Primary B-cell lymphomas of the skin

H. Kerl & L. Cerroni

Department of Dermatology, University of Graz, Austria

Summary

Primary B-cell lymphomas of the skin are not as rare as generally believed. They are defined as malignant B-cell proliferations presenting with cutaneous involvement alone and no evidence of extracutaneous manifestations over a period of at least six months when complete staging has been performed. The major subtypes are follicle center-cell lymphoma of the head and trunk, immunocytoma and large B-cell lymphoma of the leg (EORTC classification 1996). Also of interest is the recently recognized marginal-zone B-cell lymphoma. Primary B-cell lymphomas of the skin differ significantly from nodal lymphomas. Awareness of their special clinical behavior should prevent unnecessarily aggressive treatment.

Key words: diagnosis, major subtypes, primary cutaneous B-cell lymphomas, treatment

Introduction

In the past, studies on malignant lymphoproliferative disorders of the skin concerned mostly lymphomas of the T-cell type. In recent years, through the synthesis of classical morphologic studies and progress in immunology and molecular biology, it has been recognized that primary B-cell lymphomas arising in the skin (PCBCL) represent a distinct and very important group of extranodal lymphomas [1-5]. They occur far more frequently than generally believed and have been considerably underestimated. It has also become clear that many lymphoid proliferations previously classified as cutaneous B-cell pseudolymphomas are in reality examples of PCBCL with a favorable clinical behavior [6]. It is extremely important to emphasize that treatment of PCBCL is completely different from therapy schedules applied for other malignant lymphomas.

In the following discussion, we will illustrate the most common types of PCBCL employing a modified scheme of the recently proposed EORTC classification for cutaneous lymphomas, which is based on well-defined clinical criteria as well as on morphologic, immunophenotypic, and genetic patterns (Table 1) [7, 8].

PCBCL is defined as presence of cutaneous disease alone with no evidence of extracutaneous manifestations over a period of at least six months after complete staging procedures. PCBCL must be differentiated from extracutaneous B-cell lymphomas with skin involvement, which show a poor prognosis and require aggressive therapeutic regimens.

Primary cutaneous B-cell lymphomas with indolent behavior

Follicle-center lymphoma of the head and trunk

Follicle-center lymphoma (FCL) of the head and trunk is a neoplasm of B lymphocytes of the germinal center [1-3, 7, 9]. It represents a very common subtype of PCBCL. Clinically, patients present with solitary or grouped reddish papules, plaques, or tumors which, especially on the trunk, can be surrounded by erythematous patches. Preferential locations are the forehead, scalp, and back. Lesions arising on the back were classified in the past as 'reticulohistiocytoma of the dorsum' or 'Crosti's lymphoma' [10]. The prognosis of patients with cutaneous FCL is favorable. Recurrences are observed in about 50% of the cases, but dissemination to internal organs is rare.

Histopathologically, FCL is usually characterized by a diffuse growth pattern. A typical follicular pattern is observed only rarely. Centroblasts and centrocytes predominate within the neoplastic infiltrate, admixed with a variable number of immunoblasts, small lymphocytes and histiocytes, and in some cases eosinophils and plasma cells.

Table 1. EORTC classification of cutaneous B-cell lymphomas.

<table>
<thead>
<tr>
<th>Cutaneous B-cell lymphomas with indolent behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Follicle-center lymphoma of the head and trunk</td>
</tr>
<tr>
<td>• Immunocytoma</td>
</tr>
<tr>
<td>Cutaneous B-cell lymphomas with intermediate behavior</td>
</tr>
<tr>
<td>• Large B-cell lymphoma of the leg</td>
</tr>
<tr>
<td>Provisional types of cutaneous B-cell lymphomas</td>
</tr>
<tr>
<td>• Intravascular cutaneous B-cell lymphoma</td>
</tr>
<tr>
<td>• Marginal-zone B-cell lymphoma</td>
</tr>
<tr>
<td>• Plasmacytoma</td>
</tr>
</tbody>
</table>

* The EORTC Cutaneous Lymphoma Study Group held classification/consensus meetings in Berlin in 1995 and in Amsterdam in 1996.
Tumor cells express monotypic surface immunoglobulins and B-cell-associated antigens (CD19, CD20, CD79a). They are CD5 and CD43 negative. In contrast to FCL of the lymph nodes, CD10 and bcl-2 protein expression are found only rarely in primary cutaneous FCL [11]. In about 20% of FCLs of the skin, an aberrant positivity for MT2 (CD45RA) in neoplastic germinal centers can be observed [12]. MT2 positivity is never found in reactive germinal centers, and can be considered a useful tool in differentiating cutaneous FCL from B-cell pseudolymphomas (i.e., lymphocytoma cutis).

Clonal rearrangement of JH genes can be demonstrated in the majority of the cases. The interchromosomal 14;18 translocation, in contrast, is found only rarely [11].

Synthesis of morphologic, immunohistochemical, and molecular data suggests that FCLs originating in the lymph nodes and the skin, though characterized by a similar morphologic pattern, have different pathogenetic mechanisms.

