Review paper

HISTOLOGICAL AND IMMUNOHISTOCHEMICAL FEATURES OF CUTANEOUS T CELL LYMPHOMAS

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ABSTRACT

Cutaneous T-cell lymphomas are malignant neoplasms of the immune system, characterized by a proliferation of neoplastic T lymphocytes within the skin. They comprise a very heterogeneous group of disorders with respect to clinical presentation, histomorphology, and prognosis. In this paper we classify T-cell lymphomas of the skin into two main groups according to the histopathological features, namely lymphomas of T-cell precursors and peripheral T-cell lymphomas (including Mycosis fungoides/Sezary-syndrome, T chronic lymphocytic leukemia, T-pleomorphic, T-immunoblastic, and T-large cell anaplastic/ Ki1$^+$ lymphomas). In addition to histopathological classification, immunohistological examination allows a correct phenotypization of most T-cell lymphomas of the skin. This technique can be performed on routinely-fixed,paraffin-embedded tissue sections. Immunohistological features may help in differentiating malignant T-cell lymphomas from T-cell pseudolymphomas of the skin, and may provide additional prognostic criteria.

KEY WORDS:
T cell lymphomas, histology immunohistochemistry, classification

INTRODUCTION

T-cell lymphomas of the skin were designated in the past as mycosis fungoides, Sezary's syndrome, malignat reticuloses, malignat lymphoma, and histiocytic and reticulum cell sarcoma. In 1975 Edelson (1) proposed the term "cutaneous T-cell lymphoma", that has been widely used in the last decade: "...this disease results from clonal proliferation of helper T cells that have an affinity for the epidermis; this has permitted unification of an artificially splintered group of disorders into the entity of cutaneous T-cell lymphoma..." .(2). Although the idea to call all T-cell lymphomas of the skin "cutaneous T-cell lymphoma"(3) is attractive, it is an oversimplification, because T-cell lymphomas of the skin show many faces and comprise a heterogeneous group of diseases with respect to clinical presentation, histopathology, immunohistochemistry, and prognosis(4-7). In this report we will discuss the histopathological and immunohistochemical features of T-cell lymphomas of the skin.

HISTOPATHOLOGIC CLASSIFICATION OF T-CELL LYMPHOMAS OF THE SKIN

T-cell lymphomas of the skin can be classified according to the normal counterpart of the neoplastic cells in the immune system (that is, T-lymphocytes in various stages of differentiation/maturation). T-lymphocytes differentiate and proliferate in two waves: the first is antigen-independent and comprises the precursor cell pool; the second wave is antigen-dependent and has the function of amplifying antigen-reactive cells and differentiating them into memory and/or effector cells. All T cells beyond the first wave of differentiation/proliferation are called peripheral T-lymphocytes(8).

According to this scheme, four categories of T-cell lymphomas of the skin can be distinguished (Table 1): 1) Lymphomas of T-cell precursors, which include prethymic and thymic T-cell lymphoma, and lymphoblastic lymphoma/leukemia; 2) Lymphomas of peripheral T-cells (post-thymic lymphomas); 3) Other T-cell lymphomas which are rarely found in the skin (Lennert's lymphoma, angioimmunoblastic lymphoma, granulomatous slack skin, midline granuloma, lymphomatoid granulomatosis, angiocentric T-cell lymphomas of the skin, etc.); 4) Unclassifiable T-cell lymphomas. This classification system has been modified after the "Updated Kiel classification for malignant lymphomas" (9) in the European Cutaneous Lymphoma Project Group (EORTC). It must be underlined, however, that approximately 15% to 20% of cases of T-cell lymphoma of the skin do not fit into this scheme.

LYMPHOMAS OF T-CELL PRECURSORS

T-lymphoblastic lymphoma/leukemia (T-ALL) is the major subtype of thymic and prethymic lymphomas of the skin. In our experience cutaneous involvement is always secondary. Histologically multinodular or diffuse dense lymphoid infiltrates are localized within the dermis and subcutaneous fat. The cells are also arranged in strands between collagen bundles. Cytomorphologically the cells are of medium size with scant cytoplasm and uniform round or oval nuclei with fine stippled or condensed chromatin and small nucleoli. Mitotic figures are frequent.

