Webinars

Cutaneous Lymphoma

EuroBloodNet Topic on Focus

SEZARY SYNDROME part 1
Clinical, pathological and treatment data

PIETRO QUAGLINO
DERMATOLOGIC CLINIC
DEPT MEDICAL SCIENCES, UNIVERSITY OF TURIN
ITALY
Mail: pietro.quaglino@unito.it

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European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Conflicts of interest

ADVISORY BOARD AND SPEAKER FEE FROM:

- **KIOWA-KIRIN**
- **TAKEDA**
- **THERAKOS**
- **HELSINN-RECORDATI**
- **INNATE PHARMA**
- **4SC**
- **ANTHELIOS**

Learning objectives

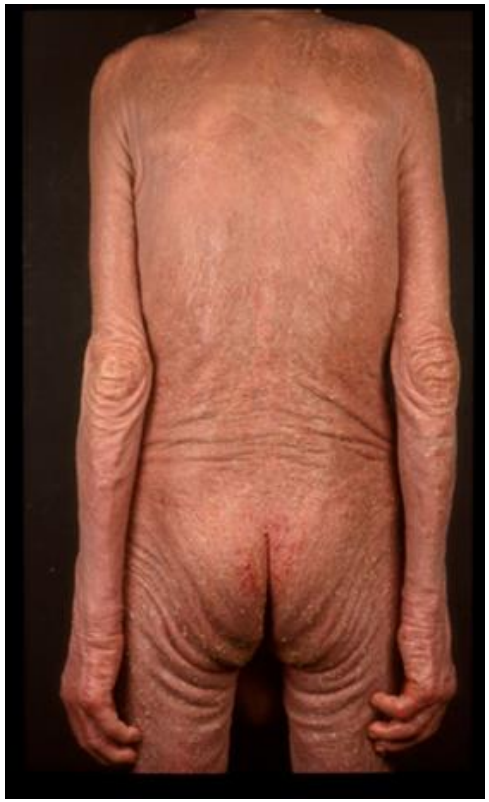
SEZARY SYNDROME

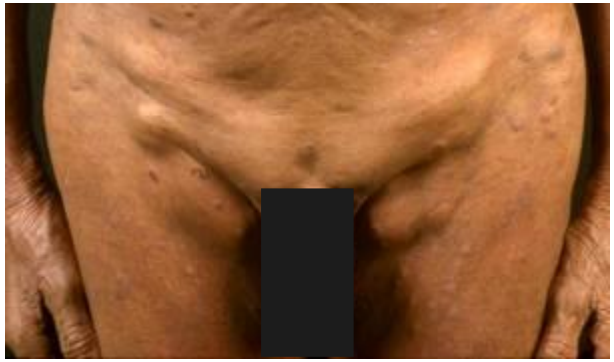
- DISEASE DEFINITION AND EPIDEMIOLOGY/DEMOGRAPHICS

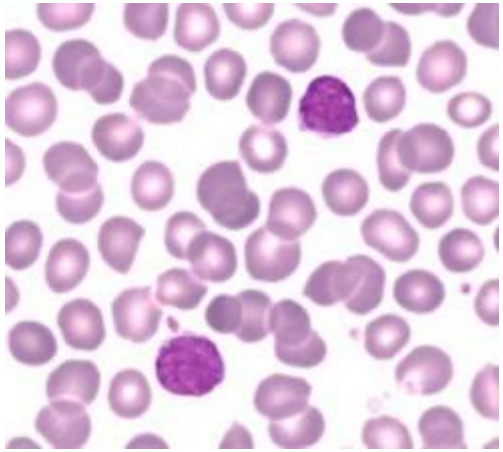
SEZARY SYNDROME

Sézary A, Bouvrain Y : Erytrodermie avec présence de cellules monstrueuses dans le derme et dans le sang circulant . 1938; Bull Soc Fr Derm Symph 45:254.

Baccaredda A : Reticulohistiocytosis cutanea hyperplastica benigna cum melanodermia. 1939 ; Archiv Dermatol Sifil 179:210.







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blood® Special Report

CME Article

The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas

Rein Willemze,[1] Lorenzo Cerroni,[2] Werner Kempf,[3] Emilio Berti,[4] Fabio Facchetti,[5] Steven H. Swerdlow,[6] and Elaine S. Jaffe[7]

[1]Department of Dermatology, Leiden University Medical Center, Leiden, The Netherlands; [2]Department of Dermatology, Medical University of Graz, Graz, Austria; [3]Kempf und Pfaltz Histologische Diagnostik and Department of Dermatology, University Hospital Zurich, Zurich, Switzerland; [4]Department of Dermatology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; [5]Department of Pathology, University of Brescia, Brescia, Italy; [6]Division of Hematopathology, University of Pittsburgh School of Medicine, Pittsburgh, PA; and [7]Hematopathology Section, Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD

SS is a rare leukemic type of CTCL, traditionally defined by the triad of pruritic erythroderma, generalized lymphadenopathy, and clonally related neoplastic T cells with cerebriform nuclei (Sezary cells) in the skin, lymph nodes, and peripheral blood.

Table 1. Relative frequency and prognosis of primary cutaneous lymphomas included in the 2018 update of the WHO-EORTC classification

WHO-EORTC Classification 2018	Frequency, %*	5-y DSS, %*
CTCL		
MF	39	88
MF variants		
Folliculotropic MF	5	75
Pagetoid reticulosis	<1	100
Granulomatous slack skin	<1	100
SS	2	36
Adult T-cell leukemia/lymphoma	<1	NDA
Primary cutaneous CD30⁺ LPDs		
C-ALCL	8	95
LyP	12	99
Subcutaneous panniculitis-like T-cell lymphoma	1	87
Extranodal NK/T-cell lymphoma, nasal type	<1	16
Chronic active EBV infection	<1	NDA
Primary cutaneous peripheral T-cell lymphoma, rare subtypes		
Primary cutaneous γ/δ T-cell lymphoma	<1	11
CD8⁺ AECTCL (provisional)	<1	31
Primary cutaneous CD4⁺ small/medium T-cell lymphoproliferative disorder (provisional)	6	100
Primary cutaneous acral CD8⁺ T-cell lymphoma (provisional)	<1	100
Primary cutaneous peripheral T-cell lymphoma, NOS	2	15

2%

36%

CTCL: 6 new cases/year/1 milion people

MALE PREVALENCE

ELDERLY AGE

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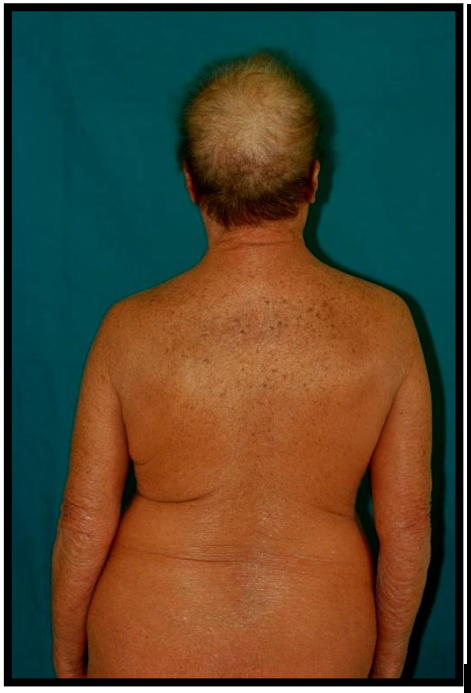
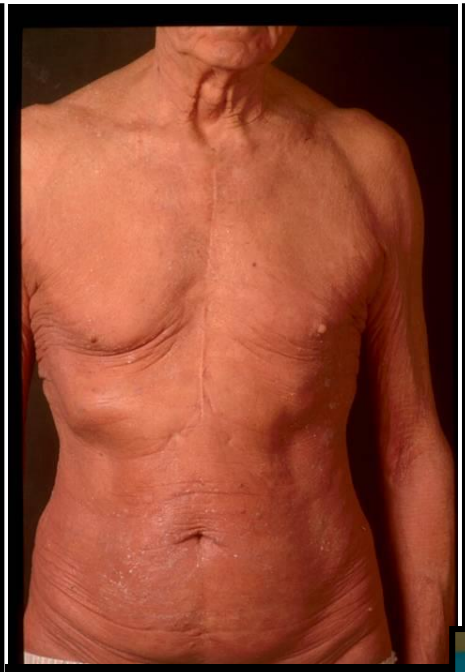
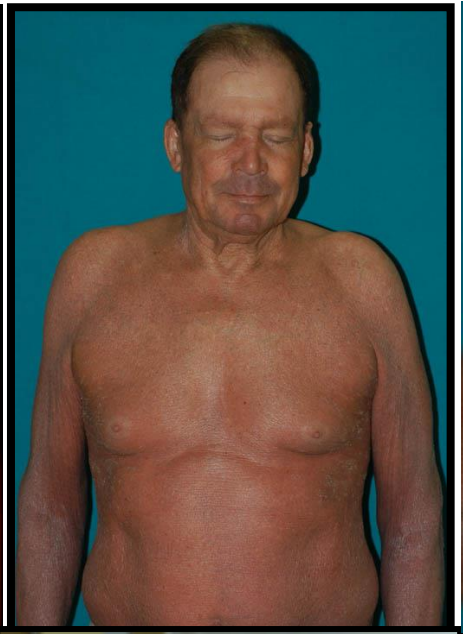
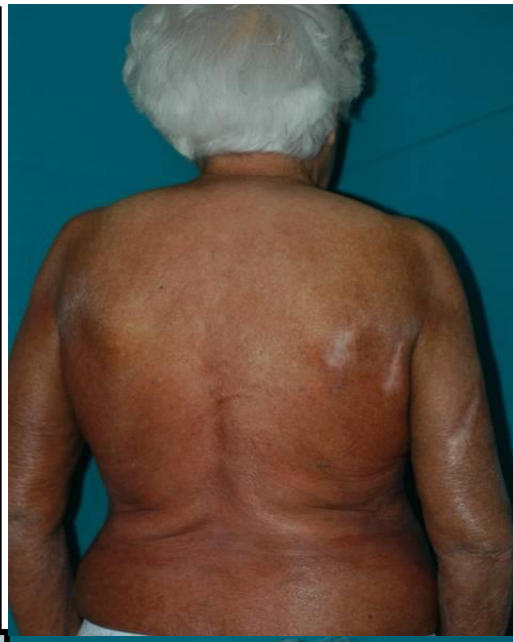
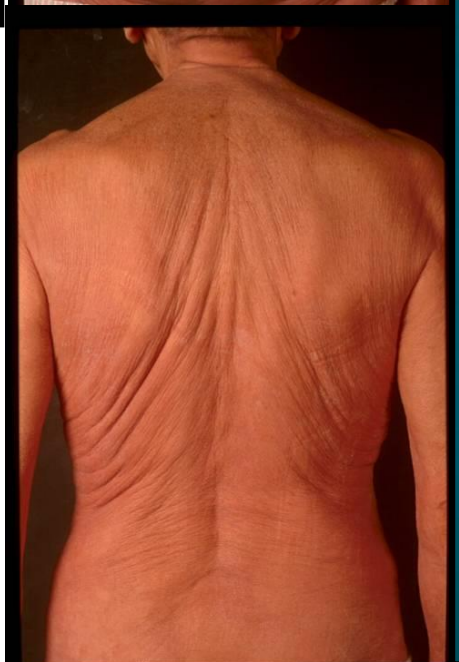
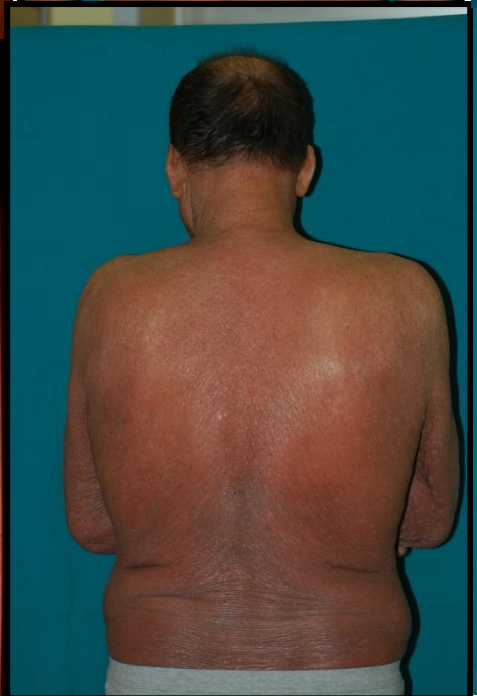
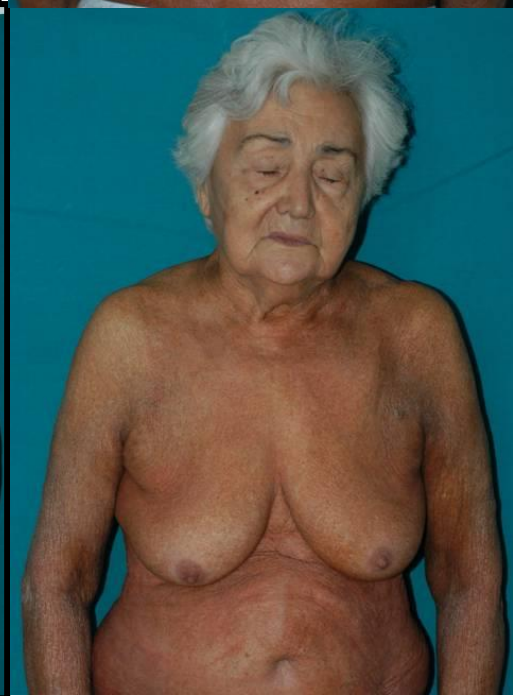
Learning objectives

