Cutaneous B-cell lymphoma : classification, prognostic factors and management recommendations

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Chapter 5.

Results of bone marrow examination in 275 patients with histological features that suggest an indolent type of cutaneous B-cell lymphoma

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Summary
Recently, discussions have started whether or not bone marrow biopsies should be performed routinely in patients with skin lesions that show histologic features consistent with an indolent B-cell lymphoma (marginal zone lymphoma (MZL) or follicle centre lymphoma (FCL). As no studies have addressed this question for this group of lymphomas, we evaluated the results of bone marrow biopsy examination in 275 patients with histologic features consistent with MZL (n = 82) or FCL (n = 193) first presenting in the skin. In the MZL group, two of 82 patients (2%) showed bone marrow involvement and in one of these patients this was the only extracutaneous localization. In the group of FCL, 22 of 193 patients (11%) had bone marrow involvement. In nine of these this was the only extracutaneous localization. FCL patients with skin lesions and a positive bone marrow had a significantly worse prognosis as compared to patients with only skin lesions (5-year disease-specific survival 63% versus 95%; p = 0.001).
These results indicate that bone marrow investigation is an essential part in staging patients with a FCL first presenting in the skin. Bone marrow examination appears to have limited value in patients with MZL presenting in the skin.

Introduction

Primary cutaneous lymphomas (PCL) are defined as a group of non-Hodgkin lymphomas of either T-cell or B-cell origin, that present in the skin without evidence of extracutaneous disease at the time of diagnosis. Distinction between PCL and systemic lymphomas involving the skin secondarily is important since they often have a completely different clinical behaviour and prognosis, and may therefore require different types of treatment.[1]

A diagnosis of PCL can only be made after adequate staging investigations have been conducted. Adequate staging procedures include, besides a detailed history and physical examination, routine laboratory tests (complete and differential blood cell count and serum biochemistry), computed tomography (CT) scan of neck, chest and abdomen and a bone marrow biopsy. At recent consensus meetings of the European Organization for Research and Treatment of Cancer (EORTC) and the International Society of Cutaneous Lymphoma (ISCL), aimed to develop staging systems and guidelines for diagnosis and treatment of PCL other than mycosis fungoïdes (MF) and Sézary syndrome (SS), the necessity to perform a bone marrow biopsy in indolent PCL was questioned. In the subsequent consensus paper, it was suggested that bone marrow examination was recommended, but not required in indolent PCL, including primary cutaneous anaplastic large cell lymphoma, primary cutaneous marginal zone lymphoma (PCMZL) and primary cutaneous follicle centre lymphoma (PCFCL), unless indicated by other staging assessments.[2] Regarding the two types of indolent cutaneous B-cell lymphoma (CBCL), this is in accordance with the National Comprehensive Cancer Network (NCCN) clinical practice guidelines [v.1.2007: available from: http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf. Accessed 31 July; 2007]. In these guidelines bone marrow biopsies are not part of the essential workup of follicular lymphoma and marginal zone lymphoma and are only advised in selected cases. However, in most other guidelines, including those of the Dutch-Belgian Hemato-Oncology Group (HOVON) [available from: http://www.hovon.nl/hovon/stream.asp?hovnhl.pdf. Accessed 31 July; 2007], unilateral trephine bone marrow biopsies are part of routine work-up in all patients with (a suspicion of) non-Hodgkin lymphoma.[3;4]

The recommendation that a bone marrow biopsy is not required in indolent types of CBCL (PCMZL and PCFCL) is confusing, since studies describing these PCMZL and PCFCL as indolent lymphomas required negative staging procedures, including a negative bone marrow biopsy.[1] Henceforth, this recommendation means that in patients who present with skin lesions that are clinically and histologically highly suggestive or consistent with a diagnosis of PCMZL or PCFCL a bone marrow is not required, if other staging procedures are negative. In case of marginal zone lymphoma the consequences of not performing a bone marrow biopsy are expected to be limited. In case staging (including a bone marrow biopsy) is negative, it concerns a PCL, which, - according to the WHO-EORTC classification for cutaneous lymphomas -, is classified as PCMZL. If, however, a bone marrow biopsy and/or other staging procedures are positive, it does not concern a PCL, and

