

Update on erythrodermic cutaneous T-cell lymphoma: Report of the International Society for Cutaneous Lymphomas

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Two conferences were sponsored by the International Society for Cutaneous Lymphomas (ISCL) to gain consensus on definitions and terminology for clinical use in erythrodermic cutaneous T-cell lymphoma (E-CTCL). Three subsets of E-CTCL were defined: Sézary syndrome ("leukemic phase" E-CTCL), erythrodermic mycosis fungoides (secondary E-CTCL that develops in patients with mycosis fungoides), and E-CTCL, not otherwise defined. The hematologic criteria recommended for Sézary syndrome are intended to identify patients with a worse prognosis compared with the other E-CTCL subsets and consist of one or more of the following: (1) an absolute Sézary cell count of 1000 cells/mm³ or more; (2) a CD4/CD8 ratio of 10 or higher caused by an increase in circulating T cells and/or an aberrant loss or expression of pan-T cell markers by flow cytometry; (3) increased lymphocyte counts with evidence of a T-cell clone in the blood by the Southern blot or polymerase chain reaction technique; or (4) a chromosomally abnormal T-cell clone. For staging purposes, it is proposed that these criteria define the B2 blood rating and that the B2 rating be considered equivalent to nodal involvement. (J Am Acad Dermatol 2002;46:95-106.)

The International Society for Cutaneous Lymphomas (ISCL) was founded in December 1992 to enhance interactions among regional and national cutaneous lymphoma groups and to build consensus on areas such as definitions, terminology, and staging criteria (ISCL Web site located at www.cutaneouslymphoma.org). In this regard the ISCL organized two conferences on erythrodermic cutaneous T-cell lymphoma (E-CTCL), a potentially confusing clinical interface that may

occur between mycosis fungoides (MF) and Sézary syndrome (SS).¹

The first conference was convened in Cologne, Germany, on May 7, 1998, with the primary purpose of compiling information about current concepts and practices at various centers concerning the diagnosis of erythrodermic MF and SS. The meeting agenda included (1) a historical review of SS (Günter Burg, MD, University of Zürich, Switzerland); (2) brief presentations by invited speakers who presented the criteria used to diagnose SS at their centers (Rein Willemze, MD, Leiden University, The Netherlands; Liliane Laroche, MD, University of Paris, France; Peter Heald, MD, Yale University, New Haven, Conn; Robin Russell-Jones, MD, St John's Institute of Dermatology, London, UK; Masahiro Takigawa, MD, Hamamatsu University, Japan; Mark Pittelkow, MD, Mayo Clinic, Rochester, Minn; and Maria Grazia Bernengo, MD, University of Turin, Italy); and (3) a review of SS from the perspective of a hematologist (Hans Tesch, MD, University of Cologne, Germany). In the discussion that followed, the results of a pre-conference questionnaire were presented (Eric

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doi:10.1067/mjd.2002.118538

Table I. Recommended definitions for subsets of erythrodermic CTCL

E-CTCL subset	Pre-existing MF	Blood findings	TNBM designation
SS	Rarely	Leukemic	T4 N0-3 B2 M0-1*
Erythrodermic MF	Always	Absent or minimal	T4 N0-3 B0-1 M0-1
E-CTCL, NOS	Absent	Absent or minimal	T4 N0-3 B0-1 M0-1

NOS, Not otherwise specified.

*B1 and B2 will be applied to cases fulfilling the proposed definition of "minimal" and "leukemic" blood involvement in E-CTCL, respectively, as defined in the text.

Vonderheid, MD, MCP Hahnemann University, Philadelphia, Pa), and opinions were obtained about how flow immunophenotyping and molecular genetics should be combined with the traditional Sézary cell count to define minimal blood involvement in CTCL (B1 blood rating) and to define the hematologic criteria for the diagnosis of SS.

The second conference was held in New Orleans on March 20, 1999. A summary of the first conference was presented, and proposed definitions and terminology for use in E-CTCL derived from the Cologne conference proceedings were presented (Eric Vonderheid, MD). In addition, current molecular genetic methods and their use in the diagnosis of SS were reviewed (Sean Whittaker, MD, St John's Institute of Dermatology). The following is a review of E-CTCL and the recommendations of the ISCL that can serve as a reference for clinicians and scientists alike.

THE CTCL CONCEPT

The close nosologic relationship between MF and SS has been appreciated for many years.^{2,3} In 1975, with the development of techniques that identified T cells, CTCL was proposed as a diagnostic term to encompass MF, SS, and other primary T-cell lymphomas originating in the skin, often with overlapping clinical and histologic features.⁴ In 1978, an international workshop sponsored by the National Cancer Institute (NCI) and the Mycosis Fungoides Cooperative Group (MFCG) embraced the CTCL concept, and a staging classification based on the TNM (*tumor, node, metastasis*) scheme was developed.⁵ The T4 skin rating was assigned to patients with erythrodermic disease, and the B1 blood rating was assigned to cases with 5% or more atypical lymphocytes on blood smears.

Distinction between erythrodermic MF (E-MF) and SS

In 1892, Besnier and Hallopeau⁶ recognized that some patients with MF develop erythroderma during their disease. Many investigators today restrict the definition of E-MF to mean a secondary erythro-

derma that occurs in patients with MF, much like erythrodermic psoriasis may develop in a patient with plaque-type psoriasis. Others view E-MF and SS to be variants of E-CTCL with differing degrees of tumor burden.⁷ At this time, no consensus exists among ISCL members as to the clinicopathologic relationship between E-MF and SS.

