

ORIGINAL ARTICLE

Early clinical manifestations of Sézary syndrome: A multicenter retrospective cohort study

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Background: Classic Sézary syndrome (SS) is defined by erythroderma, generalized lymphadenopathy, and leukemic blood involvement. Clinical observations suggest that SS begins as a nonerythrodermic disease.

Objective: To describe the early clinical characteristics of patients with SS.

Methods: A retrospective, multicenter chart review was performed for 263 confirmed cases of SS diagnosed during 1976-2015.

Results: Erythroderma was the earliest recorded skin sign of SS in only 25.5% of cases, although most patients (86.3%) eventually developed erythroderma. In patients without erythroderma during their initial visit, the first cutaneous signs of SS were nonspecific dermatitis (49%), atopic dermatitis-like eruption (4.9%), or patches and plaques of mycosis fungoides (10.6%). The mean diagnostic delay was 4.2 years overall, 2.2 years for cases involving erythroderma at the initial presentation, and 5.0 years for cases not involving erythroderma at the initial presentation.

Limitations: This study is retrospective.

Conclusion: Erythroderma is uncommon as an initial sign of SS. Early SS should be considered in cases of nonerythrodermic dermatitis that is refractory to conventional treatments. In these cases, examination of the blood by PCR for monoclonal T-cell receptor rearrangement and by flow cytometry to identify an expanded or aberrant T-cell population should be considered. (J Am Acad Dermatol <http://dx.doi.org/10.1016/j.jaad.2017.05.036>.)

Key words: cutaneous T-cell lymphoma; diagnosis; diagnostic delay; erythroderma; nonerythroderma; prognosis; Sézary syndrome; survival.

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Classically, Sézary syndrome (SS) is defined by erythroderma, the presence of circulating malignant T-cells in the peripheral blood, and generalized lymphadenopathy.¹⁻³ The International Society for Cutaneous Lymphomas (ISCL) and World Health Organization–European Organization of Research and Treatment of Cancer (EORTC) classifications include the presence of erythroderma as a necessary criterion and at least 2 of the following: Sézary cell count $>1000/\mu\text{L}$; immunophenotypic T-cell abnormalities in the peripheral blood (CD4/CD8 >10 or loss of T-cell surface markers, such as CD2, CD3, CD4, CD5, CD7, or CD26); presence of a monoclonal T-cell receptor (TCR) population in the blood; or presence of chromosomally abnormal T-cell clones.³ Other clinical signs and symptoms frequently found in SS (but not considered as strict diagnostic criteria) are alopecia, onychodystrophy, palmoplantar hyperkeratosis, and severe pruritus. The prognosis of SS is unfavorable, with a 5-year mortality of approximately 50% and a median survival of 4 years.^{1,4-6}

The diagnostic criteria for SS are based upon expert consensus rather than rigorous evidence-based guidelines and have not been validated on a large cohort of SS patients. There are numerous reports in the literature indicating that SS does not always fulfill the above diagnostic criteria of erythroderma and blood involvement.⁷⁻¹⁴ In 1974, Winkelmann et al proposed that SS might run a clinically benign course manifested with erythroderma with only minimal, if any, blood involvement.^{9,11} They coined the term pre-SS to describe this form of the disease. Similar atopic dermatitis (AD)-like presentations have been described in which SS was unmasked by iatrogenic immunosuppression.^{15,16} Another condition described involves a monoclonal T-cell dyscrasia or erythrodermic inflammatory dermatosis in which TCR clones are present in the peripheral blood and there is erythroderma or eczema-like skin involvement. Unlike SS, none of these cases developed leukemic blood involvement in their lifetime (mean follow-up of 4 years).¹⁷ On the other side of the disease presentation spectrum, SS can be preceded by a long, indolent phase of leukemic blood involvement without obvious skin involvement.^{7,14} Moreover, the relationship between SS and mycosis

fungoides (MF), especially the erythrodermic variant (E-MF), has not been well defined. According to an ISCL proposal, E-MF represents a progression of MF and should be preceded by typical patches and plaques and SS is a separate disease entity. The major differentiating feature is blood involvement: absent or minimal (B0-B1) in E-MF and substantial (B2) in SS.³ The notion that SS and MF are separate diseases is supported by genetic studies; however, MF might precede SS and, in these cases, it is recommended that the term SS preceded by MF be used.^{3,18}

To better characterize the clinical presentations of patients with SS, we have assembled a large cohort of 263 confirmed SS cases from 5 centers in the United States, Europe, and the Middle East. We describe here, that apart

from the classic clinical presentation with erythroderma and blood involvement, SS might, in the early phases, be nonerythrodermic and classified into 4 distinct and clinically relevant presentations.

