The development of more than one histologic type of lymphoma in the same patient is frequent and confers a worse prognosis

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Background and Objectives. Distinct types of lymphoma may develop in the same patient either simultaneously or sequentially. The frequency and clinical significance of this phenomenon are still only partially known.

Design and Methods. We conducted a retrospective analysis of all cases of lymphomas of different histology occurring in the same patient, denoting these cases as *multiple histology lymphoma* (MHL). The clinicopathologic characteristics of these cases were compared with those of cases with a single histology (SHL). The histologic classifications were made according to the REAL classification by the same pathologists throughout the study period.

Results. MHL were identified in 46 of 347 (13%) consecutive cases of lymphoma diagnosed at a single institution. They presented more frequently in stage III-IV (p=0.008), but the age, sex, and IPI score of patients with MHL did not differ from those of patients with SHL. Small lymphocytic/lymphoplasmacytic subtype was more frequent (16.1% vs 3%, p<0.0001) and Hodgkin's lymphoma (4% vs 16%; p=0.004) less frequent in MHL. Response rates to treatment were similar (85% vs 77.5%), whereas 5-year overall survival was significantly lower for MHL than for SHL (31% vs 67%; p=0.015). Among MHL, 14 cases were diagnosed simultaneously and 32 sequentially, after a median of 18 months. The two subgroups with simultaneous and sequential presentation did not differ in their demographic, clinicopathologic or prognostic characteristics.

Interpretation and Conclusions. Lymphomas of different histology develop frequently in the same patient, either simultaneously or sequentially. Patients with MHL form a subgroup with few peculiar presenting clinicopathologic features but a markedly worse prognosis, thus warranting prospective biological and clinical studies.

Key words: multiple histology lymphoma, clinicopathological features, prognosis.

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It has been recognized for some time that lymphomas of distinct histologic type can occur in the same patient. In most cases this happens because an indolent lymphoma of *low grade* histology transforms into an aggressive lymphoma of *high grade* histology, a process which has been known as lymphoma progression.[1,2] However a wide range of combinations of different histologic types of lymphoma have been reported.[3-11] The Working Formulation acknowledged the possibility of the occurrence of two types of lymphoma in the same lymph node, by using the term *composite lymphoma*,[12,13] but that entity was not included in either the REAL or the WHO classification.[14]

Since the phenomenon is not unusual in current clinical practice, we retrospectively analyzed a series of patients diagnosed at our Institution using the REAL classification in order to study the frequency as well as the clinicopathologic and prognostic features of lymphomas of different histology occurring in the same or in different sites and either simultaneously or at different times in the same patient. We used the term *multiple histology lymphoma* (MHL) to denote such cases and have compared them with control cases with a single diagnosis of lymphoma, denoted as *single histology lymphoma* (SHL).

Design and Methods

All 347 consecutive cases of lymphoma diagnosed at our Institution between 1994 and 2000 were retrospectively analyzed. The histopathologic diagnoses had been made by the same team of pathologists using the criteria of the REAL classification. The demographic and pathologic characteristics were representative of an unselected population of patients with lymphoma. The mean age of these patients was 55.1 years and 181 (52%) were males. Diffuse large B-cell lymphoma was the most frequent histology (121 cases: 35.9%), followed by follicular lym-

phoma (60 cases: 17.3%), Hodgkin's disease (49 cases: 14.1%), marginal zone B-cell lymphoma (37 cases: 10.7%), peripheral T-cell lymphoma (17 cases: 4.9%) and mantle cell lymphoma (16 cases: 4.6%). Other histologic subtypes accounted for less than 4.5% of the cases. Those cases in which the histologic diagnosis of any specimen analyzed at any time during the course of the disease fell into any different category of lymphoma according to the REAL classification were termed MHL. These cases of MHL were further subdivided according to the following criteria: (i) *simultaneous* MHL: different lymphomas occurring at the same time in the same lymph node or at different sites; (ii) *sequential* MHL: different lymphomas occurring at different times, in the same patient.