SS is widely regarded to be a distinctive erythrodermic and "leukemic" variant of CTCL (92% of polled ISCL members concurred with this definition). The clinical features of SS usually develop *de novo* within a short interval of time (classic SS), but some cases are preceded by a prodrome of pruritus alone or nonspecific dermatitis. Rarely, SS may follow clinically typical MF. The ISCL recommends that such cases be indicated as "SS preceded by MF" because of possible differences in clinical behavior and prognosis compared with classic SS. Patients with E-CTCL who lack the hematologic criteria of SS include patients with E-MF as defined above and other patients with undefined E-CTCL, including some patients previously classified as having "pre-SS." Patients with CTCL without erythroderma, but with the blood findings of SS, should not be diagnosed as having SS at this time; such cases should be designated as "MF with leukemic involvement." The recommended classification scheme for E-CTCL variants is summarized in Table I.

The Sézary cell

In 1938, Sézary first identified a large atypical mononuclear cell of approximately the same size as a normal monocyte ("cellules monstreuses") in a patient with a chronic erythroderma and skin histologic findings suggestive of MF.⁸ In 1959, Main, Goodall, and Swanson⁹ recognized the large Sézary cell to be a large lymphocyte that underwent nuclear division without cytoplasmic division, and in 1961, Taswell and Winkelmann¹⁰ identified the distinctive grooved nucleus that is the cellular hallmark of Sézary cells (Fig 1). In 1968, Lutzner and Jordan¹¹ showed the nucleus of Sézary cells to be lobulated, indented, and serpentine by electron microscopy. Subsequently, Lutzner and colleagues¹² described

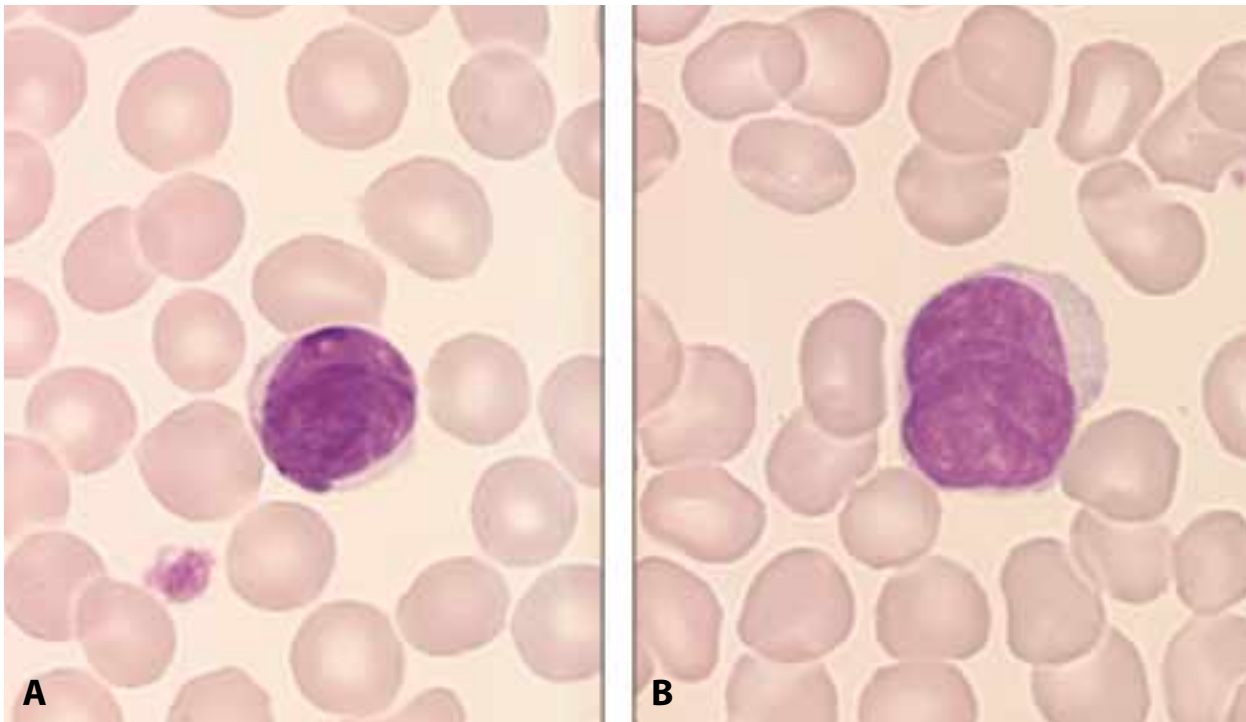


Fig 1. Photomicrograph of a small (**A**) and large (**B**) Sézary cell on blood smear from different patients with SS. Note relative cell sizes in relationship to the size of an erythrocyte that is about 7 μm in diameter. (Photograph courtesy of Georges Flandrin, MD, Paris, France.)

the “small cell” variant of the Sézary cell in which the atypical cells were the same diameter as normal resting lymphocytes (8-11 μm), and Litovitz and Lutzner¹³ performed morphometric measurements on small and large Sézary cells and found that the degree of nuclear convolutions was similar in both types of Sézary cells. In this study, the diameters of normal lymphocytes on routine blood smears ranged from 6 to 13 μm compared with 7 to 19 μm for Sézary cells.

