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The Evolution of Sézary Syndrome: Past, Present and Future

Eric C. Vonderheid*

Adjunct Professor of Oncology, Sydney Kimmel Comprehensive Cancer Center, Johns Hopkins Medical Institutes, Baltimore, MD, USA

Abstract

In this review, the author discusses the changes that have occurred in our understanding of Sézary syndrome and erythrodermic mycosis fungoides, which are currently regarded as 'leukemic' and 'non-leukemic' expressions of erythrodermic cutaneous T cell lymphoma, respectively. The neoplastic cells have highly infolded 'cerebriform' nuclei (neoplastic Sézary cells), and display properties of central memory T cells of skin-associated lymphoid tissue. Although Sézary syndrome is characterized by a myriad of genetic and epigenetic abnormalities, no one fundamental defect is common to all cases. Cytokines and colonization of the skin by Staphylococcus aureus promote phenotypic plasticity and tumor progression. The prognostic significance of blood involvement is now recognized as B ratings in a revised tumor-node-metastasis (TNM) classification system for cutaneous T cell lymphoma. Flow cytometry and evolving molecular genetic methods to quantify blood involvement are replacing traditional visual counts of Sézary cells on blood smears. Patients without erythroderma and blood findings that are typical for Sézary syndrome have been reported. The author predicts that revisions to the TNMB ratings will be required in the future.

Keywords: Cutaneous T cell lymphoma; Erythroderma; Mycosis fungoides; Sézary syndrome

Correspondence to: Eric Vonderheid, MD, 37580 S. Desert Sun Drive, Tucson, AZ, USA 85739; Tel: +520-825-2699 E-mail: evonder1@jhmi.edu

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Introduction

"There's nothing new under the sun, but there are lots of old things we don't know." — Ambrose Bierce

Our knowledge about Sézary syndrome (SS) has rapidly increased since the development of immunopathology, flow cytometry and molecular genetics in the 1970s (Figure 1). This review and commentary concerns changes that have taken place in the criteria used to define SS and other erythrodermic expressions of cutaneous T lymphoma (E-CTCL) and recent insights about pathology.

SS is currently regarded as the 'leukemic' variant of E-CTCL [1]. The remaining 'non-leukemic' variants of E-CTCL are designated as erythrodermic mycosis fungoides (E-MF) or more precisely non-Sézary E-CTCL, and rarely other primary cutaneous T cell lymphomas that develop erythroderma. Therefore, as currently defined, SS consists of three components: (1) the pathologic diagnosis of CTCL, (2) erythroderma, and (3) the hematologic criteria used to define 'leukemic' involvement. Each of these will be discussed separately below.

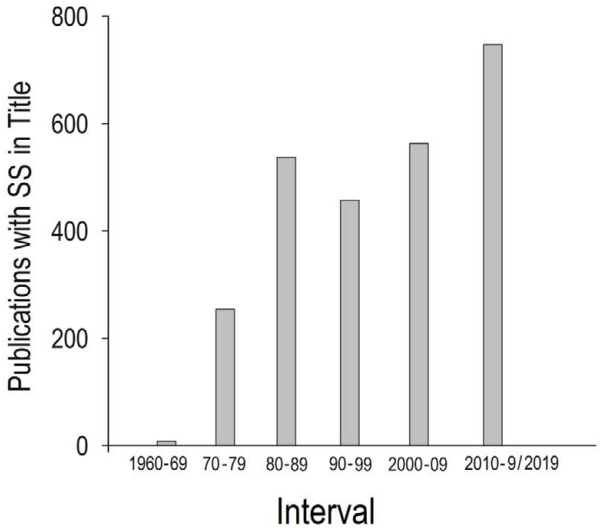

Figure 1: The number of publications with SS in the title of a Pubmed search has steadily increased since the 1970s.

Pathologic diagnosis of CTCL

A useful algorithm for the evaluation of patients with suspected E-CTCL was prepared by Russell-Jones [2] and my views on this subject were published elsewhere [3]. In general, the diagnosis of E-CTCL becomes clinically suspect if there is there is a prior diagnosis of mycosis fungoides (MF), infiltration of the skin to a degree not usually encountered in non-neoplastic erythrodermas including discrete plaques or tumors, and/or marked enlargement of peripheral lymph nodes (≥ 3 cm diameter). A prior history of an inflammatory condition that might also cause chronic erythroderma (e.g., atopic dermatitis, psoriasis, drug allergy) confounds the differential diagnosis.

In addition, chronic idiopathic erythroderma ('red man/woman syndrome') eventually may declare as CTCL.

The diagnosis of E-CTCL is usually established if a skin specimen has histopathologic findings that are either diagnostic for MF/CTCL or compatible with the diagnosis with support by an ancillary study (immunohistochemistry, molecular genetics). However, skin specimens may show non-specific or subtle histopathologic findings in up to one-third of patients with bona fide SS. In such cases, molecular genetic evidence of a T cell clone in the skin, ideally identical to one in the blood (or lymph node), provides strong support for the diagnosis of E-CTCL. The diagnosis of SS can also be established by blood studies (see section on hematologic criteria of SS below).

