Primary cutaneous B-cell lymphomas. Clinical aspects and pathology

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SUMMARY

Primary cutaneous B-cell lymphomas are defined as malignant B-cell proliferations presenting with cutaneous involvement alone and no evidence of extracutaneous manifestations when complete staging has been performed. The major subtypes are: cutaneous follicle center-cell lymphoma, cutaneous marginal zone B-cell lymphoma/immunocytoma, and large B-cell lymphoma of the leg.

A correct diagnosis can be achieved only in the context of knowledge of the clinical findings. Progress in terms of classification and biology is associated with the application of modern techniques including immunohistology and laser beam microdissection followed by molecular analysis. Future definitions of primary cutaneous B-cell lymphomas will be based on their molecular abnormalities and their etiology and pathogenesis. Awareness of the special clinical behavior of primary cutaneous B-cell lymphoma should prevent unnecessarily aggressive treatment.

Primary cutaneous B-cell lymphomas occur far more frequently than generally believed (1). Patients with cutaneous B-cell lymphomas can be divided into 2 groups: Primary cutaneous B-cell lymphomas are defined as presence of disease limited to the skin after complete staging procedures have been performed. Patients with secondary cutaneous B-cell lymphomas show extracutaneous disease and subsequent development of skin lesions.

In recent years great attention has been accorded to the group of primary cutaneous B-cell lymphomas. The European Organization for Research and Treatment of Cancer (EORTC)-Cutaneous Lymphoma Project Group proposed a new classification for primary cutaneous lymphomas in 1997 (2). The most common types of primary cutaneous B-cell lymphomas are cutaneous follicle center-cell lymphoma, cutaneous marginal zone B-cell lymphoma/immunocytoma, and large B-cell lymphoma of the leg.

KEY WORDS

B-cell lymphoma, cutaneous, primary

Follicle center cell lymphoma

Primary cutaneous follicle center-cell lymphoma (Figure 1) is a relatively common cutaneous B-cell lymphoma, characterized by the neoplastic proliferation of centrocytes and centroblasts confined to the skin (3).

Clinically solitary or grouped reddish-brown to reddish-blue papules, plaques or tumors surrounded by erythematous patches can be seen. Preferential locations are the head (scalp, forehead) and the back. 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 for patients with cutaneous follicle center-cell lymphoma is favorable (5-year survival: 94% in 60 patients, evaluated in a recent study) (4).

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 cases with follicular center-cell lymphoma as demonstrated by laser beam microdissection followed by PCR analysis of J_H gene rearrangement (3). 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 histopathologic pattern. Staining for bcl-2 protein is frequently negative, which is a major difference from nodal follicle-

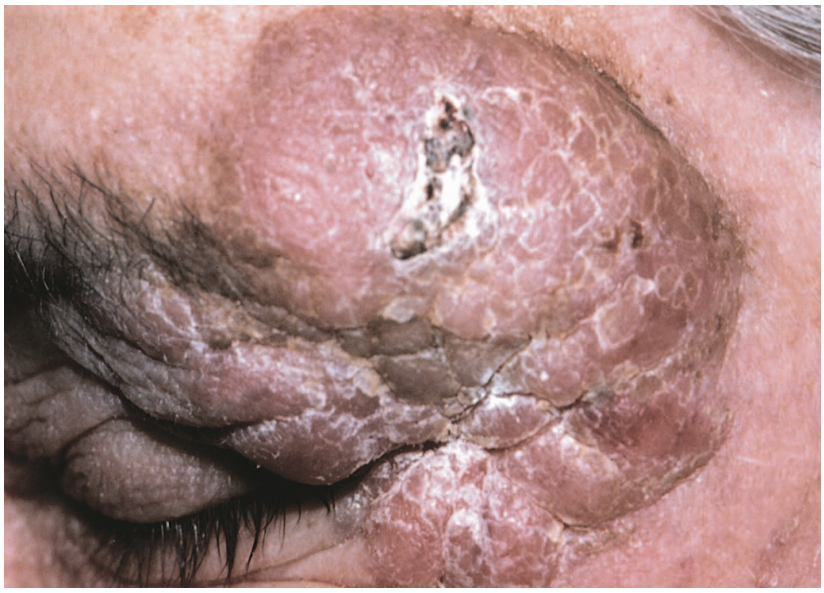


Figure 1. Primary cutaneous follicle center cell lymphoma.