MHL were analyzed separately and their characteristics were compared with those cases in which a single histologic type of lymphoma had been diagnosed, which were termed *single histology lymphoma* (SHL).

Staging procedures included thoracic and abdominal computed tomographic scans, a bone marrow trephine biopsy and an otorhinolaryngological evaluation in all cases, with additional procedures based on clinical findings. All patients were treated uniformly according to institutional guidelines, which included a *wait and see* policy in asymptomatic patients with indolent lymphoma. In patients with *simultaneous* MHL the more aggressive histologic type was considered for treatment.

Statistical analysis

Fisher's exact test and Student's T-test were used when appropriate. Actuarial survival curves were compared with log-rank analysis using Graph Pad statistical software (Prism 4). In patients with sequential MHL, survival duration was calculated from the date of the histologic diagnosis of the first lymphoma.

Results

Forty-six patients with MHL were identified among 347 cases of lymphoma, such that the cumulative frequency of MHL was 13%. Of these 46 cases, 14 were *simultaneous* MHL and 32 *sequential* MHL. In only one case among the *simultaneous* MHL did the two histologic types of lymphoma (lymphocytic + follicular) occur at the same site, i.e. as a *composite* lymphoma according to the Working Formulation. The histologic characteristics of MHL, as well as the disease sites and the time interval between the different lymphoma diagnoses are listed in Table 1. In two cases three different histologic types of lymphoma were diagnosed. Sequential MHL occurred at a median interval of 18 months (range 4 –70). Lymph node and bone marrow were the disease sites more frequently analyzed and involved in MHL, with no differences between first and subsequent lymphoma diagnoses.

Follicular lymphoma was the most frequent histology as first diagnosis (13 of 46 cases) followed by lymphocytic and marginal zone histology. Diffuse large B-cell lymphoma (DLBCL) was the most frequent second histology (25 of 46 cases) in MHL. Indeed, the most frequent histologic associations were follicular/DLBCL (10 cases), small lymphocytic/DLBCL (5 cases) and marginal zone/DLBCL (4 cases), which occurred simultaneously in 4 and sequentially in 15 cases, respectively, the latter representing typical cases of lymphoma progression. The combination of an indolent with an aggressive histologic type of the same immunologic lineage occurred in 6 of 14 (43%) cases of simultaneous MHL and in 19 of 32 (59%) *sequential* MHL.

Four patients with sequential MHL had an aggressive histology as first diagnosis followed by a diagnosis of indolent lymphoma, a phenomenon called *downgrading* MHL.[1] In eight patients a combination of different indolent histologies of the same lineage was present, and four cases showed a combination of two aggressive histologies. In 35 cases both histologies were of the B lymphocyte lineage, two had two T lineage histologies, whereas an association of lymphomas of T/null and B-cell lineage occurred in 5 cases. In four cases Hodgkin's and non-Hodgkin's lymphomas were associated.

Molecular analysis could be performed retrospectively in 14 cases of MHL, using polymerase chain reaction primers for the J-region of the IgH gene.[19] All analyzable cases showed a combination of an indolent B-cell lymphoma (follicular: 6; small lymphocytic: 4; marginal zone: 3; lymphoplasmacytoid: (i) with a DLBCL. There were 3 cases of simultaneous MHL and 11 of sequential MHL, two of which were *downgrading* MHL. Single or multiple amplification bands could be obtained in both specimens in 12 of 14 cases. Coincident amplification bands were detected in 9 cases, specifically in one simultaneous MHL and in 8 sequential MHL, including the two downgrading MHL. In two cases of sequential MHL (follicular > DLBCL and small lymphocytic > DLBCL) different bands were detected, consistent with different clonal rearrangements in the two histologic types of lymphoma. In one patient the two specimens showed a polyclonal pattern without coincident bands. Table 2 summarizes the comparison between MHL and *persistent histology* lymphoma, as well as the comparison between simultaneous and sequential MHL. As shown, MHL did not have any distinctive clinicopathological features compared to SHL, with the exception of a significantly higher frequency of advanced stage (Ann Arbor III-IV) at presentation (Fisher's exact test: p=0.003), significantly more frequent lymphocytic/lymphoplasmacytic histology (16.1% vs 3%;

Table 1. Histologic diagnosis and sites of lymphoma involvement of MHL occurring in the same lymph node (case 1), simultaneously (cases 2-14), or sequentially (cases 15-46).