Although skin and blood findings establish the diagnosis of SS in most instances, some inflammatory conditions may have high numbers of non-neoplastic lymphocytes with hyperconvoluted nuclei (Sézary-like cells) in the blood and skin findings that can be confused with SS (see comments about Sézary cells below). These pseudo-Sézary conditions include (1) drug-induced pseudolymphomatous reactions [4-6] and (2) severe photosensitivity reactions including actinic reticuloid and photosensitivity in HIV+ patients [7-10]. Because these are inflammatory rather than neoplastic conditions, they typically do not have a T cell clone or other evidence that indicates the presence of neoplastic cells such as very large Sézary cells or chromosomally abnormal cells in the blood. However, exceptions may occur. For example, Reeder described a patient with drug-induced pseudo-SS that had many of the currently accepted criteria for SS. Specifically, in addition to typical histo-immunophenotypic features of CTCL in the skin, blood studies showed > 1.0/μL atypical cells with a CD4+CD7+CD26- phenotype and an identical T cell clone in skin and blood [6]. These changes cleared on discontinuation of anti-hypertensive drugs. This remarkable case illustrates that drug-induced pseudo-SS reactions may be particularly difficult to differentiate from SS.

In addition to pseudo-SS, other neoplastic conditions may be confused with SS. These include: (1) adult T cell lymphoma [11], (2) Sézary cell variant of prolymphocytic leukemia [12], and (3) 'leukemic' peripheral T cell lymphomas with erythroderma [13]. Adult T cell lymphoma is caused by human T cell leukemia virus type 1/2 which can be diagnosed by serologic studies. The neoplastic cells often have clover-leaf nuclear morphologies and are CD7+. The Sézary cell variant of prolymphocytic leukemia is distinguished by high lymphocyte counts with bone marrow, spleen and liver involvement and CD7+ neoplastic cells. The skin shows an angiocentric non-epidermotropic lymphocytic infiltrate [14]. Chromosome studies show inversions or translocations involving 14q32 which activates TCL-1 oncogene along with other abnormalities [15]. Peripheral T cell lymphomas have lymph nodes as the primary site of involvement with neoplastic cells that infiltrate the skin as the secondary involvement. The nuclei of neoplastic cells are usually not markedly convoluted. However, if involvement of peripheral skin-associated lymph nodes proceeds erythroderma and Sézary cells are present in the blood, are these also examples of SS (see section on pathogenesis of SS below)?

Comment on erythroderma

The second requirement for the diagnosis of SS is erythroderma. Based on the consensus conference of the International Society for Cutaneous Lymphomas (ISCL) in 2002 [16], erythroderma of CTCL refers to generalized or nearly generalized redness that involves > 80% of the skin surface. Furthermore, because erythroderma associated with CTCL has a poor prognosis [17-22], it is assigned a T4 skin rating for clinical staging. However, the adverse connotation of erythroderma/T4 skin rating may be due to its linkage with SS such that the prognostic importance of erythroderma relative to B (blood), N (lymph node) and M (visceral organ) ratings adopted for clinical staging of E-CTCL needs to be reassessed.

But is generalized erythroderma sine qua non for the diagnosis of SS? With the availability of flow cytometry, patients are being identified with high numbers of circulating neoplastic cells that fulfill the hematologic criteria of SS, but lack erythroderma as currently defined [23-25]. For patients who otherwise have clinically typical MF, the designation 'leukemic MF' may be used in this circumstance together with the appropriate T rating [16].

According to one multicenter study, erythroderma as the initial skin manifestation of SS occurs in only about 25% of cases [26]. Erythroderma was preceded by patch or plaque phase MF (also known as 'secondary' SS) in about 10% of patients. In my experience, only 6 of 84 (7%) patients had a history of clinically typical MF before the diagnosis of SS.

Another common presentation of SS concerns patients with widespread, often coalescing areas of erythema that involves < 80% of the skin surface. These patients do not have the stable well-demarcated lesions of clinically typical MF and strictly speaking do not have generalized erythroderma. Although such patients might be classified as 'leukemic MF', most eventually develop generalized erythroderma and therefore I consider these patients as forme fruste SS (T4? might be indicated as the skin T rating).

In addition, patients with negligible or non-diagnostic skin changes, but with the blood findings of SS have been reported. Perhaps this is to be expected given that non-specific or eczematoid skin lesions precede the majority of cases of 'primary' SS [26]. In addition, in my experience, generalized pruritus prior to the appearance of skin lesions was reported in 16 of 84 (19%) patients, all with 'primary' SS.

