Defining early mycosis fungoides

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This editorial review summarizes the results of 5 meetings sponsored by the International Society for Cutaneous Lymphoma at which the clinicopathologic and ancillary features of early mycosis fungoides were critically examined. Based on this analysis, an algorithm was developed for the diagnosis of early mycosis fungoides involving a holistic integration of clinical, histopathologic, immunopathologic, and molecular biological characteristics. A novel aspect of this algorithm is that it relies on multiple types of criteria rather than just one, for example, histopathology. Before its finalization, the proposed diagnostic algorithm will require validation and possibly further refinement at multiple centers during the next several years. It is anticipated that a more standardized approach to the diagnosis of early mycosis fungoides will have a beneficial impact on the epidemiology, prognostication, treatment, and analysis of clinical trials pertaining to this most common type of cutaneous lymphoma. (J Am Acad Dermatol 2005;53:1053-63.)

The early diagnosis of mycosis fungoides (MF), the major subtype of cutaneous T-cell lymphoma (CTCL), has important ramifications for therapeutic options, determination of prognosis, and outcomes in clinical trials. However, the diagnosis of MF in its patch or early plaque phase is often difficult, either because of overlapping features with benign dermatoses or discordance between clinical and pathologic findings. Despite extensive clinicopathological and investigational studies of MF and its putative precursors, as well as strong biases toward particular histologic criteria, there has been no consensus on the key clinical and pathologic criteria that would ultimately facilitate

collaborative multicenter research studies of early disease.

Recognizing this persistent need to develop standardized diagnostic criteria for early MF, the International Society for Cutaneous Lymphoma (ISCL) sponsored meetings in Zurich, Switzerland on May 28-31, 1999; in Napa, California on March 9, 2000; in Bethesda, Maryland on March 1, 2001; in New Orleans, Louisiana on Feb 21, 2002; and in Washington, DC on Feb 5, 2004 with the following goals: (1) to facilitate discussion on this topic among clinicians and scientists with extensive experience in CTCL; (2) to develop a working proposal for diagnostic criteria for early MF, taking into account clinical, histologic, and ancillary (particularly immunophenotypic and genotypic) criteria; and (3) to test the validity of these criteria in an international collaborative forum. We are confident that meeting these goals will help to better evaluate the true incidence of MF, to potentially discriminate among prognostic subsets of MF, to advance the understanding of factors involved in the pathogenesis of MF and its progression, and to aid in the development of differential therapeutic approaches likely to improve current remission and survival rates. The meetings noted above accomplished the first goal. This article summarizing the meetings' proceedings addresses the second goal and creates a framework for achieving the third objective through future collaborative studies.

RELATIONSHIP BETWEEN MF AND PARAPSORIASIS EN PLAQUES: HISTORICAL PERSPECTIVE AND CURRENT IMPLICATIONS

Part of the difficulty in establishing threshold criteria for the diagnosis of early MF stems from the existence of established terminology for reputedly benign dermatoses, such as parapsoriasis en plaques (PEP), that have overlapping clinical and/or histologic features with early MF. By utilizing clinical findings only, PEP was defined by Brocq[1] in 1902 as a chronic, recurrent, erythematous, and scaling dermatosis that was part of a larger spectrum of eczematoid, psoriasiform, or lichenoid skin disorders ("les parapsoriasis") whose nosology has been reviewed elsewhere.[2] The relation between PEP and MF was first specifically addressed by Civatte[3] (Brocq's disciple) and other groups, including those of Osmundsen,[4] Samman,[5] Bonvalet et al,[6] and Binazzi[7] who made careful clinicopathologic correlations from series of patients with PEP followed over time. A "small" lesion variant, now commonly termed small-plaque parapsoriasis, was distinguished from a "large" lesion variant, now referred to as large plaque parapsoriasis, on the basis of size, preferential distribution of lesions, and the presence or absence of atrophy and/or poikiloderma.[2] The skin lesions of both small-plaque parapsoriasis and large-plaque parapsoriasis are flat patches rather than infiltrated plaques, consistent with the fact that the French term *plaque* equates to the English term *patch*. Therefore these two conditions would be termed most appropriately "small-patch parapsoriasis" and "large-patch parapsoriasis," except that these terms incorporating the word "plaque" are embedded in the literature.[8,9]

The lesions of small-plaque parapsoriasis are generally on the upper trunk, sometimes with a digitate appearance (so-called "digitate dermatosis") and without atrophy or poikiloderma.[2] Lesions are usually 2 to 6 cm in diameter; however, the long axis of digitate lesions may be up to 10 to 20 cm, imparting a "fingermark" appearance. Histologically, small-plaque parapsoriasis has been characterized by nonspecific changes (focal spongiotic and/or psoriasiform and/or lichenoid dermatitis with exocytosis of small lymphocytes). Small-plaque parapsoriasis has been judged to have little, if any, potential to evolve to typical MF.[8]

In contrast, the lesions of large-plaque parapsoriasis are usually larger than 6 cm in diameter and localized to the buttocks, lower trunk, upper thighs, inner upper arms, and inframammary areas (ie, non-sun-exposed regions) and frequently manifest atrophy and/or poikiloderma. Histologically, the pattern of lymphoid infiltration in large-plaque parapsoriasis is similar to small-plaque parapsoriasis, but the infiltrates often contain lymphocytes with cerebriform nuclei called Lutzner cells (synonymous with Sézary cells) similar to that seen in MF. Large-plaque parapsoriasis has been long regarded to be difficult to distinguish from patch-phase MF, with progression to frank MF in 7.5% to 14% of cases.[2,5-7]

In 1979, Sanchez and Ackerman[10] suggested that instead of large-plaque psoriasis evolving into frank MF only in selected cases, large-plaque parapsoriasis was synonymous with patch-stage MF. Ackerman

subsequently described typical clinical lesions of small-plaque parapsoriasis in patients who also had indubitable, biopsy-proven plaques of MF, thus challenging that even small-plaque parapsoriasis was always a benign dermatosis.[11,12] Certainly, to consider all parapsoriasis en plaques as early MF simplified a common diagnostic dilemma, but it also raised new problems in producing valid prognostic survival information for patients with "early"-stage MF (information that drives the choice of therapy), acceptable end points of therapy, interpretation of response, and ultimately the generation of risk/benefit ratios for different therapeutic interventions.

Moreover, the inclusion of patients with a "benign" course into the mix of patients who have a definite, potentially life-threatening cancer poses added risks for patients: those with "benign" disease are at risk of being treated with inappropriately aggressive therapy and those with a potential for progressive disease are at risk of being deprived of more definitive therapy.