The clinical implications of Sézary cells in the blood were discussed at a conference on the Sézary cell held at the Mayo Clinic in 1974 (published in *Mayo Clinic Proc* 1974;49:513-92). By this time, several groups had reported that Sézary cells could be detected in the peripheral blood of 20% to 25% of patients with MF, thereby suggesting a close nosologic relationship between the two disorders.^{2,14} Flandrin and Brouet¹⁵ reported finding variable numbers of Sézary cells on blood smears from 33 consecutive patients diagnosed with CTCL. Twenty-five patients with more than 40% Sézary cells per 100 lymphocytes were classified as having SS, although 7 (28%) had skin manifestations more typical of MF than erythrodermic disease. It is worth noting that lymphocytosis (>4000 cells/ μL) occurred in 17 of 25 cases (68%), and “typical” Sézary cells, defined as

Sézary cells with diameters of 12 μm or more, were not apparent on blood smears of 15 of 25 (60%) of the cases classified as SS. This study highlighted that the initial hematologic criteria for the diagnosis of SS did not necessarily require lymphocytosis or the presence of very large Sézary cells.

At the NCI/MFCG workshop on CTCL in 1978,⁵ a B1 blood rating was assigned for 5% or more atypical convoluted (Sézary) cells per 100 lymphocytes on blood smears, although this B1 rating was not used for staging of CTCL because of uncertainty about its prognostic implications. Subsequently, Schechter et al¹⁶ reported that 20% or more of Sézary cells per 100 lymphocytes had prognostic importance in CTCL, and in 1988 the NCI group presented a revised staging system with the 20% Sézary cell count as the B1 rating.¹⁷ Other groups have since confirmed the usefulness of this staging system.¹⁸

The lack of specificity of Sézary cells

Although Sézary cells are characteristically found in CTCL, smaller numbers of morphologically identical cells are often identified in skin and blood specimens of benign diseases.¹⁹⁻²¹ Small numbers of Sézary cells also can be identified in normal peripheral blood.^{22,23} In addition, Reinhold et al²⁴ recently demonstrated that normal lymphocytes stimulated

through the CD3 complex acquire a cerebriform shape indistinguishable from small Sézary cells. Because morphology alone cannot reliably distinguish malignant and normal lymphocytes, the ISCL recommends that the term *Sézary cell* be applied to any atypical lymphocyte with moderately to highly infolded or grooved nucleus. Thus defined, Sézary cells become synonymous with “mycosis cells,” “Lutzner cells,” and “cerebriform lymphocytes” identified on electron micrographs.^{19,20,25} For these reasons and the fact that the cerebriform nuclear shape of small Sézary cells is quite difficult to recognize on blood smears, many investigators do not utilize quantitative Sézary cell counts as a diagnostic criterion of SS. However, the diagnostic specificity of Sézary cell counts per se may be improved by considering the size of the cell in addition to the nuclear shape because Sézary cells larger than 12 μm may be more indicative of malignant cells.¹³ This concept was applied to work reported by Vonderheid et al²⁶ and Schechter et al¹⁶ in the mid 1980s.

Immunophenotyping

Flow immunophenotyping using murine monoclonal antibodies that react against lymphocyte subsets is a useful method to characterize SS. Most cases of SS are clonal expansions of circulating phenotypically mature $\text{TCR}\alpha\beta^+\text{CD}2^+\text{CD}3^+\text{CD}4^+\text{CD}5^+\text{CD}8^-$ T cells.^{25,27-29} However, cases of SS with expression of CD8 rather than CD4,^{7,28,30-32} coexpression of CD4 and CD8,³³⁻³⁵ loss of CD2,³⁵⁻³⁷ loss of CD3,³⁷ loss of CD4,^{27,29,35} or loss of CD5³⁷ have been encountered. In addition, expression of CD7, which is normally expressed on approximately 90% of CD4⁺ cells, is deficient on circulating malignant T cells in about 60% to 70% of SS cases.^{35,36,38,39} Antibodies that react against the variable region of the α or β chains of the T-cell receptor (TCR) (anti-V α or anti-V β antibodies) also have been used to define malignant T cells,^{40,41} and other markers of interest include altered level of CD3 or CD4 expression on T cells ($\text{CD}3^{\text{dim}}$, $\text{CD}4^{\text{dim}}$),^{38,42} the CD7-CD62L⁻ subset,⁴³ and the CD4⁺CD26⁻ subset.^{35,44}

The Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer (EORTC) has recently proposed a blood criterion for SS based on an increased number of T cells with a CD4/CD8 ratio of more than 10 and evidence of a T-cell clone in the blood.⁴⁵ These criteria define a subset of patients with an estimated 5-year survival rate of about 11%.