The expression 'invisible SS' and T0 skin rating has been suggested to describe patients presenting with pruritus and B2 blood rating [27,28]. Of note, neoplastic cells were detectable in clinically normal skin of these patients. This raises a question about semantics: should such patients be diagnosed as SS or given an alterative designation such as 'leukemic CTCL with occult skin involvement'?

My point is that salient hematologic findings of SS can be found not only in patients with erythroderma as defined by the ISCL/EORTC (i.e., primary and secondary SS), but also patients with clinically typical MF (i.e., 'leukemic' MF), patients without erythroderma and even patients with pruritus and apparently normal skin. To identify these patients with non-erythrodermic SS, the physician must screen blood samples for evidence of neoplastic cells with flow cytometry. If you do not look, you will not find.

Hematologic criteria of Sézary syndrome

Sézary cells

Since Albert Sézary reported his 3 cases between 1938 and 1942 [29-31], considerable changes have taken place in the criteria used to define 'Sézary cells' and perforce the definition of SS. In his original cases, Sézary observed large mononuclear cells (15 to 25 μm diameter) with a U-shaped nucleus that occupied most of the cell, often with several nucleoli. These 'cellules monstrueuses' were believed to be primitive cells of the reticulo-endothelial system or 'reticulosis'.

In 1959, Main et al. [32] introduced the term 'cerebriform' to describe the characteristic convoluted nucleus of large Sézary cells on blood smears. They also showed that large Sézary cells have nearly twice the amount of DNA with Feulgen staining compared to lymphocytes, and suggested that large Sézary cells may have developed from small lymphocytes by nuclear division and fusion without cytoplasmic division.

Subsequently, electron microscopic studies by Lutzner and others confirmed that large Sézary cells are T cells with highly infolded serpentine nuclei [33,34]. 'Small cell variants' of SS and MF, characterized by smaller lymphocytes with infolded nuclei and normal DNA content, were also described [35,36]. In addition, lymphocytes with morphologically similar nuclei were found in infiltrates of MF [37,38]. These cells have been called Lutzner cells, mycosis cells or cerebriform lymphocytes by various investigators.

It was also recognized in the 1970s that lymphocytes with cerebriform nuclei may be found in non-neoplastic conditions and even in the blood of normal individuals [39,40]. Of interest, cerebriform lymphocytes are commonly found in the CD4+CD7- and CD4+CD26- subsets of normal lymphocytes [41,42].

Furthermore, under certain conditions in vitro, the cerebriform nuclear shape can be induced in normal lymphocytes [43-45]. These observations indicate that the cerebriform nuclear morphology is not specific for the neoplastic cells of CTCL. Consequently, the ISCL recommended that the term 'Sézary cell' be used as a general term to describe any atypical lymphocyte with highly infolded or cerebriform nuclei [16]. This approach requires that a distinction be made between truly neoplastic Sézary cells and non-neoplastic Sézary cells, i.e., Sézary-like cells, much like defining T cell clones as being neoplastic or non-neoplastic in nature. However, in most publications, investigators continue to equate Sézary cell with neoplastic cell.

Sézary cells, particularly those with larger diameters, can be visually identified and counted on routinely stained blood smears. At the Mayo Clinic in the early 1970s, patients with erythroderma of any type were diagnosed as SS if the Sézary cell count was 1.0 K/μL or more [46], and patients with fewer Sézary cells were classified as 'pre-SS' even though not all patients eventually developed SS [47]. Some patients with SS thus defined subsequently developed aggressive lymphoma (probably transformation into large cell lymphoma) and some had a clinical course more in keeping with a non-neoplastic condition [48].

By today's standards, a Sézary cell count of ≥ 1.0 K/μL remains one established hematologic criterion of SS with the proviso that that a T cell clone is also present in the blood in order to exclude certain inflammatory mimics of SS with high number of Sézary cells, e.g. severe photosensitivity disorders/actinic reticuloid and lymphomatoid drug reactions [6-8,10]. In addition to molecular genetic evidence of a T cell clone, blood involvement can be confirmed by the presence of very large Sézary cells (cell diameter > 14 μm), abnormal chromosomal karyotypes or T cells with diminished expression levels of CD3 or restricted expression of variable beta region of the T cell receptor (TCR-Vβ) [50].

In my experience and that of others [51-52], the lymphocyte population of SS is usually composed of a mixture of variably sized Sézary cells rather than composed predominantly of very large Sézary cells (classic SS) or small Sézary cells (small cell variant of SS). Only very large Sézary cells with cell diameters > 14 μm are undoubtedly neoplastic whereas a proportion of smaller Sézary cells, which are more difficult to recognize in blood smears, are likely to be non-neoplastic in E-CTCL because up to 20% Sézary cells may be observed in common inflammatory dermatoses [51-52]. Therefore, the total Sézary cell count likely does not accurately estimate the actual neoplastic cell count when a substantial proportion of Sézary cells are small to intermediate-sized. Indeed, Sézary cells were not recognized on blood smear from one of my patients with a small cell variant of SS as shown by electron microscopy.