	First lymphoma Histology	*Site*	*Second lymphoma Histology*	*Site*	*Interval months*
1	Follicular	N	Small lymphocytic	N	0
2	Follicular	N	DLBCL + Hodgkin	Soft tissue + N	0
3	Follicular	N	DLBCL	N	0
4	Follicular	M	DLBCL	Bone	0
5	DLBCL	M	Hodgkin	N	0
6	DLBCL	N	Small lymphocytic	M	0
7	DLBCL	M	Follicular	N	0
8	Small lymphocytic	M	DLBCL	ORL	0
9	Mantle cell	Colon	Marginal zone	M	0
10	Mantle cell	S	Small lymphocytic	M	0
11	Marginal zone	N	Follicular	M	0
12	Sézary's syndrome	Skin	Immunocytoma	M	0
13	Angiocentric T	Oral cavity	Peripheral T unspec.	Skin	0
14	ALCL	Liver	DLBCL	Pleura	0
15	Follicular	N	DLBCL	N	27
16	Follicular	N	DLBCL	N	23
17	Follicular	N	DLBCL	N	13
18	Follicular	M	Marginal zone	S	22
19	Follicular	N	DLBCL	N	28
20	Follicular	N	DLBCL	N	13
21	Follicular	N	DLBCL	M	18
22	Follicular	M	DLBCL	N	7
23	Follicular	N	DLBCL	N	12
24	DLBCL	N	Small lymphocytic	M	70
25	DLBCL	ORL	Precursor T lymphoblastic	N	8
26	DLBCL	N	Small lymphocytic	M	10
27	Immunocytoma	M	DLBCL	M	20
28	DLBCL	N	Marginal zone	N	49
29	Small lymphocytic	N + M	DLBCL	Kidney + Ascites	17
30	Small lymphocytic	M	DLBCL	N	18
31	Immunocytoma	M	Plasma cell myeloma	M	21
32	Immunocytoma	M	DLBCL	Testis	48
33	Small lymphocytic	M	DLBCL	N + Liver	15
34	Small lymphocytic	M	Marginal zone	N + S	15
35	Small lymphocytic	M	Mantle cell	M	15
36	Marginal zone	M + S	DLBCL	M	35
37	Marginal zone	M	DLBCL	M	20
38	Marginal zone	M	DLBCL	N + Colon	36
39	DLBCL	Stomach	Marginal zone	Stomach	4
40	Marginal zone	Parotid gland	DLBCL	Skin	31
41	Peripheral T unspec.	N	DLBCL	N + M	39
42	ALCL	Skin + S	DLBCL	ORL	15
43	Small lymphocytic	M	ALCL	N	20
44	Peripheral T unspec.	M	Mycosis fungoides	Skin	17
45	Hodgkin	N	ALCL	N	36
46	Hodgkin	N	Peripheral T unspec.	M + tonsil	48

Disease site: N: lymph node; S: spleen; M: marrow; DLBCL: diffuse large B-cell lymphoma; ALCL: anaplastic large cell lymphoma; ORL: otorhinolaringological.

$p<0.0001$) and less frequent Hodgkin's histology (4% vs 16%; $p<0.004$). When the characteristics of MHL patients with simultaneous versus sequential lymphomas were compared, no significant differences emerged, although numbers were too small to allow proper analysis. The results of treatment and the outcome of patients with MHL and SHL are also summarized and compared in Table 2. The overall percentage of patients treated was similar, as were the probabilities of complete/partial response. On the other hand, the median survival was only 28 months in patients with MHL whereas it was not reached in patients with SHL (log-rank analysis: $p=0.015$) (Figure 1). Differences in the response rate and median survival between *simultaneous* and *sequential* cases of MHL were observed but did not reach statistical significance (Figure 2).