**Immunocytoma**

Immunocytomas (ICs) are neoplastic proliferations of lymphoplasmacytoid cells, small lymphocytes, and plasma cells [4, 13]. They appear clinically as solitary, bluish red or reddish brown plaques or dome-shaped tumors. Predilection sites are the lower extremities. In a few cases, clustered tumors or, rarely, multiple lesions may be observed. ICs can arise in areas affected by acrodermatitis chronica atrophicans, and may therefore be linked to infection by *Borrelia burgdorferi* [14]. The prognosis is excellent, although local recurrences can be observed.

The histopathologic pattern is characterized by dense nodular or diffuse infiltrates within the entire dermis and subcutis. There is no epidermal involvement. Cytomorphologically lymphoplasmacytoid cells and small lymphocytes predominate. In addition, plasma cells, which are frequently located in subepidermal aggregations or at the periphery of the infiltrate, few immunoblasts, histiocytes, and eosinophils are found. PAS-positive intranuclear inclusions (Dutcher bodies) are usually observed in lymphoplasmacytoid cells and represent a very useful diagnostic clue. Reactive germinal centers can be found scattered rarely within the infiltrate.

Tumor cells express monotypic cytoplasmic immunoglobulins. Lymphoplasmacytoid cells and plasma cells are negative with the pan-B-cell-associated antibodies CD19 and CD20, but may express CD79a. Staining with CD5 yields negative results. An aberrant positivity for CD43 is found in about 50% of the cases. Molecular analysis shows rearrangement of JH genes in the majority of the cases.

**Marginal-zone lymphoma**

Marginal-zone lymphoma (MZL) has been recently recognized as a distinct variant of low-grade malignant PCBCL [15]. It is closely related to immunocytoma and MALT lymphomas [16–18]. The term SALT (skin-associ-
Primary cutaneous B-cell lymphomas with intermediate behavior

Large B-cell lymphoma of the leg

Primary cutaneous large B-cell lymphomas (LBCLs) are neoplasms of B lymphocytes consisting predominantly of large cells with features of centroblasts, large centrocytes, and immunoblasts. Clinically, solitary or grouped tumors and plaques are located most frequently on the lower leg [22]. Tumors with similar morphologic features can arise also on body areas other than the lower extremities [23]. Ulceration is not uncommon. Older females are more frequently affected. The prognosis is more unfavorable than in other types of PCBCL, with a five-year survival rate of approximately 50%.

Histology is characterized by dense, diffuse infiltrates of large cells in the entire dermis and subcutis. Infiltration of the epidermis simulating a T-cell lymphoma can be observed sometimes. Cytomorphologically neoplastic cells resemble either immunoblasts or centroblasts. Mitotic figures are frequent. Often an exact classification is not possible. It has been proposed that most cases of LBCL represent large-cell lymphomas originating from the lymphocytes of the germinal center [23].

Immunohistology reveals monotypic surface immunoglobulins. Neoplastic cells are CD19 and CD20 positive, and frequently express the bcl-2 protein. Molecular analysis shows rearrangement of the J_H genes in most cases. The t(14;18) is not present.

LBCL must be differentiated from anaplastic large-cell lymphoma and from nonlymphoid tumors such as metastases among others. The clinicopathologic pattern, together with immunohistochemical and molecular features of the lesion, allows the correct classification of these lesions in most cases.

Treatment of primary cutaneous B-cell lymphoma

Several therapeutic options can be considered in the treatment of patients with PCBCL. The choice of one particular modality of treatment depends on several factors, including the type of PCBCL, the number of lesions, and the age and general condition of the patient.

Solitary or clustered lesions can be treated by radiotherapy, with eventual excision of smaller lesions. This treatment is usually sufficient to induce complete remission of long duration in PCBCL with indolent behavior.

There exist a few reports on the utility of systemic antibiotics in PCBCL with indolent behavior. The notion that at least a proportion of PCBCLs may be linked with infection by Borrelia burgdorferi provides a rationale for this treatment. This can be paralleled with Helicobacter pylori-associated MALT lymphomas, which in some cases can be cured by antibiotic therapy eradicating Helicobacter pylori infection [24, 25]. Also, subcutaneous injections of interferon α-2a have been used in a few patients to induce remission of generalized lesions [26].

PCBCLs with indolent behavior presenting with generalized lesions represent a difficult therapeutic problem. In the past, these patients were treated often with systemic polychemotherapy (i.e., CHOP) or with radiotherapy. The accumulation of data concerning the favorable behavior of most PCBCLs, however, also justifies a ‘watchful waiting’, at least in cases where aggressive therapies are difficult to apply owing to advanced age or general condition of the patients.

The treatment of choice of LBCL presenting with localized or grouped lesions is radiotherapy. Sometimes surgical excision can be considered systemic. Systemic involvement requires polychemotherapy according to standard regimens.

References

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Correspondence to:
H. Kerl, MD
Department of Dermatology
University of Graz
Auenbruggerplatz, 8
A-8036 Graz
Austria