Molecular genetics

Evidence of clonality in peripheral blood can be demonstrated by a number of molecular methods.⁴⁶⁻⁴⁸

Southern blot analysis is a well-validated technique with a clonal detection threshold of 1% to 5%. Because Southern blot can detect a neoplastic population representing 1:20 cells, one would normally expect it to be positive in patients with E-CTCL who have 5% or more atypical circulating cells. By contrast, polymerase chain reaction (PCR)-based methods of TCR gene analysis are at least 10 times more sensitive than Southern blot, particularly if a radioactive method of detection is utilized. Consequently peripheral blood samples from patients with early MF and precursor conditions such as parapsoriasis en plaques are commonly found to be PCR positive in the peripheral blood.⁴⁹⁻⁵⁴ Although concern has been expressed about the specificity of some PCR-based techniques, a recent study indicates that PCR evidence of T-cell clonality in peripheral blood may be an independent prognostic indicator in patients with MF.⁵⁴

A variety of electrophoretic methods are currently available to analyze PCR products, including polyacrylamide gel electrophoresis, denaturing gradient gel electrophoresis, temperature gradient gel electrophoresis, single-strand conformational polymorphism (SSCP), and heteroduplex analysis of PCR products.⁴⁶⁻⁴⁸ Although each method probably has a similar diagnostic sensitivity and specificity, a careful comparison of each technique has not been undertaken in patients with CTCL.

TCR gene analysis of peripheral blood has been reported by several groups with E-CTCL.^{7,54-65} The largest series to date involves 65 patients with a clinical diagnosis of SS as defined by erythroderma and more than 10% atypical cells in the peripheral blood.⁶⁵ TCR gene analysis was positive in 53 patients by Southern blot and in an additional 3 patients using PCR/SSCP analysis of the TCR gene. Although the 9 nonclonal subjects had a mean absolute Sézary cell count of more than 1000/ mm^3 , none died of lymphoma, whereas in the clonal group the majority of deaths were CTCL related. The most recent data (R. Russell-Jones, unpublished data) show 66 clonal patients with 49 deaths, 40 of which were due to CTCL. Russell-Jones and Whittaker⁶⁵ have argued that the nonclonal subjects may therefore have a reactive erythroderma rather than a T-cell lymphoma-leukemia.

Russell-Jones and Whittaker⁶⁵ also proposed that the minimum criteria for a diagnosis of SS should include erythroderma, compatible skin histology, more than 5% circulating mononuclear cells (Sézary cells), and evidence of a peripheral blood T-cell clone by means of at least one of the following specific tests:

- Very large Sézary cells ($>14 \mu\text{m}$ diameter)
- Cytogenetic evidence of an abnormal clone

- Loss of pan-T cell antigen by immunophenotyping
- T-cell clone shown by Southern blot or PCR analysis

The figure of 5% corresponds to the original B1 rating proposed at the NCI/MFCG workshop.⁵ However, this reflects a lower tumor burden in the peripheral blood than has been traditionally used to define SS.

DEVELOPMENT OF HEMATOLOGIC CRITERIA FOR DIAGNOSIS OF SS

It is recognized that skin specimens from bona fide cases of SS frequently show only nonspecific or suspect histologic features of CTCL⁶⁶⁻⁶⁸ and that clinical and histologic features of SS can occasionally be mimicked by benign dermatoses, particularly actinic reticuloid^{69,70} and drug-induced pseudolymphoma reactions.^{71,72} For these reasons, the ISCL recommends that the hematologic criteria selected for the diagnosis of SS be sufficiently rigorous to avoid misdiagnosis when skin or lymph node studies fail to establish the diagnosis of CTCL with certainty. The lymph nodes of SS characteristically show a rather monotonous and diffuse infiltration with Sézary cells and a varying degree of architectural effacement.^{73,74} Moreover, the hematologic criteria should reflect an increased blood tumor burden because SS is generally regarded as a "leukemic" variant of E-CTCL with a worse prognosis compared with "aleukemic" E-CTCL variants.^{45,66,75,76}

The concept of combining blood findings that reflect the increased blood tumor burden and worse prognosis of SS with more specific studies to exclude occasional cases of "pseudo-Sézary syndrome" that may show similar blood findings provides a rational approach to the problem of defining blood involvement in SS. The remainder of this article reviews possible hematologic criteria that might be utilized for the diagnosis of SS. Table II⁷⁷⁻⁸⁴ shows the frequency of each criterion in patients with E-CTCL (T4 skin rating) or patients defined as having SS with various criteria. Some studies are more useful as a measure of blood tumor burden, whereas other studies are better used to confirm the diagnosis of CTCL.

Very large Sézary cells

Prototypical very large (>14 μm in diameter) Sézary cells can be identified on smears in only a minority of patients with SS and are not found in benign disease (Table II). Therefore the presence of very large Sézary cells, when used in conjunction with other studies, is useful to confirm the diagnosis of SS. Moreover, two studies have shown that patients with E-CTCL and very large Sézary cells in the blood have a worse prognosis than patients without very large Sézary cells.^{26,35}

