Sézary syndrome—clinical and histopathologic features, differential diagnosis, and treatment

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■ **Abstract**

Sézary syndrome (SS) is a rare subtype of cutaneous T-cell lymphoma marked by erythroderma, circulating neoplastic T cells, and poor prognosis. Its low incidence has made the study of its etiology, immunologic/molecular pathways, and effective treatments difficult. Because histopathology may be nonspecific in SS, microscopic findings must be correlated with the clinical presentation and the results of blood evaluation in order to make the diagnosis. Treatments that preserve, rather than compromise, the immune system are preferred.

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In the late 1930s and early 1940s, Albert Sézary described several patients who presented with erythroderma, unique "monster cells" in the skin, blood, and occasionally the lymph node; one patient also had generalized lymphadenopathy.[1] Further patients were described by other authors, and in 1961, the constellation of findings was coined Sézary syndrome (SS).[2] It was not until the 1970s that the neoplastic "monster cells" of SS were determined to be T lymphocytes[3] and therefore SS determined to be a cutaneous T-cell lymphoma (CTCL).

Since the first patients were described in the mid-20th century, criteria to define SS have been debated. Many authorities agree that SS is defined by the presence of erythroderma and blood involvement by malignant lymphocytes that has not been preceded by typical lesions of mycosis fungoides; lymphadenopathy is also a common finding.[4,5] Criteria for blood involvement were updated in 2007[5]; however, the measures used to assess the presence and degree of blood involvement, as well as whether it represents a disorder that is distinct from erythrodermic mycosis fungoides (MF), continue to be debated.

Epidemiology and risk factors

SS is very rare and often grouped with advanced-stage MF, making the study of its epidemiology difficult. In the United States, the incidence of SS is 0.1-0.3 per 1,000,000 persons and represents 2.5% of all CTCL.[6,7] Increasing incidence of CTCL was reported[6] until recently, when incidence stabilized.[8]

SS is nearly exclusively a disease of older adults and is approximately twice as common in men as in women.[6,9] Although African American race is a risk factor for CTCL, the incidence rate of SS is higher in whites than in African Americans.[6] Many other risk factors for MF and SS have been studied,[10] and some associations have been found; however, these epidemiologic studies include so few SS patients that conclusions regarding risk factors cannot be made.

Etiology and immunologic/molecular pathways

Although the etiology of SS is not known, much work has been done to elucidate the immunologic pathways that characterize it. The malignant T-cell population in SS expresses CD3, CD4, CD45RO,[11] and CCR4,[12] indicating a mature memory T cell that traffics to the skin and CCR7, L-selectin, and CD27,[12] markers of central memory T cells. The malignant T-cell population also elaborates interleukin 4 (IL-4)[13] and IL-10,[14] consistent with a T-helper type 2 (Th2) profile, and has recently been shown to express CD25 and forkhead box protein 3 (Fox-P3),[15] consistent with a T-regulatory (also called T suppressor) profile, resulting in suppression of the normal immune response.[16] As a result of the bias toward Th2 and T-regulatory profiles, there is suppression of natural killer and CD8-positive T cells and abnormal function and differentiation of dendritic cells, thus impairing response to viral infections and tumors.[16] Furthermore, the malignant T cells have been shown to reveal impaired expression of CD40 ligand,[17] which also alters dendritic cell function. The immunosuppressed environment created by the malignant T-cell population has implications for treatment.

Recently, genomic sequencing has identified numerous abnormalities within circulating neoplastic lymphocytes in SS[18-20] and leukemic CTCL,[21] including mutations and/or chromosomal alterations in genes that control tumor suppressors, epigenetics regulators, T-cell signaling, T-cell differentiation, T-cell survival and proliferation, and T-cell trafficking to skin. These alterations may help guide development of targeted therapies.