PATIENTS AND METHODS

Patients with a confirmed diagnosis of SS were identified at the participating centers (Hospital del Mar, Barcelona, Spain; Bispebjerg Hospital, Copenhagen, Denmark; Mayo Clinic, Rochester, Minnesota, United States; Rabin Medical Center, Petah Tikva, Israel; University Hospital Zurich, Zurich, Switzerland) by review of electronic patient records. Patients from the Mayo Clinic who were no longer actively followed were identified through an institutionally approved Internet search and location service (Accurint, LexisNexis Risk Solutions, Burlington, VT). The institutional review boards of the Mayo Clinic, University Hospital Zurich (KEK-ZH-Nr. 2015-0209), and Rabin Medical Center approved this study. Ethics approval was not required in other centers because only existing, deidentified data was used for analysis.

The data set consisted of the following items: patient sex and race; age at diagnosis; date of diagnosis; date of last observation or death; diagnosis type and duration of skin signs and symptoms preceding SS diagnosis; presence or absence of SS diagnostic features (erythroderma, clinical lymphadenopathy, presence of abnormal circulating T-cell lymphocytes [Sézary cells] and Sézary cell count, presence of monoclonal TCR

CAPSULE SUMMARY

- Sézary syndrome (SS) is defined by erythroderma, generalized lymphadenopathy, and the presence of leukemic blood involvement.
- Forty-nine percent of patients with SS had a nonspecific dermatitis as the earliest cutaneous sign, and only 25.5% had erythroderma.
- Early SS should be considered in cases of nonerythrodermic, refractory dermatitis.

Abbreviations used:

AD:	atopic dermatitis
E-MF:	erythrodermic variant of mycosis fungoides
EORTC:	European Organization of Research and Treatment of Cancer
ISCL:	International Society for Cutaneous Lymphomas
MF:	mycosis fungoides
SD:	standard deviation
SS:	Sézary syndrome
TCR:	T-cell receptor

rearrangement in skin or blood assessed by PCR or Southern blot, lymph node histopathology, bone marrow biopsy, or skin biopsy showing features of MF or an atypical lymphocytic infiltrate); and classification of clinical phenotype at diagnosis (erythroderma, nonspecific dermatitis, AD-like, compatible with MF, or other). Imaging results (chest radiograph, computed tomography, or positron emission tomography) were not included. Because of the length of the study period and the different approaches in different centers, the diagnostic criteria that identified patients varied and could not be standardized. However, in all cases the diagnosis of SS was consistent with the 2007 ISCL/EORTC diagnostic criteria or a typical pattern of clinical and histopathologic evolution of SS was observed.

Survival was defined as the time from diagnosis of SS to death. Time to diagnosis was defined as the time of onset of any persistent cutaneous symptoms compatible with SS to the time of SS diagnosis.

The early clinical features before the diagnosis of SS were categorized as 1) typical erythroderma (defined as confluent erythema involving >80% of the body surface area) with or without blood involvement; 2) prolonged (>1 year) dermatitis (defined as nonspecific eczema, nummular dermatitis, contact dermatitis, drug eruption—like rash) without erythroderma; 3) AD-like (defined as preferential head and neck involvement, pruritus, nonspecific reactions to multiple contact allergens, elevated IgE, and eosinophilia); 4) patches and plaques of MF (defined as clinical and histopathologic features consistent with MF); 5) leukemia (defined as Sézary cell count >1000/uL [if clonal testing was not available], Sézary cell count >1000/uL and a positive T-cell clone [if flow cytometry was not available], and clonally expanded CD3⁺ or CD4⁺ T-cell population with a CD4/CD8 >10 by flow cytometry or abnormal clonal phenotype CD4⁺CD7[−] ≥40% or CD4⁺CD26[−] ≥30% [if flow cytometry was available]^{3,19–21} without initial erythroderma; and 6)

other. In cases with overlapping features of dermatitis and AD-like presentation, the dominant phenotype was chosen. The patients from the Mayo Clinic and select patients from the Zurich cohort have previously been included in other studies.^{4,22} Two patients from Copenhagen have been published in a case report.¹⁵