Absolute Sézary cell count

Quantitative Sézary cell count for the diagnosis of SS has been in use for more than 25 years. At the Mayo Clinic, Sézary cell counts initially were expressed as a percentage of the total leukocyte count with 10%, and then 15%, considered to be diagnostically significant for SS.^{85,86} However, it was subsequently recognized that the Sézary cell count expressed as an absolute number per cubic millimeter was more reliable to monitor patients than percentage of white blood cells,⁸⁷ and a persistent absolute Sézary cell count of 1000 cells/mm³ was adopted as the hematologic criterion of SS. Patients with fewer than 1000/mm³ absolute Sézary cell counts were defined as having "pre-SS," although only some of these patients actually developed SS.^{88,89} In addition, absolute Sézary cell counts of 1000/mm³ or more have been reported in about 5% of patients with severe benign dermatoses, most often erythroderma (Table II).^{77,79} A notable exception is the report of Pincelli, Dean, and Warin⁷⁸ in which no Sézary cells were observed in benign inflammatory skin diseases, a finding that presumably reflects use of different cytomorphologic criteria to define Sézary cells than was used by others. To avoid potential misdiagnosis in the absence of diagnostic skin or lymph node finding, the ISCL recommends that additional evidence of blood involvement be provided to substantiate the diagnosis of SS. In patients with E-CTCL, an absolute Sézary cell count of 1000/mm³ or more appears to have prognostic significance (E. Vonderheid, unpublished data).

Percentage of Sézary cells per 100 lymphocytes

An alternative method to quantitate Sézary cells is to determine the percentage of Sézary cells observed within the lymphocyte population on blood smears. The potential advantage of this method over absolute Sézary counts derived directly from the leukocyte differential count is that a diagnosis of SS might be rendered in patients who have low leukocyte counts as a result of previous systemic treatment or concurrent bone marrow myelodysplasia. However, the relevant Sézary cell percentage for the diagnosis of SS has not been established. Vonderheid et al²⁶ reported that more than 15% small and large Sézary cells on blood smears were not usually encountered in common benign dermatoses and that this count correlated to the presence of a cytogenetically abnormal clone in the blood. Schechter et al¹⁶ found 20% to be a useful cut point to distinguish benign disease from CTCL, and this finding was supported by Willemze et al²⁵ who counted lymphocytes with

high nuclear contour indexes on electron micrographs. Thus a Sézary cell percentage of 20% has become widely regarded as a criterion that differentiates CTCL from benign disease, but current experience indicates that more severe benign erythrodermas occasionally have Sézary cell percentages exceeding 20%. This is particularly true in cases of actinic reticuloid^{69,70} and drug-induced pseudolymphomas.^{71,72}

From a prognostic point of view, several groups have found that patients with CTCL and 20 Sézary cells per 100 lymphocytes or more on blood smears have a worse prognosis than patients with fewer cells.^{16-18,26} However, when subjected to multivariate analysis with erythroderma (T4 skin rating) in the model, the 20% cut point no longer retained significance, indicating that the prognostic importance of 20% Sézary cells was derived mostly from being associated with erythroderma.¹⁷ This finding is directly supported by Vonderheid who found no significant difference in survival of patients with E-CTCL who had 20% or more Sézary cell counts compared with fewer than 20% Sézary cell counts (E. Vonderheid, unpublished data). Conversely, Kim et al⁷⁶ found a 5% Sézary cell count to be prognostically significant in E-CTCL. The reason for this apparently discordant result is unclear, but may relate to the definition of Sézary cells. These observations indicate that 20% or more Sézary cells in the lymphocyte population per se is not adequate as a diagnostic criterion for SS because of the potential for false-positive results and uncertain prognostic significance, but it remains useful for screening purposes because of its high sensitivity (Table II). Therefore at this time the ISCL recommends that an absolute Sézary cell count of 1000 cells/mm³ or more be utilized as a diagnostic criterion of SS.

CD4/CD8 ratio

An increase in CD4⁺ lymphocytes that results in a CD4/CD8 ratio of 10 or more occurs in about 80% of patients with SS and occasionally in patients with benign erythroderma (Table II). As mentioned previously, this criterion together with molecular evidence of T-cell clonality has been proposed by the Cutaneous Lymphoma Study Group of the EORTC to be a diagnostic criterion of SS.⁴⁵ The estimated 5-year survival rate of such patients is 11%, which may be less than the 5-year survival rate of patients with SS defined by other diagnostic criteria. The ISCL consensus is that a CD4/CD8 ratio of 10 or more is appropriate as a hematologic criterion of SS, but additional evidence of blood involvement is required in the absence of diagnostic skin or lymph node finding.

Aberrant immunophenotype and percentage of CD4⁺CD7⁻ cells

The ISCL recognizes that SS can be diagnosed by flow cytometry in patients with E-CTCL and lymphocytosis if the T cells express an aberrant phenotype (eg, loss of CD2, CD3, CD4, or CD5 or coexpression of CD4 and CD8). However, such cases occur infrequently. In addition, an increase in the percentage of CD4⁺CD7⁻ cells ($\geq 40\%$ of cells in the lymphocyte gate) occurs in only some cases of SS (Table II). Of patients with SS defined by absolute Sézary cell counts of 1000/mm³ or more, Harmon et al³⁷ and Bernengo et al³⁵ found that 6 of 13 patients (46%) and 12 of 22 (55%), respectively, had 40% or more CD4⁺CD7⁻ cells in the blood. None of the patients with benign inflammatory diseases were positive, suggesting that this criterion has high specificity for CTCL. Moreover, Laetsch et al⁵³ found a significant correlation between the percentage of CD4⁺CD7⁻ cells and Sézary cell counts. However, Dummer et al⁹⁰ demonstrated that the expanded CD4⁺CD7⁻ population in some cases of SS does not represent the dominant T-cell clone, and the prognostic significance of this criterion has not been established. For these reasons, at this time the ISCL recommends that 40% or more of CD4⁺CD7⁻ cells be regarded as a tentative blood criterion of SS.