LYMPHOMAS OF PERIPHERAL T-CELLS (ACTIVATED OR MEMORY/EFFECTOR CELLS)

Chronic lymphocytic leukemia, T-cell type (T-CLL) has been reported in the skin only in a few instances. Histology shows the features of mycosis fungoides or Sezary's syndrome. The infiltrate is bandlike in the upper dermis with epidermotropism,

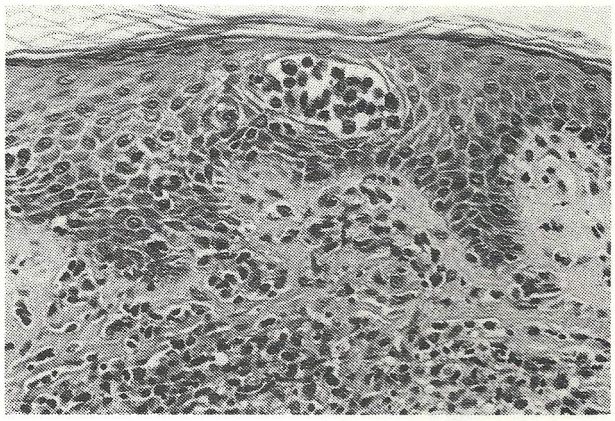

Figure 1. Mycosis fungoides. Collection of intraepidermal neoplastic lymphocytes (Pautrier's abscess) (haematoxylin-eosin).

or perivascular and periadnexal. Cytomorphologically, small lymphocytes with roundish or slightly irregular nuclei, coarse chromatin and sparse cytoplasm predominate.

Mycosis fungoides and Sezary's syndrome represent the main morphological group of T-cell lymphomas of the skin. Histologically, in the early stages they are characterized by bandlike infiltrates in the upper dermis with epidermotropism. The lymphoid cells within the epidermis are arranged in the so-called Pautrier abscesses (Figure 1) or may be aligned along the basal layer. Coarse collagen bundles are frequently found within the superficial dermis. Cytomorphologically small to medium-sized cerebriform or pleomorphic cells

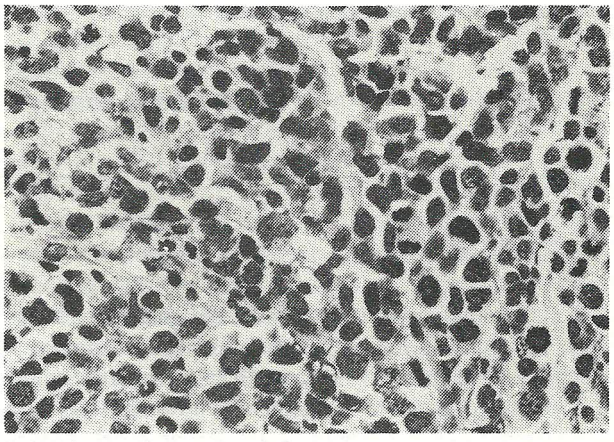

Figure2. Medium-and large-sized T-pleomorphic lymphoma. Pleomorphic lymphocytes with irregular nuclear contour. Several mitoses are present (haematoxylin-eosin).

Table 1. Classification of T-cell lymphomas of the skin according to the cytologic spectrum (From Kerl et al.,ref.5)

* Lymphomas of T-cell precursors
T-lymphoblastic lymphoma/leukemia
* Lymphomas of peripheral T-cells
T-chronic lymphocityc leukemia
Mycosis fungoides, Sezary's syndrome
T-pleomorphic lymphoma (HTLV-I-)
T-immunoblastic lymphoma
T-large cell anaplastic lymphoma ($Ki1^+$)
*Other T-cell lymphomas
* Unclassifiable T-cell lymphomas

predominate. A distinction between cerebriform and small and medium pleomorphic cells is, in our opinion, impossible. Cerebriform and pleomorphic cells probably represent the same cell type morphologically, which apparently develops in response to some type of antigens. In the late stages of the disease dense lymphoid infiltrate involve the entire dermis, often extending into the subcutaneous fat. Epidermotropism may be absent. Cytomorphological transformation into a large cell lymphoma (T immunoblastic, T medium-and large-sized pleomorphic, and T large cell anaplastic) occurs in approximately 50-60% of the cases, and is usually associated with poor prognosis and short survival(10).