RESULTS

Patient characteristics

Patient characteristics are given in Table 1. The cohort included 263 patients from the following centers given a diagnosis of SS during the indicated periods: Hospital del Mar (n = 11, 2003–2015); Bispebjerg Hospital (n = 18, 2002–2014); Mayo Clinic (n = 191, 1976–2010); Rabin Medical Center (n = 18, 1996–2015); and University Hospital Zurich (n = 25, 2000–2015). There was a male preponderance by a factor of 1.5; disease onset was in the sixth decade of life, and the mean overall survival was 4.4 years after SS diagnosis. In our cohort, the mean survival measured from diagnosis was 4.1 years for men and 4.9 years for women (Kaplan-Meier analysis, nonsignificant difference).

Clinical features at diagnosis

The following features were used for the diagnosis of SS: presence of erythroderma, lymphadenopathy, skin biopsy compatible with cutaneous T-cell lymphoma, leukemic blood involvement (defined in Patients and methods), presence of monoclonal TCR rearrangement in the peripheral blood, and bone marrow involvement. All cases met at least 2 criteria. In our patient subset, 40.2% exhibited 4 criteria, 28.8% exhibited 3 criteria, 18.2% exhibited 5 criteria, 10.8% exhibited 2 criteria, and 2% exhibited all 6 criteria.

In most patients (227/263, 86.3%), erythroderma was present at the time of diagnosis of SS. However, erythroderma, often considered sine qua non for the diagnosis of SS, was absent in 34 (13.0%) patients at the time of diagnosis (Table 1). With long-term follow-up, 19/34 (56%) of the nonerythrodermic SS patients went on to develop erythroderma; however, it was absent in the remaining 15 patients throughout the median observation time of 5.4 (range 1.5–13.0) years.

Early signs of SS

We examined the earliest recorded skin and blood manifestations in patients who were eventually given a diagnosis of SS. Early signs of SS fell into 5 distinct skin categories: erythroderma (type 1), dermatitis (type 2), AD-like (type 3), MF-like (type 4),

Table I. Patient characteristics

Characteristic	Value, N = 263
Sex, female:male, n (%)	107:156 (40.7:59.3)
Age at diagnosis, mean (SD)	61.9 (16.2)
Race	
White, n (%)	246 (93.5)
Black, n (%)	5 (1.9)
Hispanic, n (%)	2 (0.8)
Middle Eastern, n (%)	8 (3.0)
Unknown, n (%)	2 (0.8)
Alive:Dead, n (%)	55:208 (20.9:79.1)
Survival after diagnosis, years, mean (95% confidence interval)	4.2 (3.8-4.7)*
Clinical features	
Duration of symptoms before presentation, years, mean (SD)	4.3 (4.3)
Erythroderma	
Present at diagnosis or before diagnosis, n (%)	227 (86.3)
Absent at diagnosis and throughout follow-up, n (%)	15 (5.7)
Absent at diagnosis but develops during follow-up, n (%)	19 (7.2)
Unknown, n (%)	2 (0.8)
Earliest recorded signs	
Nonspecific dermatitis, n (%) [†]	129 (49.0)
Erythroderma, n (%)	66 (25.1)
Patches and plaques suggestive of MF or parapsoriasis, n (%)	28 (10.6)
Leukemia without erythroderma, n (%)	23 (8.7)
AD-like lesions, n (%)	13 (4.9)
Isolated lymphadenopathy, n (%)	1 (0.4)
Urticaria followed by dermatitis, n (%)	1 (0.4)
Unknown, n (%)	2 (0.8)
Diagnostic criteria	
Sézary cell count >1000/uL, n (%)	222 (84.4)
Lymph node biopsy consistent with SS, n (%)	66 (25.1)
Clonal TCR rearrangement in blood, n (%)	168 (63.9)
Flow cytometry CD4/CD8 >10, n (%)	128 (48.7)
Bone marrow biopsy consistent with SS, n (%)	41 (15.6)
Skin biopsy consistent with MF and SS, n (%)	214 (81.4)

MF, Mycosis fungoides; SD, standard deviation; SS, Sézary syndrome; TCR, T-cell receptor.