Clinical presentation

Most patients with SS are older adults (most commonly white males) who present with erythroderma (defined as greater than or equal to 80% body surface area involved by erythema) that is often exfoliative (Figure 1), intensely pruritic, and has been present for months to years prior to diagnosis.[4,9] Lymphadenopathy (≥1.5 cm in size) is common.[9] Palmoplantar keratoderma (Figure 2), nail abnormalities, and alopecia are other commonly associated findings.[9] Leonine facies (Figure 3) is rare.[22]

Recently published series have described a subset of SS patients who present without erythroderma.[23-25] Skin findings at diagnosis were variable and included unremarkable skin in some patients, patches and plaques of MF-like lesions in others, and nonspecific dermatitis or atopic dermatitis-like lesions in still others. Some nonerythrodermic SS patients eventually progressed to erythroderma.[24,25] Biopsies of normal-appearing skin revealed a perivascular

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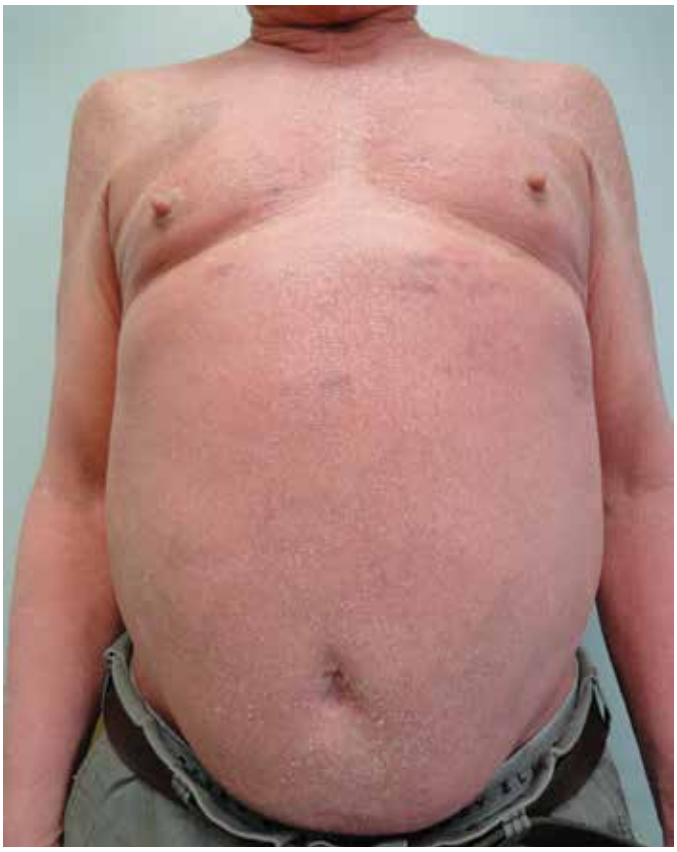

FIGURE 1. Erythroderma with scaling in a patient with SS. SS, Sézary syndrome. Courtesy of Diya F Mutasim, MD.

infiltrate of large atypical lymphocytes with focal epidermotropism, indicating subclinical disease.[23]

Histopathology

The most common histopathologic finding in SS is a superficial perivascular (Figure 4) or band-like infiltrate of large lymphocytes that may reveal atypia (defined as large, hyperchromatic or convoluted nuclei).[26,27] Epidermotropism may be present (Figure 5).[27,28]

However, nondiagnostic histopathology is common in SS. One series reported nondiagnostic microscopic findings in 39% of specimens taken from 41 SS patients.[27] Another revealed absent or minimal epidermotropism in 19 of 31 SS patients, a finding that is considered characteristic of MF, arguing that epidermotropism is less common in SS than MF.[29] Furthermore, in the erythrodermic manifestation of any inflammatory skin disorder, histopathology is nondiagnostic in approximately 50% of patients, in part because the diagnostic microscopic features are milder than in nonerythrodermic presentations.[30] Therefore, when faced with nondiagnostic histopathology in erythroderma, flow cytometry of blood may be useful.[31]

The neoplastic T lymphocytes of SS are usually CD3 and CD4 positive and CD8 negative. Loss of CD7 (a pan-T-cell marker) labeling by more than 50% of infiltrating T cells and presence of programmed cell death protein 1 (PD-1) labeling by infiltrating T cells support a diagnosis of SS over inflammatory causes of erythroderma