SEZARY SYNDROME

- DISEASE DEFINITION AND EPIDEMIOLOGY/DEMOGRAPHICS
- CLINICAL ASPECTS

T4 (TNMB classification)= Confluence of erythema covering>=80% body surface area

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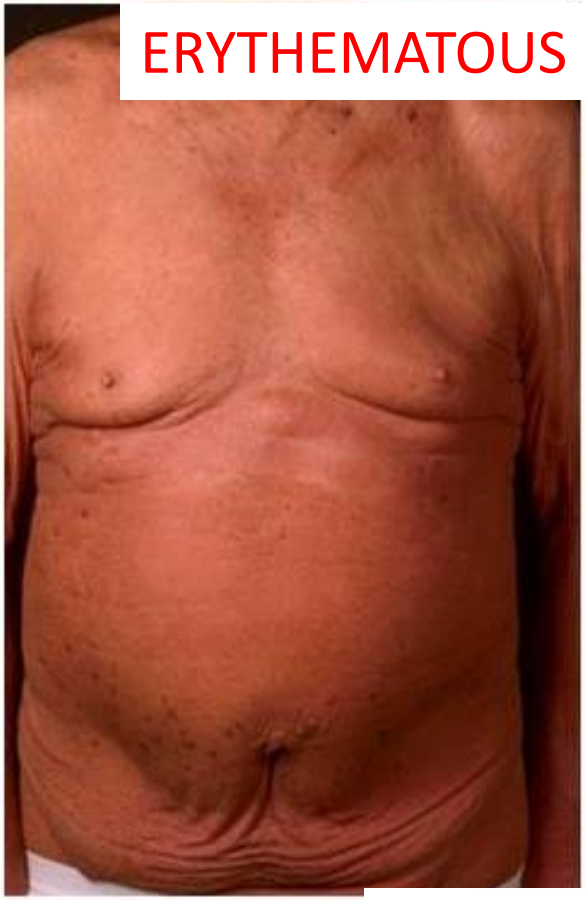
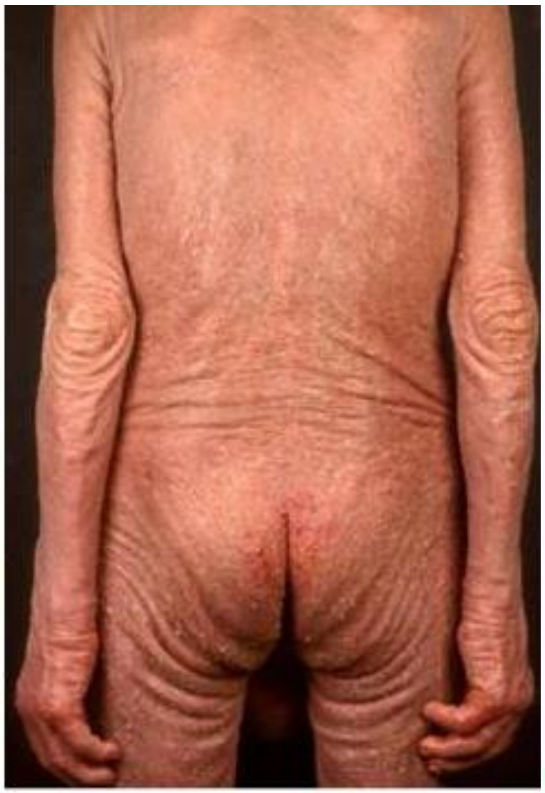
ERYTHRODERMA MORPHOTYPES

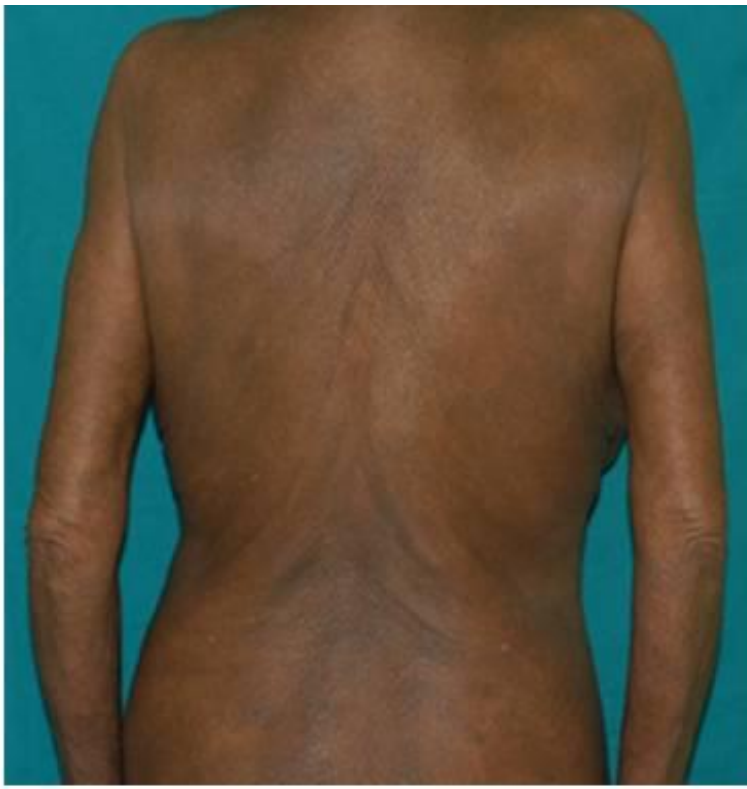
ERYTHEMATOUS



INFILTRATIVE



MELANODERMIC



DIAGNOSIS

Erythematous
85/119
(71.4%)

Infiltrative
25/119
(21%)

Melanodermic
9/119
(7.6%)

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EORTC 2018 ST GALLEN, EUR J CANCER 2018 abstract

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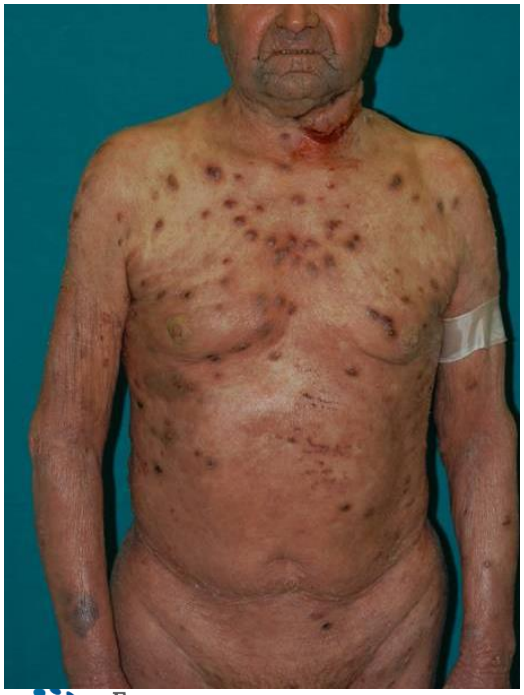
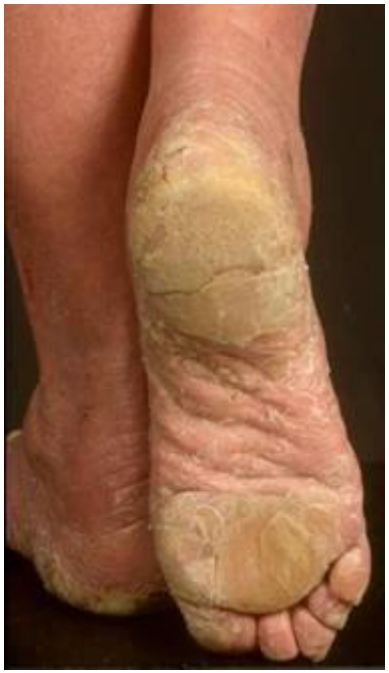
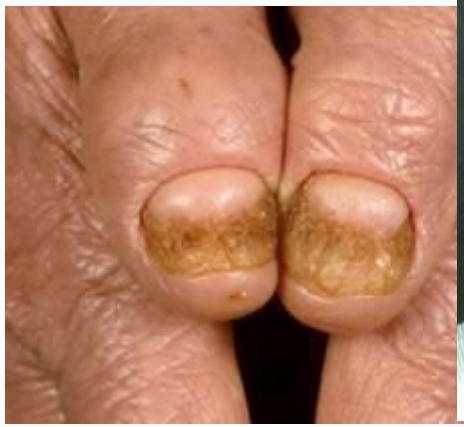
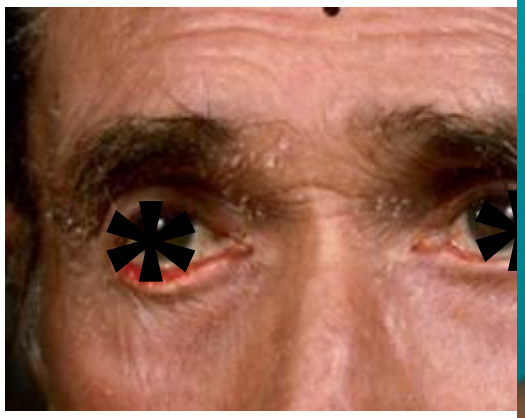
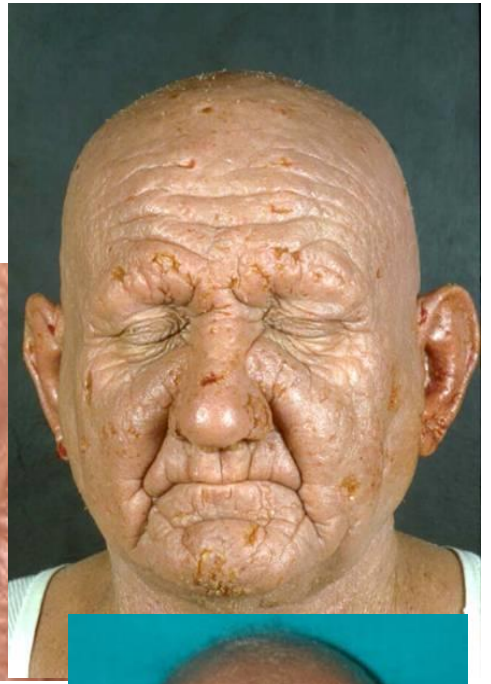
- Alopecia (40-70%)
- Palmo-plantar keratoderma (60-80%)
- Ectropion (40-60%)
- "Leonine" facies (30-40%)
- Nails alterations (60-70%)











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Bernengo MG, Quaglino P, Novelli M, et al. Prognostic factors in Sézary syndrome: a multivariate analysis of clinical, haematological and immunological features. Ann Oncol 1998; 9: 857-863.