Flow cytometry

The most significant change in the hematologic criteria used for SS since the 1970s has been flow cytometry and antibodies that define subsets of lymphocytes. Quantitative counts of Sézary cells in the blood have been replaced at most centers by measurement of lymphocyte populations that have phenotypic features of neoplastic cells vis-à-vis normal lymphocytes. Usually this involves quantitation of cells that have lost expression of CD7 or CD26, i.e., lymphocytes with a CD4+CD7- or CD4+CD26- phenotype. Because expression of CD7 and CD26 by neoplastic cells are partially or completely lost in about 60% and 90% of SS cases, respectively, it has been recommended that both CD4+CD7- or CD4+CD26- subsets be measured and the subset with the highest value be used to determine the absolute count [53,54]. As shown in Figure 2, these subsets correlate well with morphologic Sézary cell counts and usually provide a higher absolute count [42,53]. Thus, the most recent recommended hematologic criterion for the B2 blood rating and perforce SS is an absolute count of CD4+CD7- or CD4+CD26- cells ≥ 1.0 K/μL plus evidence of a T cell clone (or other test that confirms the presence of neoplastic cells) [53,54]. Provided the neoplastic cells have total loss of either CD7 or CD26 expression, the maximum count of either CD4+CD7- or CD4+/CD26- lymphocytes provides a good estimate of blood tumor burden. However, this criterion would underestimate neoplastic involvement if both CD7 and CD26 are variably or completely expressed, i.e., CD4+CD7 ± CD26 ± or CD4+CD7+CD26+, as well as partial or complete loss of CD4 expression.

It also should be noted that non-neoplastic erythrodermas have increased percentages of CD4+CD7- or CD4+CD26- lymphocytes (up to 40% and 45% of lymphocytes, respectively, in some series)

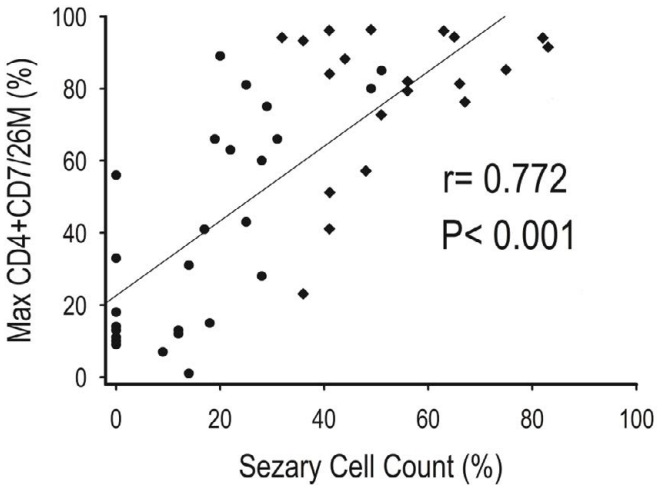

Figure 2: In the author's experience, a significant positive correlation exists between Sézary cell percentage determined by morphology and the highest CD4+CD7- or CD4+CD26- percentage in blood lymphocytes of patients with erythrodermic cutaneous T cell lymphoma. The diamonds indicate patients with Sézary cell count ≥ 1.0 K/μL.

[16,42,53,55]. It remains to be determined if inflammatory conditions that mimic SS have even higher values, perhaps exceeding the 1.0 K/μL threshold used to define SS.

A second approach is to use antibodies that react against the TCRVβ region. Measurement of expanded populations of CD4+TCRVβ+ neoplastic cells could potentially be used to quantify blood tumor burden. The problems with this approach in addition to cost considerations are: (1) commercially available anti-TCRVβ antibody panel covers only 70% of the Vβ family repertoire, (2) the antibodies also react against normal CD4+ cells expressing the same Vβ segment, and (3) the antibody may fail to react to the appropriate Vβ segment (false negative reactivity) or react to a different Vβ segment (false positive reactivity) [54,56,57].

My experience with TCRVβ, CD4+CD7- and CD4+CD26- measurements on lymphocytes collected by leukapheresis from with 30 patients with SS is shown in Figure 3 [58]. The correlation between percentage of cells with a restricted Vß expression and maximum percentage of either CD4+CD7- or CD4+CD26- cells was significant (rho= 0.593, P= 0.001; r= 0.494, P= 0.006). Of interest, the neoplastic cells of two patients co-expressed CD7 and CD26 which resulted in low maximum percentages of CD4+CD7- or CD4+CD26- vis-à-vis percentage of Vβ+ cells (shown lower right corner of plot). If these 2 patients are excluded from the analysis, the correlation between maximum percentage of either CD4+CD7- or CD4+CD26- cells and Vβ+ cells became even stronger (rho= 0.845, P< 0.001) (Figure 3).