Figure 2. Primary cutaneous marginal B.cell lymphoma.

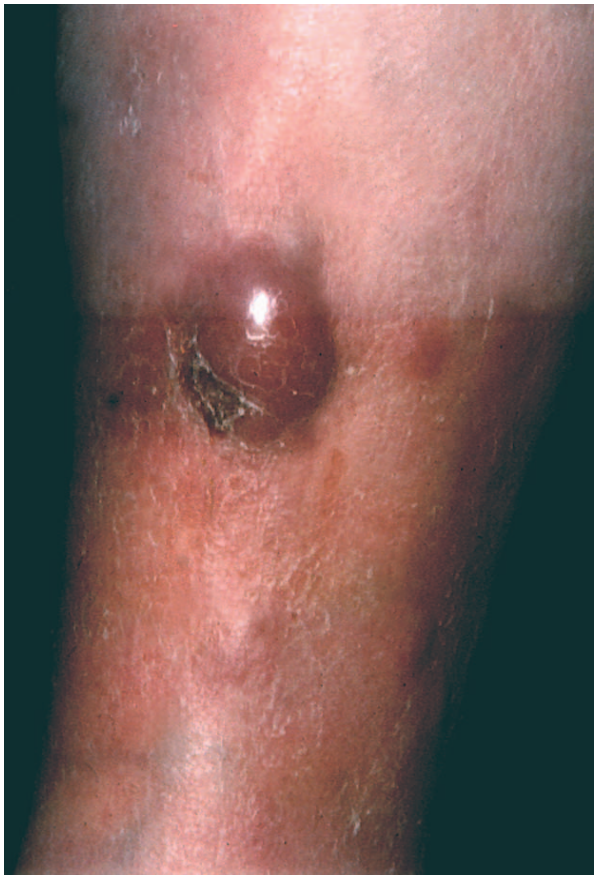
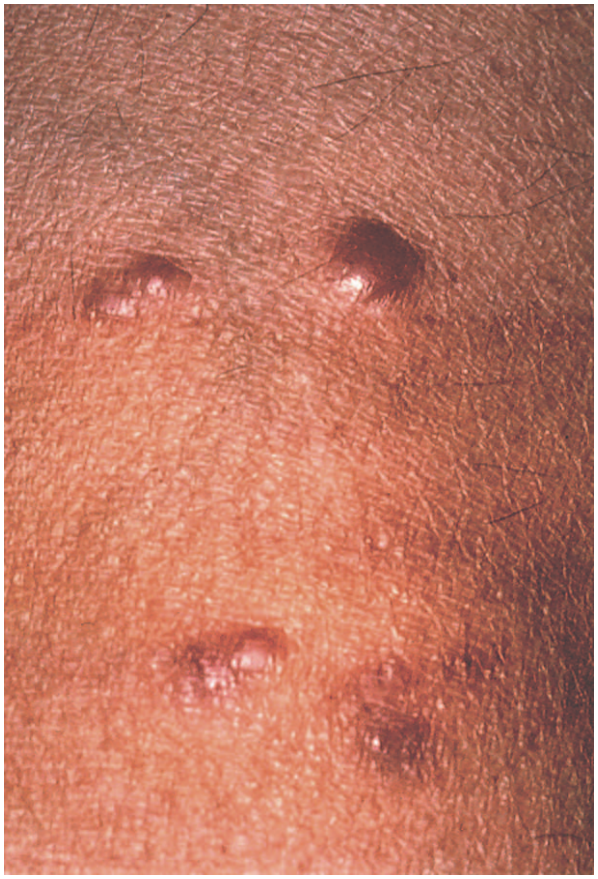


Figure 3. Primary cutaneous large B-cell lymphoma of the leg.



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

Synthesis of morphologic, immunohistochemical and molecular data suggests that follicle center cell lymphomas originating in the lymph nodes and the skin, though characterized by a similar morphologic pattern, have different pathogenetic mechanisms. However, patients with primary cutaneous follicle center cell lymphomas show an indolent course, irrespective of the histopathologic and cytomorphologic features of the infiltrate, and aggressive therapy is not justified.

Table. Therapy of primary cutaneous B-cell lymphomas.