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American Journal of Clinical Dermatology (2020) 21:383–391
https://doi.org/10.1007/s40257-020-00501-7

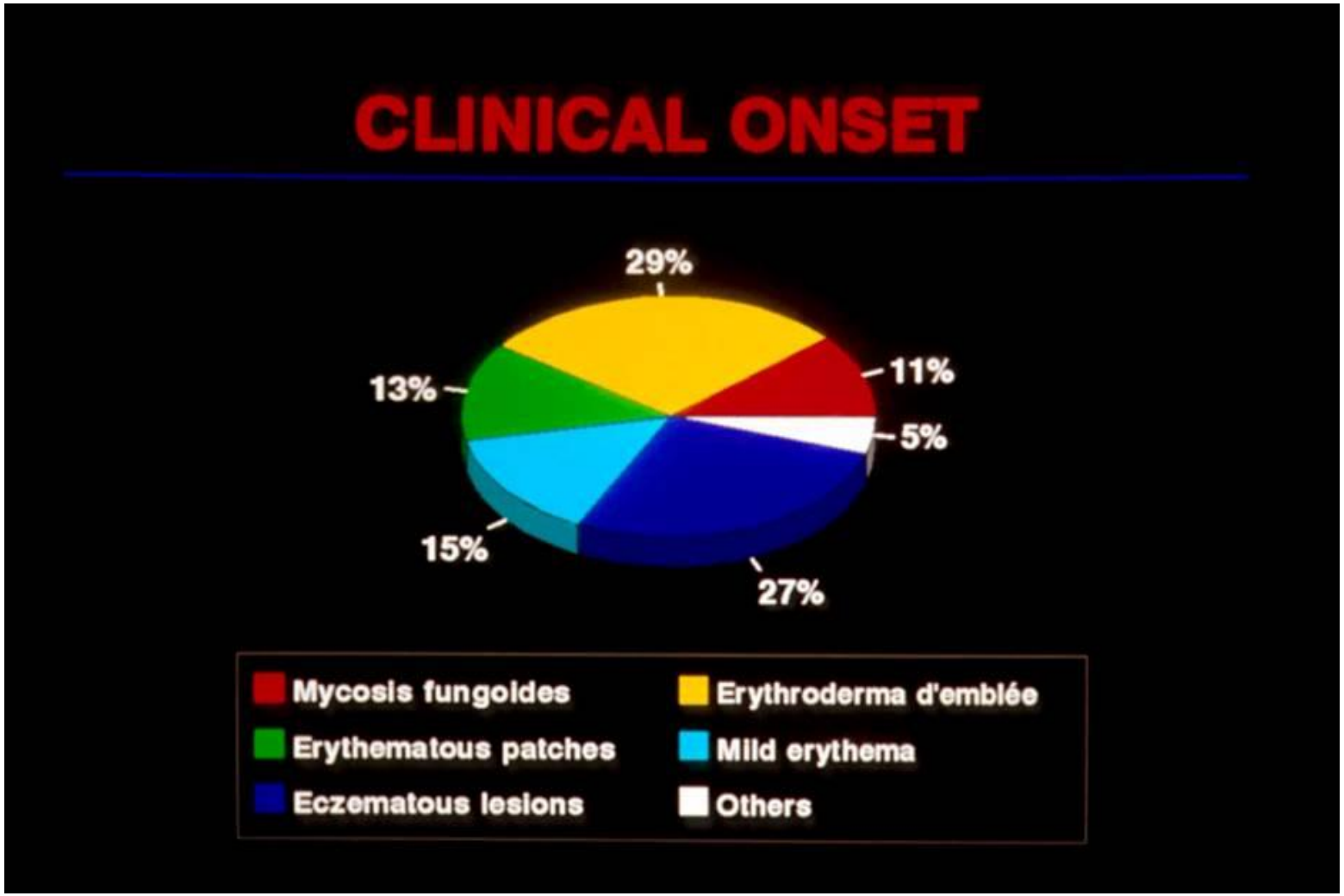
REVIEW ARTICLE

Non-Classic Signs of Sézary Syndrome: A Review

Lisa Morris[1] · Jessica Tran[2,3] · Madeleine Duvic[3]

Table 1 Non-classic signs and symptoms associated with Sézary syndrome

Non-classic sign/symptom	Number of patients reported (% of total reported)
Keratoderma [3, 4, 6, 11, 15–20, 37–47]	190 (37.6)
Onychodystrophy [16, 18, 19, 21, 27, 44, 46, 48–50]	79 (15.6)
Alopecia [3, 4, 19, 21, 30, 35, 42, 43, 46, 47, 50–53]	55 (10.9)
Leonine facies [4, 14, 30–32, 43, 45, 54, 55]	18 (3.6)
Ectropion [4, 6, 15, 19, 41, 46, 47, 52]	17 (3.4)
B symptoms (fever/chills, sweats, weight loss) [4, 18, 31, 32, 34, 52, 56, 57]	8 (1.6)
Peripheral neuropathy [35, 58–60]	4 (0.8)
Burning/stinging [39, 47, 61]	3 (0.6)
Arthritis [35, 62]	2 (0.4)
Papuloerythroderma of Ofuji [63, 64]	2 (0.4)
Lower-extremity edema [46, 52]	2 (0.4)



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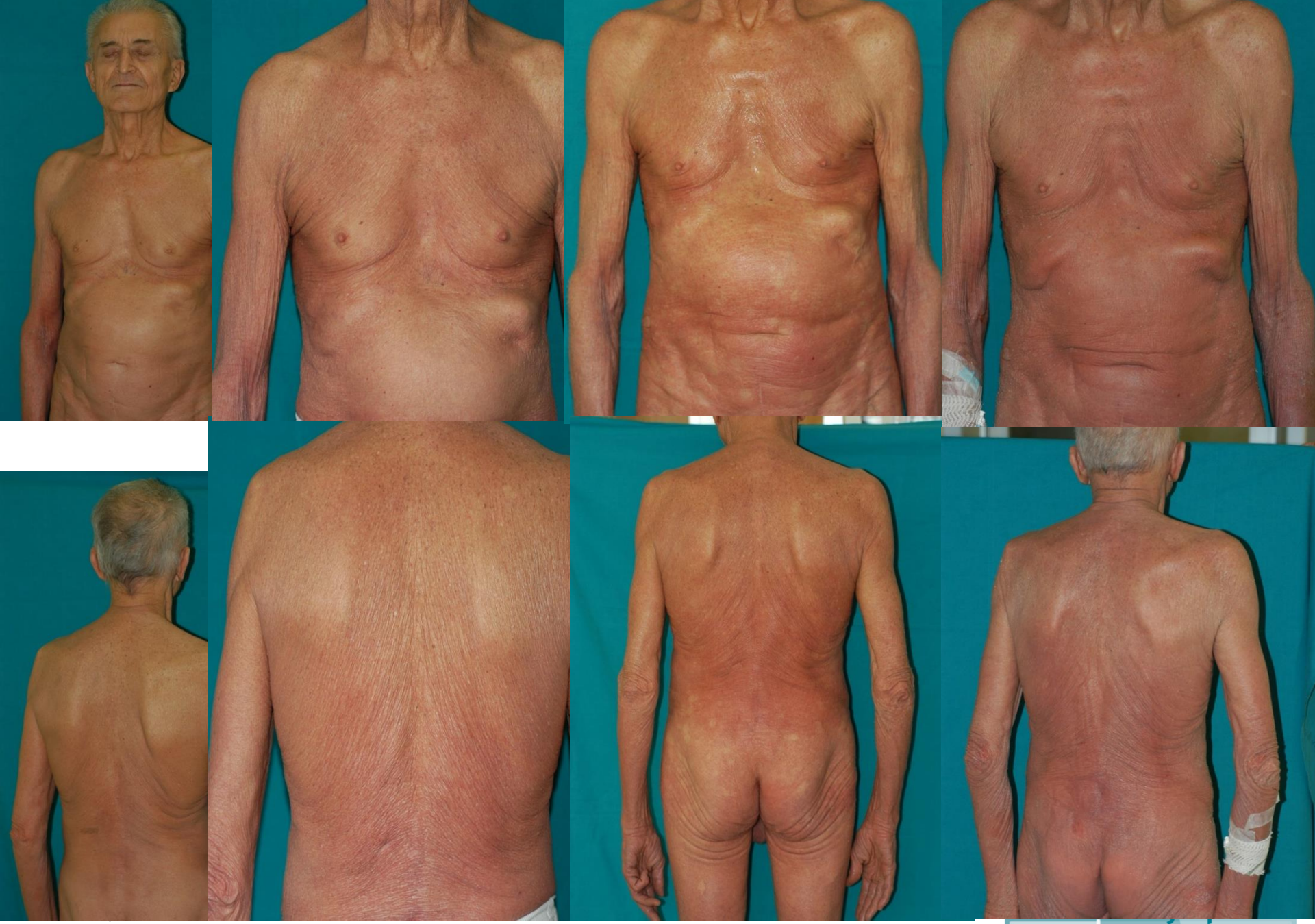