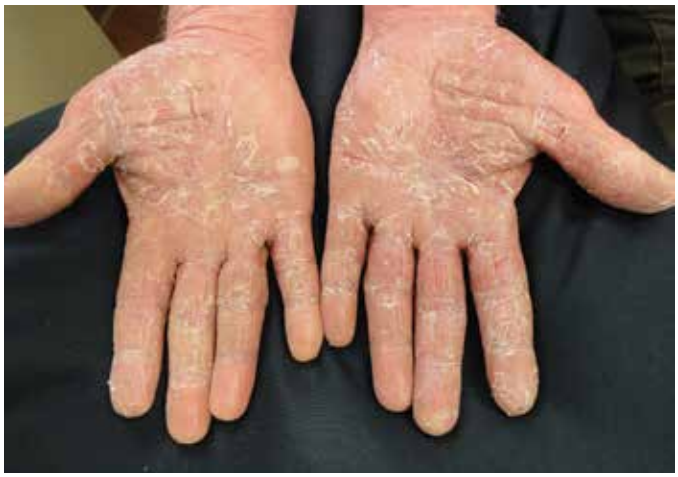

FIGURE 2. Palmoplantar hyperkeratosis with fissuring in a patient with SS. SS, Sézary syndrome. Courtesy of Diya F Mutasim, MD.

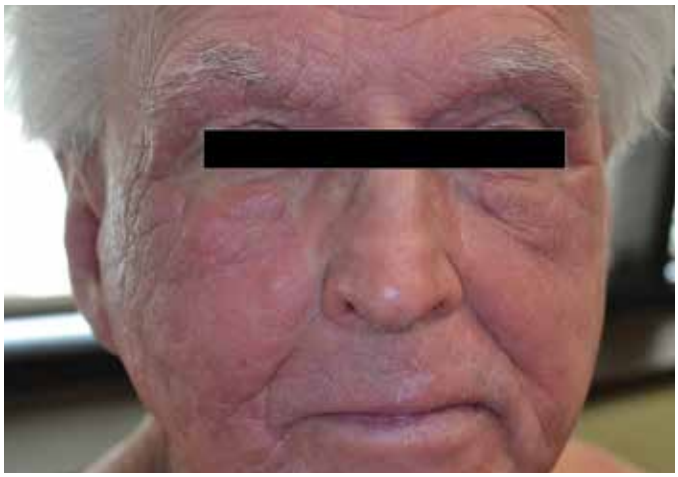

FIGURE 3. Leonine facies in a patient with SS. SS, Sézary syndrome. Courtesy of Diya F Mutasim, MD.

in skin biopsies.[28] Low numbers (less than 10%) of CD8-positive T cells within the cutaneous infiltrate also favor SS in skin biopsies.[28]

The percentage of CTCL skin biopsies that reveal a monoclonal T-cell receptor (TCR) gene rearrangement by polymerase chain reaction (PCR) varies widely across the literature and may depend on amplification method; however, a recent report detected a T-cell clone by PCR within the skin biopsies of 27 out of 30 patients with SS.[32] Nonetheless, several inflammatory conditions may reveal monoclonality, therefore the results of TCR gene rearrangement studies must be considered in the context of other data. Detection of identical T-cell clones in the skin and blood may favor SS over inflammatory causes of erythroderma.[33] High-throughput sequencing of CTCL lesions has recently been shown to have more specificity and sensitivity in the detection of a T-cell clone than PCR.[34]

In summary, the diagnosis of SS cannot be based on histopathology alone but must be correlated with the clinical presentation and the results of blood evaluation. Multiple long shave biopsies[30] that extend to the superficial reticular dermis may increase the chance of identifying characteristic microscopic findings.