From an epidemiologic point of view, changes in the histologic criteria that favor the diagnosis of early MF instead of parapsoriasis en plaques may have profound effects on disease incidence and prognosis. In the past 20 years, a clear-cut increase in the incidence of MF and, in parallel, improved overall survival time have been observed.[13,14] It is unknown to what degree these observations are the consequence of a substantial modification of the histologic criteria for the diagnosis of early MF, earlier biopsy of unexplained dermatitis, or an increase in the environmental or genetic influences that may affect the true incidence of MF. These questions are similar to those posed regarding "atypical nevi" and melanoma. Finally, the classification of small-plaque parapsoriasis, particularly the digitate variant, as a form of MF obscures the issue of whether small-plaque parapsoriasis is one step along the path of MF tumor progression or is truly an unrelated biologic entity.[8,9,15-17]

EARLY DIAGNOSIS OF MF: THE ROLE OF CLINICAL ASSESSMENT

The diagnosis of MF relies heavily on clinical assessment, particularly in providing a supportive history, confirming one of several typical or suspect clinical presentations of MF and directing the choice of the critical biopsy site(s). The clinical diagnosis of MF may be difficult to make in patch- or early plaque-phase disease because many of its clinical features may also be found in benign inflammatory diseases. However, certain findings are quite characteristic of early MF and, when present, are helpful in establishing the diagnosis. The ISCL Task Force for

the Clinical Definition of Early MF* has identified several clinical criteria that it believes are most important for recognizing classic MF at its initial presentation (patch phase) (Table I).

A. History

The most important aspect of the medical history as it pertains to the diagnosis of MF is the persistent nature of the disease. In addition, MF lesions tend to increase in size and number over time, although this is not an invariable finding. Although topical corticosteroids have a salutary effect in MF[18] and may even clear very early lesions,[19] the lesions of MF typically either incompletely clear with topical corticosteroids and recur when therapy is discontinued or continue to develop in untreated areas. Because some drug-induced eruptions (reviewed in Gul, Kilic, and Dursun[20]) may share both clinical and light microscopic features with MF, a trial off of a potentially offending drug may be indicated to eliminate this possibility.

B. Morphology of lesions

The clinical presentation of classic patch-phase MF is characterized by variability in the size, shape, and color of individual lesions. Most MF patch lesions are large (>5 cm in diameter). Uniformly small (<3 cm in width), even though sometimes very "long" (up to 10 cm or more in length), digitate lesions are uncommon in MF and would make one suspect the "digitate dermatosis" variant of small-plaque parapsoriasis. Untreated lesions of MF often expand slowly to form well-demarcated lesions that vary in size with or without coalescence and may also undergo spontaneous clearing in areas. This phenomenon of progression and regression of individual lesions, when present, produces lesions that are irregularly shaped.

Another important clinical feature that is relatively specific for early MF is the presence of poikiloderma.[2] Poikiloderma is defined clinically as the local juxtaposition of mottled pigmentation, telangiectasia, and epidermal atrophy (cigarette paper wrinkling) interspersed with slight infiltration. In some cases of MF, there may be epidermal atrophy alone. Poikiloderma may rarely be seen with the cutaneous lesions of other subtypes of CTCL such as granulomatous slack skin, the regressing lesions of anaplastic

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Table I. Algorithm for diagnosis of early MF*

Criteria	Scoring system
Clinical	
Basic	2 points for basic criteria and two additional criteria
Persistent and/or progressive patches/thin plaques	1 point for basic criteria and one additional criterion
Additional	
1) Non-sun exposed location	
2) Size/shape variation	
3) Poikiloderma	
Histopathologic	
Basic	2 points for basic criteria and two additional criteria
Superficial lymphoid infiltrate	1 point for basic criteria and one additional criterion
Additional	
1) Epidermotropism without spongiosis	
2) Lymphoid atypia[†]	
Molecular biological	
1) Clonal TCR gene rearrangement	1 point for clonality
Immunopathologic	
1) <50% CD2+, CD3+, and/or CD5+ T cells	1 point for one or more criteria
2) <10% CD7+ T cells	
3) Epidermal/dermal discordance of CD2, CD3, CD5, or CD7[‡]	

MF, Mycosis fungoides; *TCR,* T-cell receptor.
*A total of 4 points is required for the diagnosis of MF based on any combination of points from the clinical, histopathologic, molecular biological, and immunopathologic criteria.
[†]Lymphoid atypia is defined as cells with enlarged hyperchromatic nuclei and irregular or cerebriform nuclear contours.
[‡]T-cell antigen deficiency confined to the epidermis.

T-cell lymphoma, connective tissue disease such as dermatomyositis, and certain genodermatoses. Poikiloderma is not a feature of atopic dermatitis, nummular eczema, psoriasis, lichen planus, drug eruptions, tinea corporis, erythema chronicum migrans, small-plaque parapsoriasis/digitate dermatosis, pityriasis rosea, or other benign dermatoses likely to be clinically confused with MF. Poikiloderma is, however, commonly seen with large-plaque parapsoriasis, where it has been referred to as poikiloderma vasculare atrophicans. Persistent poikilodermatous patches on non-sun-exposed skin, particularly the buttocks, should be considered MF until proven otherwise by biopsy.

C. Number of lesions

Although MF may occur as a single lesion (unilesional MF),[21-23] most patients with classic MF typically present with multiple lesions and several sites of involvement. In particular, certain drugs may lead to a fixed drug reaction and produce solitary lesions that may be confused with unilesional MF. Other disorders that might be confused with unilesional MF include nummular eczema, lichen simplex chronicus, erythema chronicum migrans, and tinea corporis.

D. Distribution of lesions

MF has a proclivity to develop initially on relatively non-sun-exposed areas of the skin, such as the trunk below the waistline ("bathing suit" distribution), flanks, breasts, inner thighs, inner arms, and periaxillary areas. This characteristic distribution may be less apparent in dark-skinned patients. However, lesions may appear on the face or scalp early in the course of disease particularly if there is a component of follicular involvement. Occasionally, MF may present as a refractory dermatosis of the palms or soles.[24]

EARLY DIAGNOSIS OF MF: THE ROLE OF HISTOPATHOLOGY

The definition of histopathologic features to differentiate early MF from benign inflammatory diseases is by far the most difficult, debated, and yet crucial issue. To enhance the chance of establishing a histologic diagnosis of MF, multiple biopsies from a variety of lesions may be required, including the oldest, well-developed, most infiltrated lesions as well as the newest lesions. With the exception of emollients, it is important that all topical treatments, but especially topical corticosteroids and systemic immunosuppressants, be discontinued at least 2 to 4 weeks before performing a biopsy or else the salient histologic features of MF may be suppressed.