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2002---> 2006

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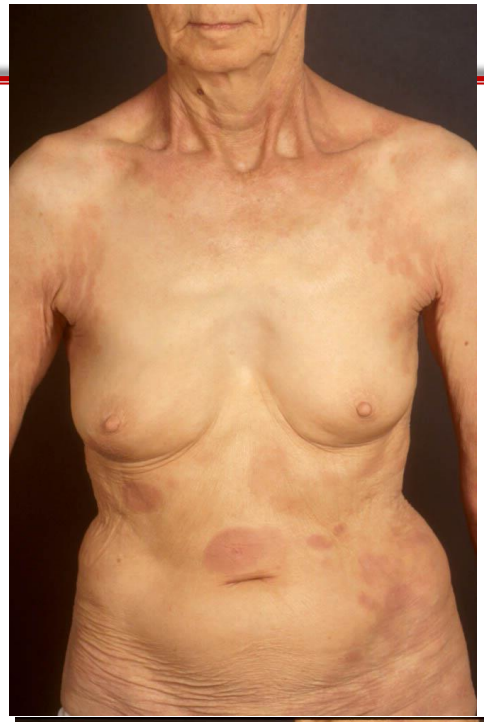
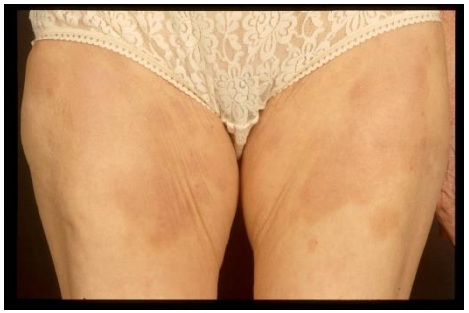
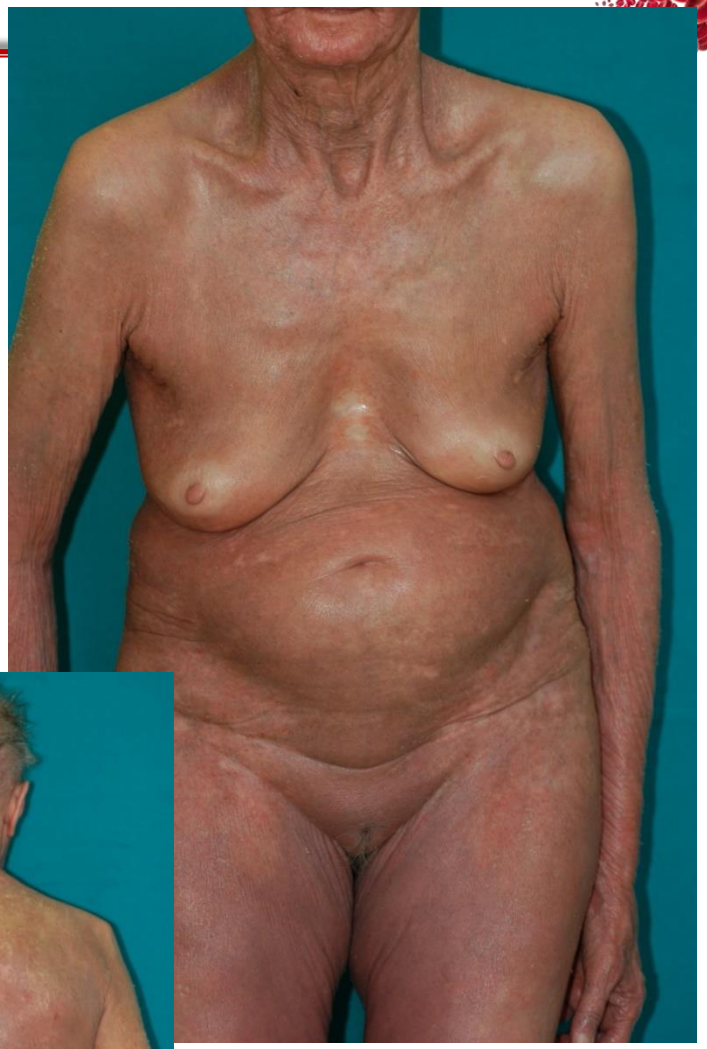
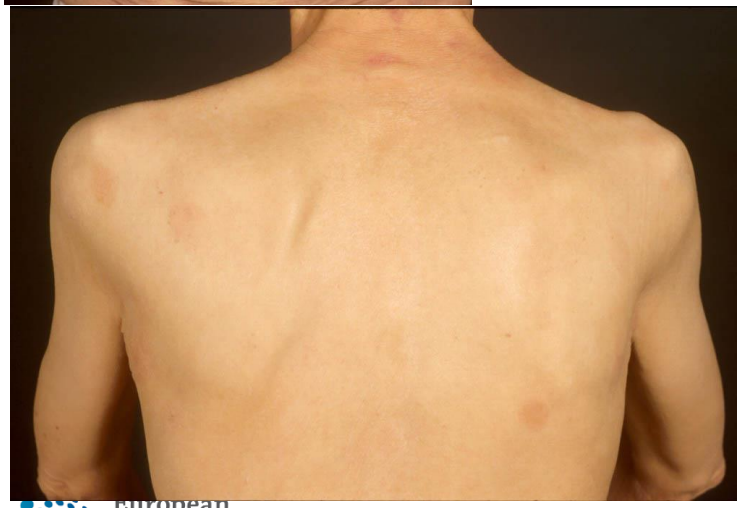
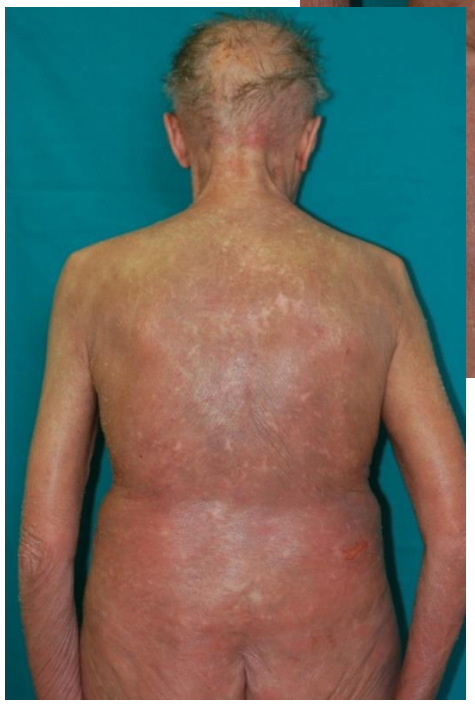
1998-2004











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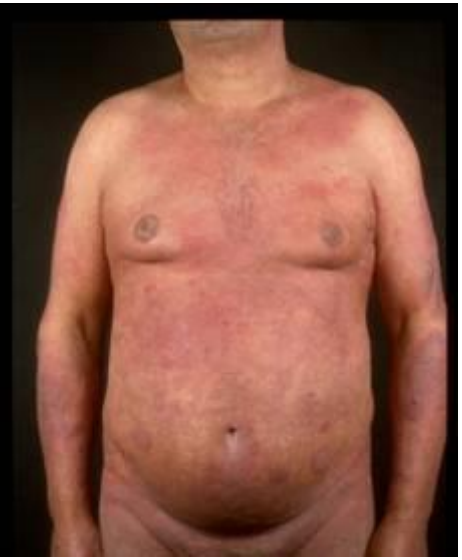
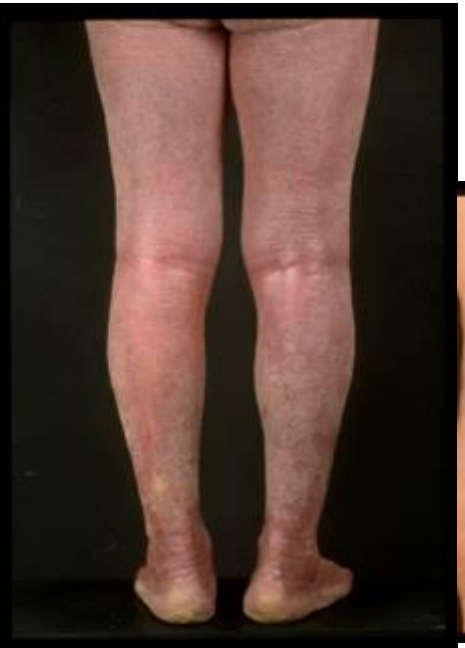
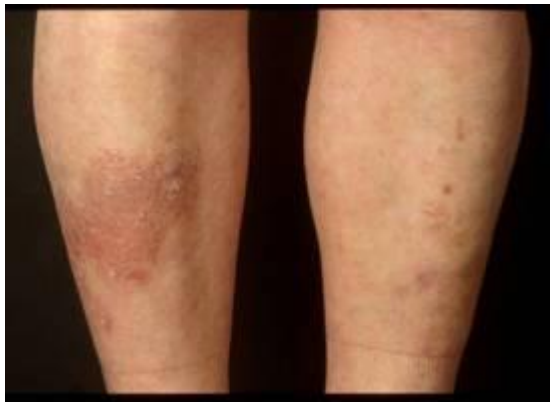
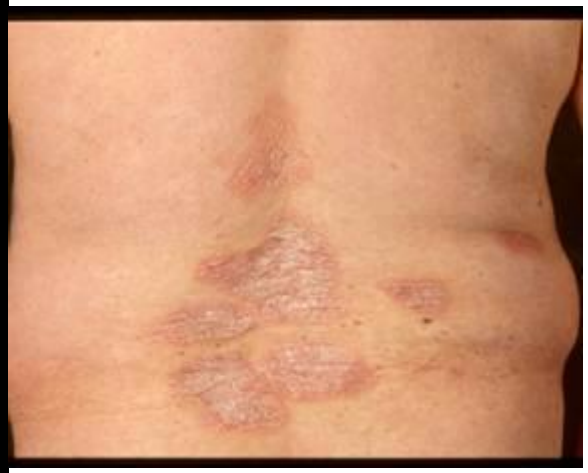
1986



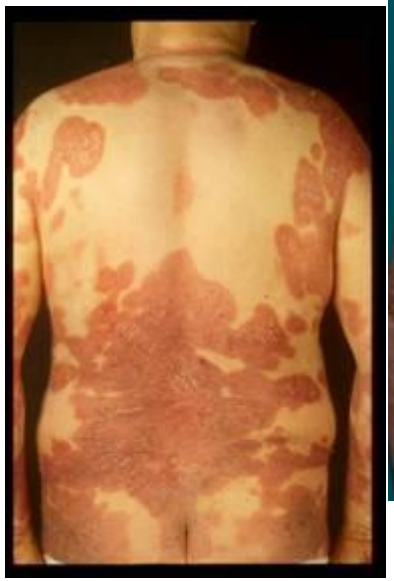


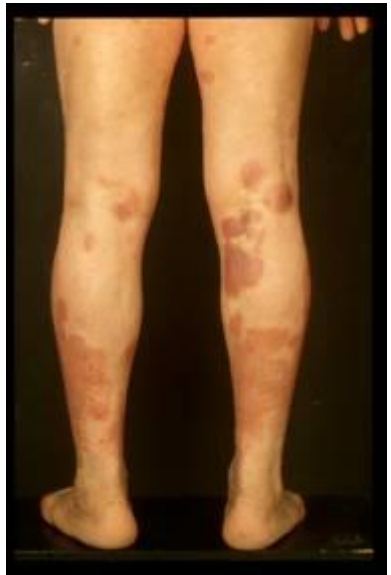
1993



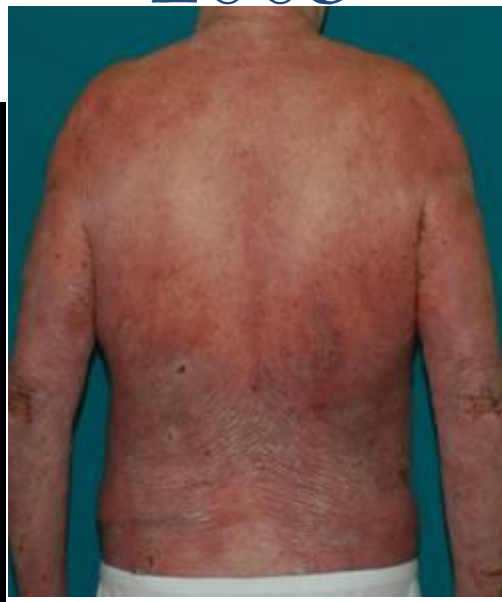


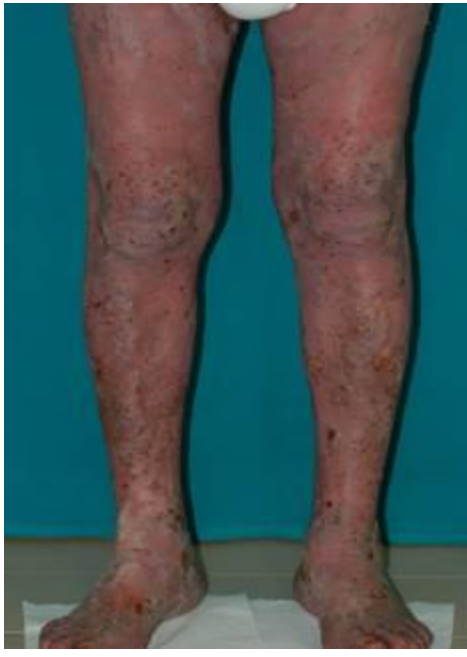
1998





2005





GENERAL DERMATOLOGY

BJD
British Journal of Dermatology

The PROCLIPI international registry of early-stage mycosis fungoides identifies substantial diagnostic delay in most patients