the WHO-EORTC classification should not be applied. Such cases should be classified according to the WHO classification as an extranodal marginal zone lymphoma with skin localizations. In both instances it concerns an indolent type of B-cell non-Hodgkin lymphoma, and the therapeutic consequences will be minimal. In case of PCFCL the situation is more complex. PCFCL are defined as tumors of neoplastic follicle center cells, usually a mixture of centrocytes and variable numbers of centroblasts, which may show a follicular (5%), follicular and diffuse (30%) or diffuse growth pattern (65%).[5] These PCFCL are preferably treated with radiotherapy and have an excellent prognosis with a 5-year-survival of 95%, irrespective of the growth pattern (follicular and/or diffuse) or the number of blast cells.[1] However, if in a patient with clinicopathologic features suggesting a PCFCL, a bone marrow biopsy and/or other staging procedure prove to be positive, a diagnosis of PCFCL can not be made. Such cases concern a secondary cutaneous lymphoma and should be classified according to the WHO classification as either follicular lymphoma or, in most cases, as a diffuse large B-cell lymphoma, which will have major therapeutic consequences. One would therefore assume that not performing a bone marrow biopsy in such cases may result in inappropriate treatment.
Studies on the frequency of extracutaneous manifestations and in particular a positive bone marrow biopsy in patients presenting with skin lesions otherwise consistent with a PCMZL or PCFCL have never been performed. In the present study we therefore evaluated retrospectively staging results of a large group of patients presenting with skin lesions that showed histological features consistent with a diagnosis of marginal zone lymphomas (MZL) or follicle centre lymphomas (FCL). The aim was to evaluate the frequency of bone marrow involvement in these patients in order to find out whether our current policy to perform a bone marrow biopsy in all patients with a histological diagnosis of cutaneous MZL or FCL should be maintained or that it should only be performed in selected cases as suggested recently.[2]

Patients and Methods

All patients who presented with skin lesions showing histologic and immunophenotypical features consistent with a diagnosis of MZL (n = 107) or FCL (n = 250) between 1985 and 2006 were retrieved from the database of the Dutch Cutaneous Lymphoma Group. The term FCL is herein used for tumors of neoplastic follicle centre cells with either a follicular, a follicular and diffuse or a diffuse growth pattern, which should be classified as PCFCL, in case staging procedures were negative. All cases had been reviewed by a panel of hematopathologists and dermato(patho)logists and classified by consensus prior to entry in the database. For each patient in this registry follow-up is collected yearly. Patients with a history of a prior systemic B-cell lymphoma (n = 16; 2 MZL and 14 FCL) and patients in whom a bone marrow biopsy was not performed (n = 66; 23 MZL and 43 FCL) were excluded from the study. The final study group consisted of 82 MZL and 193 FCL (Table 1). Median follow-up for the whole group was 43 months (range 1 – 443 months). Staging

procedures had included physical examination, complete and differential blood cell counts and serum biochemistry, CT-scan of neck, chest and abdomen and a bone marrow biopsy. The results of the staging investigations were extracted from the patient's files.
Statistical calculations were performed using SPSS 14.0 (SPSS Inc, Chicago, IL). Overall survival (OS) was calculated from the date of diagnosis until the patient's death or date of last follow-up. Disease-specific survival (DSS) was calculated from the date of diagnosis until death from lymphoma (including therapy-related death) or censoring. Patients who were alive at last follow-up or patients who died of other causes were considered censored. Survival curves were estimated using the method of Kaplan and Meier and statistical comparison between curves was done by log-rank testing.

Table 1. Selection of cases and results of bone marrow biopsy and disease-specific survival (DSS) in marginal zone lymphomas and follicle center lymphomas first presenting in the skin.