Several cytologic and architectural histopathologic criteria, variably grouped to identify the categories of "diagnostic of," "consistent with," and "suggestive of" MF, have been proposed in the past two decades. These include the following:

1. Presence of atypical lymphoid cells that are slightly larger than normal lymphocytes and have hyperchromatic, irregularly contoured (convoluted) nuclei.[25] Such cells have been variably termed "mycosis cells," "Lutzner cells," or "Sézary cells."[26]
2. Presence of individual haloed atypical lymphocytes within the epidermis[27]

3. Presence of single lymphoid cells linearly arranged along the basal layer of the epidermis with pagetoid spread (ie, buckshot distribution with pericellular halos)[10]

4. Presence of an increased or skewed number of lymphocytes (not necessarily atypical) relative to typical dermatitis, distributed singly or in small collections in an epidermis devoid of spongiotic microvesiculation.[10,28] The term "disproportionate epidermotropism" has been used to express this concept.

5. Presence of vacuolar interface dermatitis[29]

6. Presence of papillary dermal fibrosis[10,27,28,30]

In 2001, Guitart et al[31] published an integrated grading system, reflecting the pathologist's degree of diagnostic certainty, based on the sequential evaluation of major criteria (density of the infiltrate, evaluated at low power; nature and extent of epidermotropism, evaluated at medium power; and grade of lymphocytic atypia, evaluated at high power), which were scored 0 to 3 points according to the degree of their presence, and minor criteria (presence of atypia primarily in the intraepidermal compartment [low grade atypia:1 point; high grade: 2 points], lack of associated inflammatory features [1 point], reticular/wiry fibroplasia within the papillary dermis [1 point]). The diagnoses rendered under this system were reached by adding the components to obtain the total score and were specifically as follows: (1) perivascular/interface lymphocytic dermatitis (total score: 0-2 points); (2) atypical lymphocytic infiltrate (MF cannot be excluded) (total score: 3-4 points); (3) atypical lymphocytic infiltrate suggestive of MF (total score: 5-6 points); and (4) MF (total score 7). Within the confines of this study, there was improvement shown with this approach (ie, using histologic criteria and a training session for evaluators) compared with independent assessment alone. Specifically, there was an increase in the agreement rate among pathologists as reflected by an increase in overall precision weighted κ values from 0.630 to 0.854. However, as is true of all the histopathologic studies to date, this method has not been adopted widely or validated by others yet. Nevertheless, two other studies warrant specific mention because of their international nature.

In 2000, the European Organisation for Research and Treatment of Cancer's Cutaneous Lymphoma Study Group addressed the issue of histologic definition of early MF by publishing a retrospective review of 24 biopsy specimens obtained from 18 patients with limited patch-stage lesions whose diagnosis of MF was based on clear-cut clinical and histologic progression to more advanced disease

over time.[32] As controls, 13 biopsies of spongiotic, lichenoid, or psoriasiform simulators of MF were randomly intermixed with the 24 MF biopsies by a participant uninvolved in the biopsy assessments. The panel, composed of 3 physicians well trained in the histopathology of lymphoproliferative disorders (one dermatologist/dermatopathologist, one hematopathologist, and one pathologist experienced in dermatopathology), used a multiheaded microscope to review the slides together for the presence of a large series of histologic criteria. They found that the presence of medium-sized to large (7- to 9-μm nuclear diameter, ie, approximately the same diameter as the nuclei of basal keratinocytes) cerebriform mononuclear cells was the most important histologic feature for the diagnosis of MF (multivariate log linear analysis $P < .001$). When these cells were distributed either singly or in small clusters in the epidermis, the sensitivity and specificity for the diagnosis of MF were 100% and 92.3%, respectively. When the cells were in clusters in the dermis, the sensitivity and specificity were 91.7% and 100%, respectively. Moreover, the absence of papillary dermal fibrosis (66.7% sensitivity and 100% specificity), the presence of epidermotropism with linearly arranged single lymphoid cells (closely apposed to basal keratinocytes and lined up along contiguous rete ridges like a necklace on the epidermal side of the derm0epidermal junction) (45.8% sensitivity and 100% specificity), and absence of dermal blast-like cells (41.7% sensitivity and 100% specificity) were found to yield additional independent diagnostic information (multivariate log linear analysis $P < .001$). Further evaluation is necessary to determine whether these findings can be confirmed in larger studies and in clinical practice or have predictive value for progressive disease.

Finally, another attempt to reach an international consensus about the histologic definition of early MF was made with an ISCL-sponsored workshop held in Zurich, Switzerland (May 28-31, 1999) devoted to assessing a number of preselected potential histologic criteria for the diagnosis of early MF. An international panel of dermatopathologists with specific expertise in cutaneous lymphomas* independently reviewed 33 MF cases, the diagnosis of which had been conclusively confirmed with long-term

follow-up, 33 cases of small-plaque parapsoriasis, and 33 inflammatory disease controls. The findings (unpublished data) were as follows:

- Lymphoid cells with variable nuclear and cytoplasmic features and/or with strikingly irregular nuclear contours (53.3% sensitivity and 88.9% specificity; odds ratio [OR] 9.14, 95% confidence interval [CI] 3.16-26.49) and/or presence of lymphocytes larger than those usually seen in inflammatory dermatoses (36.7% sensitivity and 92.1% specificity; OR 6.72, 95% CI 2.07-21.80) constituted the major criteria for the diagnosis of MF.
- Haloed lymphoid cells (13.3% sensitivity and 98.4% specificity; OR 9.54, 95% CI 1.02-89.48), disproportionate epitheliotropism (36.7% sensitivity and 84.1% specificity; OR 3.07, 95% CI 1.12-8.37), and presence of an epidermotropic, band-like infiltrate of lymphocytes (50% sensitivity and 73% specificity; OR 2.71, 95% CI 1.09-6.70) were documented to have a limited impact on the diagnosis of MF.
- In this study of early MF, the finding of Pautrier microabscesses, considered a highly specific criterion in MF in general, did not reach statistical significance (16.7% sensitivity, 92.1% specificity; OR 2.95, 95% CI 0.73-11.91). Similarly, the presence of: (1) wiry bundles of collagen (papillary dermal fibrosis), (2) lymphocytes in the epidermis larger than those in the dermis, and (3) admixed inflammatory cells (eg, eosinophils, plasma cells) yielded negative results.
- Small-plaque parapsoriasis showed histologic features indistinguishable from those of inflammatory controls.

The multivariate analysis determined that the best combination for the identification of MF was the presence of lymphoid cells with variable nuclear and cytoplasmic features and with striking irregular nuclear contours (log rank test = 22.08, *P* value = .000), with a misclassification error rate of 21.51%. Adding the other criteria, useful according to the univariate analysis, did not improve the final results, that is, it did not reduce the misclassification error rate. The consensus was hampered, however, by the high interobserver variability. The criterion-specific κ for statistically significant criteria ranged from 0.3762 to 0.4332, documenting a fair to moderate agreement beyond chance.