J.J. Scarisbrick,[1,2,3,4] P. Quaglino,[2,3] H.M. Prince,[3] E. Papadavid,[2,3] E. Hodak,[2,3] M. Bagot,[2,3] O. Servitje,[2,3] E. Berti,[2,3] P. Ortiz-Romero,[2,3] R. Stadler,[2,3] A. Patsatsi,[2,3] R. Knobler,[2,3] E. Guenova,[2,3] F. Child,[2,4] S. Whittaker,[2,3,4] V. Nikolaou,[2,3] C. Tomasini,[2] I. Amitay,[2,3] H. Prag Naveh,[2,3] C. Ram-Wolff,[2] M Battistella,[2,3] S. Alberti-Violetti,[2] R. Stranzenbach,[2,3] V. Gargallo,[2] C. Muniesa,[2] T. Koletsa,[2] C. Jonak,[2,3] S. Porkert,[2] C. Mitteldorf,[2] T. Estrach,[2] A. Combalia,[2] M. Marschalko,[2] J. Csomor,[2] A. Szepesi,[2] A. Cozzio,[2,3] R. Dummer,[2] N. Pimpinelli,[2] V. Grandi,[2] M. Beylot-Barry,[2] A. Pham-Ledard,[2] M. Wobser,[2] E. Geissinger,[2] U. Wehkamp,[2,3] M. Weichenthal,[2] R. Cowan,[2,4] E. Parry,[2,4] J. Harris,[4] R. Wachsmuth,[2,4] D. Turner,[4] A. Bates,[4] E. Healy,[4] F. Trautinger,[2,3] J. Latzka,[2] J. Yoo,[1,2] B. Vydianath,[1] R. Amel-Kashipaz,[1] L. Marinos,[2] A. Oikonomidi,[2] A. Stratigos,[2] M.-D. Vignon-Pennamen,[2] M. Battistella,[2] F. Climent,[2] E. Gonzalez-Barca,[2] E. Georgiou,[2]

What's already known about this topic?

- Mycosis fungoides (MF) is a rare skin cancer that may closely mimic common inflammatory dermatoses in early-stage disease.
- There is no singular diagnostic test for MF.
- Diagnosis of early-stage MF requires close clinical, pathological and genotypic correlation.

What does this study add?

- This study reports on the clinical characteristics of a large international cohort of patients with early-stage MF whose diagnosis has been confirmed following clinicopathological review.
- The median age of presentation is 57 years, which is significantly younger than those presenting with advanced-stage MF (66 years).
- This study confirmed a worldwide male predominance in early-stage MF (1·7 males : 1 female).
- A diagnostic delay is frequent (median 3 years).

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

Aaron R. Mangold, MD,[a] Agnieszka K. Thompson, MD,[b,c] Mark D. Davis, MD,[b] Ieva Saulite, MD,[d] Antonio Cozzio, MD,[d,e] Emmanuella Guenova, MD, PhD,[d,e] Emmilia Hodak, MD, PhD,[f] Iris Amitay-Laish, MD,[f] Ramon M. Pujol, MD, PhD,[g] Mark R. Pittelkow, MD,[b] and Robert Gniadecki, MD, PhD[h,i]
Scottsdale, Arizona; Rochester, Minnesota; New York, New York; Zurich and St. Gallen, Switzerland; Petah Tikva, Israel; Barcelona, Spain; Edmonton, Canada; and Copenhagen, Denmark

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

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.

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)

DURATION OF LESIONS BEFORE DIAGNOSIS: 4,3 YEARS

Journal of the American Academy of Dermatology [0190-9622] Mangold, Aaron anno:2017 vol:77 fasc:4 pag:719 -727

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Webinars Cutaneous Lymphoma
EuroBloodNet Topic on Focus

Sézary syndrome without erythroderma

Aurélia Henn, MD,[a] Laurence Michel, PhD,[b] Charlotte Fite, MD,[a,c] Lydia Deschamps, MD,[c,d] Nicolas Ortonne, MD, PhD,[e,f] Saskia Ingen-Housz-Oro, MD,[g] Eduardo Marinho, MD,[c,d] Marie Beylot-Barry, MD, PhD,[h,i] Martine Bagot, MD, PhD,[c,i] Liliane Laroche, MD, PhD,[g,j] Béatrice Crickx, MD, PhD,[a,c] and Eve Maubec, MD, PhD[a,c]
Paris, Créteil, Bordeaux, and Bobigny, France

Background: Sézary syndrome is a cutaneous T-cell lymphoma characterized by erythroderma and leukemic involvement.

Objective: We sought to define the clinical, biologic, and histopathologic features of Sézary syndrome

Table I. Clinical features of Sézary syndrome without erythroderma at diagnosis

Patient	Gender	Age at diagnosis, y	Pruritus	Pruritus duration before diagnosis, y	Specific CTCL lesions	Peripheral/central lymph nodes
1	F	82	Yes	6	None	–/–
2	F	73	Yes	8	None	–/–
3	F	93	Yes	0.5	None	–/–
4	F	76	Yes	4	None	–/–
5	F	67	Yes	2	Patch (T1*)	–/–
6	M	47	Yes	1	Infiltrated skin, PPK	+†/–

CTCL, Cutaneous T-cell lymphoma; *F*, female; *M*, male; *PPK*, palmoplantar keratoderma.
*Patches involving <10% of total body surface area.
†Axillary: 1.5 cm.

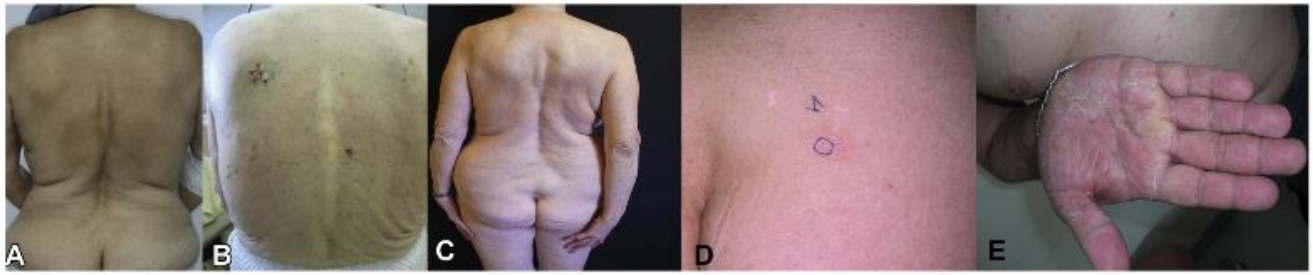


Fig. 1 Initial clinical presentations of Sézary syndrome without erythroderma. Normal-

GENERAL DERMATOLOGY

BJD
British Journal of Dermatology

Characteristics associated with significantly worse quality of life in mycosis fungoides/Sézary syndrome from the Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study

K. Molloy,[1] C. Jonak,[2] F.J.S.H. Woei-A-Jin,[3] E. Guenova,[4] A.M. Busschots,[3] A. Bervoets,[3] E. Hauben,[3] R. Knobler,[2] S. Porkert,[2] C. Fassnacht,[4] R. Cowan,[5] E. Papadavid,[6] M. Beylot-Barry,[7] E. Berti,[8] S. Alberti Violetti,[8] T. Estrach,[9] R. Matin,[10] O. Akilov,[11] L. Vakeva,[12] M. Prince,[13] A. Bates,[14] M. Bayne,[15] R. Wachsmuch,[16] U. Wehkamp,[17] M. Marschalko,[18] O. Servitje,[19] D. Turner,[20] S. Weatherhead,[21] M. Wobser,[22] J.A. Sanches,[23] P. McKay,[24] D. Klemke,[25] C. Peng,[1] A. Howles,[1] J. Yoo,[1] F. Evison[1] and J. Scarisbrick[1]

[1]University Hospitals Birmingham, Birmingham, U.K.
[2]Medical University of Vienna, Vienna, Austria
[3]University Hospitals Leuven, Belgium
[4]University Hospital Zurich, Switzerland
[5]Christie Hospital, Manchester, U.K.
[6]Athens University Medical School, Athens, Greece
[7]Centre Hospitalier Universitaire Hospital de Bordeaux, Bordeaux, France
[8]Department of Dermatology, Fondazione Ca' Granda, IRCCS, OMP, Milan, Italy

"dramatic itching" and "cold" sensation

Table 4 Multiple linear regression analysis of factors influencing Skindex-29 scores in patients with mycosis fungoides/Sézary syndrome (SS)

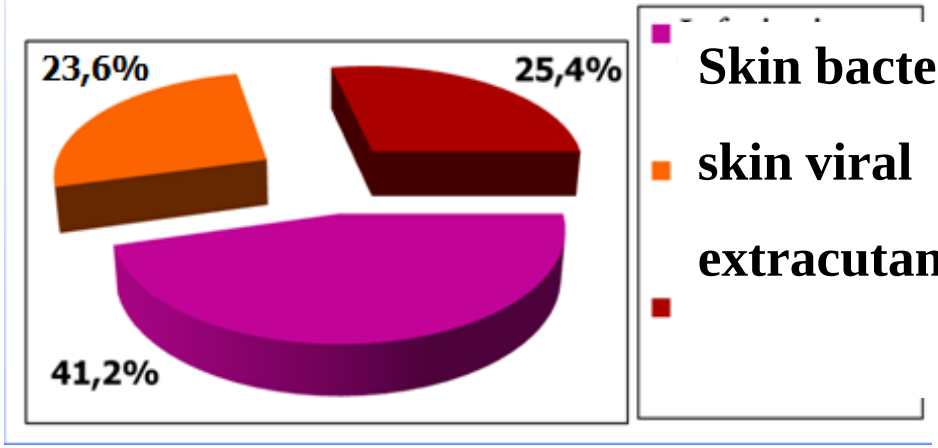
		Global			Symptoms			Emotions			Functioning		
Variable	n	β	SE	P-value	β	SE	P-value	β	SE	P-value	β	SE	P-value
Age	–	−0·06	0·09	0·48	−0·04	0·09	0·67	−0·11	0·10	0·28	−0·04	0·10	0·71
Female gender	94	8·61	2·84	0·003**	9·95	3·07	0·001**	9·08	3·20	0·005**	6·80	3·17	0·03*
SS	26	6·65	5·89	0·26	6·44	6·36	0·31	4·30	6·65	0·52	9·21	6·57	0·16
Late-stage disease	58	4·87	4·21	0·25	5·24	4·55	0·25	4·53	4·76	0·34	4·83	4·70	0·31
Alopecia	35	9·71	4·00	0·02*	8·43	4·32	0·05	12·70	4·52	0·01**	8·02	4·47	0·07
Confluent erythema	54	8·13	4·08	0·05	10·95	4·40	0·01**	3·66	4·60	0·43	9·77	4·55	0·03*

Linear regression coefficient (β) with standard errors (SE). *P < 0·05; ** P ≤ 0·01.