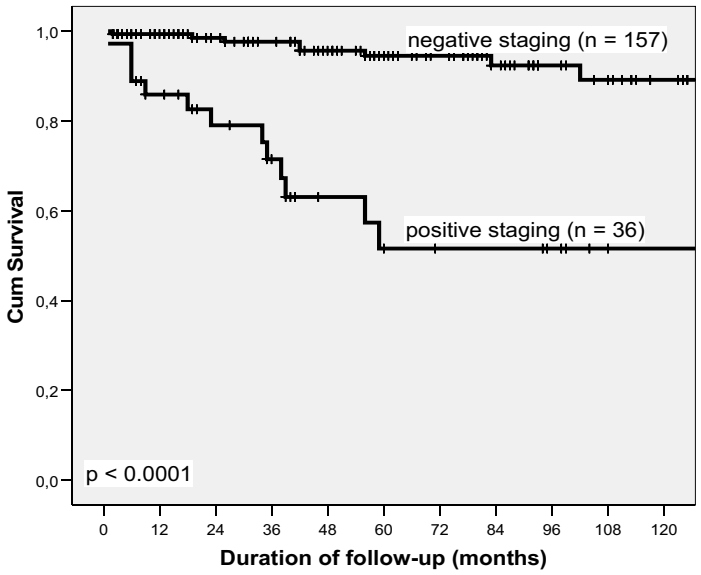
Histology	Marginal zone lymphoma	Follicle centre lymphoma
Total number present in database DCLG (*)	107	250
History of non-cutaneous lymphoma	2	14
Bone marrow biopsy not performed (5-year DSS)	23 (100%)	43 (86%)
Final study group (5-year DSS)	**82 (92%)**	**193 (86%)**
Male: female	52:30	118:75
Median age (range)	57 (23-90)	59 (21-90)
Median duration of follow-up, months (range)	31 (1-334)	51 (1-443)
Staging negative (5-yr DSS)	76 (98%)	157 (95%)
Staging positive (5-yr DSS)	6 (50%)	36 (51%)
Bone marrow involvement (5-yr DSS)	2 (50%)	22 (51%)
Only bone marrow involvement (5-yr DSS)	1 (100%)	9 (63%)

Results

Marginal zone lymphoma

In the group of 82 MZL patients, 76 patients showed no signs of extracutaneous involvement during staging investigations and were diagnosed as PCMZL (see Table 1).[1] In six cases (7%) extracutaneous localizations were found, including five patients with enlarged lymph nodes on the CT-scan. Bone marrow involvement was found in two of these six patients, in one of them as part of widespread disease with involvement of central lymph nodes and peripheral blood as well, and in the other patient as the only evidence of extracutaneous disease. The first patient was treated with chemotherapy, but died from secondary acute myeloid leukaemia three years after diagnosis. The second patient is in complete remission for over five years following an autologous bone marrow transplantation and radiotherapy for a skin relapse during follow-up. Patients with and without extracutaneous involvement had a 5-year OS of 33% and 91%, respectively and a 5-year DSS of 50% and 98% respectively (Table 1).

Figure 1: Disease-specific survival of follicle center lymphomas first presenting in the skin; cases with positive staging (n = 36) versus cases with negative staging (i.e. true PCFCL; n = 157).

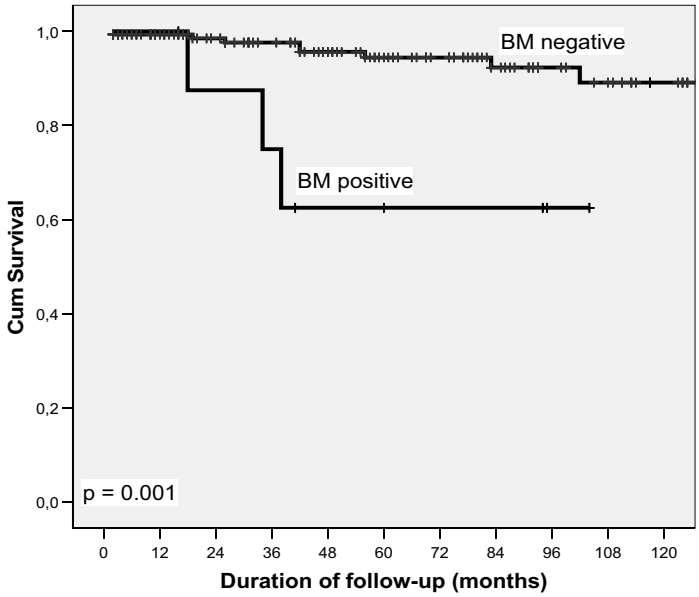


Follicle centre lymphoma

Of 193 FCL patients with complete staging work-up 157 patients showed no evidence of extracutaneous disease and were classified as PCFCL.[1] Extracutaneous disease was detected at the time of diagnosis in 36 cases (19%). Nine of 36 cases showed the characteristics of a follicular lymphoma, while the other 28 cases lacked a follicular component and were classified as diffuse large B-cell lymphoma. Taken together, in 22 of these 36 cases the bone marrow biopsy was positive or contained lymphoid aggregates highly suspect for lymphoma involvement (Table 1). In 13 patients, bone marrow involvement was accompanied by more extensive involvement of other organs or lymph nodes as assessed by CT-scans and/or lymph node histology. In the remaining nine cases the bone marrow was the only extracutaneous localization. The 14 patients with extracutaneous disease, but no bone marrow involvement showed nodal disease as assessed by CT-scan and/or lymph node biopsy (n = 13), while one patient showed bone involvement.