T-cell pleomorphic lymphomas are characterized by small- or medium to large-sized cells. Designations that have been used to describe the nuclear irregularities of the pleomorphic cells include maple-leaf, walnut seedlike, jelly fish, banana bunch appearance, embryolike, etc. Histologically the infiltrates are dense nodular or diffuse, distributed at all levels of the dermis till the subcutaneous fat. Cytomorphologically many nuclei are twisted, lobulated, or cerebriform (Figure 2). The cytoplasm is pale grey with Giemsa staining. Mitotic figures are frequent.

T-immunoblastic lymphoma is usually found in association with mycosis fungoides/Sezary's syndrome or with systemic disease. We have observed the skin as primary site of manifestation of T-immunoblastic lymphoma only rarely. Histologic examination shows infiltrates of relatively monomorphous large cells with round, oval or slightly irregular vesicular nuclei and mostly one central prominent nucleolus (Figure 3). Cytoplasm is basophilic or pale with Giemsa staining.

T large cell anaplastic lymphoma ($Ki1^+$ lymphoma) is a recently described entity(11). Occurrence in the skin without lymph node involvement is usually associated with good

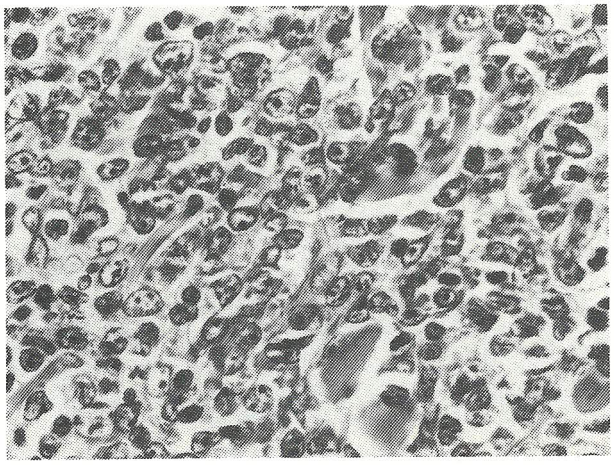

Figure 3. T-immunoblastic lymphoma. Large lymphocytes with vesicular nuclei and prominent centraly located nucleolus (haematoxylin-eosin).

prognosis and prolonged survival (12,13). Histologic examination displays infiltrates of large cells with histiocyte-like features. The nuclei are large, round or irregularly shaped, and contain one or more prominent nucleoli. Bi-nucleated cells with Reed-Sternberg-like features and multi-nucleated giant cells with bizarre shapes may also be observed (Figure 4). Cytoplasm is abundant and pale with Giemsa staining.

OTHER T-CELL LYMPHOMAS OF THE SKIN

Angiocentric immunoproliferative lesions (angiocentric lymphoma) is a term proposed by Lipford et al. in 1988 for a group of lymphoid proliferations that show prominent angiocentricity and angiodestruction (14). To this group belong also "lymphomatoid granulomatosis" and "midline granuloma". Histologically dense perivascular infiltrates are located within the superficial and deep dermis. Blood vessels are invaded and may be destroyed by the neoplastic cells. Cytomorphologically the infiltrate is often characterized by small-to medium-sized pleomorphic cells.

Lymphoepithelioid lymphoma (Lennert's lymphoma) of the skin occurs only as a secondary manifestation of a nodal lymphoma. Histologically lesions show dense nodular or diffuse infiltrates composed of small lymphocytes and large epithelioid cells. Rare immunoblasts and Reed-Sternberg-like cells may also be found.