SIGNS & SYMPTOMS

INFECTIOUS COMPLICATIONS

- Edema, skin exudation
- Protein/iron/metabolite loss through the altered skin barrier



- 69 out of 114 SS patients (60.6%)

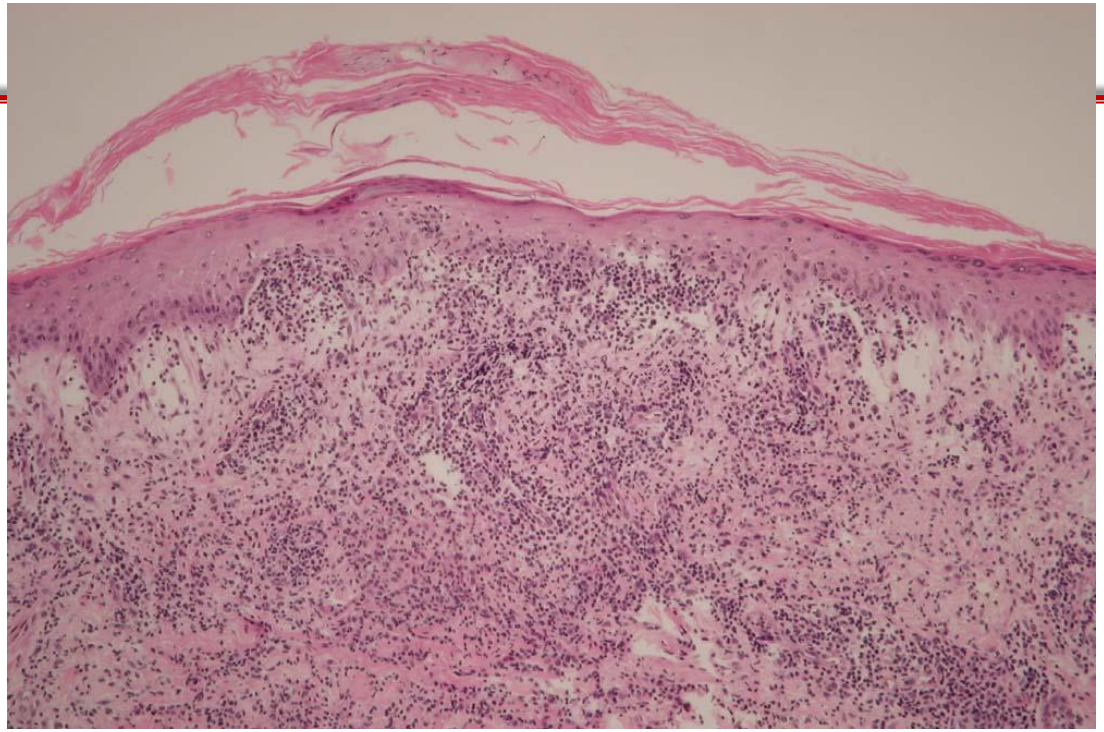
Main cause of death

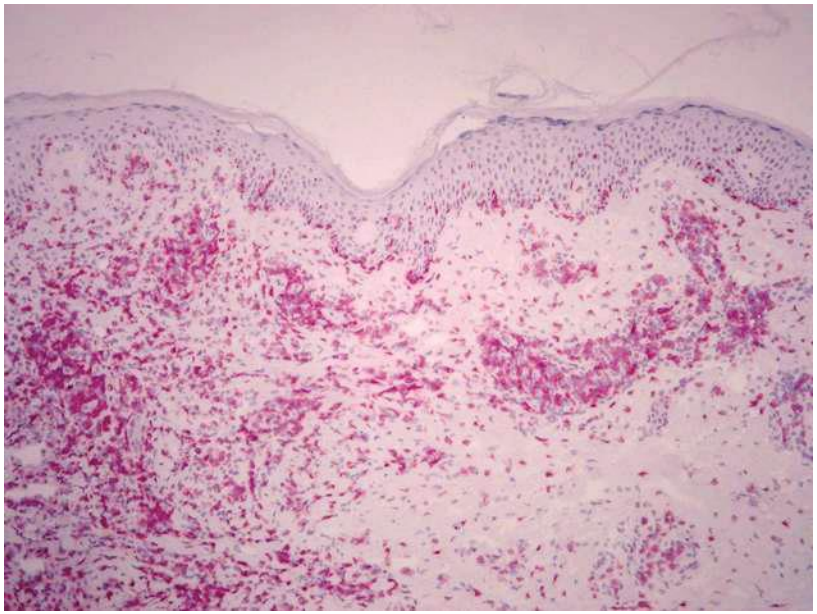
QUAGLINO P, et al. JAAD 2020 in press

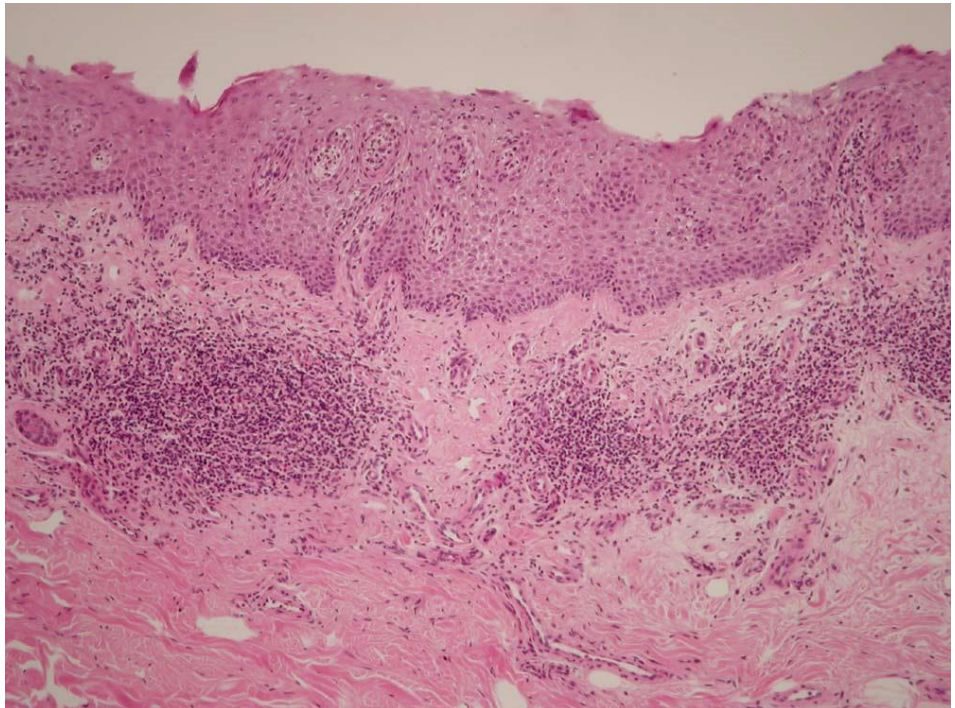
Learning objectives

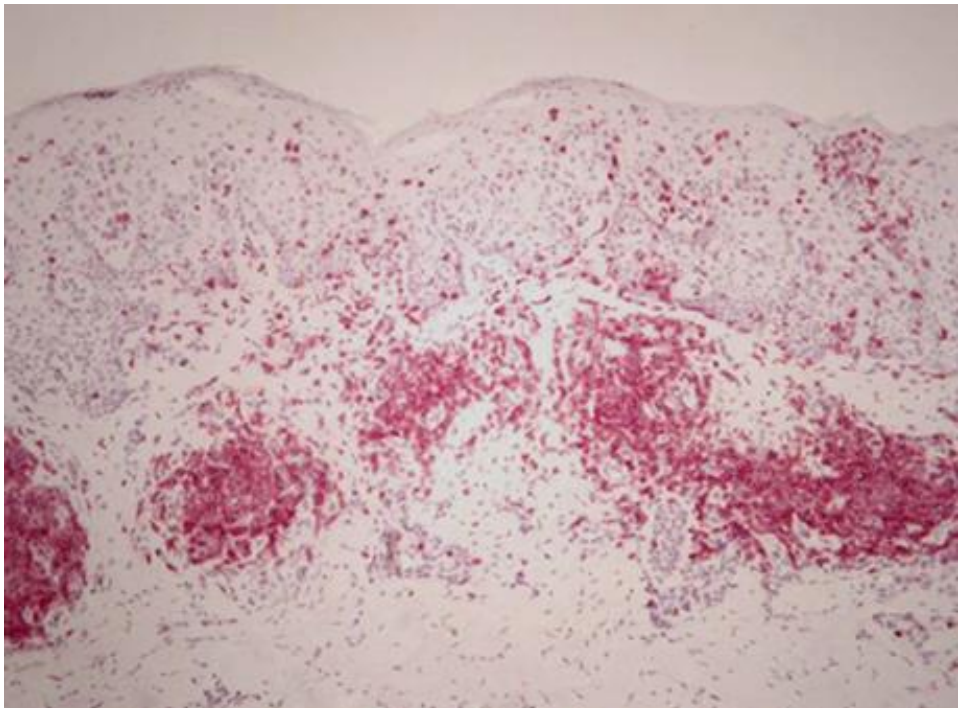
SEZARY SYNDROME

- DISEASE DEFINITION AND EPIDEMIOLOGY/DEMOGRAPHICS
- CLINICAL ASPECTS
- HISTOLOGY & IMMUNOPHENOTYPE

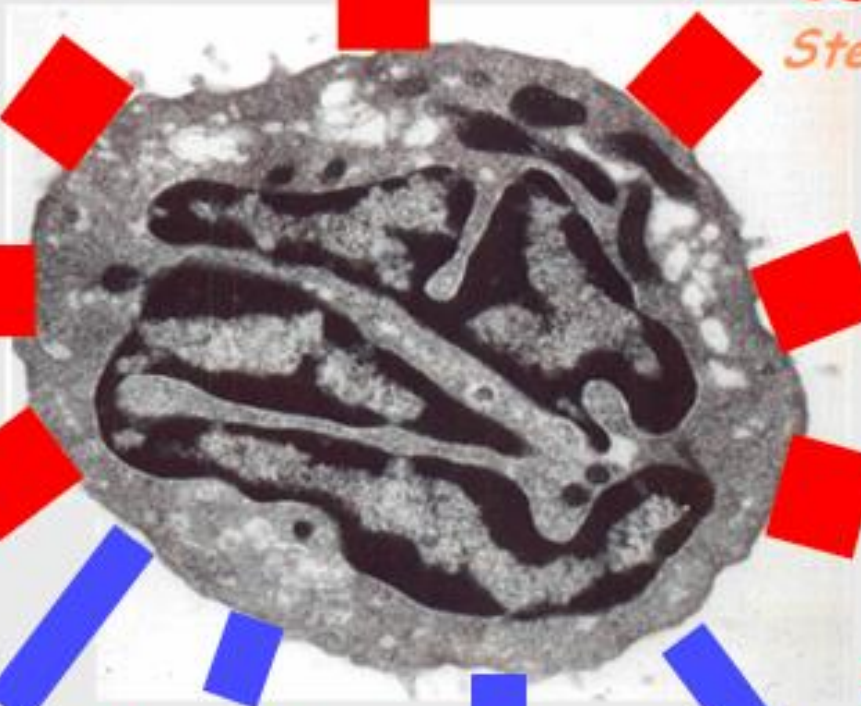








SEZARY CELL PHENOTYPE



T CD4+ *Broder, 1974*

CD7 neg
Wood, 1990

CD45RO+
Sterry, 1989

CD26 neg
Bernengo, 2001

vβ restr.
Vonderheid, 2005

Loss/"dim"
Lima, 2003

CLA+ CCR4+
Picker 1990

T plastin
Su, 2003

Vimentin
Huet, 2006

CD158k
Bagot, 2004

central memory phenotype
CD27/CCR4
Campbell, 2010

MF express markers of skin-resident effector memory T-cells

British Journal of Dermatology 2001; 144: 125–135.

The relevance of the CD4+ CD26− subset in the identification of circulating Sézary cells

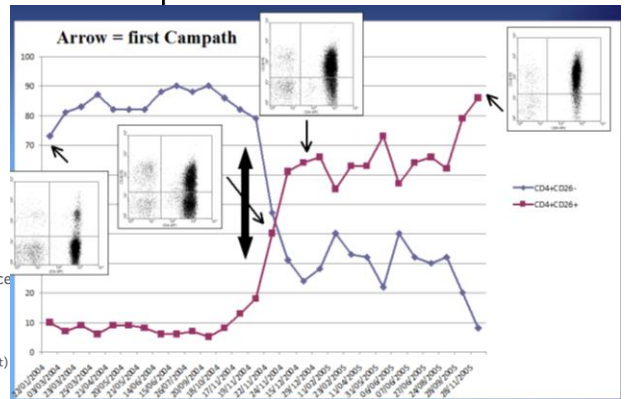
M.G.BERNENGO, M.NOVELLI, P.QUAGLINO, F.LISA, A.DE MATTEIS, P.SAVOIA, N.CAPPELLO* AND M.T.FIERRO

*Department of Medical and Surgical Specialities, First Dermatologic Clinic and *Department of Genetics, Biology and Medical Chemistry, Section of Medical Statistics, University of Turin, Via Cherasco 23, 10126 Torino, Italy*

Accepted for publication 16 August 2000

PHENOTYPIC HETEROGENEITY IN SS PATIENTS: THE CD26 AND CD7 PUZZLE

107 cases: % values		stable CD7			"changing" CD7					
		negative	"mixed"	positive	negative		"mixed"		positive	