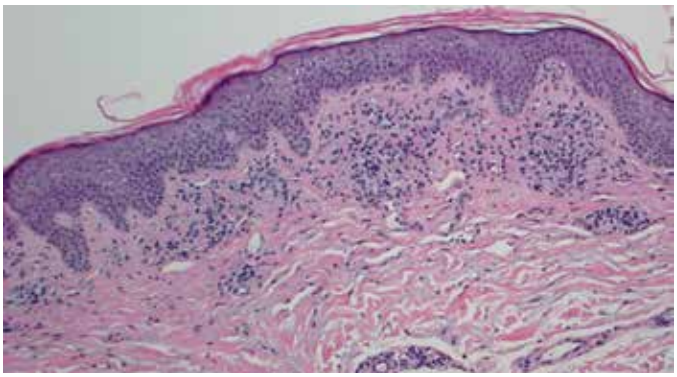

FIGURE 4. An example of a perivascular infiltrate without epidermal involvement in SS: the medium-sized hyperchromatic lymphocytes revealed marked predominance of CD4 over CD8 expression by immunohistochemistry (H+E, 20x). Abbreviation: H+E, hematoxylin-eosin; SS, Sézary syndrome.

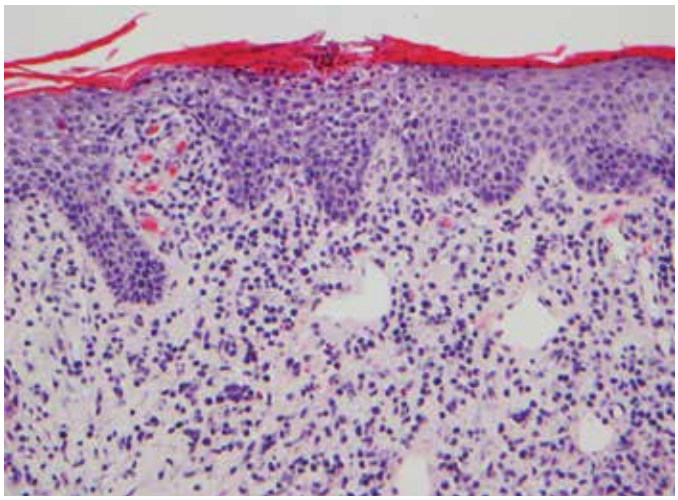

FIGURE 5. An example of SS with epidermotropism of medium-sized lymphocytes and superficial dermal infiltrate of similar lymphocytes (H+E, 20x). Abbreviations: H+E, hematoxylin-eosin; SS, Sézary syndrome.

Differential diagnosis

The differential diagnosis of SS includes other causes of erythroderma and non-SS leukemias with cutaneous involvement. Because the clinical features of erythroderma are often invariable regardless of cause and because the histopathology may not be specific, history and evaluation of the blood are often necessary to distinguish SS from the conditions discussed below.[31]

Erythrodermic psoriasis and erythrodermic atopic dermatitis may be difficult to differentiate clinically from SS but only very uncommonly occur in a patient without history of their localized forms.[35] Erythroderma secondary to drug must also be distinguished on the basis of history, response to drug withdrawal, and rechallenge. Prior history of patches, plaques, and/or tumors will be elicited in patients with erythrodermic MF. Classical adult-onset pityriasis rubra pilaris (PRP) is an uncommon cause of erythroderma; PRP may reveal palmoplantar keratoderma identical to SS but may be distinguished by history of preceding localized involvement and cephalocaudal progression.

Non-SS T-cell leukemias with a CD4-positive phenotype that may be accompanied by skin involvement include adult T-cell leukemia/lymphoma (ATLL) and pro-T-cell prolymphocytic leukemia (T-PLL). ATLL is rare in the United States, and erythroderma is an uncommon cutaneous presentation of ATLL[36]; nevertheless, ATLL is well known to mimic MF and should be considered in any T-cell leukemia with cutaneous involvement. ATLL can be excluded when serology is negative for human T-lymphotropic virus 1 (HTLV-1) , the virus that causes ATLL. T-PLL may also present with cutaneous involvement although, like ATLL, erythroderma is rare[37]; patients with T-PLL often present with B symptoms, hepatomegaly, and a markedly elevated white blood count—features not commonly present in SS. Furthermore, cytogenetic studies of T-PLL usually reveal abnormalities in chromosome 14.