- Radiotherapy (local)
- Surgical excision
- Alpha-interferon
- Chemotherapy
- Anti-CD20 (Rituximab)
- Corticosteroids
- Antibiotic treatment

Frequently combinations are used (example: CHOP + Rituximab for large B-cell lymphoma [11]).

Marginal zone B-cell lymphoma

Marginal zone B-cell lymphoma (Figure 2) is a distinct variant of primary cutaneous B-cell lymphoma (5, 6). It is closely related to immunocytoma and MALT lymphomas. The term SALT (skin-associated lymphoid tissue) lymphoma has also been used for these tumors (7). Clinically there are solitary or clustered erythematous patches, papules, nodules, or plaques located on the upper extremities or trunk. 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 B-cell lymphoma/immunocytoma we found a 5-year survival of 98% (4).

Histology is characterized by dense nodular, diffuse or patchy perivascular/periadnexal 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 reveals a monotypic intracytoplasmic expression of immunoglobulins in about 70% of cases. Neoplastic cells are positive for B-cell-associated markers (CD 20, 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 J_H genes in about 2/3 of the cases.

There is controversy concerning the distinction of primary cutaneous marginal zone lymphoma from immunocytoma (8). Clinically, immunocytomas usually appear as solitary or clustered bluish-red or reddish-brown plaques, or dome-shaped tumors with a smooth surface. The prognosis is excellent. The histopathologic features are characterized by dense nodular or diffuse infiltreates within the entire dermis extending into the subcutis. The pattern of growth and the infiltrates look monomorphous and differ from the "marginal zone pattern" of cutaneous marginal zone lymphoma. Cytomorphologically a predominance of small lymphocytes and lymphoplasmacytoid cells is found. A diagnostic clue is PAS-positive intranuclear inclusions (Dutcher bodies) which are sometimes observed. *Borrelia burgdorferi* probably plays a role in the pathogenesis of this lymphoma (9). This provides a rationale for treatment with antibiotics (see Table). Immunocytomas can arise in areas affected by acrodermatitis chronica atrophicans or in association with erythema chronicum migrans. There are clinical and histopathologic differences between the two groups, but because of similarities in prognosis and treatment marginal zone B-cell lymphomas and immunocytomas are classified as one single category in the EORTC-classification.

Large B-cell-lymphoma of the leg

Primary cutaneous large B-cell lymphomas are neoplasms of B lymphocytes consisiting predominantly of large cells with features of centroblasts, large centrocytes, and immunoblasts (10). Clinically, reddish-brown to bluish-red solitary or grouped tumors and plaques which are located most frequently on the lower legs can be observed (Figure 3). Tumors with similar morphological 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 58% in our recent study (4).

Histology is characterized by dense, diffuse infiltrates

of large cells in the entire dermis and subcutis. Cytomorphologically neoplastic cells resemble either immunoblasts or centroblasts. Mitotic figures are frequent. An exact classification is often not possible. It has been proposed that most cases of large B-cell lymphoma of the leg represent large-cell lymphomas originating from the lymphocytes of the germinal center.

Immunohistology shows monotypic surface immunoglobulins and/or cytoplasmic immunoglobulin. Neoplastic cells are CD20+ and bcl2+. Molecular analysis shows rearrangement of J_H genes in most cases. The t(14;18) is not present.

Large B-cell lymphoma of the leg must be differentiated from anaplastic large-cell lymphoma and from non-lymphoid tumors such as metastases among others. It represents a category that should be clearly seperated from the "diffuse" type of primary cutaneous follicle center cell lymphoma, because cytomorphology and prognosis are clearly different. The clinicopathologic pattern, together with immunohistochemical and molecular features of the tumors, allows the correct classification in most cases.

Management of primary cutaneous B-cell lymphomas

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 (4). Staging procedures for primary cutaneous B-cell lymphomas include examination of the entire integument, representative photographs of skin lesions, skin biopsies, blood investigations, bone-marrow biopsy, chest X-ray, and ultrasound sonography (superficial lymph nodes and abdomen). In cases of pathologic findings computed tomographic scans are indicated. Whole body emission tomography (PET-scan) has revealed an excellent accuracy in diagnostic imaging and treatment monitoring of lymphomas.

Several therapeutic options can be considered in the treatment of patients with primary cutaneous B-cell lymphomas (Table). The choice of one particular modality of treatment depends on several factors, including the type of lymphoma, the number of lesions, and the age and general condition of the patient.

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