Abstract. Primary B-cell lymphomas of the skin 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, marginal zone lymphoma and large B-cell lymphoma of the leg (EORTC classification 1997). Primary B-cell lymphomas of the skin differ significantly from nodal lymphomas especially with respect to their clinical behavior. Pseudolymphomas of the skin are inflammatory diseases that simulate malignant lymphomas either clinically, histopathologically, or both. Particular pseudolymphomas may mimic cutaneous B-cell lymphomas. The most important examples are: lymphomatoid drug reactions, lymphocytoma (Borrelia burgdorferi as causative agent), arthropod reactions, pseudolymphomas associated with vaccinations or tattoos and inflammatory pseudotumors. In recent years, new immunohistological and molecular techniques have added important criteria for the differentiation of cutaneous lymphomas from pseudolymphomas. (Keio J Med 50 (4): 269-273, December 2001)

Key words: primary cutaneous B-cell lymphomas, cutaneous pseudolymphomas, immunohistology, genetic features, differential diagnosis

Studies on malignant lymphoproliferative disorders of the skin have especially concerned lymphomas of the T-cell type. In recent years great attention has been also accorded to the group of primary cutaneous B-cell lymphomas, which occur far more frequently than generally believed. Patients with primary cutaneous B-cell lymphomas can be divided into 2 groups: primary cutaneous B-cell lymphomas reveal cutaneous disease alone with no evidence of extracutaneous manifestations over a period of at least 6 months when a complete staging examination has been performed. Patients with secondary cutaneous B-cell lymphomas show extracutaneous disease and subsequent development of skin lesions. The European Organization for Research and Treatment of Cancer (EORTC)-Cutaneous Lymphoma Project Group proposed a new classification for primary cutaneous lymphomas in 1997. The most common types of primary cutaneous B-cell lymphomas are cutaneous follicle center-cell lymphoma, cutaneous marginal zone B-cell lymphoma, and large B-cell lymphoma of the leg. It is extremely important to emphasize that primary cutaneous B-cell lymphomas differ significantly from their nodal counterparts revealing in most patients an excellent prognosis. Awareness of these special prognostic aspects (Fig. 1) should prevent unnecessarily aggressive treatment schemes.

Follicle Center-cell Lymphoma

Primary cutaneous follicle center-cell lymphoma is a relatively common cutaneous B-cell lymphoma, characterized by the neoplastic proliferation of centrocytes and centroblasts confined to the skin. To this group belong most of the patients diagnosed in the past as "reticulohistiocytoma of the dorsum" or "Crosti's lymphoma", typically located on the back. The prognosis of patients with cutaneous follicle center-cell lymphoma is favorable (survival rate 94%) (Fig. 1A). Clinically solitary or grouped reddish-brown to reddish-blue papules, plaques or tumors surrounded by

Presented at the 1203rd Meeting of The Keio Medical Society in Tokyo, April 10, 2001.
Reprint request to: Dr. Helmut Kerl, Department of Dermatology, University of Graz Auenbruggerplatz 8, A-8036 Graz, Austria, e-mail: helmut.kerl@uni-graz.at

Fig. 1 Survival curves of different groups of primary cutaneous B-cell lymphomas. A) Primary cutaneous follicle center-cell lymphoma. B) Primary cutaneous immunocytoma/marginal zone B-cell lymphoma. C) Large B-cell lymphoma of the leg.

Erythematous patches can be seen. Preferential locations are the head (scalp, forehead) and the back. Recurrences are observed in about 50% of the cases, but dissemination to internal organs is rare.

Histopathologically, follicle center-cell lymphoma is usually characterized by a diffuse growth pattern with proliferation of neoplastic centrocytes and centroblasts. A typical follicular pattern, however, is observed in a distinct proportion of patients with follicle center-cell lymphoma as demonstrated by laser beam microdissection followed by PCR-analysis of $J_H$ gene rearrangement (Fig. 2). Within the neoplastic infiltrate of centrocytes and centroblasts, a variable number of immunoblasts, small lymphocytes, histiocytes, and in some cases eosinophils and plasma cells can be admixed. The tumor cells express monotypic surface Ig- and B-cell-associated antigens (CD20, CD79a), reveal CD21 (DRC = dendritic reticulum cells)-positivity and are CD5 negative, whereas variable results are found for CD10 (+/-) and bcl-6 (+/-) depending on the histopathological pattern. Staining for bcl-2 protein frequently yields negative results, which is a major difference from nodal follicle center-cell lymphoma.