Laboratory and imaging findings

Detailed evaluation of the peripheral blood is essential in patients suspected to have SS in order to determine the degree of blood burden (and potentially monitor response to treatment), identify comorbidities that may direct treatment, and exclude other T-cell leukemias. Blood evaluation should include complete blood count with differential, lactate dehydrogenase (LDH), flow cytometry, T-cell gene rearrangement studies, complete metabolic panel, and HTLV-1 serology. Although quantification of circulating Sézary cells (large, cerebriform lymphocytes) was initially used to determine the degree of blood involvement in SS,[38] this technique has been replaced by a combination of blood flow cytometry and TCR gene rearrangement studies at many institutions, which may be a more objective measure of circulating malignant T cells.

Complete blood count is often normal in SS; however, eosinophilia has been associated with poor prognosis.[39] Elevated LDH also portends a poorer prognosis in MF/SS.[40] Blood flow cytometry reveals an expanded population of $CD4^+$ cells with loss of CD7 and/or CD26.[41] The most accurate way to define and categorize blood involvement has long been debated. Most recently, in 2007, authorities[5] revised the criteria for blood involvement in SS, now defined as a clonal rearrangement of the TCR in the blood plus either 1000 Sézary cells per microliter or one of the following: increased $CD4^+$ or $CD3^+$ cells with CD4/CD8 ratio greater than or equal to 10 to 1 or increased $CD4^+$ cells with an abnormal phenotype (such as ≥40% loss of CD7 or ≥30% loss of CD26). It is important to note that aberrant T-cell phenotypes[42] (and Sézary cells[43]) have been detected in patients with inflammatory skin conditions, although in smaller numbers than in SS patients.

Circulating T cells with a clonally rearranged TCR can be identified by molecular techniques, commonly by PCR. Although the detection of TCR monoclonality in the blood is required in SS, its sensitivity and specificity for SS are not 100%; some patients with SS will lack, and some elderly healthy controls will reveal, monoclonality.[44,45]

Recently, skewed usage of the variable region of the ß chain of the TCR as detected by flow cytometry (known as the Vß repertoire) has been shown to correlate with TCR monoclonality detected by PCR in SS.[46] It is faster and may have a higher specificity[47] in SS than PCR; however, it has not been incorporated into the

blood staging system for MF/SS, and thus it is uncertain how results should be incorporated into the diagnosis and monitoring of patients with SS.

Because assessment of the size of superficial lymph nodes by physical examination may be inaccurate,[48] imaging is used in diagnosis and staging, although the best technique has not been determined. Integrated positron emission tomography and computed tomography (CT) may be more sensitive than CT alone.[49] If imaging findings suggest enlarged or hypermetabolic lymph nodes, a biopsy may be performed to assess histopathologic grading, although the prognostic significance of this grading in SS is uncertain.

Prognosis and survival

Because it is rare and usually grouped with MF in the literature, prognostic factors in SS are not well known. Advanced age[50] and elevated LDH[9,50] may predict poor prognosis. In the largest study of SS patients to date, the median survival after diagnosis was 4.0 years, with overall survival of 42.3% at 5 years after diagnosis.[9]

Treatment

The literature on treatment efficacy in SS faces many challenges, including the following: SS is very rare, making it difficult to acquire the sample sizes needed to adequately power clinical trials; SS has historically been poorly defined, making it difficult to apply study results to everyday practice; SS is often grouped with erythrodermic MF (and other advanced stages of MF) with or without blood involvement when they may represent distinct diseases; and finally, until recently, there was no consensus on clinical endpoints.[16,51] As a result, treatment of SS has been driven by expert experience and may vary considerably between referral centers.[52]

Although many treatments are available, most responses are partial and not durable, therefore the course of therapy in SS is that of successive treatments either alone or in combination. Furthermore, the effect of treatment on overall survival is unknown. An exception may be allogeneic bone marrow transplantation (BMT), which has provided durable complete remissions in SS.[53]

An important principle in SS treatment is the preference for treatments that preserve, rather than suppress, the patient's immune system. As already discussed, SS is associated with dysfunction of cellular immunity resulting in impaired response to infections and tumors, therefore the use of immunosuppressing therapies may lead to overwhelming infection. Furthermore, while SS often responds well to multiagent chemotherapy,[54] patients relapse quickly and because of long-term toxicities of chemotherapeutic agents cannot be maintained on them long term.