Angioimmunoblastic lymphadenopathy ("Angioimmunoblastic lymphadenopathy with disproteinemia", "Lymphogranulomatosis X") shows a polymorphic infiltrate of plasma

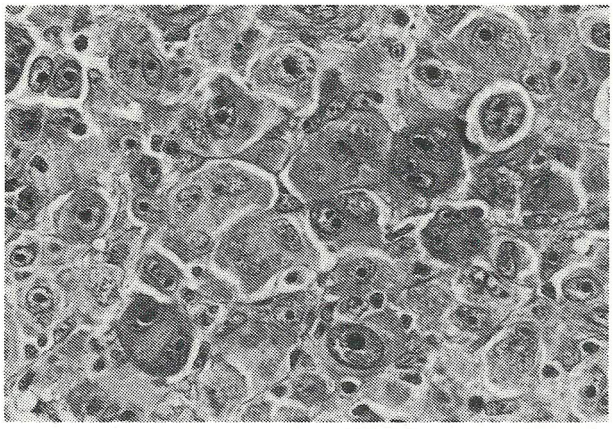

Figure 4. Large cell anaplastic (Ki1+/CD30 +) lymphoma. Large cells, binucleated cells and multinucleated giant cells with bizarre shape, prominent nucleoli and abundant cytoplasm. The patient had secondary skin involvement from nodal lymphoma (haematoxylin-eosin).

cells and immunoblasts, with pronounced proliferation of small capillaries. The histopathologic features, however, are not distinctive.

Intravascular lymphomatosis ("malignant angioendotheliomatosis", "angiotropic lymphoma") may show, in rare cases, a T-cell phenotype. Histologically dilated blood vessels in the dermis and the subcutis (venules, capillaries and arterioles) are filled with atypical lymphocytes characterized by irregular nuclei, prominent nucleoli and scant cytoplasm. Neoplastic cells are commonly enmeshed in fibrin and platelet thrombi.

T-zone lymphoma is characterized by neoplastic T-lymphocytes (mainly small lymphocytes and immunoblasts) and reactive B-cells, which may or may not form germinal centers.

Granulomatous slack skin is regarded by some authors as a granulomatous variant of mycosis fungoides. Hystologically is characterized by dense tubercoloid granulomas within the dermis with destruction of elastic tissue. Cytomorphologically pleomorphic lymphocytes and histiocytic giant cells (showing up to forty nuclei per cross section) predominate. The epidermis may show changes similar to those found in mycosis fungoides.

UNCLASSIFIABLE T-CELL LYMPHOMAS OF THE SKIN

In some cases the histopathological features of the neoplastic infiltrates do not allow a definitive classification of the lesions (i.e., presence of several cell types within the infiltrate). In other instances, the quality of the slide does not permit a proper evaluation of architectural and cytological features of the infiltrate.

IMMUNOHISTOCHEMISTRY OF T-CELL LYMPHOMAS OF THE SKIN

For nearly one century the diagnosis of cutaneous lymphomas has been based only upon clinico-pathologic correlations. Immunohistochemical techniques during the last two decades added new criteria for the differentiation of these diseases. A wide range of antibodies reactive with lymphocyte subsets and accessory cells (macrophages, dentric reticulum cells and interdigitating cells) on cryostat sections is available since more than 10 years. Recently, the development of a new generation of markers working on fixed biopsy specimens has allowed the investigation of routine histopathologic sections (15,16). Table 2 displays a rational panel of antibodies which can be used on paraffin-embedded tissue sections. The use of fixed specimens may require predigestion with proteolytic enzymes (i.e., trypsine) or pre-treatment with microwaves.