					changing to positive	changing to "mixed"	changing to negative	changing to positive	changing to "mixed"	
stable CD26	negative	36,4	19,6	18,7	0,9	1,9	1,9	0,9		87.9 %
	"mixed"	2,8	2,8	0,9						
	positive			0,9						
"changing" CD26	negative to positive		0,9	0,9	0,9		0,9			12.1 %
	negative to "mixed"	3,7		2,8						
	"mixed" to negative	0,9							0,9	
		91.6 %			8.4 %					



Novelli M & Quaglino P, et al, AJCP 2014

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

Webinars Cutaneous Lymphoma

EuroBloodNet Topic on Focus

REGULAR ARTICLE

blood advances

Single-cell heterogeneity in Sézary syndrome

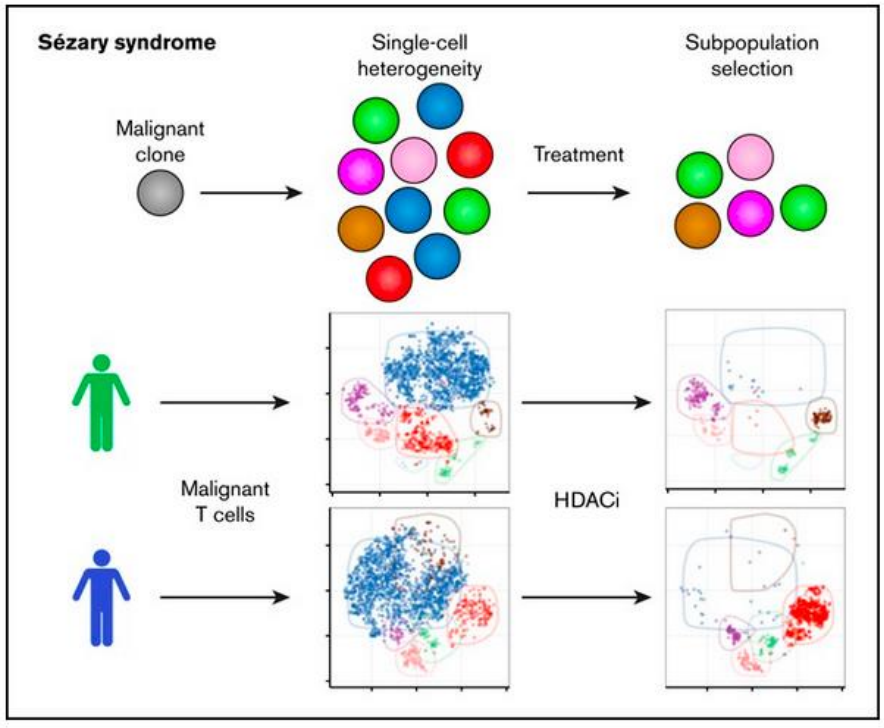
Terkild Brink Buus,[1] Andreas Willerslev-Olsen,[1] Simon Fredholm,[1] Edda Blümel,[1] Claudia Nastasi,[1] Maria Gluud,[1] Tengpeng Hu,[1] Lise M. Lindahl,[2] Lars Iversen,[2] Hanne Fogh,[3] Robert Gniadecki,[3] Ivan V. Litvinov,[4] Jenny L. Persson,[5,6] Charlotte Menné Bonefeld,[1] Carsten Geisler,[1] Jan Pravsgaard Christensen,[1] Thorbjørn Krejsgaard,[1] Thomas Litman,[1] Anders Woetmann,[1] and Niels Ødum[1]

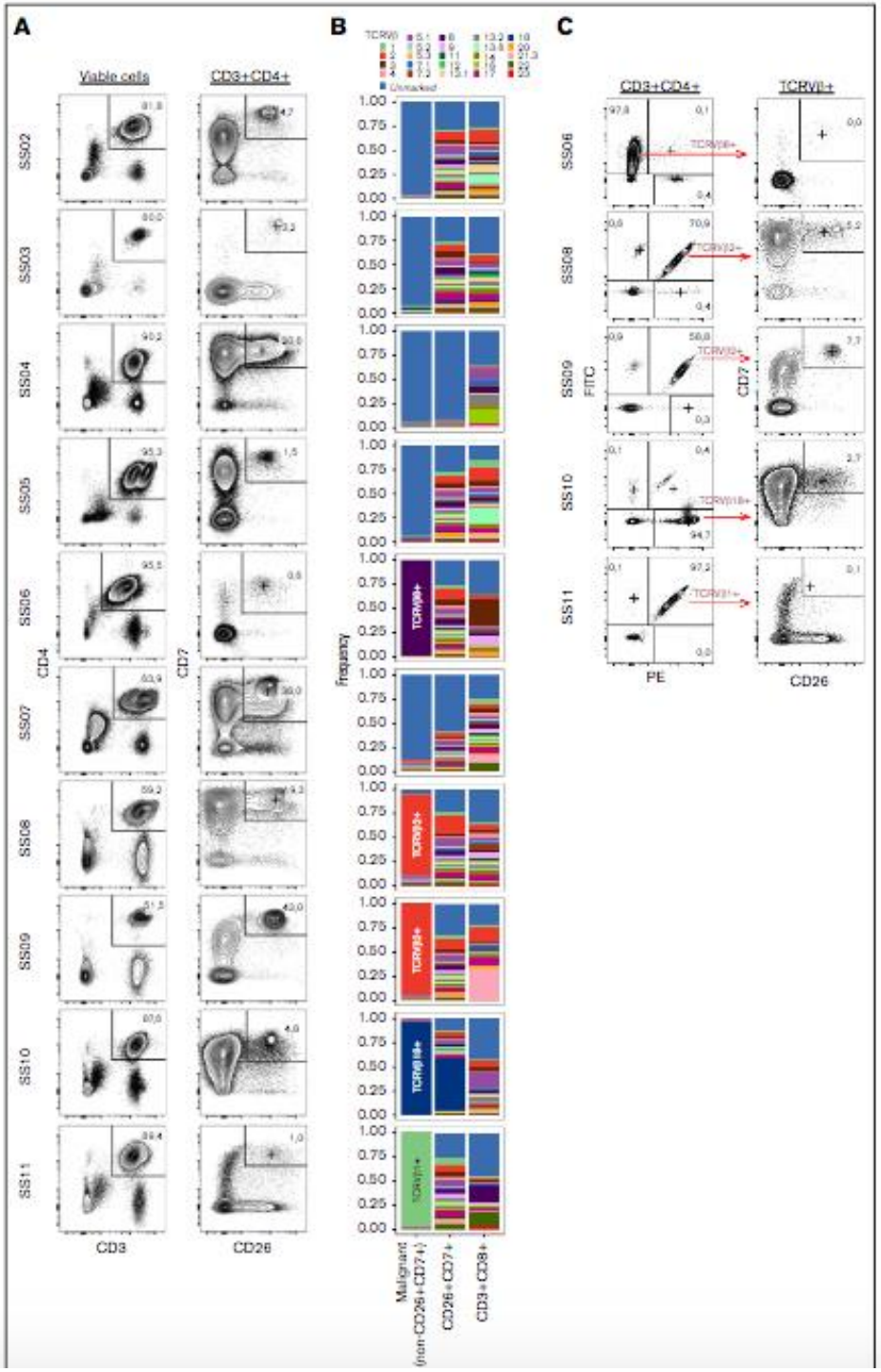
[1]Department of Immunology and Microbiology, University of Copenhagen, Copenhagen, Denmark; [2]Department of Dermatology, Aarhus University, Hospital, Skejby, Aarhus, Denmark; [3]Department of Dermatology, Copenhagen University Hospital, Bispebjerg, Copenhagen, Denmark; [4]Division of Dermatology, McGill University, Montreal, QC, Canada; [5]Clinical Research Center, Lund University, Malmö, Sweden; and [6]Department of Molecular Biology, Umeå University, Umeå, Sweden.

Key Points

- Individual patients with Sézary syndrome contain several distinct malignant subpopulations and show marked single-cell heterogeneity.