Another possibility is to measure T cells that have diminished expression levels of CD3 (e.g., CD3dim cells) or other pan T markers [59,60]. However, it has not been established that such cells represent all or only some of the neoplastic cells. Moreover, inflammatory conditions might also have T cells with altered expression levels.

Finally, efforts continue to identify antibodies that react against moieties highly expressed by neoplastic cells, but not by normal or activated T cells or other cells. Of these, the killer immunoglobulin-like receptor KIR3DL2/CD158k on T cells has been extensively studied and seems promising, but is not always expressed by neoplastic cells [61,62]. Other potentially useful neoplastic markers are CD164 [63,64] and CD39 [65].

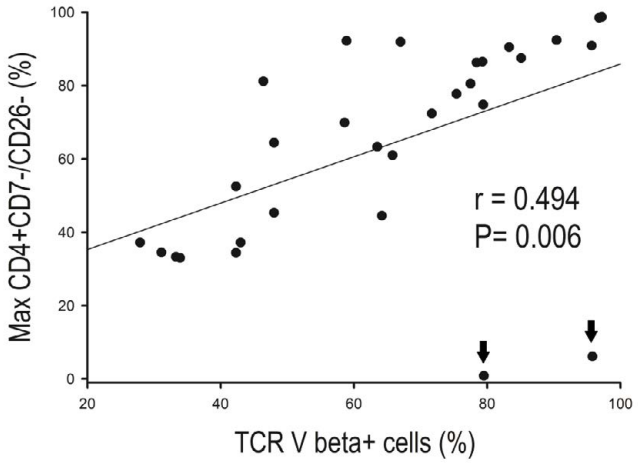

Figure 3: Significant correlation between maximum percentage of CD4+CD7- or CD4+CD26- and TCRVβ+ lymphocytes collected from 30 patients with Sézary syndrome. The arrows identify 2 patients with CD7+CD26+ neoplastic cells.

Molecular genetics

SS is characterized by a myriad of genetic and epigenetic abnormalities, but unlike other lymphomas and most leukemias, no one mutation has emerged as being instrumental in the early pathogenesis of SS [66]. Nevertheless, several groups have identified combinations of genetic or epigenetic abnormalities that allow for differentiation of SS from inflammatory skin disease [61,67,68]. For example, the genetic profile of ↓STAT4, ↑TWIST1, and ↑DNM3 (or ↑PLS3) gene expression identifies 98% of patients with SS with 100% specificity [61]. However, it is unclear whether screening for these abnormalities should define SS vis-à-vis non-Sézary E-CTCL because of lack of a quantitative component.

Ultimately, molecular methods that can quantify tumor burden in blood, skin and other tissues such as high-throughput sequencing of the TCR-β gene, may provide the best criterion for B ratings and SS [69,70]. The method also allows measurement of reactive clones in the same sample [71].

Erythrodermic mycosis fungoides

In 1892, Hallopeau and Besnier observed that erythroderma can precede or follow MF [72]. This original definition of erythrodermic mycosis fungoides (E-MF) included patients that now would be diagnosed as SS. At the 1992 ISCL consensus conference, it was proposed that the diagnosis of E-MF be applied when patients with clinically typical MF develop erythroderma, assuming blood studies are not those of SS (a.k.a. 'secondary SS') [16]. The remaining non-Sézary patients whose erythroderma was not preceded by typical MF were to be diagnosed as E-CTCL, not otherwise specified. However, this clinical distinction has not been widely accepted, including the World Health Organization Classification of Tumors [1]. Therefore, the current definition of E-MF refers to most patients with E-CTCL that lack the blood criteria for SS, i.e., non-Sézary E-CTCL.

As already discussed, in most instances, the pathologic diagnosis of E-MF (non-Sézary E-CTCL) can be rendered with a high degree of certainty with skin histology and supporting ancillary studies. In addition, a proportion of patients will have neoplastic cells in the blood albeit at numbers that do not reach the threshold used to define SS. However, if the erythrodermic specimen shows non-specific histopathologic findings and blood studies are not helpful for diagnosis, it can be very difficult to distinguish E-MF from erythrodermic inflammatory skin diseases (EISD). The problem is confounded by the fact that E-CTCL may be preceded by skin diseases that also have the potential to become erythrodermic such as psoriasis and atopic dermatitis [73,74]. It is even possible that the erythroderma associated with MF may be a reactive process rather than true neoplastic progression.

In such problematic situations when skin histopathology shows equivocal or non-diagnostic findings, demonstration of a T cell clone in the skin provides evidence in favor of E-MF because T cell clones are almost always not detectable in EISD, i.e., high diagnostic specificity [75-78]. Nevertheless, with modern PCR-based methods that have a 1% or less detection threshold for T cell clones, a small proportion of EISD will have a detectable clone in the skin. For example, Klemke detected a T cell clone in 98% of skin samples of SS, but also 2/15 (13%) samples of EISD [78]. It also should be noted that high-throughput sequencing of the TCR-Vβ CDR3 region may be even more sensitive than the TCR-γ/GeneScan method [79]. Consequently, it is likely that non-neoplastic clones will be detected by high throughput sequencing in the skin of EISD at a frequency

as high or higher than with other PCR-based methods.