Most cases of mycosis fungoides (MF) and Sezary's

Table 2. Rational panel of antibodies for the immunohistochemical diagnosis of cutaneous lymphoproliferative diseases in routinely-fixed biopsy specimens

Antibody	CD	Specificity
anti-CD3*	3	pan-T lymphocytes
UCHL1	45RO	T lymphocytes, myeloid cells
MT1	43	T lymphocytes,myeloid cells,some B lymphocytes
MT2	45R	B-and T-lymphocytes
MB2		B lymphocytes,macrophages
L26	20	B lymphocytes
LN1	w75	B lymphocytes (germinal center)
1F8	21	dendric reticulum cells
LN2	74	HLA invariant chain
M1	15	Reed-Sternberg cells,myeloid cells
BerH2	30	activated lymphocytes,Reed-Sternberg cells
Ig		immunoglobulin's heavy and light chains
S100*		T-zone histiocytes
Mac387		macrophages, myeloid cells
KP1	68	macrophages, myeloid cells
PCNA		proliferating cells

**polyclonal antibody*

Figure 5. Sezary's syndrome. Band-like infiltrate of T-helper lymphocytes (immunoperoxidase, frozen tissue section, antibody Leu3/CD4).

syndrome in the early phases show a T-helper phenotype (CD2+, CD3+, CD4+, CD5+, CD8-), indistinguishable from that seen in benign chronic inflammatory dermatoses (Figure 5) (17-20). Only a minority of cases exhibit a T-suppressor lineage (CD2 +, CD3 +, CD4 +, CD5 +, CD8 +) (21-23). However, cases that underwent change of the phenotype from CD4-/CD8 + to CD4 +/CD8 - during the course of the disease have been described (24). The two phenotypes, helper and suppressor, bear no prognostic differences (19).

It has been previously suggested that in early stages of MF there is a loss of expression of the T-cell-associated antigens Leu8 and Leu9 (CD7), in contrast to what is seen in benign (inflammatory) cutaneous infiltrates of T lymphocytes (25,26). However, this finding has not been supported by subsequent studies showing normal Leu8 + /Leu9 + populations in early MF(18,23,27,28). In addition, some cases of benign inflammatory dermatosis also can show partial loss of one or both antigens (28-30).

Recently, we observed substantial differences between intraepidermal T-cell populations in early MF and chronic contact dermatitis (31). In inflammatory skin diseases most if not all, intraepidermal T lymphocytes express a suppressor phenotype, whereas in early MF T-suppressor lymphocytes are the minority of the intraepidermal T-cell population.

Immunohistochemical analysis of the T-cell antigen receptor (TCR) also has been advocated for differentiation of early MF from chronic, benign inflammatory conditions. The TCR consists of a constant and a variable region (32). Two types of TCR may be distinguished in respect of the constant regions, namely α/β and γ/δ heterodimers. Analysis of these receptors shows in most early MF cases (βF1+,TCRδ1-) phenotype, similar to that seen in benign cutaneous T-cell infiltrates (33). More interesting results have been obtained with the analysis of the variable regions of TCR. In benign T-cell infiltrates these differ from one cell to another, whereas malignant proliferations usually exhibit a monoclonal expression of these determinants (34-36). Jack et al. (37) could show a monoclonal population in 10 out of 16 cases of plaque or tumor stage MF using antibodies specific for the Vß8 and the Vß5 determinants. However, monoclonality could not be demonstrated in patch stage MF. The frequent expression of the same variable region in different cases of MF could reflect similarities in the etiology and/or pathogenesis (i.e.,a distinct population of virus-infected cells) of this condition (37).

In high-grade malignant cutaneous T-cell lymphoma, or advanced stages of MF-Sezary's syndrome, immunohistochemical criteria for diagnosis of malignancy include partial loss of one or more T-cell-associated antigens, aberrant helper/suppressor (CD4 +/CD8 + or CD4 -/CD8 -) phenotype, and aberrant expression of TCR (ßF1-, δ1-) (23,33,34,38,39). Activation - (CD25, CD30, CD71, HLA-DR) and proliferation-associated (Ki67, PCNA) antibodies usually are positive in these cases (23). The latter (PCNA = proliferating cell nuclear antigen/cyclin) detects a formalin-resistant antigen, and is useful for the analysis of the proliferation rate in routinely fixed biopsy specimens (40). Beside high-grade malignant T-cell lymphomas, aberrant antigen expression is a frequent finding also in lymphomatoid papulosis (41,42). This condition ca progress to lymphoma in 10-20% of the cases (43,44), and must be distinguished from CD30 + large cell anaplastic lymphoma (Ki1+ lymphoma) and from specific cutaneous manifestations of Hodgkin's disease. However, histopathologic and immunohistologic criteria often are not helpful, and in several cases differentiation can be achieved only upon clinical criteria