Similarly, a high percentage of lymphocytes (eg, $\geq 40\%$ of cells in the lymphocyte gate) that react with an anti-V β antibody, or express low levels of CD3 (CD3^{dim}) or CD4 (CD4^{dim}), or are CD7-CD62L⁻ or CD4⁺CD26⁻ might also be useful to diagnose SS, but the experience with these markers is limited at this time. Bernengo et al⁴⁴ recently reported that the CD4⁺CD26⁻ subset is typically greater than 30% in patients with evidence of leukemic involvement based on blood smears.

T-cell clonality by molecular genetics

Because PCR-based methods are at least 10-fold more sensitive than Southern blot, it is not surprising that PCR-based methods detect T-cell clones in the blood of more patients with E-CTCL than does the Southern blot technique (Table II). Most patients with SS have evidence of a T-cell clone by either method, and clones may be detected occasionally in the blood of patients with benign skin diseases or normal elderly people. In addition, the higher sensitivity of PCR-based methods often detects T-cell clones in the blood of patients with parapsoriasis and nonerythrodermic CTCL who otherwise have no evidence of blood involvement.⁴⁹⁻⁵⁴ For these reasons, the ISCL suggests that molecular evidence of T-cell clonality be combined with some measure of tumor burden such as absolute Sézary cell count or

Table II. Frequency of hematologic findings in erythrodermic CTCL

Diagnostic criterion	Study	No. of positive/total cases	
		E-CTCL subset	Benign ISD
Sézary cells $\geq 14 \mu\text{m}$ diameter	Vonderheid et al ²⁶	T4:33/49 (67%)	0/70 (0%)
	Bernengo et al ³⁵	SS:20/62 (32%)	ND
Sézary cells $\geq 1000/\text{mm}^3$	Duncan & Winkelmann ⁷⁷	ND	2/63 (3%)
	Pincelli et al ⁷⁸	T4:1/2 (50%)	0/40 (0%)
	Duangurai et al ⁷⁹	SS:2/2 (100%)	6/67 (9%)*
	Thangavelu et al ^{80†}	T4:7/14 (50%)	ND
	Duncan & Winkelmann ⁷⁷	ND	4/63 (6%)
Sézary cells $\geq 20\%$ of lymphocytes	Pincelli et al ⁷⁸	ND	0/40 (0%)
	Vonderheid et al ²⁶	T4:30/49 (61%)	0/70 (0%)
	Schechter et al ¹⁶	T4:46/51 (90%)	1/25 (4%)
	Laetsch et al ^{53†}	T4:8/13 (62%)‡	ND
	Dutch group ^{25,60,64,70§}	T4:20/25 (80%)	3/37 (8%)
CD4/CD8 ratio ≥ 10	Solbach et al ⁸¹	SS:3/5 (80%)	ND
	Laroche & Bach ²⁷	SS:6/8 (75%)	ND
	Yale group ^{58,82,83}	SS:20/27 (74%)	ND
	Chu et al ⁶⁹	SS:5/8 (63%)	0/4 (0%)
	Boumsell et al ²⁸	SS:4/5 (80%)	ND
	Bernengo et al ^{35†}	SS:27/56 (48%)	ND
	Jakob et al ^{84†}	T4:7/8 (88%)	0/15 (0%)
	Harmon et al ^{37†}	SS:15/18 (83%)	6/30 (20%)
	Jakob et al ^{84†}	T4:6/8 (75%)	0/15 (0%)
	Bernengo et al ^{35†}	SS:12/22 (55%)	ND
	Harmon et al ^{37†}	SS:6/13 (46%)	0/30 (0%)
	Laetsch et al ^{53†}	T4:8/13 (62%)‡	ND
	T-cell clonality by Southern blot	Bertness et al ⁵⁵	SS:11/11 (100%)
Waldmann et al ⁵⁶		SS:5/5 (100%)	ND
Ralfkiaer et al ⁵⁷		SS:4/4 (100%)	ND
Berger et al ⁵⁸		SS:13/13 (100%)	ND
Dutch group ^{25,60,64,70§}		T4:10/12 (83%)	1/18 (6%)¶
Weiss et al ⁵⁹		T4:3/3 (100%)	ND
Whittaker et al ⁶²		T4:10/17 (59%)	ND
Zelickson et al ⁶¹		SS:19/21 (90%)	0/16 (0%)
Vonderheid et al ⁷		T4:9/18 (50%)	ND
Weinberg et al ⁶³		SS:8/11 (73%)	1/11 (9%)
Russell-Jones & Whittaker ⁶⁵		SS:53/65 (82%)#	ND
Dutch group ^{25,60,64,70§}		T4:10/11 (91%)	1/23 (4%)
Theodorou et al ⁵⁰		SS:3/3 (100%)	0/10 (0%)
T-cell clonality by PCR	Muche et al ⁵¹	SS:6/7 (86%)	1/40 (3%)
	Russell-Jones & Whittaker ⁶⁵	SS:56/65 (86%)#	ND
	Laetsch et al ^{53†}	T4:10/13 (77%)‡	ND

ISD, Inflammatory skin disease; ND, not done; SS, Sézary syndrome as defined by the author; T4, erythrodermic CTCL including SS.