EARLY DIAGNOSIS OF MF: THE ROLE OF ANCILLARY TECHNIQUES

DNA cytophotometry,[33-37] nuclear morphometry,[38-41] immunohistochemistry,[42-57] chromosomal studies,[58-60] and, more recently, molecular genetic analysis of T-cell clonality[8,55-57,61-78] have generated a significant amount of data that suggest their utility not only in the early diagnosis of MF but also potentially in the clinical management of MF patients. How these data may be integrated with light microscopy to aid in the definitive diagnosis of CTCL has not been standardized. The ISCL Task Force on the Role of Ancillary Techniques in the Diagnosis of Early MF,* based on critical review of the literature and the experience accumulated in different institutions, has addressed these issues with the analysis and conclusions detailed below.

Sensitivity and specificity are crucial issues in the detection of T-cell anomalies in early MF. They depend on several factors, including type of assay, tissue processing, and selection of controls. In the case of clonality, polymerase chain reaction (PCR)—based assays are more sensitive than Southern blot analysis (eg, 90% vs 59% in a direct comparison).[63] The overall sensitivity of PCR methods varies from 60% to 100%. One recommended method utilizes DNA extracted from fresh-frozen tissue and PCR-based clonality analysis of T-cell receptor γ gene rearrangements using denaturing gradient gel electrophoresis (PCR/DGGE). Alternative PCR assays with a similar 1% clonal detection threshold are also acceptable.[79] Unpublished direct comparisons of PCR/DGGE analysis of frozen versus formalin-fixed, paraffin-embedded samples have shown both false-positive and false-negative results in archival specimens relative to fresh-frozen ones (Gary Wood, unpublished data). Specificity has been as high as 100% but depends heavily on selection of controls; several clinically benign skin diseases, such as lymphomatoid papulosis and pityriasis lichenoides, can show dominant clonality in at least some cases and should be excluded from assessments of specificity.[62,63]

The detection of a clonal T-cell population by sensitive PCR techniques on frozen specimens that otherwise do not have diagnostic histopathologic features of MF has generated the concepts of "clonal dermatitis"[62,63] and/or "abortive/latent lymphoma."[8,15,17] Long-term follow-up of patients categorized as having "clonal dermatitis" indicates that progression to overt MF occurs at a rate that may be as much as 4 times higher than that for large-plaque

parapsoriasis defined by clinicopathological criteria alone.[63,79] This suggests the existence of a specific category of patients (those with clonal dermatitis) who are at significant risk of progression to MF in the absence of definite clinicopathologic features of MF. In addition, recent studies stress the importance of combining clinical features with the evidence of a clone for the diagnosis of early MF.[80] That the more sensitive molecular studies may be able to unmask this subset of "benign" dermatoses is supported by studies showing clonal populations,[81,82] aberrant immunophenotypes,[57] and/or MF-like T-cell cytokine production profiles[83] in the peripheral blood of some patients diagnosed as "parapsoriasis en plaques." More recently developed techniques, such as single-cell PCR combined with laser-assisted microdissection, that exceed the current sensitivity of PCR-based methods (~1% clonal detection threshold)[76,77] need further evaluation regarding their specificity.

Among genetic studies, some previous reports[60] indicate that both skin-homing T cells and peripheral blood mononuclear cells of CTCL patients have high telomerase activity and short telomere length compared with healthy control subjects. In addition, molecular cytogenetics using G-banding,[59] comparative genomic hybridization, multifluor fluorescence in-situ hybridization, and cDNA microarrays[84] have been proposed as adjunctive diagnostic tools. The possible role of these assays in the diagnostic definition of MF needs further evaluation. DNA flow cytometry and morphometry of blood alone have limited value in establishing an early diagnosis of MF.

The sensitivity and specificity for early MF of immunopathologic criteria involving antigen deficiencies also depend on multiple factors. These include the precise definition of antigen deficiency, tissue processing, primary antibody used, patient age, and selection of controls.[45,52,56,85-89] For frozen tissue, primary antibodies Leu-9, B-B7, and 3A1 that define CD7 have been used. The best sensitivity in frozen sections (59%-88%) has been achieved with Leu-9 and B-B7, with reported specificity of 87%-98%. CD7-272 is the best marker for CD7 in paraffin sections. In paraffin sections, CD7-272 has a sensitivity of 81% and a specificity of 100%; however, these results were based on a study that included advanced as well as early cases of MF.[88] The cutpoint for defining antigen deficiency has varied with the particular antigen in question and the method of quantitation. For total lesional infiltrates, CD2, CD3, and CD5 expression by less than 50% of T cells is virtually 100% specific for T-cell lymphoma but only about 10% sensitive for MF. This is also true for epidermal/dermal discordance for CD2, CD3, CD5,

and CD7.[90] Discordance refers to antigen deficiency restricted to the epidermis. For total lesional infiltrates, CD7 expression of less than 33% has been reported to be 59% sensitive and 97% specific for MF.[85] CD7 expression of less than 10% has been reported to be 41% sensitive and 100% specific for MF,[85] although larger unpublished experience suggests that the specificity is closer to 80% (Gary Wood, unpublished data).

The status of CD13,[47] CD26, CD49d, and CD60 antigens[91-93] and the possible role of T-cell receptor V-beta repertoire analysis[51,53] requires further study at this time.

DIAGNOSTIC ALGORITHM: AN ISCL PROPOSAL

Based on the literature reviewed herein, the proceedings of the ISCL meetings in Zurich, Napa, Bethesda, New Orleans, and Washington, DC, as well as our aggregate experience evaluating early MF, we have proposed an algorithm for the diagnosis of early "classic" MF that incorporates clinical, histopathologic, molecular biologic, and immunopathologic features (Table I). The diagnosis of early MF requires a total of 4 points. Because molecular biologic and immunopathologic criteria represent no more than 1 point each, they always require additional clinical and/or histopathologic criteria to establish the diagnosis of early MF. Conversely, if sufficient clinical and histopathologic criteria are met, then molecular and immunopathologic criteria are not necessary.

This algorithm represents a major departure from several past proposals of criteria for diagnosing MF, especially histopathologic ones, because there is no undue reliance on any one type of criteria. This is a crucial feature of this algorithm: it relies on up to 4 types of criteria, not just one. Because no single criterion needs to stand alone, none has to be entirely specific in and of itself. Furthermore, each criterion can be relatively simple and therefore reproducible in both an interobserver and an intraobserver capacity. This algorithm is intended to be used for 3 major purposes: first, to define minimal diagnostic criteria for general purposes of interinstitutional uniformity needed for multicenter studies and comparison among different studies; second, to aid diagnosis in individual cases involving the common presentations of early MF; and third, to aid in the diagnosis of recurrent MF in patients previously in remission who have new cutaneous lesions of uncertain origin.