Discussion

The possibility that different types of lymphoma can develop in the same patient has been recognized for many years. In addition to the well known cases of lymphoma progression,[1] there are many reports of different lymphomas occurring in the same patient, often

Table 2. Clinicodemographic and prognostic characteristics compared between *multiple histology* lymphomas (MHL) and control lymphomas with *single histology* (SHL), as well as between the subgroups of MHL occurring simultaneously or sequentially.

	SHL	*MHL Total*	*MHL Sequential*	*MHL Simultaneous*
#	301	46	32	14
Mean age	55,0	59,9	60,3	59,2
M/F	155/146	26/20	17/15	9/5
Stage III-IV	145/246* (59%)°	35/42* (83%)°	24/29 (83%)	11/13 (85%)
IPI score HI-H°	99/214* (46%)	17/37* (46%)	11/24 (46%)	6/13 (46%)
Response (CR/PR)	169/199* (85%)	27/35* (77%)	20/23 (87%)	7/12 (58%)
Survival (median)	Not reached@	28 months@	52 months^	22 months^

*°HI-H denotes high-intermediate and high risk according to the international prognostic index; *number of evaluable patients; °Fisher's exact test: p=0.003; @log-rank analysis: p=0.0149; ^log-rank analysis: p=0.153.*

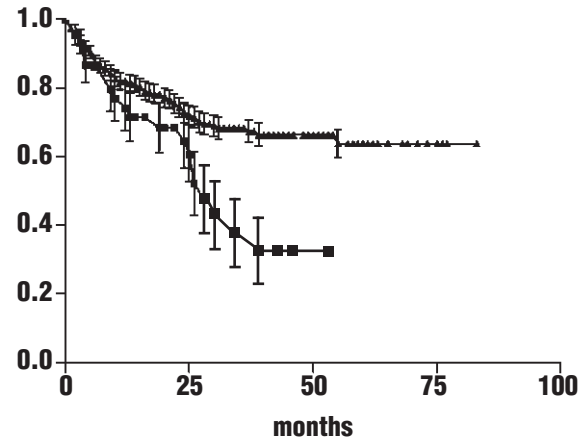

Figure 1. Overall actuarial survival of patients with *persistent* lymphoma (▲) (median survival was not reached) compared to that of patients with MHL (■) (median survival: 28 months). The curves are significantly different (log-rank analysis: *p*=0.0149).

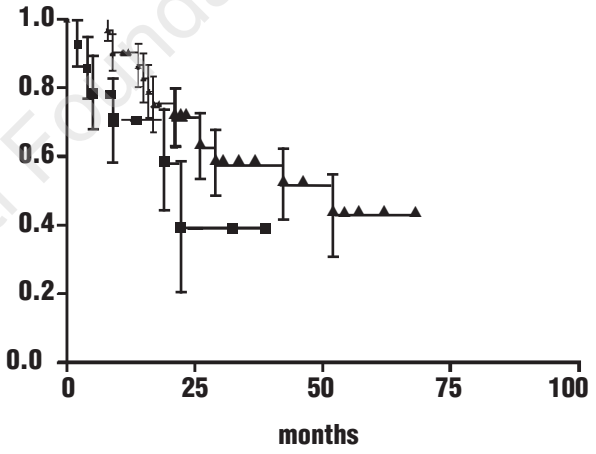

Figure 2. Overall actuarial survival of patients with *sequential* MHL (▲) (median survival: 52 months) compared to that of patients with *simultaneous* MHL (■) (median survival: 22 months). The curves are not significantly different (log-rank analysis: *p*=0.153).

at the same time.[12,13] However, since most of the reports dealt with a single case or small numbers of patients, the exact frequency of this phenomenon, as well as its clinical correlates and prognostic consequences are not well known. A further reason to investigate the problem derives from the fact that the recent REAL[14] and WHO classifications have attempted to define single disease entities among the wide spectrum of lymphomas. It therefore becomes important to identify possible associations between such different disease entities, which may have similar clinical presentations but different immunological and molecular characteristics. Their non-random development in the same patient could be of particular significance and could help to understand some aspects of lymphoma pathogenesis better.