Clonal rearrangement of $J_H$ genes can be demonstrated in the majority of the cases. The interchromosomal 14;18 translocation typically observed in nodal follicular lymphomas is usually not found in primary cutaneous follicle center-cell lymphoma.
Marginal Zone B-cell Lymphoma

Marginal zone B-cell lymphoma has been recognized as a distinct variant of a primary cutaneous B-cell lymphoma. It is closely related to immunocytoma and MALT-lymphomas. The term SALT (skin-associated lymphoid tissue)-lymphoma has also been used for these tumors. Clinically, there are solitary or clustered erythematous patches, papules, nodules, or plaques located on the upper extremities or trunk (Fig. 3). Generalized lesions can be observed in a minority of patients. The prognosis is excellent despite frequent recurrences. In a recent study of 62 patients with primary cutaneous marginal zone B-cell lymphoma we found a survival of 98% (Fig. 1B).

Histology is characterized by dense nodular, diffuse or patchy perivascular/periadnexial infiltrates throughout the entire dermis and subcutaneous fat. At scanning power, a characteristic pattern can be observed: dark areas composed of small lymphocytes (lymphoid nodules) are surrounded by and contrast with pale areas containing medium-sized cells with indented nuclei and abundant pale cytoplasm (marginal zone cells, centrocyte-like cells). Reactive (polytypic) germinal centers are a frequent finding; lymphoplasmacytoid cells, plasma cells, blasts, and eosinophils are also present. Immunohistology shows a monotypic intracytoplasmic expression of immunoglobulins in about 70% of cases (Fig. 4). Neoplastic cells are positive for B-cell-associated markers (CD20, CD79a) and display negativity for CD5, CD10 and bcl-6. A typical intracytoplasmic granular reactivity for the monocytoid B-cell-associated antibody KiM1p is frequently found. Molecular analysis reveals rearrangement of JH genes in about 2/3 of the cases.

Large B-cell Lymphoma of the Leg

Primary cutaneous large B-cell lymphomas are neoplasms of B-lymphocytes consisting predominantly of large cells with features of centroblasts, large centrocytes, and immunoblasts. Clinically, reddish-brown to bluish-red solitary or grouped tumors and plaques which are located most frequently on the lower legs can be observed (Fig. 5). Tumors with similar morphologic features can arise also on body areas other than the lower extremities. Ulceration is not uncommon. Older females are frequently affected. The prognosis is more unfavorable than in other types of primary cutaneous B-cell lymphoma, with a 5-year survival rate of approximately 60% (Fig. 1C).

Histology is characterized by dense, diffuse infiltrates of large cells in the entire dermis and subcutis. Cyto-morphologically neoplastic cells resemble either immunoblasts or centroblasts. Mitotic figures are frequent. It has been proposed that most cases of primary cutaneous large B-cell lymphoma represent large-cell lym-
important cutaneous B-cell pseudolymphomas originating from lymphocytes of the germinal center.

Immunohistology reveals monotypic surface immunoglobulins and/or cytoplasmic Ig. Neoplastic cells are CD20- and bcl-2-positive.

Molecular analysis shows rearrangement of JH genes in most cases. The t(14;18) is not present.

Criteria for the Differential Diagnosis of Cutaneous B-cell Lymphomas from B-cell Pseudolymphomas

Cutaneous pseudolymphomas are inflammatory diseases that simulate malignant lymphomas either clinically, histopathologically, or both. They can be divided into T-cell predominant types (examples: chronic actinic dermatitis, lymphomatoid contact dermatitis) and B-cell predominant pseudolymphomas (Table 1).