Clinical criteria

To fulfill any of the clinical criteria, lesions must be persistent and/or progressive patches/thin plaques

in addition to having two of the following additional features for 2 points or one of the following for 1 point:

- Non-sun-exposed location
- Size/shape variation *or*
- Poikiloderma.

Histopathologic criteria

To fulfill any of the histologic criteria, biopsy specimens must first have a superficial lymphoid infiltrate. Epidermotropism without spongiosis and lymphoid atypia each qualify as 1 point. Atypia is manifested as cells with enlarged, hyperchromatic nuclei with irregular or cerebriform nuclear contours. Note that these criteria are not entirely specific for MF. For example, the criterion of epidermotropism alone might be seen in collagen vascular diseases. Epidermotropism and/or lymphoid atypia might be seen in some drug-induced pseudolymphomas. Atypia might also be seen in lymphomatoid contact dermatitis, a spongiotic simulant of MF. However, the utility of the histopathologic criteria is preserved by their interdependence on the other criteria (clinical, molecular, and immunopathologic) in order to achieve the 4 points needed to establish the diagnosis of early MF. An important caveat is that the overall clinicopathological features cannot suggest a specific non-MF diagnosis.

Molecular biological criteria

To fulfill this criterion, a dominant T-cell clonal pattern must be detected by PCR-based analysis of T-cell receptor gene rearrangements. This is worth 1 point. The PCR/DGGE method (or a related technique such as PCR/temperature gradient gel electrophoresis or PCR/single stranded conformational polymorphism analysis) is preferred because the clonal detection threshold of these assays has been determined to be approximately 1%, which is reasonably sensitive and specific for early CTCL. In contrast, methods like PCR/ribonuclease protection analysis are too sensitive (clonal detection threshold 0.001%-0.01%) and could detect reactive, inflammatory T-cell clones. Southern blot analysis is too insensitive (clonal detection threshold 5%-20%) and would fail to detect tumor clones in many cases of early MF.[79] Although the presence of a matching clone in multiple skin lesions has shown a strong association with eventual clear-cut evidence of MF,[94] this can also occur in clonal dermatitis. Therefore we did not make matching clones a criterion in the algorithm. This avoids undue emphasis on clonality.

Immunopathologic criteria

Any one of 3 features must be present to generate 1 point: less than 50% of T cells expressing CD2, CD3, and/or CD5; less than 10% of T cells expressing CD7; or epidermal/dermal discordance for expression of CD2, CD3, CD5, and/or CD7. The first and last of these features are virtually 100% specific for T-cell lymphoma but only about 10% sensitive for early MF.[45,85,89,90] CD7 deficiency is about 40% sensitive and 80% specific based on the same literature and our general experience.

Caveats concerning the algorithm

It is difficult if not impossible to create an algorithm that is both straightforward and entirely specific for early MF. Nevertheless, its specificity will be enhanced by recognition of the following points. First, the algorithm is designed for classic presentations of early MF. It is not intended for atypical clinical and histologic variants including follicular, hypopigmented, purpuric, or palmoplantar MF. They will require their own algorithms. Second, regardless of any individual feature, if the overall clinicopathologic correlation in a case suggests a specific diagnosis other than MF, then the algorithm ceases to apply. For example, this might occur in some connective tissue diseases. In addition, some drug-induced pseudo-MF lesions can closely mimic true MF clinically, histopathologically, and in regard to ancillary studies. Here the history is key. If the history suggests a pseudo-MF drug eruption, then a confirmatory trial off of the suspected medication should be undertaken.

CONCLUSIONS

It is hoped that this proposed algorithm will prove useful in the standardization of the diagnosis of early MF. Having such standardization is critical to predicting and tracking prognosis, designing clinical trials, and implementing stage-appropriate treatment. The ISCL has developed this algorithm only as a first step toward establishing firm diagnostic criteria for classic early MF (Table I). The next step will be multicenter testing of this algorithm in order to identify areas of weakness, refine the proposed criteria, and validate its applicability. This will be achieved initially by retrospective studies and later by prospective analysis. Recently, cDNA microarrays have demonstrated promise for the diagnosis of MF[84] and Sézary syndrome.[95] However, issues of validation, availability, and cost will need to be resolved before this method can gain widespread application for the diagnosis of early MF.