*All patients with erythroderma.

†Additional data by personal communication from Maria Grazia Bernengo et al,³⁵ Thilo Jakob, MD,⁸⁴ Thomas Witzig, MD (Harmon et al³⁷), Reinhard Dummer, MD (Laetsch et al⁵³), and Timothy Kuzel, MD (Thangavelu et al⁸⁰).

‡In the series reported by Laetsch et al,⁵³ all patients were diagnosed to have SS. However, because Sézary cells were not observed in all patients, T4 is being used to describe the patients.

§Data compiled from series reported by Willemze et al,²⁵ Bakels et al,^{60,64} and Preesman et al.⁷⁰

||Data compiled from series reported by Berger et al,⁵⁸ Kono et al,⁸² and Heald et al.⁸³

¶Excludes two equivocally Southern blot-positive cases in series.

#If nonclonal SS patients are shown to be reactive, then diagnostic sensitivity exceeds 90% for Southern blot and approaches 100% for PCR.

CD4/CD8 ratio for defining the hematologic criterion of SS. In this regard, the “minimum” criterion for the diagnosis of SS proposed by Russell-Jones and Whittaker⁶⁵ may not serve to identify patients with

“leukemic” blood involvement that is implicit for the diagnosis of SS. Moreover, the prognostic connotations of minimal blood involvement in the setting of E-CTCL have not yet been determined.

Cytogenetics

Although no specific chromosomal abnormality characterizes SS, random numeric and structural abnormalities of chromosomes are encountered quite commonly.^{80,91-94} A chromosomally abnormal clone, conventionally defined as the same structural aberration or extra chromosome in 2 or more mitoses or missing chromosome in 3 or more mitoses, is demonstrable in only some patients with SS, but when present, it is highly specific for SS and identifies patients with a relatively poor prognosis. Of 24 cases of erythrodermic CTCL studied at MCP Hahnemann University, 13 (54%) had evidence of a T-cell clone on the initial study.⁷ Thangavelu et al⁸⁰ found that 11 of 19 patients (53%) with advanced MF/SS (11/14 patients with erythroderma) had evidence of a T-cell clone in the blood (T. Kuzel, personal communication). The ISCL recommends that a chromosomally abnormal clone in patients with E-CTCL be adopted as an independent hematologic criterion of SS.

PROPOSED HEMATOLOGIC CRITERIA OF SS

The criteria for SS require generalized erythroderma plus evidence of an increased number of malignant T cells in the blood associated with a relatively poor prognosis. The proposed hematologic criteria that signify "leukemic" blood involvement of SS will be assigned a "B2" blood rating to distinguish from the B1 blood rating and include the following:

1. An absolute Sézary cell count of 1000 cells/mm³ or more*
2. A CD4/CD8 ratio of 10 or more due to an increase in CD3⁺ or CD4⁺ cells by flow cytometry*
3. Aberrant expression of pan-T cell markers (CD2, CD3, CD4, CD5) by flow cytometry. Deficient CD7 expression on T cells (or expanded CD4⁺CD7⁻ cells \geq 40%) represents a tentative criterion of SS at this time.
4. Increased lymphocyte counts with evidence of a T-cell clone in the blood by Southern blot or PCR technique*
5. A chromosomally abnormal T-cell clone

IMPLICATIONS FOR STAGING

The T4 skin rating utilized in the NCI/MFCG staging classification scheme should be applied to all

* If the diagnosis of CTCL was not substantiated on skin or lymph node studies, then additional evidence of malignancy is required to avoid a misdiagnosis of SS, such as the presence of very large Sézary cells (>14 μ m in diameter) on smears, evidence of T cells with aberrant expression of T-cell markers or abnormally large size by flow cytometry, or demonstration of the identical T-cell clone in the skin and blood by Southern blot or PCR-based method.

cases of E-CTCL; the T rating may be further designated as "T4 (T1-2)" or "T4 (T3)" when coexisting plaques or tumors are present, respectively. The ISCL consensus is that the B1 blood rating should be applied to cases of CTCL with cytologic evidence of abnormal lymphocytes (Sézary cells) on blood smears (\geq 5% per 100 lymphocytes) *plus* PCR or other evidence of a T-cell clone in the blood. If only Sézary cell counts are available, then 20% or more abnormal lymphocytes should be utilized as the criterion for minimal blood involvement. However, these proposed definitions of B1 are not sufficient for the diagnosis of SS, which requires demonstration of a greater number of abnormal T cells in the blood as defined above. Although the prognostic significance of the proposed hematologic criteria of SS vis-à-vis other staging parameters has not been determined, the ISCL recommends that the proposed blood involvement of SS be designated as a B2 rating (leukemic involvement) to distinguish from the proposed B1 rating (minimal blood involvement) and that the adverse connotation of such involvement be recognized to be equivalent to nodal involvement for staging purposes, that is, T4 N0-1 B2 M0 equals stage IVa. The staging designation of E-MF and E-CTCL, NOS (not otherwise specified) remains unaffected by the modified B rating, that is, T4 N0-1 B0-1 M0 equals stage III, until additional studies are available.