In summary, although detection of a T cell clone in the skin of an erythrodermic patient with non-diagnostic histopathologic findings supports the diagnosis of E-MF, it is not conclusive particularly with highly sensitive PCR methods. The presence of an identical clone in the blood increases the chance that the patient has E-MF rather than EISD, but even this circumstance has been reported in EISD [6].

Blood studies are also helpful to differentiate some patients with E-MF from EISD based on the idea that low levels of neoplastic cells are present in the blood. The first study used for this purpose was the presence of ≥ 20% Sézary cells in the lymphocyte population [51,52]. However, this criterion was based on studies that compared E-CTCL with various non-neoplastic skin disorders, most of which were not erythrodermic.

In my experience with 30 patients diagnosed with EISD, the percentage of Sézary cells ranged up to 42% (median, 12.5%) and 6 patients (20%) had Sézary cell counts exceeding 20%. The highest absolute count was 440 Sézary cells/μL. The EISD diagnoses with Sézary cells > 20%. were drug reactions (3 patients) and idiopathic erythroderma (3 patients). Of note, none of the 6 patients had very large Sézary cells (> 14 μm diameter), no clone was detected in 4 studied patients, and the CD4/CD8 ratio for 5 patients ranged from 2.1 to 8.3. This observation indicates that the ≥ 20% Sézary cell criterion does not reliably separate E-CTCL from EISD (depending on the morphologic criteria used for Sézary cells, this experience may be different at other centers). Furthermore, other studies have shown that even higher numbers of Sézary cells may be encountered in pseudo-Sézary inflammatory diseases.

More recently, flow cytometry has been used to distinguish E-MF from EISD. One hematologic criterion is based on the observation that neoplastic T cells have partial or complete loss of CD7 or CD26. As a result, patients with E-MF often have increased percentages of CD4+CD7- or CD4+CD26- lymphocytes compared to healthy individuals. However, these populations also expand in EISD such that percentages ≥ 40% for CD4+CD7- and ≥ 30% for CD4+CD26- lymphocytes have been recommended to distinguish E-CTCL from EISD [16,42,53,55]. Because patients with EISD occasionally have CD4/CD8 ratio ≥ 10, CD4+CD7- ≥ 40% or CD4+CD26- ≥ 30%, the ISCL/EORTC recommends that evidence of a T cell clone also be demonstrated to confirm the presence of neoplastic cells and to exclude 'false positives'.

In my experience with various inflammatory skin diseases, no patient had CD4+CD7- ≥ 40% whereas CD4+CD26- lymphocytes exceeded 30% in 2 of 54 (4%) patients [53]. For 18 patients with EISD, the median percentage of CD4+CD7- lymphocytes was 10% (range, 2 to 20%). For 15 EISD patients studied for CD4+CD26-, the median percentage was 14% (range, 7 to 43%). Only one patient diagnosed with erythrodermic atopic dermatitis exceeded the 30% threshold. This patient had a Sézary cell count of 11% (252 Sézary cells/μL), a CD4/CD8 ratio of 75%/14% (5.4), CD4+CD7- lymphocytes of 10%, and no clone in the blood by PCR-TCRγ analysis.

Another useful finding by flow cytometry is the detection of T cells that have altered expression levels of CD3 (e.g., CD3dim cells) or other pan T cell markers [59,60,80]. Such cells are presumed to be neoplastic cells because they are not found in healthy blood samples. However, I reserve judgment on this until sorting experiments are performed and more information is available on whether EISD might also have activated T cells with altered expression levels.

Another finding is the presence of large lymphocytes on flow cytometry histograms [81]. Possibly these cells correspond to large Sézary cells on blood smears. Finally, the killer immunoglobulin-like receptor Kir3DL2/CD158k and CD164 are other potential markers expressed by neoplastic T cells that might be useful to differentiate E-MF from EISD [63,64,82].

Comment on B rating and clinical staging of E-CTCL

Because of improved methods to measure neoplastic cells in the blood and the prognostic importance of blood tumor burden, the ISCL/EORTC added a blood B rating to the tumor-node-metastasis (TNM) staging classification of CTCL. The B2 rating is currently defined as: Sézary cells ≥ 1.0K/L, CD4+CD7- or CD4+CD26- lymphocytes ≥ 1.0K/L or increased CD4+ T cells with CD4/CD8 ratio > 10 in the blood plus evidence of a T cell clone (or other confirmatory test in my opinion) [50]. These hematologic criteria signify 'leukemic' involvement and therefore may be used for the diagnosis of SS in patients with E-CTCL, i.e., T4B2. Thus defined, the clinical stages of SS are IVA1 (T4N0-2M0B2), IVA2 (T4N3M0B2) or IVB (T4N0-3M1B2).

