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

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.
Multiple lymphomas in the same patient

MHL: different lymphomas occurring

MHL: different lymphomas

All 19

In eight patients a combination of different histologic types of lymphoma were diagnosed. In only one MHL did the two histologic types of lymphoma (lymphocytic + follicular) occur 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 GraphPad 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. 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. All analyzable cases showed a combination of an indolent B-cell lymphoma (follicular: 6; small lymphocytic: 4; marginal zone: 3; lymphoplasmacytoid: 1) 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%;
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).

### 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).

<table>
<thead>
<tr>
<th>First lymphoma</th>
<th>Second lymphoma</th>
<th>Site</th>
<th>Histology</th>
<th>Site</th>
<th>Histology</th>
<th>Interval months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Follicular</td>
<td>Follicular</td>
<td>N</td>
<td>Small lymphocytic</td>
<td>N</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>2 Follicular</td>
<td>Follicular</td>
<td>N</td>
<td>DLBCL + Hodgkin</td>
<td>Soft tissue + N</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3 Follicular</td>
<td>Follicular</td>
<td>N</td>
<td>DLBCL</td>
<td>N</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>4 Follicular</td>
<td>DLBCL</td>
<td>M</td>
<td>Hodgkin</td>
<td>N</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>5 DLBCL</td>
<td>DLBCL</td>
<td>N</td>
<td>Small lymphocytic</td>
<td>M</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>6 DLBCL</td>
<td>DLBCL</td>
<td>M</td>
<td>Follicular</td>
<td>N</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>7 Small lymphocytic</td>
<td>Mantle cell</td>
<td>Colon</td>
<td>Marginal zone</td>
<td>M</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>8 Mantle cell</td>
<td>S</td>
<td>Small lymphocytic</td>
<td>N</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9 Marginal zone</td>
<td>Follicular</td>
<td>M</td>
<td>N</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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, there are many reports of different lymphomas occurring in the same patient, often.
Multiple lymphomas in the same patient

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 REAL14 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-
animal which best explains the occurrence of MHL. Molecular analysis of selected cases in this series supports 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 the end of this study, we also realized that one third of the cases of MHL were not clearly distinguishable from DLBCL, because of the CD10 expression, which is a characteristic of the latter. This expression, which may be responsible for the decreased survival of MHL, was found in 13 of 17 evaluable cases in our series.


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