The 5-year OS for the 36 patients with and the 157 patients without extracutaneous involvement was 42% and 84%, respectively, whereas the 5-year DSS was 52% and 95% respectively ($p < 0.001$; Figure 1). Patients with bone marrow involvement with or without extracutaneous localizations at other sites had a 5-year OS of 30% and 44% and a 5-year DSS of 30% and 63%, respectively (Table 1).

Figure 2: Disease-specific survival of follicle center lymphomas first presenting in the skin; cases with only bone marrow in addition to skin lesions (n = 9) versus true PCFCL (n = 157).



Discussion

Recently, discussions have started whether or not bone marrow biopsies should be routinely performed in patients with a MZL or FCL first presenting in the skin.[2] Since there are, to the best of our knowledge, no studies that have addressed this question for this particular group of lymphomas, we evaluated the results of bone marrow biopsy examinations in 275 patients with a MZL or FCL first presenting in the skin. Considering the whole group of 275 patients, 24 patients (9%) had bone marrow involvement at initial diagnosis, while in 10 patients (4%) this was the only evidence of extracutaneous disease.

In the group of MZL, bone marrow was involved in only two of 82 (2%) patients, and in one of these two patients it was the only evidence of extracutaneous disease. Thus, if bone marrow biopsies would not have been performed in this group, only one of 82 cases would have been misdiagnosed as PCMZL.

Recent studies on large cohorts of nongastric extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), report bone marrow involvement at initial diagnosis in 14% to 28% of patients.[6-8] Cutaneous MZL included in these studies showed bone marrow involvement in zero of seven[7] and two of 22 (9%)[8] cases, respectively. Since MALT lymphomas present with disseminated disease in a considerable proportion of cases, these studies emphasize the need of extensive staging procedures, including a bone marrow biopsy. In addition, in these studies bone marrow involvement was associated with an inferior prognosis. In contrast, a recent Austrian study found bone marrow involvement in only three of 140 (2%) MALT lymphomas, including one of 79 (1%) nongastric MALT lymphomas, thus arguing against the necessity of a routine bone marrow biopsy. [9]The different frequencies of bone marrow involvement in these studies are as yet unexplained.

The results of the present study and data from the literature indicate that bone marrow involvement is uncommon in MZL first presenting in the skin, and that it is rarely the only manifestation of extracutaneous disease. Moreover, treatment of MZL with skin lesions and isolated bone marrow involvement will not be different from that of MZL presenting with only skin lesions (PCMZL). In both cases, radiotherapy will be the primary option, although the (known) presence of bone marrow involvement will ask for a closer follow-up of such a patient compared to the patient with only skin involvement. It is also interesting to note that the 23 patients with cutaneous MZL in whom no bone marrow biopsy was performed, and who were excluded from the present study, had a 5-yr DSS of 100% (see Table 1). Thus, from a clinical point of view, there does not seem to be a good reason to consider a bone marrow biopsy mandatory in these patients. However, if bone marrow biopsies are no longer performed, a definite diagnosis of PCMZL can no longer be made with certainty. Given the major pathogenetic differences in terms of translocations and antigenic stimuli involved in the development of MALT lymphomas at different sites[10-12],

not performing a bone marrow biopsy may obscure distinction between primary and secondary cutaneous cases and hamper elucidation of the pathogenesis of genuine PCMZL.

In the group of FCL first presenting in the skin, bone marrow was involved in 22 of 193 cases (11%), whereas bone marrow involvement was the only evidence of extracutaneous disease in nine of them. Thus, if bone marrow biopsies had not been performed in this group, nine cases would have been incorrectly classified as PCFCL. The finding of bone marrow involvement in these nine patients appears clinically relevant, since they had a significantly worse survival as compared to the 157 PCFCL patients (5-year OS 44% versus 84%; p = 0.001; 5-year DSS 63% versus 95%; p = 0.001; Figure 2). In addition, although the clinical presentation (site and extent of skin lesions) in these nine patients did not differ from patients with a PCFCL, the presence of bone marrow involvement may also have therapeutic consequences.
In three of nine cases the skin infiltrates showed a partial follicular growth pattern and were classified as follicular lymphoma with skin and bone marrow involvement. In the other six cases the skin biopsies showed a diffuse population of large cleaved cells without a follicular component and were classified as diffuse large B-cell lymphoma according to the WHO classification. Taken together, these data indicate that a bone marrow biopsy is mandatory in patients with a FCL first presenting in the skin.