*Kaplan-Meier analysis.

[†]Comprises contact dermatitis, nummular eczema, nonspecific dermatitis, or drug rash-like eruption of the duration of >1 year.

and leukemia without initial erythroderma (type 5) (Table II; Figs 1-5). Three cases did not fit into any of the 5 categories: 2 cases were not classifiable because of inadequate clinical information and 1 case presented with adenopathy. Patients with signs and symptoms characteristic of type 2 or 3 disease tended to be younger and have longer survival, measured from the onset of the disease (not from the time of diagnosis of classic SS), even after adjustment for age in the Cox regression analysis.

The initial clinical presentation often determined the magnitude of diagnostic delay, measured as the time from emergence of skin lesions to the diagnosis of SS. The mean diagnostic delay of the entire cohort was 4.2 years (median 2.8 years, standard deviation [SD] 4.2 years) and varied from 1 month to 32 years. Patients given a diagnosis of SS early (<4 years,

n = 150) were older than those given one later (≥ 4 years, n = 113) (64.8 years [SD 14.0] vs 58.2 years [SD 18.1], $P = .002$ [Cox regression]) and often presented with typical erythroderma (35.3% vs 12.3%, $P < .001$ [Chi square test]). The mean diagnostic delay of the classic type 1 erythrodermic variant was only 2.2 years (SD 2.4 years) versus 5.0 years (SD 4.5) in nonerythrodermic variants ($P = .001$).

DISCUSSION

This study is unique in its large size and focus on the early manifestations of SS. The demographic features of SS patients in our cohort were consistent with prior reports with respect to sex, age, and survival.^{4,6,23} In contrast with prior reports, we found no association with sex or age of onset and poor

Table II. Clinical classification of early SS on the basis of the presenting skin signs

Feature	Type 1 erythroderma n = 67	Type 2 dermatitis n = 129	Type 3 AD-like n = 13	Type 4 MF-like n = 28	Type 5 leukemia w/o initial erythroderma n = 23	Remarks
Essential clinical features at initial presentation	Erythroderma involving >80% body	Pruritic, scaly, ill-demarcated lesions; hand eczema; neurodermatitis	Head and neck dermatitis; eczematous lesions on the trunk and flexural areas	Scaly patches and thin plaques mostly on the trunk and gluteal area resembling early lesions of MF; parapsoriasis or psoriasis	Pruritus sometimes with excoriations and eczematous lesions	
Presence of erythroderma						
Never, n (%)	0 (0)	0 (0)	0 (0)	2 (7.1)	13 (56.5)	N = 261 (data missing for 2 cases)
Present at diagnosis, n (%)	66 (98.5)	128 (99.2)	10 (76.9)	19 (67.9)	2 (8.7)	
Develops after SS diagnosis, n (%)	0 (0)	1 (0.8)	3 (23.1)	7 (25.0)	7 (30.4)	
Skin biopsy at initial presentation	Spongiotic dermatitis (n = 9); lymphocytic infiltrate (n = 9); psoriasiform dermatitis (n = 1)	Spongiotic dermatitis (n = 17); lymphocytic infiltrate (n = 16); psoriasiform dermatitis (n = 1)	Spongiotic dermatitis (n = 7)	Spongiotic, lymphocytic infiltrate (n = 7); lymphocytic infiltrate compatible with MF (n = 8); psoriasiform dermatitis (n = 1)	Psoriasiform dermatitis (n = 1); spongiotic dermatitis (n = 2); psoriasiform dermatitis (n = 1); lymphocytic infiltrate (n = 3)	
Age at diagnosis, mean (SD)	64.4 (16.0)	59.2 (16.3)*	60.2 (14.2)*	62.9 (16.8)	68.6 (14.8)	P = .047 for intergroup difference
Sex, male: female, n (%)	42:25 (62.7:37.3)	78:51 (60.5:39.5)	5:8 (38.5:61.5)	17:11 (60.7:39.3)	12:11 (52.2:47.8)	Not significant
OS after diagnosis, years, mean (95% CI)	4.9 (3.7-6.2)	4.3 (3.7-5.0)	4.0 (2.1-5.9)	3.1 (2.0-4.1)	3.4 (2.3-4.4)	Not significant
OS after first visit to clinic, years, mean (95% CI)	7.1 (5.5-8.7)	9.2 (8.1-10.3) [†]	11.5 (7.3-15.6) [†]	8.1 (5.8-10.3)	6.9 (4.9-8.9)	
Diagnostic delay, years, mean (SD)	2.2 (2.4)	4.9 (4.4)	7.2 (4.4)	5.2 (4.1)	4.2 (4.4)	P = .001 erythroderma vs nonerythroderma P < .001 for intergroup ANOVA