REFERENCES

1. Brocq L. Les parapsoriasis. Ann Dermatol Syphilol (Paris) 1902;3:433-68.
2. Lambert WC, Everett MA. The nosology of parapsoriasis. J Am Acad Dermatol 1981;5:373-95.
3. Civatte A. Le cinquantenaire du parapsoriasis. Ann Dermatol Syphilol (Paris) 1951;78:5-22.
4. Osmundsen PE. Parapsoriasis en plaques: a follow-up study. Acta Derm Venereol 1968;48:345-54.
5. Samman PD. The natural history of parapsoriasis en plaques (chronic superficial dermatitis) and prereticulotic poikiloderma. Br J Dermatol 1972;87:405-11.
6. Bonvalet D, Colau-Gohm K, Belaich S, Civatte J, Degos R. Les differentes formes du parapsoriasis en plaques, a propos de 90 cases. Ann Dermatol Venereol 1977;104:18-25.
7. Binazzi M. Some research on parapsoriasis and lymphoma. Arch Dermatol Res 1977;258:17-23.
8. Burg G, Dummer R, Nestle FO, Doebbeling U, Haeffner AC. Cutaneous lymphomas consist of a spectrum of nosologically different entities including mycosis fungoides and small plaque parapsoriasis. Arch Dermatol 1996;132:567-72.
9. Burg G, Kempf W, Haeffner AC, Nestle FO, Hess Schmid M, Doebbeling U, et al. Cutaneous lymphomas. Curr Probl Dermatol 1997;9:137-204.
10. Sanchez JL, Ackerman AB. The patch stage of mycosis fungoides: criteria for histologic diagnosis. Am J Dermatopathol 1979;1:5-26.
11. King-Ismael D, Ackerman AB. Guttate parapsoriasis/digitate dermatosis (small plaque parapsoriasis) is mycosis fungoides. Am J Dermatopathol 1992;14:518-30.
12. Ackerman AB. If small plaque (digitate) parapsoriasis is a cutaneous T-cell lymphoma, even an "abortive" one, it must be mycosis fungoides. Arch Dermatol 1996;132:562-6.
13. Weinstock MA, Gardstein B. Twenty-year trends in the reported incidence of mycosis fungoides and associated mortality. Am J Public Health 1999;89:1240-4.
14. Weinstock MA, Reynes JF. The changing survival of patients with mycosis fungoides: a population-based assessment of trends in the United States. Cancer 1999;85:208-12.
15. Burg G, Dummer R. Small plaque (digitate) parapsoriasis is an "abortive" cutaneous T-cell lymphoma. Arch Dermatol 1995; 131:336-8.
16. Haeffner AC, Smoller BR, Zepter K, Wood GS. Differentiation and clonality of lesional lymphocytes in small plaque parapsoriasis. Arch Dermatol 1995;131:321-4.
17. Burg G, Dummer R, Haeffner AC, Kempf W, Kadin M. From inflammation to neoplasia: mycosis fungoides evolves from reactive inflammatory conditions (lymphoid infiltrates) transforming into neoplastic plaques and tumors. Arch Dermatol 2001;137:949-52.
18. Vonderheid EC. Treatment planning in cutaneous T-cell lymphoma. Dermatol Ther 2003;16:276-82.
19. Zackheim HS. Treatment of patch stage mycosis fungoides with topical corticosteroids. Dermatol Ther 2003;16:283-7.
20. Gul U, Kilic A, Dursun A. Carbamazepine-induced pseudo mycosis fungoides. Ann Pharmacother 2003;37:1441-3.
21. Oliver GF, Winkelmann RK. Unilesional mycosis fungoides: a distinct entity. J Am Acad Dermatol 1989;20:63-70.
22. Heald PW, Glusac EJ. Unilesional cutaneous T-cell lymphoma: clinical features, therapy, and follow-up of 10 patients with a treatment-responsive mycosis fungoides variant. J Am Acad Dermatol 2000;42:283-5.
23. Hodak E, Phening E, Amichai B, Feinmesswer M, Kuten A, Maron L, et al. Unilesional mycosis fungoides: a study of seven cases. Dermatology 2000;201:300-6.
24. McNiff JM, Schechner JS, Crotty PL, Glusac EJ. Mycosis fungoides palmaris et plantaris or acral pagetoid reticulosis? Am J Dermatopathol 1998;20:271-5.
25. Freeman RG. Questions to the editorial board and other authorities [letter]. Am J Dermatopathol 1986;8:536.
26. Reed R. Questions to the editorial board and other authorities [letter]. Am J Dermatopathol 1986;8:539-41.
27. Smoller BR, Bishop K, Glusac EJ, Kim YH, Hendrickson M. Reassessment of histologic parameters in the diagnosis of mycosis fungoides. Am J Surg Pathol 1995;19:1423-30.
28. Nickoloff BJ. Light microscopic assessment of 100 patients with patch/plaque stage mycosis fungoides. Am J Dermatopathol 1988;10:469-77.
29. Everett MA. Early diagnosis of mycosis fungoides: vacuolar interface dermatitis. J Cutan Pathol 1985;12:271-8.
30. Shapiro PE, Pinto FJ. The histologic spectrum of mycosis fungoides/Sézary syndrome (cutaneous T-cell lymphoma). Am J Surg Pathol 1994;18:645-67.
31. Guitart J, Kennedy J, Ronan S, Chmiel JS, Hsiegh YC, Variakojis D. Histologic criteria for the diagnosis of mycosis fungoides: proposal for a grading system to standardize pathology reporting. J Cutan Pathol 2001;28:174-83.
32. Santucci M, Biggeri A, Feller AC, Massi D, Burg G. Efficacy of histologic criteria for diagnosing early mycosis fungoides. Am J Surg Pathol 2000;24:40-50.
33. van Vloten WA, van Duijn P, Schaberg A. Cytodiagnostic use of Feulgen-DNA measurements in cell imprints from the skin of patients with mycosis fungoides. Br J Dermatol 1974; 91:365-71.
34. Hagedorn M, Kiefer G. DNA content of mycosis fungoides cells. Arch Dermatol Res 1977;258:127-34.
35. Wantzin GL, Larsen JK, Christensen IJ, Ralfkiaer E, Thomsen K. Early diagnosis of cutaneous T-cell lymphoma by DNA flow cytometry on skin biopsies. Cancer 1984;54:1348-52.
36. Ralfkiaer E, Larsen JK, Christensen IJ, Thomsen K, Wantzin GL. DNA analysis by flow cytometry in cutaneous T-cell lymphomas. Br J Dermatol 1989;120:597-605.
37. Altomare G, Capella GL, Pigatto PD, Biondo B, Lavezzi AM. Densitometry of Pautrier's microabscess cells in cutaneous T cell lymphoma. Int J Dermatol 1995;34:535-7.
38. Meyer CJ, van Leeuwen AW, van der Loo EM, van de Putte LB, van Vloten WA. Cerebriform (Sézary-like) mononuclear cells in healthy individuals: a morphologically distinct population of T cells. Relationship with mycosis fungoides and Sezary's syndrome. Virchows Arch B 1977;25:95-104.
39. Payne CM, Grogan TM, Lynch PJ. An ultrastructural morphometric and immunohistochemical analysis of cutaneous lymphomas and benign lymphocytic infiltrates of skin. Useful criteria for diagnosis. Arch Dermatol 1986;122: 1139-54.
40. Simon GT. The value of morphometry in the ultrastructural diagnosis of mycosis fungoides. Ultrastruct Pathol 1987; 11:687-91.
41. Payne CM, Grogan TM, Spier CM, Bjore CG Jr, Richter LC, Cromey DW, et al. A multidisciplinary approach to the diagnosis of cutaneous T-cell lymphomas. Ultrastruct Pathol 1992; 16:99-125.
42. Chu A, Patterson J, Berger C, Vonderheid E, Edelson R. In situ study of T-cell subpopulations in cutaneous T-cell lymphoma. Diagnostic criteria. Cancer 1984;54:2414-22.
43. Ralfkiaer E, Wantzin GL, Mason DY, Hou-Jensen K, Stein H, Thomsen K. Phenotypic characterization of lymphocyte subsets in mycosis fungoides. Comparison with large plaque parapsoriasis and benign chronic dermatoses. Am J Clin Pathol 1985;84:610-9.

44. Vonderheid EC, Tan E, Sobel EL, Schwab E, Micaily B, Jegasothy BV. Clinical implications of immunologic phenotyping in cutaneous T cell lymphoma. J Am Acad Dermatol 1987;17: 40-52.

45. Lindae ML, Abel EA, Hoppe RT, Wood GS. Poikilodermatous mycosis fungoides and atrophic large-plaque parapsoriasis exhibit similar abnormalities of T-cell antigen expression. Arch Dermatol 1988;124:366-72.

