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Original article

Report of the Symposium on Cutaneous Lymphomas: Sixth International Conference on Malignant Lymphoma*

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Summary

The symposium discussed the pathobiology, classification, and treatment of cutaneous lymphomas. Drs. Burg and Kadin commented on the pathophysiology of mycosis fungoides/Sézary syndrome and cutaneous CD30+ lymphoproliferative disorders, respectively. A proposed classification of primary cutaneous lymphomas from the EORTC was presented by Drs. Kerl and Sterry. Dr. Jaffe presented a classification of cutaneous lymphomas based on the REAL classification. All speakers agreed that primary cutaneous lymphomas are usually distinctive in their clinical behavior and biology, and differ from their nodal counterparts. The symposium concluded with remarks from Drs. Vonderheid and Hoppe on the therapeutic approach to primary cutaneous lymphoid malignancies.

Key words: cutaneous lymphoma, T cell, B cell, lymphocyte biology, skin

A symposium chaired by Prof. Gunter Burg and Dr. Elaine S. Jaffe focused on the pathophysiology, classification, and treatment of cutaneous lymphomas. Primary lymphomas of the skin differ in many ways from their nodal counterparts, and these malignancies require special consideration from the specialist. The program began with a review of the pathogenesis of cutaneous T-cell lymphoma (CTCL) or mycosis fungoides/Sézary syndrome (MF/SS) by Gunter Burg. He noted that the pathologic and clinical manifestations of CTCL follow from complex interactions between the neoplastic T cells and the cells of the cutaneous microenvironment, mainly keratinocytes and dendritic cells. An important factor may be a switch from TH (T helper) 1 cells to TH 2 cells during tumor development. The cytokines elaborated by the neoplastic cells and bystander cells play a role both in tumor development and the ensuing clinical manifestations. CTCL, like most other malignancies, goes through stages of tumor evolution. Tumor progression may be explained by stepwise accumulation of mutations involving DNA repair- and tumor-suppressor genes. The risk for the accumulation of gene mutations increases with the number of cell divisions, which normally is limited by cell death owing to apoptosis or senescence of the cell. These events depend on *bcl*-2 expression and telomerase activity, both of which are increased in CTCL and, therefore, may be important factors in promoting unlimited cell proliferation, driven by persistent antigenic stimulation.

CD30+ lymphoproliferative disorders (LPDs) of the skin include lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large-cell lymphoma (ALCL). These disorders, which were reviewed by Marshall Kadin, exhibit a spectrum in both their pathologic features and clinical behavior. Multiple cytokines (TNF-α and TGF-β) produced by the T-cell clone appear to influence the histologic features and clinical regression of the cutaneous lesions. CD30+ cutaneous LPDs appear distinct from classical ALCL, and lack the t(2;5)(p23;q35) of the latter malignancy. The most common cytogenetic abnormalities involve chromosomal breakpoints at 1p36 and 10q24–26. Although the disease typically remains confined to the skin for many years, extracutaneous disease is seen in 25% of patients and is associated with a more aggressive clinical course.

The symposium proceeded to a discussion of the classification of primary cutaneous lymphomas. The EORTC, noting that cutaneous lymphomas differ from nodal lymphomas in clinical behavior and functional markers, has proposed a classification for these diseases (Table 1). Helmut Kerl presented an overview of cutaneous B-cell lymphomas and Wolfram Sterry presented the EORTC perspective on T-cell malignancies. The tumors are classified according to their usual clinical behavior, indolent or aggressive. In addition, some entities have been identified as provisional, and still others are undergoing continued discussion regarding their inclusion. The EORTC group identifies a primary cutaneous lymphoma as one presenting solely with cutaneous disease, without detected extracutaneous spread for at least six months.

Elaine Jaffe presented a classification of cutaneous lymphomas based on the principles of the revised European–American lymphoma (REAL) classification proposed by the International Lymphoma Study Group (ILSG). She noted that the premise of the REAL classification is the identification of disease entities, based on pathologic, immunophenotypic, genetic and clinical features. Therefore, if cutaneous involvement is a unique aspect of a disease entity, this clinical fact is considered integral to disease recognition. Indeed, there are a num-

Table 1. EORTC classification of primary cutaneous lymphomas

Primary cutaneous T-cell lymphomas	Primary cutaneous B-cell lymphomas
Indolent	*Indolent*
Mycosis fungoides	Follicle center cell lymphoma of head and trunk
Sézary syndrome	Immunocytoma
Pagetoid reticulosis	
Lymphomatoid papulosis	
Large-cell CTCL, CD30+, including anaplastic, immunoblastic, pleomorphic	
	Intermediate
	Large B-cell lymphoma of the leg
Aggressive	
Large-cell CTCL, CD30−, including immunoblastic, pleomorphic	
Provisional	*Provisional*
Granulomatous slack skin disease	Intravascular CBL
CTCL pleomorphic small/ medium sized	Marginal-zone B-cell lymphoma
CD8+ CTCL	Plasmacytoma

For discussion: angiocentricity, gamma/delta CTCL, marginal-zone B-cell lymphoma, and subcutaneous lymphoma.
Abbreviations: CTCL – cutaneous T-cell lymphoma; CBL – cutaneous B cell.