The differentiation of cutaneous B-cell lymphomas from B-cell pseudolymphomas represents one of the most difficult problems in dermatology. Certain clinical features may be helpful. Pseudolymphomas present themselves often as a single papule or nodule with a smooth surface on a special location (e.g., earlobe), whereas lymphomas tend to be associated with many tumors and can reveal ulceration. Pseudolymphomas occur frequently in children, in contrast to lymphomas.

In pseudolymphomas there may be a history of a causative event (e.g., borrelia infection), whereas in lymphomas the cause is usually obscure.

By conventional microscopy, as a rule, infiltrates in pseudolymphomas are less dense and less deep than those of lymphomas. They usually are relatively symmetrical, rather well circumscribed, and more dense in the upper part of the dermis than in the lower part. Often the infiltrates assume a wedge-shaped pattern. In contrast, the infiltrates of lymphomas tend to be more massive, asymmetrical, and poorly circumscribed. Because there are many exceptions to each of these “rules”, differentiation between the inflammatory and neoplastic processes of entirely different prognostic potentiality often is impossible on histopathologic grounds alone.

Immunohistological features can be studied on routinely fixed, paraffin-embedded biopsy specimens. Malignant cell populations of B-lymphocytes usually show a monoclonal restriction to either κ or λ light chain, whereas benign infiltrates exhibit a polyclonal pattern with expression of both light chains. Unfortunately, however, there are several cases of B-cell lymphoproliferative disorders, both benign and malignant, in which the cells do not express immunoglobulins. A useful clue for the diagnosis of follicle center-cell lymphomas with a follicular growth pattern is the diminished proliferation activity of malignant germinal centers as outlined by the Ki67/MIB-1 antibody. Reactive germinal centers show a high proliferation, whereas malignant ones often are characterized by a much lesser degree of positivity.

About 80% of follicular lymphomas and 15% to 30% of high-grade malignant non-Hodgkin’s lymphomas in the lymph nodes are characterized by the t(14;18), which is associated with an overexpression of the bcl-2 oncogene. By contrast, investigation of cutaneous cases showed that the t(14;18) and the bcl-2 protein expression are rare in primary cutaneous B-cell lymphomas. Thus, in the skin bcl-2 protein expression cannot be used as a criterion for differentiation of follicle center-cell lymphoma from B-pseudolymphoma with follicular pattern.

It has been demonstrated recently, that CD10 and bcl-6 expression, which support a germinal center-cell origin, may be useful in the differential diagnosis of follicle center-cell lymphomas from pseudolymphomas.

Low-grade malignant lymphomas of B-cell lineage may show aberrant expression of some T-cell-associated markers. CD5 is a pan-T-cell marker that reacts with the cells of most cases of B-cell chronic lymphocytic leukemia. Normal B-lymphocytes are CD43 negative, but several low-grade B-cell lymphomas are CD43 positive. The detection of an aberrant phenotype of the B-
Fig. 6 Primary cutaneous follicle center-cell lymphoma. CD10 positivity of the follicle center-cells. CD10 is also expressed in aggregated cells within extrafollicular areas. Cutaneous pseudolymphomas, by contrast to cutaneous follicle center-cell lymphoma, reveal CD10 immunoreactivity limited to the follicle centers.

lymphocytes (CD20+, CD5+, CD43+) is considered as a sign of malignancy.

High-grade malignant cutaneous B-cell lymphomas often show partial loss of one or more B-cell-associated antigens (CD20).

Concerning the molecular analysis of cutaneous B-cell lymphoid proliferations the detection of clonal IgH-gene rearrangements using PCR is a very valuable method for assessing clonality. Highly sensitive and specific PCR methods are however required. A helpful technique for the determination of the lineage of neoplastic cells in cutaneous follicle center-cell lymphoma is represented by molecular genetic analysis of single cells isolated by a laser-based microdissection technique. This method allows to isolate a group of cells or single cells for PCR analysis of IgH genes (Fig. 2B).

Looking towards the future cutaneous lymphomas and pseudolymphomas will soon be defined in relation to their molecular abnormalities and their etiology or pathogenesis. This information will encourage further progress and the development of better therapies.

References


