Cutaneous lymphomas: update of laboratory diagnosis.

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SUMMARY

The term primary cutaneous lymphomas designates a heterogeneous group of lymphoproliferative disorders arising from skin-homing T and B cells. The European Organization for Research and Treatment of Cancer (EORTC) classification for primary cutaneous lymphomas recognizes a limited number of cutaneous T-cell lymphomas and cutaneous B-cell lymphomas and provides a working classification for cutaneous lymphomas. Herein, the diagnostic procedures for the diagnoses of cutaneous lymphomas are discussed. Recent developments regarding immunophenotyping and immunogenotyping of cutaneous T-cell lymphomas and cutaneous B-cell lymphomas recognized in the EORTC classification are presented.

KEY WORDS

cutaneous lymphomas, T cell, B cell, classification, immunophenotyping, immunogenotyping, review

The term primary cutaneous lymphomas designates a heterogeneous group of lymphoproliferative disorders arising from skin-homing T and B cells which present in the skin with no evidence of extracutaneous disease at the time of diagnosis and six months thereafter (1-3). They are after the group of gastrointestinal lymphomas the second most common group of extranodal non-Hodgkin lymphomas with an annual incidence of 1-1.5/100,000.

Classification.

The European Organization for Research and Treatment of Cancer Classification (EORTC) uses a combination of clinical, histological, immunophenotypic, and molecular biological characteristics and provides a working classification for cutaneous lymphomas (Table I) (4). The diagnosis of cutaneous lymphomas is made by recognizing the clinical manifestations and is supported by laboratory tests. Immunophenotyping (immunologic analysis of cellular antigen expression) and immunogenotyping (molecular biology analysis of antigen receptor genes) support the conventional clinical and histopathologic analyses.

Immunophenotyping of cutaneous lymphomas.

The distinction between cutaneous lymphomas and non-lymphoid tumors of the skin is a common problem. The most useful immunohistochemical marker in

this situation is the CD45 antibody reacting with all the known isotypes of the CD45 family, also called the leukocyte common antigen family (LCA family). The antibody labels the cell membrane of almost all leukocytes and is absent on non-haematopoietic cells (5).

Mycosis fungoides is a neoplasm of T helper lymphocytes expressing the CD4 molecule and the pan-T-cell antigens CD2 and CD3 (1). They generally express the T-cell receptor molecules that consist of α and β chains (TCRαβ) (6). Partial or complete loss of the T cell associated antigens CD5 and CD7 can sometimes be observed particularly among the intraepidermal T cells and in the late stage of the disease (7, 8). This aberrant phenotype is considered circumstantial evidence of a neoplastic proliferation of T-cells. A small percentage of cases express CD8 rather than CD4. Benign reactive cutaneous diseases such as chronic eczema and psoriasis show the same pattern as that in early stage of mycosis fungoides (9). However cutaneous infiltrations in early mycosis fungoides contain significantly more CD4+ cells than those of benign lymphoid disorders. The CD4/CD8 ratio has been shown to be 4/1 in benign lymphoid infiltrates, 7/1 in the patch stage of mycosis fungoides, 14/1 in the plaque stage of MF and 24/1 in the tumor stage (9).

Patients may have atypical lymphocytes with cerebriform nuclei (Sezary cells) in the peripheral blood. The current practice is to use a criterion of at least 20% cerebriform lymphocytes to define Sezary syndrome (10). Immunophenotypic studies of the peripheral blood may show expansion of a CD4+CD7- population reflective of circulating atypical lymphocytes (10).

Primary cutaneous large T-cell CD30+ lymphoma is the most common form on non-MF primary CTCL. The spectrum of primary cutaneous CD30+ lymphoproliferative disorders includes lymphomatoid papulosis, primary cutaneous large T-cell CD30+ lymphoma and intermediate forms (11). Lymphomatoid papulosis is characterized by scattered CD30+ blast cells whereas primary cutaneous large T-cell CD30+ lymphomas demonstrate diffuse infiltrates of large anaplastic CD30+ T cells (11, 12). The CD30 molecule is expressed on the majority (>75%) of neoplastic cells. Most cases express the CD4+CD30+ phenotype with variable loss of pan-T cell antigens (CD2, CD3, CD5, or CD7). A small minority of cases is CD8+CD30+(12).

Primary cutaneous large T-cell CD30- lymphomas are characterized by minimal or absent CD30 expression (11, 13). Tumor cells express a phenotype of the CD4+ lymphocyte subset. Occasional cases express CD8.