Due to the fact that these patients were collected during a 20-year period, all data were retrieved from a database or patient's files, and some of these could not be reviewed. The quality of CT scans has very much improved, and PET scans have recently contributed to the upgrading of staging procedures. As far as bone marrow biopsies are concerned, much has changed during the last decade. The Cheson guidelines[3] request a well-defined quality, regarding length of the specimen (>2 cm) with sufficient marrow fields, and in the case of doubtful infiltration additional immunohistochemistry, which obviously was not available in the early years of this study. Although some *false-positive* marrows might have been present, one would rather expect *false-negative* bone marrows. We therefore believe that there are two reasons why the percentage of positive bone marrow biopsies might be even higher than found in our study. First, in the absence of a histologic review of the bone marrow biopsies, it can not be excluded that some designated negative, were in fact of insufficient quality to allow a definite conclusion. Exclusion of such 'false-negative' bone marrow biopsies would result in a higher percentage of positive bone marrow examinations. Second, one of the main goals of the Dutch Cutaneous Lymphoma Group is to assist referring dermatologists and pathologists in making a correct diagnosis of patients with (suspicion of) a *cutaneous* lymphoma. Although the database contains both primary and secondary cutaneous lymphomas, patients presenting with skin lesions and extensive extracutaneous disease, and who were primarily referred to a haematologist, may not have been included in the Dutch Cutaneous Lymphoma Group database. If such patients would

have been included, the percentage of positive bone marrow biopsies would definitely have been higher. However, we believe that this will apply to only a few patients as compared to the large number of cases included in this study, and therefore will not significantly influence our conclusions.

In conclusion, the results of our study indicate that bone marrow investigation is an essential part of staging procedures in patients with a FCL first presenting in the skin. From a clinical point of view, bone marrow examination appears to have limited value in patients with MZL presenting in the skin, and may be considered only in selected cases, as previously suggested.[2]

References

1. Willemze R, Jaffe ES, Burg G et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768-3785.

2. Kim YH, Willemze R, Pimpinelli N et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:479-484.

3. Cheson BD, Horning SJ, Coiffier B et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J.Clin.Oncol. 1999;17:1244.

4. Cheson BD, Pfistner B, Juweid ME et al. Revised response criteria for malignant lymphoma. J.Clin.Oncol. 2007;25:579-586.

5. Senff NJ, Hoefnagel JJ, Jansen PM et al. Reclassification of 300 primary cutaneous B-Cell lymphomas according to the new WHO-EORTC classification for cutaneous lymphomas: comparison with previous classifications and identification of prognostic markers. J.Clin.Oncol. 2007;25:1581-1587.

6. Arcaini L, Burcheri S, Rossi A et al. Nongastric marginal-zone B-cell MALT lymphoma: prognostic value of disease dissemination. Oncologist. 2006;11:285-291.

7. Zinzani PL, Magagnoli M, Galieni P et al. Nongastrointestinal low-grade mucosa-associated lymphoid tissue lymphoma: analysis of 75 patients. J.Clin.Oncol. 1999;17:1254.

8. Zucca E, Conconi A, Pedrinis E et al. Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. Blood 2003;101:2489-2495.

9. Raderer M, Wohrer S, Streubel B et al. Assessment of disease dissemination in gastric compared with extragastric mucosa-associated lymphoid tissue lymphoma using extensive staging: a single-center experience. J.Clin.Oncol. 2006;24:3136-3141.

10. Cohen SM, Petryk M, Varma M et al. Non-Hodgkin's lymphoma of mucosa-associated lymphoid tissue. Oncologist. 2006;11:1100-1117.

11. Ferreri AJ, Zucca E. Marginal-zone lymphoma. Crit Rev.Oncol.Hematol. 2007;63:245-256.

12. Inagaki H. Mucosa-associated lymphoid tissue lymphoma: molecular pathogenesis and clinicopathological significance. Pathol.Int. 2007;57:474-484.