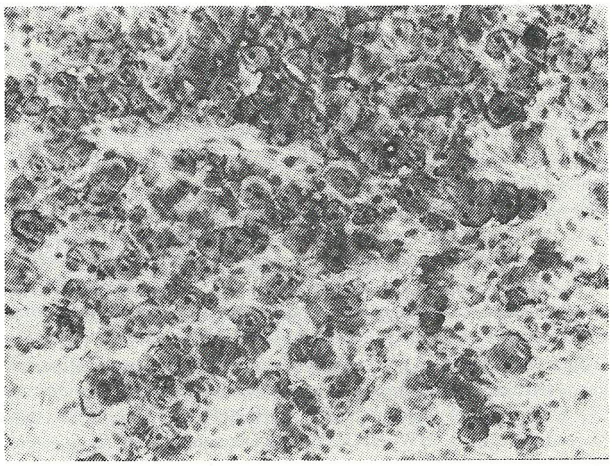

Figure 6. Large cell anaplastic (Ki1 +/CD30+) lymphoma. Neoplastic cells are positive for CD 30 (Immunoperoxidase, paraffin-embedded tissue section, antibody BerH2/CD30)

(self-healing, recurrence, size of the lesions, history, etc.).

Most of the criteria just mentioned are repeatable only on unifixed, frozen tissue sections. Antibodies reactive on routine biopsy specimens are useful in establishing the phenotype of the neoplastic cells, but, with the exception of rare cases of high-grade malignant T-cell lymphomas in which aberrant expression of B-cell associated antibodies can be observed (L26-CD20,LN1-CDw75,MB2)(45-47) do not allow the differentiation of benign from malignant cutaneous T-cell proliferations (15).

It must be emphasized that a distinct B-cell compartment, sometimes with germinal center formation, can be observed in about 30% of the cases of cutaneous T-cell lymphomas, in both the early and the advanced stages of the disease (48,49). The presence of B-cell clusters should not mislead to a diagnosis of B-cell lymphoma. Useful clues are the "normal" phenotypic features of the B lymphocytes, the polyclonal immunoglobulin expression, and the cytomorphologic-phenotypic correlatin which can be achieved in paraffin-embedded sections. In rare instances, however, the B-cells may constitute the majority of the infiltrate.

Prognosis of cutaneous T-cell lymphomas has been related to the expression of CD30, Ki67, and CD44 antigens. CD30 (BerH2,K1) is expressed on activated lymphocytes, on Hodgkin and Reed-Sternberg cells of Hodgkin's disease, and lymphocytes of so-called Ki1 + (CD30+) lymphoma (Figure 6) (12). It has been reported that primary cutaneous CD30+ lymphomas have a more favourable prognosis than primary cutaneous CD30- lymphomas (5,13,14).Ki67 detects an antigen present in proliferating cells, and is expressed in higher amounts in lymphomas with less favourable prognosis (50). Anti-CD44 is an antibody raised against the lymphocyte homing receptor (LHR), and may be related to the spreading potential of the neoplastic cells (51,52). Other adhesion molecules (LFA1-CD18,ICAM1-CD54) could be related neither to prognostic features nor to the stage of the disease (53).

CONCLUSIONS

T-cell lymphomas of the skin include a widely heterogeneous group of tumors that are difficult to classify. However, histopathological features may provide a basis for a reliable and repeatable classification. In addition, immunohistological techniques offer a new, powerful tool for the investigation of T-cell lymphomas of the skin. Examination with monoclonal antibodies also may prove useful in cases in which differentiation from benign conditions is not possible on histopathologic ground alone. However, it cannot be emphasized too strongly that the diagnosis of lymphoid proliferations in the skin must be rendered only in the context of knowledge of clinical features and findings by classical microscopy.

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