS
CD29	NS	S	S
CD44	NA	NA	NA
CD54	NS	S	S
CD62	NA	NA	NA

CLL = chronic lymphocytic leukemia; MCL = mantle-cell lymphoma; MZL = marginal B-cell lymphoma; S = differences are significant ($P \leq 0.05$); NS = differences are nonsignificant; NA = not applicable.

expressed together by a non-covalent bond, the higher expression of this adhesion molecule observed in marginal B-cell lymphoma is probably the result of the concomitant higher expression of CD49d in this subtype of B-NHL.

The presence of the myelomonocytic antigens CD11b and CD11c on cells of chronic lymphocytic leukemia has been previously reported (24,25). CD11b has a heterogeneous expression in chronic lymphocytic leukemia. Whereas some publications described a high expression of this adhesion molecule in chronic lymphocytic leukemia (20), others reported a low expression (21,25). The data presented in the current study are in agreement with these latter reports, and since the mantle-cell lymphoma and the marginal B-cell lymphoma showed a higher expression of CD11b compared to chronic lymphocytic leukemia, this adhesion molecule could eventually be used to help differentiate between chronic lymphocytic leukemia and the other B-NHL in the leukemic phase. Moreover, CD11b may have other biological functions in chronic lymphocytic leukemia since it has been reported to be associated with a higher probability of disease progression and poor survival (26), as well as to prevent the induction of apoptosis in this disease (27). Our findings add more information about the expression of CD11b in mantle-cell lymphoma and in marginal B-cell lymphoma since there are only a few studies in the literature regarding this adhesion molecule in these diseases (28).

The role of CD11c in the dissemination of B-NHL is still controversial. Angelopoulou et al. (28) and Bairey et al. (29) found a higher frequency of splenic involvement in cases of chronic lymphocytic leukemia with strong CD11c positivity. Moreover, this adhesion molecule is usually over-expressed in splenic marginal B-cell lymphoma (28) and in hairy cell leukemia (30,31), both diseases characterized by large splenomegaly, which could suggest a role for CD11c in the

infiltration of the spleen. However, our data do not support this hypothesis, since 14 of 17 of our patients with the diagnosis of mantle-cell lymphoma presented an enlarged spleen, but showed a very low expression of CD11c. In agreement with our results, Angelopoulou et al. (32), in a study of 11 patients with mantle-cell lymphoma, observed that the CD11c was negative in all patients, including a subgroup of 6 patients with exclusively splenic disease.

CD54 is a member of the immunoglobulin superfamily that normally has a lower expression in peripheral blood mononuclear cells when compared with the lymph node (33). In our series, marginal B-cell lymphoma presented the highest expression of this adhesion molecule. Similarly, Csanaky et al. (34), studying 7 patients with this disease, found a higher level of CD54 expression when compared with chronic lymphocytic leukemia. Stauder et al. (35) and Horst et al. (36) showed that the lower expression of CD54 in indolent B-NHL correlates with a higher frequency of invasion of peripheral blood. In addition, Terol et al. (37) showed that low expression or absence of CD54 was associated with a higher frequency of disseminated disease (stage IV), extranodal involvement and bone marrow infiltration. Down-regulation of CD54 seems to favor the dissemination of tumor cells by a still unknown biological pathway and little information is available about the expression of this adhesion molecule in splenic marginal B-cell lymphoma.

The results of the present study allow us to conclude that chronic lymphocytic leukemia, mantle-cell lymphoma and marginal B-cell lymphoma have different adhesion molecule profiles, and these differences may be responsible for the distinct capacities of these diseases to disseminate into the blood stream. Moreover, our data reinforce the hypothesis that the peripheral blood invasion always present in chronic lymphocytic leukemia is the consequence of an imbalance of adhesion

molecule expression in tumor cells. Furthermore, we demonstrated that the CD49c/CD49d pair consistently presented a distinct pattern of expression in chronic lymphocytic leukemia compared to mantle-cell lymphoma and marginal B-cell lymphoma, which could be help-

ful for the differential diagnosis.

Future studies comparing the expression of adhesion molecules in peripheral blood and lymph nodes could better address their role in the phenomenon of peripheral blood invasion in B-NHL.

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