The frequency of MHL was 13% in this unselected, population-based series of patient. This figure underscores the importance of the problem, since it derives from a retrospective study in which biopsies were performed only based on clinical judgement. Therefore, it may even be an underestimate, since a precise evaluation would require histologic analysis of all disease sites at presentation and at lymphoma progression or relapse.

The risk of developing a second type of lymphoma could not be predicted in our series. When compared to patients with a single diagnosis of lymphoma, patients with MHL had similar presenting demographic and clinical features, although patients in advanced stage had a higher risk of MHL. The pathologic features did not differ significantly, except for a higher frequency of lymphocytic lymphoma, which was mainly associated with DLBCL, and a lower frequency of Hodgkin's lymphoma in MHL. While the majority of MHL developed at different times, nearly one third of them were actually diagnosed simultaneously, at different sites, except in one case of true *composite* lymphoma. This observation would support the policy of obtaining a tissue specimen from any disease site whose presentation characteristics are not in agreement with the first diagnosis of lymphoma, to avoid overlooking a second histologic type of lymphoma which could substantially modify the prognosis and the treatment program.

Lymphoma progression, i.e. the transformation of an indolent histology to a more aggressive one of the same immunologic origin, is the pathogenetic mech-

anism which best explains the occurrence of MHL. Molecular analysis of selected cases in this series support this hypothesis, since 9 of 11 evaluable MHL showed the same clonal rearrangement of the IgH gene. It accounted for the majority of sequential MHL in our series, as expected, but also likely accounted for a substantial proportion of simultaneous MHL, which may represent cases of lymphoma progression diagnosed fortuitously at the same time, in different sites, as was demonstrated by molecular studies in one of our cases. Even the so-called *downgrading* lymphoma may represent a different aspect of the same pathogenetic mechanism, as in two of our cases. Indeed, in *downgrading* lymphoma, the first biopsy may have disclosed a *transformed* DLBCL, and the second biopsy a previously unrecognized indolent lymphoma, which may have relapsed because it had not been fully eradicated by the treatment originally given for the DLBCL.

On the other hand, a number of cases in this series cannot be interpreted as lymphoma progression, including the two cases of sequential MHL showing different clonal rearrangements in the two types of lymphoma at molecular analysis, but also the 8 cases showing a combination of lymphomas of different immunologic origins, the 4 cases of simultaneous MHL and 3 of sequential MHL in which two indolent histologic types were diagnosed and in which molecular analysis was, unfortunately, unavailable. While chance occurrence or technical problems could well account for some MHL, other and more interesting biological phenomena may be hypothesized to explain these associations, which were observed at a significant frequency. Genetic instability, both intrinsic or therapy-related, microenvironmental effects on lymphoma characteristics, spontaneous or treatment-induced differentiation, defects in immune surveillance, and oncogenic viral infections are among the mechanisms proposed to interpret some cases of MHL; further prospective studies addressing this point are clearly needed.

A most important result of our study derived from the analysis of the outcome of patients with MHL. While their initial response to treatment did not differ from that of patients with SHL, the overall survival of patients with MHL was significantly inferior, being a median of 28 months; the 5-year survival was only 33% for the entire group, which was less than half that of the patients with SHL. Of note, the poor outcome of MHL was similar both for patients with *sequential* lymphoma, whose bad prognosis could be expected considering the frequent progression of lymphoma in this subgroup, and for patients with *simultaneous* MHL, a subgroup in which this worse prognosis may be related to different pathogenetic mechanisms and which merits further analysis in prospective studies.

AT and GRo designed the study, carried out the analyses and wrote the manuscript; MU, AU and FF contributed to the histopathological diagnoses and molecular analyses; MM, EB, GRu and CC were responsible for the collection and analysis of data. The authors declare that they have no potential conflict of interest.

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