The handle http://hdl.handle.net/1887/20106 holds various files of this Leiden University dissertation.

Author: Benner, Marchina Frederika  
Title: Cutaneous CD30-positive lymphoproliferations: clinical and molecular aspects and differential diagnosis  
Date: 2012-11-07
Bone marrow examination has limited value in the staging of patients with an anaplastic large cell lymphoma first presenting in the skin. Retrospective analysis of 107 patients

M.F. Benner and R. Willemze

Department of Dermatology, Leiden University Medical Center, Leiden, the Netherlands.

*British Journal of Dermatology* 2008;159:1148-1151
SUMMARY

Background: According to criteria of the World Health Organization-European Organization for Research and Treatment of Cancer classification for cutaneous lymphomas a diagnosis of primary cutaneous CD30-positive anaplastic large cell lymphoma (C-ALCL) should be made only when systemic localizations have been excluded by adequate staging procedures, including a bone marrow biopsy. It has recently been questioned whether or not bone marrow examination should be performed routinely in indolent cutaneous lymphomas such as C-ALCL. Studies addressing this issue have never been performed.

Objectives: To determine the incidence of bone marrow involvement in patients with an ALCL first presenting in the skin to find out if the current policy to advice bone marrow examination should be maintained or whether a bone marrow biopsy should be performed only in selected cases.

Methods: All patients presenting with skin lesions with histological and immunophenotypical features of an ALCL were retrieved from the database of the Dutch Cutaneous Lymphoma Group. Patients with a history of systemic ALCL and patients without bone marrow examination were excluded from the study. The final study group included 107 patients with an ALCL first presenting in the skin, who had been staged completely.

Results: Staging procedures showed the presence of extracutaneous disease in 20 patients, but bone marrow involvement was not detected in any of the 107 patients. Moreover, only one patient developed bone marrow involvement during follow-up (median follow-up period: 69 months)

Conclusions: Bone marrow examination has limited value in the staging of patients with an ALCL first presenting in the skin, and should be performed only in selected cases.
INTRODUCTION

Primary cutaneous CD30-positive anaplastic large cell lymphoma (C-ALCL) is defined as a malignant lymphoma composed of large cells with an anaplastic, pleomorphic or immunoblastic cytomorphology and expression of the CD30 antigen by more than 75% of tumour cells. Clinically, C-ALCL most often present with solitary or localized skin lesions; they may regress spontaneously, often relapse in the skin, but uncommonly disseminate to extracutaneous sites and have an excellent prognosis with a 10-year disease-specific survival (DSS) of approximately 90%. Radiotherapy or, in cases of a small solitary tumour surgical excision are the preferred modes of treatment, while systemic chemotherapy is only required in exceptional cases.

C-ALCL must be differentiated from systemic ALCL involving the skin secondarily. These systemic ALCLs consist of lymphomas which are associated with the t(2;5) translocation resulting in expression of the anaplastic large cell lymphoma kinase (ALK) protein (ALK-positive ALCLs) and of lymphomas which are not (ALK-negative ALCLs). Importantly, C-ALCLs are not associated with the t(2;5) translocation and do not express ALK protein. Both ALK-positive and ALK-negative ALCL with secondary cutaneous involvement have a worse prognosis and require a completely different therapeutic approach as compared to C-ALCL.

According to the criteria of the World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) classification for cutaneous lymphomas a diagnosis of C-ALCL can only be made after adequate staging procedures have been conducted, including a bone marrow biopsy. Consistently, current guidelines of the Dutch Cutaneous Lymphoma Group (DCLG) require complete staging including a bone marrow biopsy. However, recent data from the registry of the DCLG show that in an increasing number of patients with an ALCL presenting in the skin, in particular those presenting with a solitary tumour that has resolved spontaneously or has been excised completely, staging is incomplete and particularly a bone marrow biopsy is not always performed. Moreover, in a recently published consensus paper from the International Society for Cutaneous Lymphomas (ISCL) and the European Organization of Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Group, it was suggested that in indolent cutaneous lymphomas such as C-ALCL, bone marrow examination is recommended, but not required, unless indicated by other staging investigations.

Studies on the incidence of extracutaneous manifestations and, in particular, a positive bone marrow biopsy, in patients with an ALCL first presenting in the skin have never been published. In the present study, we therefore evaluated retrospectively the results of staging in a large group of such patients. The main purpose of this study was to determine the incidence of bone marrow involvement in these patients in order to find out if our current policy to advice bone marrow examination in all patients with an ALCL first presenting in the skin should be maintained or that a bone marrow biopsy should be performed only in selected cases.

PATIENTS AND METHODS

All patients presenting with skin lesions with the histological and immunophenotypical features of an ALCL between 1986 and 2007 were retrieved from the database of the DCLG (n = 157). All cases in the Dutch registry have been reviewed by an expert panel of dermatologists and
hematopathologists before entry in this database. Moreover, for each patient in this database follow-up is collected yearly. These procedures guarantee that this initial study group did not contain patients with lymphomatoid papulosis or transformed mycosis fungoides, both of which may show histological features similar to a (C-)ALCL. From the initial group of 157 patients, patients with a history of systemic ALCL who developed specific skin lesions during follow-up (n = 4) and patients without bone marrow examination (n = 46) were excluded from the study. The final study group consisted of 107 patients with an ALCL first presenting in the skin. Staging investigations had consisted of physical examination, full and differential blood cell count and serum biochemistry, computed tomographic scanning of chest and abdomen and other imaging studies if required, and a bone marrow biopsy.