46. van der Putte SC, Toonstra J, van Wichen DF, van Unnik JA, van Vloten WA. Aberrant immunophenotypes in mycosis fungoides. Arch Dermatol 1988;124:272-80.

47. Dreno B, Bureau B, Stalder JF, Litoux P. MY7 monoclonal antibody for diagnosis of cutaneous T-cell lymphoma. Arch Dermatol 1990;126:1454-6.

48. Verga M, Braverman IM. The use of immunohistologic analysis in differentiating cutaneous T-cell lymphoma from psoriasis and dermatitis. Arch Dermatol 1991;127:1503-10.

49. Fivenson DP, Rheins LA, Nordlund JJ, Pomaranski M, Douglass MC, Krull EA. Thy-1 and T-cell receptor antigen expression in mycosis fungoides and benign inflammatory dermatoses. J Natl Cancer Inst 1991;83:1088-92.

50. Rijlaarsdam JU, Scheffer E, Meijer CJ, Willemze R. Cutaneous pseudo-T-cell lymphomas. A clinicopathologic study of 20 patients. Cancer 1992;69:717-24.

51. Bagot M, Wechsler J, Lescs MC, Revuz J, Farcet JP, Gaulard P. Intraepidermal localization of the clone in cutaneous T-cell lymphoma. J Am Acad Dermatol 1992;27:589-93.

52. Ralfkiaer E, Wollf-Sneedorff A, Thomsen K, Vejlsgaard GL. Immunophenotypic studies in cutaneous T-cell lymphomas: clinical implications. Br J Dermatol 1993;129:655-9.

53. Potoczna N, Boehncke WH, Nestle FO, Kuenzlen C, Sterry W, Burg G, et al. T-cell receptor beta variable region (V beta) usage in cutaneous T-cell lymphomas (CTCL) in comparison to normal and eczematous skin. J Cutan Pathol 1996;23: 298-305.

54. Harmon CB, Witzig TE, Katzmann JA, Pittelkow MR. Detection of circulating T cells with CD4+CD7- immunophenotype in patients with benign and malignant lymphoproliferative dermatoses. J Am Acad Dermatol 1996;35:404-10.

55. Bakels V, van Oostveen JW, van der Putte SC, Meijer CJ, Willemze R. Immunophenotyping and gene rearrangement analysis provide additional criteria to differentiate between cutaneous T-cell lymphomas and pseudo-T-cell lymphomas. Am J Pathol 1997;150:1941-9.

56. Bergman R, Faclieru D, Sahar D, Sander CA, Kerner H, Ben-Aryeh Y, et al. Immunophenotyping and T-cell receptor gamma gene rearrangement analysis as an adjunct to the histopathologic diagnosis of mycosis fungoides. J Am Acad Dermatol 1998;39:554-9.

57. Fucich LF, Freeman SF, Boh EE, McBurney E, Marrogi AJ. Atypical cutaneous lymphocytic infiltrate and a role for quantitative immunohistochemistry and gene rearrangement studies. Int J Dermatol 1999;38:749-56.

58. Shapiro PE, Warburton D, Berger CL, Edelson RL. Clonal chromosomal abnormalities in cutaneous T-cell lymphoma. Cancer Genet Cytogenet 1987;28:267-76.

59. Karenko L, Hyytinen E, Sarna S, Ranki A. Chromosomal abnormalities in cutaneous T-cell lymphoma and in its premalignant conditions as detected by G-banding and interphase cytogenetic methods. J Invest Dermatol 1997;108:22-9.

60. Wu K, Lund M, Bang K, Thestrup-Pedersen K. Telomerase activity and telomere length in lymphocytes from patients with cutaneous T-cell lymphoma. Cancer 1999;86:1056-63.

61. Kikuchi A, Naka W, Harada T, Sakuraoka K, Harada R, Nishikawa T. Parapsoriasis en plaques: its potential for progression to malignant lymphoma. J Am Acad Dermatol 1993;29: 419-22.

62. Wood GS, Haeffner A, Dummer R, Crooks CF. Molecular biology techniques for the diagnosis of cutaneous T-cell lymphoma. Dermatol Clin 1994;12:231-41.

63. Wood GS, Tung RM, Haeffner AC, Crooks CF, Liao S, Orozco R, et al. Detection of clonal T-cell receptor gamma gene rearrangements in early mycosis fungoides/Sezary syndrome by polymerase chain reaction and denaturing gradient gel electrophoresis (PCR/DGGE). J Invest Dermatol 1994; 103:34-41.

64. Kikuchi A, Naka W, Nishikawa T. Cutaneous T-cell lymphoma arising from parakeratosis variegata: long-term observation with monitoring of T-cell receptor gene rearrangements. Dermatology 1995;190:124-7.

65. Bachelez H, Bioul L, Flageul B, Baccard M, Moulonguet-Michau I, Verola O, et al. Detection of clonal T-cell receptor gamma gene rearrangements with the use of the polymerase chain reaction in cutaneous lesions of mycosis fungoides and Sezary syndrome. Arch Dermatol 1995;131:1027-31.

66. Wolff-Sneedorff A, Ralfkiaer E, Thomsen K, Vejlsgaard GL. Analyses of T-cell receptor beta-chain genes by Southern blotting in known and suspected cutaneous T-cell lymphoma. A study of 67 samples from 32 patients. Clin Exp Dermatol 1995;20:115-22.

67. Menke MA, Tiemann M, Vogelsang D, Boie C, Parwaresch R. Temperature gradient gel electrophoresis for analysis of a polymerase chain reaction-based diagnostic clonality assay in the early stages of cutaneous T-cell lymphomas. Electrophoresis 1995;16:733-8.

68. Curco N, Servitje O, Llucia M, Bertran J, Limon A, Carmona M, et al. Genotypic analysis of cutaneous T-cell lymphoma: a comparative study of Southern blot analysis with polymerase chain reaction amplification of the T-cell receptor-gamma gene. Br J Dermatol 1997;137:673-9.

69. Ashton-Key M, Diss TC, Du MQ, Kirkham N, Wotherspoon A, Isaacson PG. The value of the polymerase chain reaction in the diagnosis of cutaneous T-cell infiltrates. Am J Surg Pathol 1997;21:743-7.

70. Scheller U, Muche JM, Sterry W, Lukowsky A. Detection of clonal T cells in cutaneous T cell lymphoma by polymerase chain reaction: comparison of mutation detection enhancement-polyacrylamide gel electrophoresis, temperature gradient gel electrophoresis and fragment analysis of sequencing gels. Electrophoresis 1998;19:653-8.