N = 260; 3 cases were not included in analysis: 2 because adequate clinical information for early classification was unavailable and 1 because lymphadenopathy was the initial sign of disease. AD, Atopic dermatitis; ANOVA, analysis of variance; CI, confidence interval; MF, mycosis fungoides; OS, overall survival; SD, standard deviation; SS, Sézary syndrome.

*P = .004 versus type 1.

[†]P = .001 for type 2 or 3 versus types 1, 4, or 5 by age-adjusted Cox regression analysis.



Fig 1. Erythroderma (type 1) form of early Sézary syndrome. Typical exfoliative erythroderma.



Fig 2. Dermatitis (type 2) form of early Sézary syndrome. Focused over the groin and lower abdomen are numerous well-margined pink patches with minimal overlying scale.

overall survival.⁶ The demographic features of SS patients in our cohort were consistent with prior reports.

Erythroderma is considered a diagnostic requisite for SS, even though few studies have focused on the clinical nuances of skin involvement over time. Therefore, our primary objective was to analyze the clinical findings of SS patients at the time of diagnosis and compare them with early clinical features recorded before a definitive diagnosis of SS. Erythroderma (type 1 SS; Fig 1) was the initial presenting sign in 25.5% of the patients and never developed in 5.7% of patients. It is evident from our analysis that the strict application of ISCL diagnostic

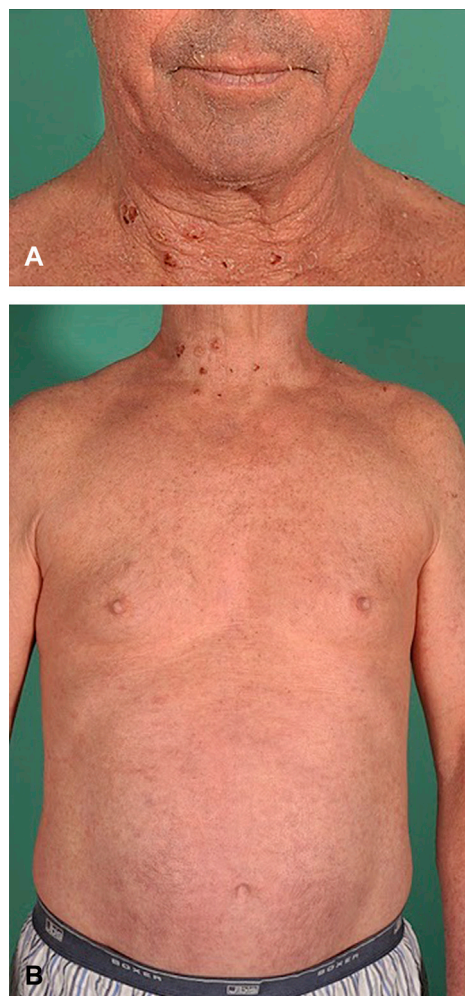


Fig 3. A and B, Atopic dermatitis-like (type 3) form of early Sézary syndrome. Focused on the head, neck, and torso are numerous, poorly marginated, dull-pink papules and patches with overlying scale and a mottled erythematous background. Excoriations are noted on the neck.

criteria will lead to the underdiagnosis of SS or misclassification as E-MF and delay the diagnosis by up to 2.8 years.³

A detailed analysis of clinical data allowed early SS to be classified into 5 clinically distinct categories (Table II). Nearly half (49.6%) of the cases presented with a nonspecific dermatitis (type 2 SS, Fig 2). Type 2 SS is a heterogeneous group that includes eczema, nummular dermatitis, contact dermatitis, and drug eruption-like rash as primary manifestations of disease. The early dermatitic appearance of SS is likely secondary to T_H2 polarization caused by malignant T-cells stimulating the release of interleukins 4, 5, and 18.²⁴ A future prospective examination of the differential features of type 2 SS is required to delineate which clinical features are predictive of SS.