PROPOSED TERMS AND DEFINITIONS

- I. Sézary cell: An atypical lymphocyte with a moderately to highly infolded or grooved nucleus (eg, a cerebriform lymphocyte with nuclear contour index of 6.5 or more). Sézary cells, mycosis cells, Lutzner cells, and cerebriform lymphocytes are synonymous terms. Although characteristically found in tissues of patients with CTCL, Sézary cells may be found in benign and other malignant diseases. In certain inflammatory diseases such as actinic reticuloid, certain drug eruptions, and severe eczemas, Sézary cells may be numerous, thereby mimicking SS.
 - A. Small Sézary cell: A Sézary cell with cell diameter <12 μ m, that is, the size of a normal resting lymphocyte (Fig 1, A).
 - B. Large Sézary cell: A Sézary cell with cell diameter \geq 12 μ m, that is, larger than the size of a normal resting lymphocyte (Fig 1, B). A very large Sézary cell with cell diameter >14 μ m is clearly neoplastic.
- II. Erythroderma: A disease state characterized by diffuse erythema involving more than 80% of the skin surface with or without scaling. Erythroderma may occur in many disorders including CTCL. The term "idiopathic" erythro-

derma should be applied to cases lacking a definite diagnosis.

A. Erythrodermic CTCL (E-CTCL): A variant of CTCL characterized by chronic erythroderma. The E-CTCL category may be further divided into 3 clinical groups depending on clinical history and blood findings.

1. SS: A leukemic expression of E-CTCL characterized by numerous Sézary cells in the skin, blood, and other tissues, typically with evidence of T-cell clonality. Additional clinical findings that occur frequently in SS, but which are not essential for the diagnosis, include lymphadenopathy, hepatosplenomegaly, palmo-plantar keratoderma, ectropion, and alopecia. The manifestations of SS typically develop de novo (classic SS), but may be preceded by a prodrome of pruritus alone or nonspecific dermatitis. Rarely, the clinical and pathologic features of SS may be preceded by mycosis fungoides, and the ISCL recommends that such cases be designated as "SS preceded by MF" to distinguish from the more typical presentation of SS. To be diagnosed as SS, cases must fulfill one of the criteria of "leukemic" involvement as already proposed.

Cases of SS may be further classified by using cytomorphologic criteria as small-cell variant of SS when more than 80% of the Sézary cells are small ($<12\ \mu\text{m}$ in diameter) and very large ($>14\ \mu\text{m}$ in diameter) Sézary cells are absent. Cases of SS may be classified as large-cell variant of SS when 20% or more of the Sézary cells are very large ($>14\ \mu\text{m}$ in diameter). Cases with an intermediate picture may be referred to as mixed cell variant.

2. E-MF: E-CTCL lacking the blood findings of SS that develops during the course of disease in patients with otherwise clinically typical MF.

3. E-CTCL, not otherwise specified (NOS): Cases of E-CTCL that fail to fulfill the diagnostic criteria for either E-MF or SS as defined above. This category would encompass cases previously designated as "pre-SS."

B. Adult T-cell leukemia with features of SS: Cases of adult T-cell leukemia that mimic the blood findings of SS. The diagnosis requires incorporation of human T-lymphotropic virus type 1 DNA into the tumor cell genome.

C. Pseudo-CTCL erythroderma: Benign non-malignant inflammatory conditions characterized by erythroderma and other findings that suggest the diagnosis of CTCL. Typically this refers to compatible skin histology, but occasionally cases of actinic reticuloid and certain drug eruptions may have increased numbers of Sézary cells in the blood that are suspected to be SS. If the absolute number of Sézary cells is $1000/\text{mm}^3$ or more or the CD4/CD8 ratio is 10 or more, such cases should be designated as pseudo-SS.

UNRESOLVED ISSUES AND FUTURE WORK

The proposed definitions and terms for describing patients with E-CTCL are intended to improve the communication among investigators involved in the study of CTCL. As such, they are not meant to be dogmatic, but rather subject to modification as new information accumulates about the disease. Some unresolved issues raised at the conferences were as follows: Should the definition of SS be restricted to erythrodermic patients or should the definition be expanded to also include patients with nonerythrodermic manifestations as originally proposed by Schein, Macdonald, and Edelson³? Is the clinical behavior and prognosis of SS that develops after MF different from classic SS? How reliable are Sézary cell counts, and should the study be abandoned as a measure of tumor burden? What additional hematologic criteria are appropriate for the diagnosis of SS, for example, percentage of CD4⁺CD7⁻, CD7-CD62L⁻, CD4⁺CD26⁻, TCR V β ⁺, or CD3^{dim}/CD4^{dim} cells in the lymphocyte gate by flow cytometry? How do newer, more sensitive techniques to detect neoplastic T cells in tissues affect staging and prognosis of patients with E-CTCL? How do the criteria of "minimal" blood involvement for SS proposed by Russell-Jones compare with the recommended ISCL definition of "leukemic" involvement in E-CTCL? Can blood tumor burden in E-CTCL be further stratified into prognostically useful categories?

To address these issues, the ISCL plans to establish a registry for newly diagnosed patients with E-CTCL to determine the prognostic relevance of the proposed blood criteria for SS vis-à-vis other established prognosticators, for example, nodal involvement, transformation to high-grade lymphoma, and level of soluble interleukin 2 in the blood. One expected outcome of this effort is the development of additional B ratings based on blood tumor burden that have clinical usefulness for the staging of patients with E-CTCL.

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