Another principle in SS treatment is vigilant surveillance for, and prompt treatment of, microbial colonization and infection because infection is a common cause of death. Eradication of staphylococcal nasal carriage may result in clinical improvement in SS.[55] Ongoing use of mupirocin, dilute bleach baths, chlorhexidine wash, and/or oral antimicrobials may be used to control bacterial colonization and infection. Invasive procedures, including the placement of indwelling catheters, should be avoided.

Despite the nearly universal presence of pruritus in SS, only recently have researchers begun to assess the effect of SS therapies on pruritus. Histone deacetylase inhibitors (HDACi) may improve pruritus.[56] Because treatment response in SS is usually partial and short lived, other agents not specific to the treatment of CTCL may be used in an attempt to relieve pruritus.[57] Emollients and topical corticosteroids may be helpful. First-line systemic agents include antihistamines, doxepin, and gabapentin. Second-line systemic agents include aprepitant, mirtazapine, and selective serotonin reuptake inhibitors.

Three groups[16,57,58] have recently published treatment recommendations for SS based on literature review and consensus opinion—these recommendations are summarized below. The reader is referred to Olsen et al 2011[16] for an exhaustive literature review that includes mechanisms, dosing regimens, and toxicities of each treatment.

First-line therapies for SS include the following: extracorporeal photophoresis (ECP); subcutaneous interferon-α (IFN-α); oral bexarotene; and low-dose oral, subcutaneous, or intramuscular methotrexate (MTX; ≤100 mg per week). Many combination regimens are possible, including the following: bexarotene and IFN-α; bexarotene and ECP; IFN-α and ECP; bexarotene, IFN-α, and ECP; IFN-α and low-dose MTX; and IFN-α, low-dose MTX, and ECP. One group[58] recommends chlorambucil and prednisone as a first-line therapy. The combination of MTX and bexarotene is avoided due to the potential for hepatotoxicity. Systemic therapy may also be combined with skin-directed therapy, including the following: psoralen plus ultraviolet A (PUVA) with bexarotene, IFN-α, and ECP; low-dose MTX and topical nitrogen mustard; PUVA and bexarotene; and total skin electron beam therapy (TSEBT) may be combined with ECP, IFN-α, and bexarotene. Because it is a radiosensitizer, MTX is not administered at the same time as TSEBT. Topical corticosteroids may be used in combination with any systemic therapy.

Second-line therapies for SS include single-agent chemotherapy (liposomal doxorubicin, gemcitabine, low-dose pralatrexate, pentostatin, chlorambucil, etoposide, cyclophosphamide, temozolomide, and high-dose MTX), HDACi (oral vorinostat and intravenous romidepsin), multiagent chemotherapy (fludarabine and cyclophosphamide; cyclophosphamide, doxorubicine, vincristine, prednsione [CHOP]), or targeted immunotherapy including brentuximab (anti-CD30), alemtuzumab (anti-CD52), and mogalumizumab (anti-CCR4). Allogeneic BMT is a potentially curative treatment option[53]; however, it is associated with high morbidity and mortality and is currently only considered in young, relatively healthy patients with advanced disease.

Several new agents for the treatment of MF/SS are in development,[59] including those that target KIR3DL2 (a marker that is overexpressed in SS[60]), CD3 (a pan-T-cell marker), CD25 (IL-2 receptor, the target of denileukin diftitox), PD-1 receptor (an immune checkpoint targeted by pembrolizumab), and PI-3KINASE (a signal transducer inhibited by duvelisib).

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