Studies indicate that the prognosis of patients with SS (T4B2) is worse than E-MF (non-Sézary E-CTCL) patients (T4B0-1). Furthermore, my experience indicates that the survival curves of SS at stages IVA1 and IVA2 are similar, indicating that these stages can be consolidated into one stage IV [50]. This also has been shown in some, but not series of CTCL [20,21,83]. One advantage of a combined stage IVA may be that the survival curves for E-MF at stages IIIA (T4N0-2M0B0) and stage IIIB (T4N0-2M0B1) become statistically different [50].

Comment on the pathogenesis of SS

Nowadays SS (and CTCL in general) are understood to be neoplasms of skin-associated lymphoid tissue (SALT) which includes skin and peripheral lymph nodes that drain the skin [84]. Recent studies indicate that the neoplastic T cells of SS typically have an immunophenotype consistent with central memory T (T_{CM}) cells (CD27) and express both skin-homing receptors (CLA and CCR4) and lymph node-homing molecules (CCR7 and CD62L/L-selectin) [85]. This would explain the circulatory pattern between skin, blood and lymph nodes.

Of interest, CD62L can also bind to peripheral node address in that may be induced on dermal endothelial cells in chronic inflammatory skin disorders [86,87]. This may provide an additional pathway for CD62L+ neoplastic cells of SS to enter and accumulate in the skin [88].

The current dogma about primary CTCL including SS is that the skin is the origin of the neoplastic process with secondary involvement of peripheral 'skin-associated' lymph nodes. This skin-first concept originated with Sézary's observation that lymph node enlargement occurs after the appearance of erythroderma and that the bone marrow is not involved. Examples of 'secondary' SS also support the hypothesis.

On the other hand, why couldn't the neoplastic process of some, perhaps most cases of 'primary' SS begin in peripheral lymph nodes with subsequent trafficking of cells into the skin? An extra-cutaneous origin of 'primary' SS would not only explain the phenomenon of 'invisible' SS, but also rare examples of patients who are diagnosed with a T cell lymphoma in their lymph nodes prior to otherwise

typical SS (such cases might otherwise be considered to be composite lymphomas).

If the initial neoplastic event of 'primary' SS occurs somewhere other than the skin, a prime candidate for this location would be skin-associated peripheral lymph nodes which theoretically can harbor precursor neoplastic T_{CM} that have the capacity for self replication. Furthermore, peripheral lymph nodes provide an ideal environment for continued antigenic stimulation that might play a role in promoting clonal expansion and genetic instability of neoplastic cells. These neoplastic cells might emerge from regional lymph nodes and infiltrate the skin. In this regard, isotopic and some radioautographic studies of SS in the 1980s that indicated that peripheral lymph nodes, not the skin, was the likely primary source of neoplastic cell proliferation [89-92]. Bacterial colonization of erythrodermic skin by *Staphylococcus aureus* further stimulate and modulate the neoplastic clones which emerge back into blood and regional lymph nodes. Lymph node enlargement results from the combination of dermatopathic lymphadenopathy and accumulation of neoplastic cells which expand the paracortical T zone and ultimately efface nodal architecture in fully developed SS.

Finally, recent evidence suggests that the bone marrow can provide a sanctuary for memory T cells [93]. This may account for the presence of small clusters of neoplastic cells in bone marrow samples of SS [94-96]. Nevertheless, bone marrow involvement in SS does not connote a worse prognosis [96].

Comment on neoplastic plasticity and differentiation of SS

With repetitive antigenic exposure, normal T_{CM} cells differentiate into effector memory cells and eventually terminal effector cells which are capable of immediate inflammatory cytokine production and cytotoxicity, yet with little proliferative capacity. The terminal differentiation of CD4+ T cells into TH-1, TH-2, TH-17, iTreg, TH-9, TH-22 and T follicle helper cells is determined by lineage-specific transcription factors ('master regulators') that activate differentiation-associated genes [97]. In general, cytokines bind to their cognate cytokine receptors that then engage Janus-activated kinases (mostly JAK3) which phosphorylate signal transducer and activator of transcription proteins (STATS) that mediate activation of transcription factors including master regulators in the nucleus.

It is now thought that neoplastic T_{CM} undergo similar changes depending on cytokine and bacterial stimuli received in the microenvironment of the skin and presumably regional lymph nodes. This phenomenon is called 'neoplastic plasticity' and accounts for phenotypic heterogeneity within the neoplastic cell population [98-100].