Table 2. Classification of cutaneous lymphomas based on the REAL classification.

Cutaneous T-cell lymphomas
Mycosis fungoides/ Sézary syndrome
Pagetoid reticulosis (α/β and γ/δ)
Granulomatous slack skin disease
Follicular mucinosis
CD30+ cutaneous lymphoproliferative disease
Lymphomatoid papulosis
Cutaneous anaplastic large cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Other T-cell lymphomas with cutaneous involvement (nearly all)
T-PLL/T-CLL
Aggressive NK-cell leukemias
NK/T-cell 'angiocentric' lymphomas
Angioimmunoblastic T-cell lymphoma
Peripheral T-cell lymphoma, NOS
Adult T-cell leukemia/lymphoma
Classical anaplastic large-cell lymphoma
Cutaneous B-cell lymphomas
Cutaneous follicle-center lymphoma
(Usually *bcl*-2 rearrangement/expression–negative)
Cutaneous marginal-zone B-cell lymphoma (cutaneous MALT-type lymphoma)
So-called 'cutaneous immunocytoma'
Large B-cell lymphoma
Intravascular large B-cell lymphoma
Precursor B-lymphoblastic lymphoma

Abbreviations: T-PLL/T-CLL – T-cell prolymphocytic leukemia/T-cell chronic lymphocytic leukemia; NK – natural killer; NOS – not otherwise specified; MALT – mucosal-associated lymphoid tissue.

ber of T-cell malignancies for which cutaneous involvement is essential (Table 2). B-cell lymphomas restricted to the skin are rare, with the possible exception of cutaneous follicle-center lymphoma. It differs from its morphologically similar nodal counterpart clinically, immunophenotypically, and at the genetic level (*bcl*-2 rearrangement-negative). So-called cutaneous immunocytoma is felt to be an extranodal marginal-zone lymphoma of MALT-type. Cutaneous large B-cell lymphoma is usually associated with a good prognosis, but it is not clear whether this clinical behavior is related to low stage or to an intrinsically different biology.

Dr. Jaffe concluded that the principles of the REAL classification are applicable to cutaneous lymphomas, and that organ-specific classification schemes are not required. Indeed, such schemes may impede the recognition of features common to diseases involving multiple anatomic sites; e.g., MALT-type lymphomas. Nevertheless, primary cutaneous lymphomas are frequently distinctive in their clinical behavior and biology.

The symposium concluded with an overview of the treatment of primary cutaneous lymphomas from the dermatologist's perspective by Eric Vonderheid, and from the oncologist's perspective by Richard T. Hoppe. Dr. Vonderheid reaffirmed the principles presented by Dr. Burg, that MF/SS represent a continuum with respect to tumor aggressiveness and risk for transformation. Both parapsoriasis en plaques and patch-stage MF are considered part of this continuum, with plaque- and tumor-stage MF representing the opposite extreme. In patients with limited cutaneous disease, skin-directed chemotherapy and/or radiotherapy may be curative in 30%–50% of patients. Such approaches are also useful in palliating patients with more advanced disease. Biological response modifiers and cytotoxics or immunotoxins targeted against T cells hold promise for the future.

Dr. Hoppe confirmed the effectiveness of topical therapies in control of disease. Because systemic disease at presentation is rare, only limited staging is required (chest radiographs, hematological evaluation with Sézary cell counts, and routine chemistries). If significant lymphadenopathy is present, lymph node biopsy may be indicated. Electron beam and topical nitrogen mustards are both effective. Visceral disease requires systemic chemotherapy, but chemotherapy generally has not been effective. Interferon has shown some promise, and other investigational approaches are indicated in patients with advanced disease. Primary localized cutaneous B-cell lymphoma is often treated successfully with localized radiation therapy.

In conclusion, all speakers agreed that primary cutaneous lymphomas differ significantly from nodal and most extranodal lymphomas, and that these malignancies require specialized diagnostic and therapeutic approaches. The site of presentation must be taken into consideration by both the pathologist and the clinician.

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