Five percent of cases presented with an AD-like phenotype (type 3 SS, Fig 3, A and B). The AD-like

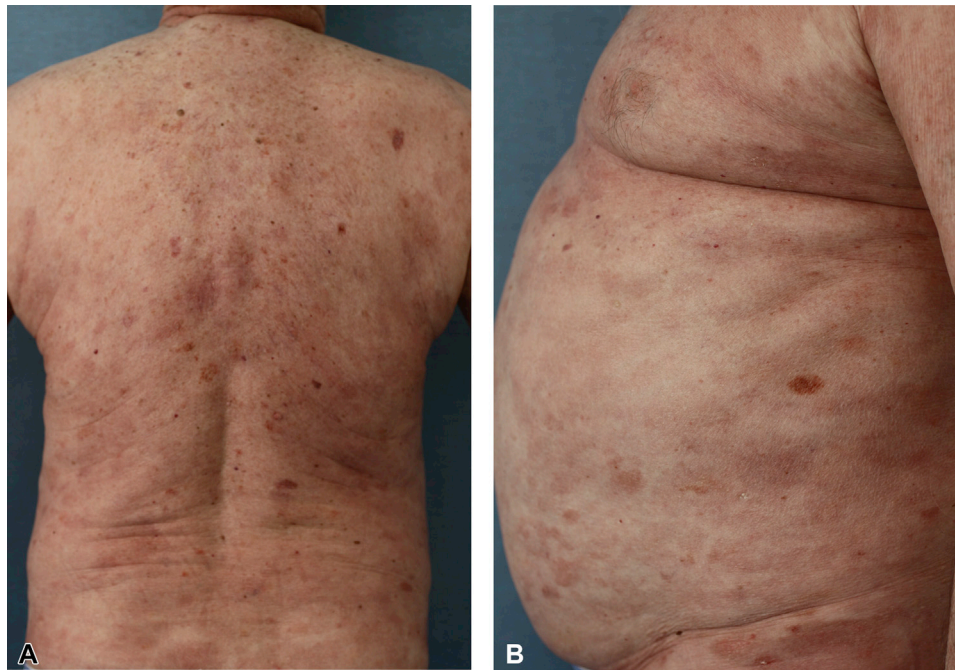


Fig 4. **A** and **B**, Mycosis fungoides-like (type 4) form of early Sézary syndrome. Over the torso are typical dull-pink to red-brown patches and plaques of mycosis fungoides.

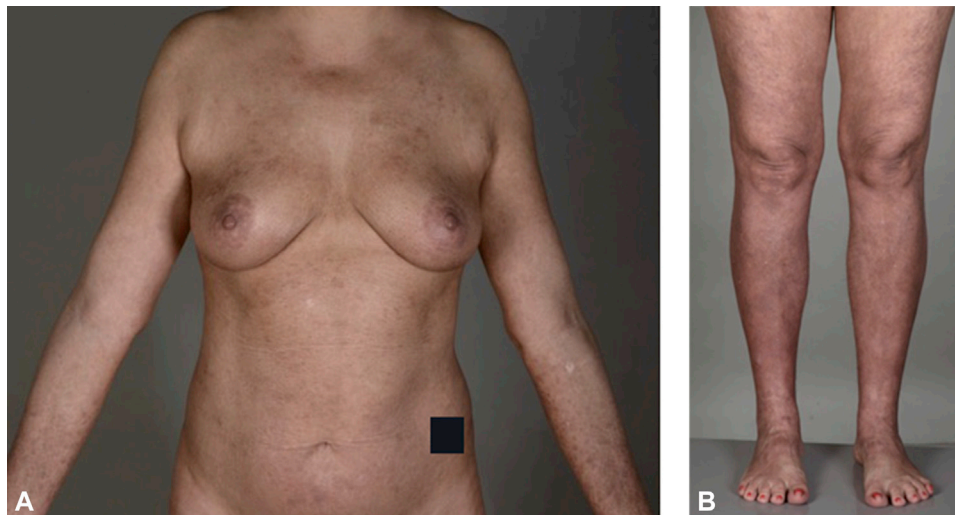


Fig 5. The leukemia without initial erythroderma (type 5) form of early Sézary syndrome. Scattered over the torso (**A**) and legs (**B**) are patches of postinflammatory hyperpigmentation secondary to excoriation and a faint dull-purple mottling of the skin on the proximal thighs that was physiologic in nature. Minimal skin disease is noted.