In most cases of SS, neoplastic cells develop the phenotype of TH-2 differentiated cells via the STAT5→GATA3 pathway. These cells have the capacity to secrete IL-4, IL-5 and IL-13. This contributes to the eosinophilia (IL-5) and increased total serum IgE levels (IL-4, IL-13) that frequently occur in SS. Conversely, neoplastic cells lose responsiveness to IL-12 (via loss of IL-12β2 receptor signaling), which mediates TH-1 differentiation via the STAT4→T-bet pathway. Indeed, low expression of the STAT4 gene occurs in 90% of Sézary blood samples and is useful as a genetic biomarker for blood involvement [61,67].

Activation of STAT5 and TGFβ-dependent Smad3 pathway also may activate FoxP3 transcription and induction of a Treg phenotype characterized by secretion of immunosuppressive cytokines IL-10 and TGF-β [101]. These cytokines contribute to the profound depression of cell mediated immunity of SS [102]. In my patients, FoxP3 mRNA transcripts were detected in 6 of 25 (25%) of Sézary blood samples and notably these patients had a worse prognosis [103]. Using anti-TCR Vβ antibodies to identify neoplastic cells, Heid showed that 6 of 15 (40%) Sézary patients had FoxP3+CD25-Vβ+ neoplastic cells with functional suppressive properties as well as a highly demethylated Foxp3 gene locus [104]. However, these patients did not have an impaired prognosis. Taken together, a subset of SS may acquire the properties of induced Treg (iTreg) cells, consistent with the plasticity model of neoplastic cells [101]. A 2019 study suggests that FoxP3 expression is a transitional phase that precedes GATA3 driven transition to TH-2 cells [105].

However, the neoplastic cells of a small number of Sézary patients have constitutive properties of classic CD25+ Treg cells, presumably as a result of intrinsic genetic alterations [106]. One of my patients with SS developed a transformed aggressive large cell lymphoma that was FoxP3+ presumably as a result of genetic alterations [107].

Neoplastic plasticity also accounts for the differentiation of neoplastic T cells into TH-17 cells via STAT3→RORγt pathway. In addition to many cytokines, STAT3 can be activated by bacterial toxins including Staphylococcal enterotoxins [108,109]. The secretion of IL-21 by TH-17 differentiated neoplastic cells may act as an autocrine growth factor [110]. Consequently, IL-21 joins the list of other TH-2 cytokines, namely IL-2, IL-7, IL-9, IL-13 and IL-15, that have been implicated in neoplastic cell survival and proliferation [111-114]. Dysregulated STAT3 activation is thought to be a major factor in the pathogenesis and neoplastic progression of SS [115,116].

Finally, it is even possible that neoplastic T cells can acquire the lineage properties of IL-9 or T follicle helper cells. In this regard, it has been reported that activation of STAT3/STAT5 with increased expression of the master regulator Interferon regulatory factor 4 (IRF4), also known as MUM1, along with decreased expression of BCL6 promotes IL-9 differentiation in MF [117]. The observation that neoplastic cells of SS have diffuse staining for MUM1 by immunohistochemistry suggests that a similar phenomenon might also occur in SS [118]. Conversely, IL-6-mediated activation of the STAT3→BCL6 pathway favors differentiation into T follicle helper cells. A few cases of SS have been reported that express combinations of surface markers used to identify follicle helper T cells, i.e., PD-1, CXCL-13, ICOS, Bcl-6, and CD10 [118,119]. Follicle helper T cells provide help to B cells for generation of high-affinity antibodies, and it is interesting that serum immunoglobulins are normal or increased in SS [120].

Final thoughts

Today, the diagnosis of SS is based more on hematologic findings by flow cytometry and molecular genetic studies and less on quantitative counts of Sézary cells and even skin manifestations. As methods to quantify blood tumor burden improve, hematologic criteria used to define prognostic subgroups based on B ratings will be reevaluated in the context of the TNMB system. Whether the definitions of 'leukemic involvement' and diagnosis of SS will continue to be linked to B ratings as is the current practice (i.e., SS = T4B2) remains to be seen.

The inclusive diagnosis of CTCL for MF, SS and other T cell lymphomas with initial manifestations in the skin was based on pioneering studies by Edelson and others in the 1970s [121]. It was also proposed that the terms MF and SS were archaic and should be

replaced with 'aleukemic' and 'leukemic' variants of CTCL, respectively, because of overlapping clinical findings [122]. One could also argue that 'primary' SS is not always a primary CTCL. Perhaps a more general designation 'skin-associated T-cell lymphoma/leukemia' (SALL) based on the concept of skin-associated lymphoid tissue as proposed by Streilein in the 1980s might be more appropriate than CTCL [84].

Most dermatologists continue to regard MF and SS as distinctive entities because of the differences in clinical-pathologic findings and approach to treatment. Furthermore, recent studies have provided evidence that MF and SS should be distinguished on biologic grounds. Specifically, MF is a disorder of resident memory T cells and SS is a disorder of T_{CM} cells [85,123].

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