Primary cutaneous pleomorphic small/medium-sized T-cell lymphomas are characterized by deep and diffuse infiltrates composed of small-to-medium sized atypical lymphoid cells expressing the CD4 molecule (11, 14). CD8+ cutaneous pleomorphic lymphomas are rarely observed. A small minority expresses the γδ TCR and is characterized by an aggressive behavior. The loss of one or more pan-T antigens (CD2, CD3, CD5, or CD7) can be observed.

Primary cutaneous B-cell lymphomas are characterized by a dense infiltrate of tumor cells expressing B-cell surface antigens, notably CD19, CD20, CD22 and CD79a (15, 16). Neoplastic cells may be Ig+ or Ig-. Ig+ B-cell lymphomas are monoclonal, ie, all tumor cells express the same Ig light chain, either κ or λ (15). This phenomenon is denominated light chain restriction. Reactive polyclonal B-cell infiltrates are composed of a mixture of κ and λ cells, tipically with approximately

Table 1. EORTC classification for primary cutaneous lymphomas.

Cutaneous T-cell lymphoma (CTCL)
Indolent clinical behaviour
Mycosis fungoides
Mycosis fungoides variants: follicular MF and pagetoid reticulosis
CTCL, large cell, CD30-positive (anaplastic, immunoblastic and large pleomorphic)
Lymphomatoid papulosis
Aggressive clinical behaviour
Sezary syndrome
CTCL, large cell, CD30-negative (immunoblastic and large pleomorphic)
Provisional entities
CTCL, pleomorphic, small/medium-sized
Subcutaneous panniculitis-like T-cell lymphoma
Cutaneous B-cell lymphoma (CBCL)
Indolent clinical behaviour
Primary cutaneous immunocytoma/marginal zone B-cell lymphoma
Primary cutaneous follicle center cell lymphoma
Intermediate clinical behaviour
Primary cutaneous large B-cell lymphoma of the leg
Provisional entities
Primary cutaneous plasmacytoma
Intravascular large B-cell lymphoma

2.:1 κ predominance. Therefore, the presence of light chain restriction is consistent with the presence of a CBCL.

Immunogenotyping of cutaneous lymphomas.

The use of molecular biologic techniques has improved our ability to diagnose lymphocytic infiltrate of the skin and provided additional diagnostic parameters to complement clinical, histologic and immunophenotipic analysis. Molecular characterization involves the identification of a monoclonal population of lymphocytes which is based upon the detection of specific rearrangements in the genes coding for antigen receptor in B-cells (Ig) and T-cells (the T-cell antigen receptor) (16,17). Southern blot analysis of genes coding for Ig or for T-cell receptor was the method used in initial studies, which showed evidence for the monoclonal nature of both cutaneous T cell lymphoma (CTCL) and cutaneous B cell lymphoma (CBCL). More recently, Southern blot hybridization has been challenged by the polymerase chain reaction (PCR) for the routine analysis of clonality (18).

Studies of clonality by means of PCR in patients with MF revealed clonal patterns in tumorous lesions, in erythrodermal stages, and in most infiltrated plaques, whereas a dominant clone was not found in 40% of non-infiltrated patch lesions (19-21).

The immunogenotyping studies of primary cutaneous CD30+ lymphoproliferative disorders have shown the clonal T-cell nature of these disorders (11). In particular the TCR gene rearrangement analysis of lymphomatoid papulosis, which is characterized by a clinically benign course, has shown evidence of monoclonality in the cases analyzed (22). A similar monoclonal pattern has been observed in the other subtypes of CTCL, notably primary cutaneous large T-cell CD30- lymphomas and primary cutaneous pleomorphic small/medium-sized T-cell lymphomas (11).

Immunogenotyping studies in CBCL have shown in most cases a monoclonal process; however, they differ from nodal lymphoma in that they rarely show the t (14,18) translocation (23-25).

Since polyclonal patterns of TCR and immunoglobulin rearrangements were found in most benign inflammatory dermatosis one might argue that the molecular demonstration of clonal proliferation of lymphocytes provides strong evidence for malignancy. However recent studies have shown monoclonality in patients with benign cutaneous lymphoid infiltrate (18). These results indicate that monoclonality is not conclusive evidence for malignancy and that results from clonality studies should be interpreted in the context of histopathological, immunohistochemical and clinical data.

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