Statistical calculations were performed using SPSS 14.0 (SPSS Inc., Chicago, IL, U.S.A.). DSS and overall survival (OS) were calculated from date of diagnosis until death from lymphoma and death from any cause respectively, or last follow-up without an event. Survival curves were estimated using the Kaplan-Meier technique and comparison between curves was done by log-rank testing.

RESULTS

The median age at diagnosis of our final study group was 57 years (Table 1). In total 72 patients were male (67%) and 35 patients were female (33%). Median follow-up was 69 months (range 1-308 months). Staging investigations showed no evidence of extracutaneous disease in 87 of 107 cases (81%), which were therefore classified as C-ALCL. In the remaining 20 patients staging was positive. In 11 of these 20 cases there was only involvement of peripheral lymph nodes draining a skin area containing ALCL lesions, suggesting that these were C-ALCLs with secondary lymph node involvement. The other nine patients showed more widespread disease with involvement of central lymph nodes and/or other extracutaneous localizations such as lung (three patients), central nervous system (two patients), bone (two patients), liver and spleen (one patient) and nasopharynx (one patient). Bone marrow involvement by ALCL was not observed in any of the 107 cases investigated. However, bone marrow biopsies showed B-cell chronic lymphocytic leukemia (B-CLL) in four cases (4%) and myelodysplastic syndrome in one case (1%). Patients with negative staging results and patients with positive staging results had a 5-year DSS of 90% and 51%, respectively (p = 0.001; Figure 1), whereas the 5-year OS was 80% and 51%, respectively (p = 0.144).

DISCUSSION

The results of the present study indicate that bone marrow examination has limited clinical value in normal staging work-up of patients with an ALCL first presenting in the skin. Bone marrow involvement was not detected at the time of diagnosis in any of the 107 patients investigated, including 20 patients with extracutaneous disease at other sites. Moreover, in the database of the DCLG, which collects follow-up information for every included patient every year, bone marrow involvement during follow-up had only once been recorded. In this particular patient all staging investigations at diagnosis were negative, but six months after diagnosis involvement of multiple
Peripheral lymph nodes, spleen, adenoid and bone marrow was observed. In addition, none of the 46 patients in whom bone marrow examination had not been performed initially, and who were therefore not included in the present study, had developed bone marrow involvement during follow-up. Taken together, these observations indicate that bone marrow involvement is not or is rarely found in ALCL first presenting in the skin, and argue against bone marrow examination as an essential part of initial staging procedures.

An unexpected finding in our study was the presence of a B-CLL in bone marrow biopsies of 4 of 107 patients. The coexistence of C-ALCL and B-CLL is uncommon with only a few cases published. Several hypotheses exist for the coexistence of both T- and B-cell malignancies, including an origin from a common stem cell progenitor, exposure to carcinogens or viruses affecting oncogenes or tumour suppressor genes of both T- and B-cell precursors, and coincidental occurrence of two unrelated neoplasms.

A limitation of the present study is that the results of bone marrow examinations were obtained from a database, and not by review of the original bone marrow specimens. Current guidelines for bone marrow evaluation request a biopsy specimen with a length of at least 2 cm and with sufficient marrow fields, and in the case of doubtful infiltration additional immunohistochemistry. Consistently, in a study of ALK-positive ALCL, the incidence of bone marrow involvement increased from approximately 10% when only haematoxylin and eosin sections were analyzed, to 30%, when immunohistochemical stainings for CD30, epithelial membrane antigen and/or ALK were used. Considering the fact that our patients were collected during a period of 20 years, it cannot be excluded that our series contain a number of false-negative marrows, as some biopsies from the early years might not meet current standards.
and immunohistochemistry was not widely used at that time. However, no differences were observed between bone marrows included in the database before and after 2000, and we therefore believe that the number of false-negative bone marrows will be minimal, and will not significantly influence our conclusions. Moreover, even if we assume a small number of false-negative bone marrows, the clinical consequences of not performing a bone marrow biopsy are expected to be minimal. It is of interest that the 5-year DSS and OS for the 46 patients in whom a bone marrow biopsy had initially not been performed were 95% and 72%, respectively, which is similar to that of the group of C-ALCL (Table 1).

In conclusion, the results of the present study indicate that bone marrow examination has limited value in the staging of patients with an ALCL first presenting in the skin, and should be performed only in selected cases, such as patients with other positive staging assessments (e.g. involved lymph nodes) or rare patients requiring multiagent chemotherapy.

Table 1. Staging results and survival data of anaplastic large cell lymphomas first presenting in the skin, from the database of the DCLG.

<table>
<thead>
<tr>
<th>Metric</th>
<th>Number</th>
<th>5-year DSS (OS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients with ALCL</td>
<td>157</td>
<td>-</td>
</tr>
<tr>
<td>History of non-cutaneous ALCL</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Bone marrow not investigated</td>
<td>46</td>
<td>95% (72%)</td>
</tr>
<tr>
<td>Final study group</td>
<td>107</td>
<td>81% (74%)</td>
</tr>
<tr>
<td>Male:female</td>
<td>72:35</td>
<td>-</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>57 (7-88)</td>
<td>-</td>
</tr>
<tr>
<td>Median duration of follow-up, months (range)</td>
<td>69 (1-308)</td>
<td>-</td>
</tr>
<tr>
<td>Staging negative</td>
<td>87</td>
<td>90% (80%)</td>
</tr>
<tr>
<td>Staging positive*</td>
<td>20</td>
<td>51% (51%)</td>
</tr>
<tr>
<td>Involvement of bone marrow</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

*Bone marrow involvement by B-CLL is not included in this category
REFERENCES