71. Delfau-Larue MH, Petrella T, Lahet C, Lebozec C, Bagot M, Roudot-Thoraval F, et al. Value of clonality studies of cutaneous T lymphocytes in the diagnosis and follow-up of patients with mycosis fungoides. J Pathol 1987;184:185-90.

72. Delfau-Larue MH, Dalac S, Lepage E, Petrella T, Wechsler J, Farcet JP, et al. Prognostic significance of a polymerase chain reaction-detectable dominant T-lymphocyte clone in cutaneous lesions of patients with mycosis fungoides. Blood 1998; 92:3376-80.

73. Tok J, Szabolcs MJ, Silvers DN, Zhong J, Matsushima AY. Detection of clonal T-cell receptor gamma chain gene rearrangements by polymerase chain reaction and denaturing gradient gel electrophoresis (PCR/DGGE) in archival specimens from patients with early cutaneous T-cell lymphoma: correlation of histologic findings with PCR/DGGE. J Am Acad Dermatol 1998;38:453-60.

74. Wood GS, Uluer AZ. Polymerase chain reaction/denaturing gradient gel electrophoresis (PCR/DGGE): sensitivity, band pattern analysis, and methodologic optimization. Am J Dermatopathol 1999;21:547-51.

75. Murphy M, Signoretti S, Kadin ME, Loda M. Detection of TCR-gamma gene rearrangements in early mycosis fungoides by non-radioactive PCR-SSCP. J Cutan Pathol 2000;27: 228-34.

76. Cerroni L, Arzberger E, Ardigo M, Putz B, Kerl H. Monoclonality of intraepidermal T lymphocytes in early mycosis fungoides detected by molecular analysis after laser-beam-based microdissection. J Invest Dermatol 2000;114:1154-7.

77. Gellrich S, Lukowsky A, Schilling T, Rutz S, Muche JM, Jahn S, et al. Microanatomical compartments of clonal and reactive T cells in mycosis fungoides: molecular demonstration by single cell polymerase chain reaction of T cell receptor gene rearrangements. J Invest Dermatol 2000;115:620-4.

78. Simon M, Flaig MJ, Kind P, Sander CA, Kaudewitz P. Large plaque parapsoriasis: clinical and genotypic correlations. J Cutan Pathol 2000;27:57-60.

79. Wood GS. Analysis of clonality in cutaneous T cell lymphoma and associated diseases. Ann N Y Acad Sci 2001;941:26-30.

80. Stevens SR, Ke MS, Birol A, Terhune MH, Parry EJ, Ross C, et al. A simple clinical scoring system to improve the sensitivity and standardization of the diagnosis of mycosis fungoides type cutaneous T-cell lymphoma: logistic regression of clinical and laboratory data. Br J Dermatol 2003; 149:513-22.

81. Dommann SN, Dommann-Scherrer CC, Dours-Zimmermann MT, Zimmermann DR, Kural-Serbes B, Burg G. Clonal disease in extracutaneous compartments in cutaneous T-cell lymphomas. A comparative study between cutaneous T-cell lymphomas and pseudo lymphomas. Arch Dermatol Res 1996; 288:163-7.

82. Muche JM, Lukowsky A, Ahnhudt C, Gellrich S, Sterry W. Peripheral blood T cell clonality in mycosis fungoides—an independent prognostic marker? Blood 1999;94:1409-17.

83. Rubegni P, De Aloe G, Di Renzo M, Pompella G, Pasqui AL, Auteri A, et al. Cytokine production profile of peripheral blood mononuclear cells in patients with large-plaque parapsoriasis. Arch Dermatol 2001;137:966-7.

84. Tracey L, Villuendas R, Dotor AM, Spiteri I, Ortiz P, Garcia JF, et al. Mycosis fungoides shows concurrent deregulation of multiple genes involved in the TNF signaling pathway: an expression profile study. Blood 2003;102:1042-50.

85. Wood GS, Hong SR, Sasaki DT, Abel EA, Hoppe RT, Warnke RA, et al. Leu-8/CD7 antigen expression by CD3+ T cells: comparative analysis of skin and blood in mycosis fungoides/

86. Borowitz MJ, Weidner A, Olsen EA, Picker LJ. Abnormalities of circulating T-cell subpopulations in patients with cutaneous T-cell lymphoma: cutaneous lymphocyte-associated antigen expression on T cells correlates with extent of disease. Leukemia 1993;7:859-63.

87. Reinhold U, Abken H. Cutaneous T-cell lymphoma: molecular genetics, immunology and pathogenesis. Eur J Cancer 1995; 31A:793-9.

88. Ormsby A, Bergfeld WF, Tubbs RR, Hsi ED. Evaluation of a new paraffin-reactive CD7 T-cell deletion marker and a polymerase chain reaction-based T-cell receptor gene rearrangement assay: implications for diagnosis of mycosis fungoides in community clinical practice. J Am Acad Dermatol 2001;45:405-13.

89. Smoller BR, Santucci M, Wood GS, Whittaker SJ. Histopathology and genetics of cutaneous T-cell lymphoma. Hematol Oncol Clin North Am 2003;17:1277-311.

90. Michie SA, Abel EA, Hoppe RT, Warnke RA, Wood GS. Discordant expression of antigens between intraepidermal and intradermal T cells in mycosis fungoides. Am J Pathol 1990; 137:1447-51.

91. Scala E, Russo G, Cadoni S, Narducci MG, Girardelli CR, De Pita O, et al. Skewed expression of activation, differentiation and homing-related antigens in circulating cells from patients with cutaneous T cell lymphoma associated with CD7- T helper lymphocyte expansion. J Invest Dermatol 1999;113:622-7.

92. Scala E, Narducci MG, Amerio P, Baliva G, Simoni R, Giovannetti A, et al. T cell receptor-Vbeta analysis identifies a dominant CD60+ CD26- CD49d- T cell clone in the peripheral blood of Sezary syndrome patients. J Invest Dermatol 2002;119:193-6.

93. Novelli M, Comessati A, Quaglino P, Savoia P, Fierro MT, Bernengo MG. CD26 expression on cutaneous infiltrates from patients with cutaneous T-cell lymphoma (CTCL) CD26 in cutaneous T-cell lymphoma patients. Adv Exp Med Biol 2003; 524:223-34.

94. Vega F, Luthra R, Medeiros LJ, Dunmire V, Lee SJ, Duvic M, et al. Clonal heterogeneity in mycosis fungoides and its relationship to clinical course. Blood 2002;100:3369-73.

95. Kari L, Loboda A, Nebozhyn M, Rook AH, Vonderheid EC, Nichols C, et al. Classification and prediction of survival in patients with the leukemic phase of cutaneous T cell lymphoma. J Exp Med 2003;197:1477-88.

Sézary syndrome relative to normal blood values. J Am Acad Dermatol 1990;22:602-7.