phenotype of SS closely mimics AD, including the preferential involvement of the head and neck, pruritus, multiple nonspecific reactions to contact allergens, and (less commonly) elevated IgE and eosinophilia.^{15,16,25,26} Clinical clues to the diagnosis of AD-like SS are a lack of signs and symptoms of AD in childhood, late onset of AD after the fourth decade of life, and a lack of response to treatment. In

general, normal-to-mildly elevated IgE levels, a normal eosinophil count, negative radioallergosorbent test reactions, and T-regulatory phenotype and C-C chemokine receptor 10-positive cells present in lesional skin might help distinguish AD-like SS from AD, but this remains unconfirmed.^{25,27} Early skin biopsies and TCR gene rearrangements might be inconclusive, which often leads to delays in

diagnosis. Awareness of the nonerythrodermic manifestation of SS is needed because the incorrect treatment with immunosuppression, such as cyclosporine, can accelerate the disease and result in poor outcomes.¹⁵

Some nonerythrodermic patients (14.2%) presented with skin lesions compatible with patches and plaques of MF (type 4 SS, Fig 4, A and B). This category is analogous to the SS-preceded-by-MF type suggested by the ISCL.³ We do not have sufficient data to speculate whether this category represents an overlap of MF and SS (as is the case with clonally related lymphomatoid papulosis coexistent with MF) or is a true evolution of MF into SS.

The nonerythrodermic, leukemic variant of SS (type 5 SS; Fig 5, A and B) was first reported in a Japanese patient and was subsequently confirmed with additional case reports.^{7,12-14} We found 23 cases of type 5 SS in our cohort. This leukemic variant is more common than previously reported and comprised 11.8% of our nonerythrodermic cases. Pruritus was the main reason for referral to a dermatologist. Sixteen patients developed the following skin lesions: dermatitis (n = 3), patches and plaques compatible with MF (n = 2), papuloerythroderma (n = 1), urticaria (n = 1), or erythroderma (n = 9). Interestingly, 56.5% of SS patients in the leukemic group never developed erythroderma, which is in stark contrast with the other clinical groups in which the emergence of erythroderma occurred later during the disease. The prognosis of type 5 SS is no different from the prognosis of classic, erythrodermic (type 1) SS. The prognosis of nonerythrodermic SS is mixed, with 1 case series reporting an indolent course and another reporting a similar prognosis to classic erythrodermic SS (note that the latter series included 16 patients from the current study).^{7,28} The etiology of nonerythrodermic SS remains speculative; however, both the ineffective skin homing of malignant T cells and dampened inflammatory response might play roles.^{14,29} Future studies are needed to determine the immunophenotypical features and the prognosis of type 5 SS.

This study was limited by the retrospective, multicenter design, which led to diagnostic variability of SS between the centers. The patient population was largely white (93.5%), which limits the generalizability. The Sézary cell count was consistently reported in all Mayo Clinic patients, and blood involvement at the other participating centers was assessed by flow cytometry or TCR monoclonality. Therefore, patients could not be staged according to the current guideline recommendations.²¹ However, all patients included in this cohort satisfied at least 2 ISCL criteria for SS, which,

together with the long follow-up (in most cases life-long), allowed a confident diagnosis of SS.

Conclusion

This study establishes the common clinical features of early SS. Erythroderma was the earliest recorded skin sign in only 25.5% of cases, although most patients (86.3%) developed erythroderma by the time of their diagnosis with SS. The nonerythrodermic presentations could be subclassified into 5 clinical subtypes. Types 2 through 5 of SS did not initially present with erythroderma and had an additional diagnostic delay of 2.8 years compared with the classic erythrodermic form (type 1). Awareness of the nonerythrodermic manifestations of SS will allow for earlier diagnosis, treatment, and relevant follow-up. The Prospective Cutaneous Lymphoma International Prognostic Index study is currently underway to identify prognostic markers during late stage MF and SS and is an ideal tool to help delineate the diagnostic and prognostic features of the early manifestations of SS.

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