Sézary syndrome (SS) is an aggressive leukemic variant of cutaneous T-cell lymphoma (CTCL) with a median life expectancy of less than 4 years. Although initial treatment responses are often good, the vast majority of patients with SS fail to respond to ongoing therapy. We hypothesize that malignant T cells are highly heterogeneous and harbor subpopulations of SS cells that are both sensitive and resistant to treatment. Here, we investigate the presence of single-cell heterogeneity and resistance to histone deacetylase inhibitors (HDACi) within primary malignant T cells from patients with SS. Using single-cell RNA sequencing and flow cytometry, we find that malignant T cells from all investigated patients with SS display a high degree of single-cell heterogeneity at both the mRNA and





Vonderheid EC, Bernengo MG, Burg G, et al.
Update on erythrodermic cutaneous T-cell lymphoma: report of the ISCL
J Am Acad Dermatol. 2002 Jan;46(1):95-106.

LEUKEMIC BLOOD INVOLVEMENT

- Absolute Sézary cell count > 1,000/mm^3
- CD4/CD8 ratio> 10
- CD4+CD7- >= 40%
- Aberrant expression of T cell markers
- Evidence of a T cell clone (SB, PCR)
- A chromosomally-abnormal T cell clone
- Circulating CD4+CD26- > 30%

European Journal of Cancer 93 (2018) 47–56

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Review

Blood classification and blood response criteria in mycosis fungoides and Sézary syndrome using flow cytometry: recommendations from the EORTC cutaneous lymphoma task force

Julia J. Scarisbrick [a,*], Emmilia Hodak [b], Martine Bagot [c], Rene Stranzenbach [d], Rudolf Stadler [d], Pablo L. Ortiz-Romero [e], Evangelia Papadavid [f], Felicity Evison [a,1], Robert Knobler [g], Pietro Quaglino [h], Maarten H. Vermeer [i]

European Journal of Cancer 101 (2018) 278–280

Available online at www.sciencedirect.com

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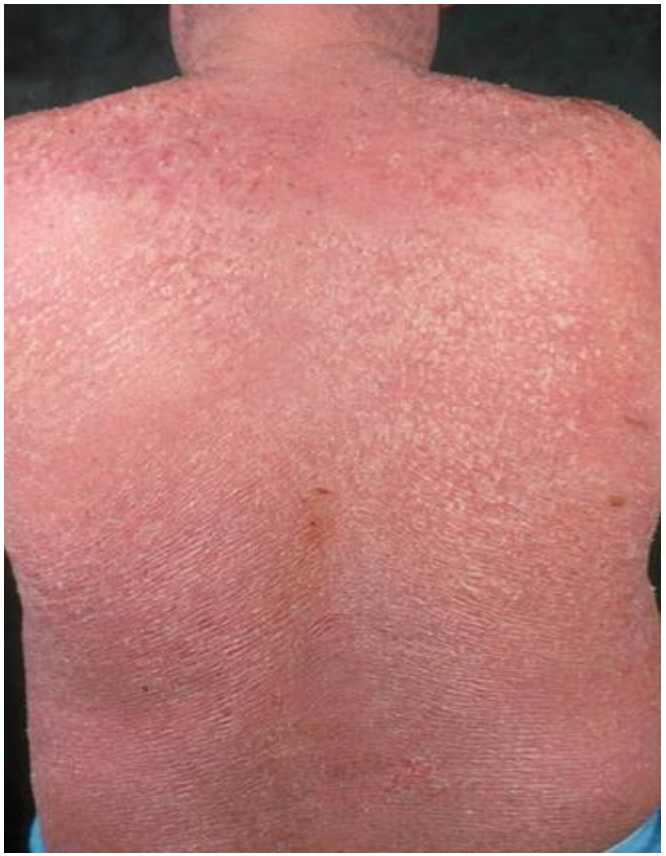
journal homepage: www.ejcancer.com

Letter to the Editor

Developments in the understanding of blood involvement and stage in mycosis fungoides/Sezary syndrome

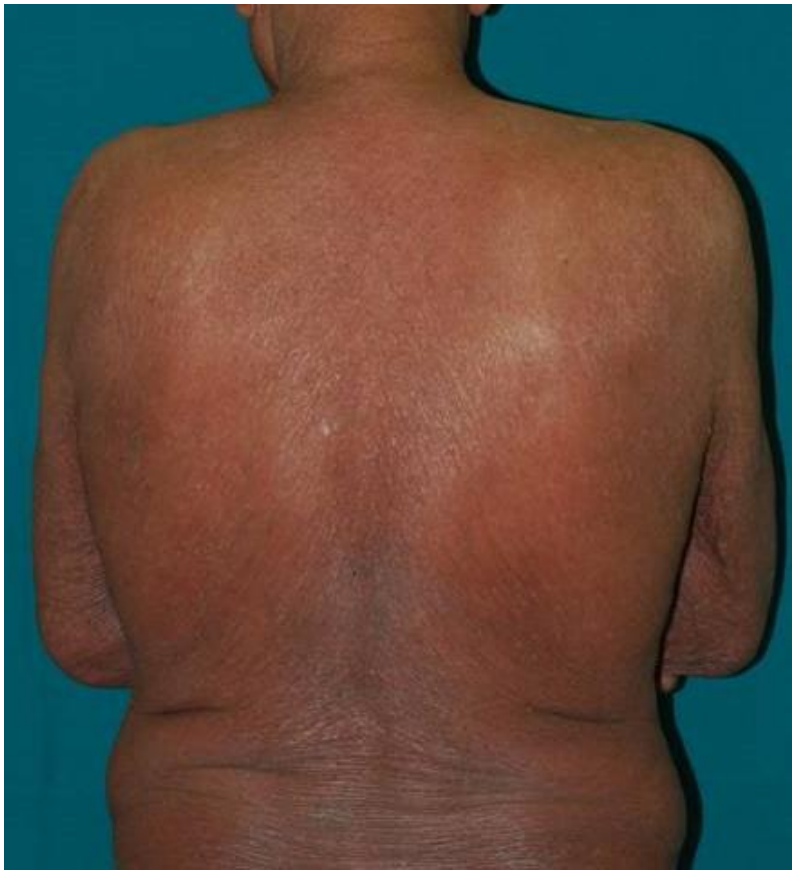
Julia J. Scarisbrick [a,*], Emmilia Hodak [b], Martine Bagot [c], Rene Stranzenbach [d], Rudolf Stadler [d], Pablo L. Ortiz-Romero [e], Evangelia Papadavid [f], Robert Knobler [g], Pietro Quaglino [h], Maarten Vermeer [i]

B	definition
B0	Absence of blood involvement: absolute counts of CD4+CD7-or CD4+CD26- <250/mL
B1	absolute counts of CD4+CD7- or CD4+CD26-<1000/mL
B2	> 1000/mL CD4+CD7- or CD4+CD26- with a positive cell clone



ERYTHRODERMIC MYCOSIS FUNGOIDES

B-SCORE: B0-B1



SEZARY SYNDROME

B-SCORE: B2

Learning objectives

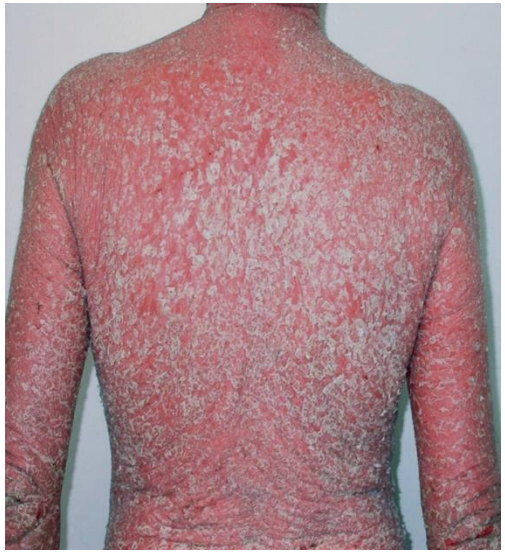
SEZARY SYNDROME

- DISEASE DEFINITION AND EPIDEMIOLOGY/DEMOGRAPHICS
- CLINICAL ASPECTS
- HISTOLOGY & IMMUNOPHENOTYPE
- DIFFERENTIAL DIAGNOSIS

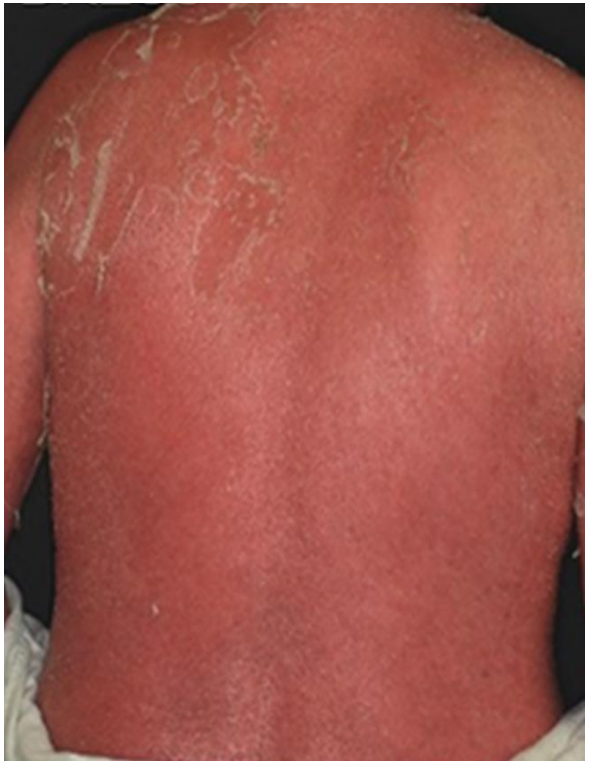
Authors, year	Number of patients	Male: Female	Median age at diagnosis (years)	Pre-existing dermatoses (%)	Drug reaction (%)	CTCL (%)	Paraneoplastic (%)	Miscellaneous (%)	Idiopathic (%)
Nicolis and Helwig (1973)[70]	135	11.3:1	49	27	40	8	3	10	12
Hasan and Jansen (1983)[11]	50	1.94:1	61	54	10	4	0	0	32
King *et al.* (1986)[71]	82			31	34	18	0	1	16
Sehgal *et al.* (1986)[13]	80	2.6:1	41.9	58	20	0	0	0	22
Thestrhup-Pedersen *et al.* (1988)[29]	204	2.24:1	32–69	38.2	25	0	5	16	19
Wilson *et al.* (1993)[30]	50	2.3:1	55	48	8	4	0	4	38
Botella-Estradas *et al.* (1994)[26]	56	4:1	57	66	12.5	12.5	0	0	9
Vasconcellos *et al.* (1995)[31]	247	1,9:1		59	7.3	4.1	0	0.4	29.2
Sigurdsson *et al.* (1996)[32]	102	2.6:1	61	53	5	13	2	1	26
Pal and Haroon (1998)[42]	90	2.8:1	41.6	74	5.5	5.5	0	0	14.6
Leenutaphong *et al.* (1999)[12]	49	2:1	51.7	26.5	38.7	0	2.04	0	32.65
Morar *et al.* (1999)[57]	138	1.9:1	34.7	64.7	22.5	2.2	0	0	10
El Euch *et al.* (2003)[33]	94	1.54:1	39	66	13	11.5	0	1	8.5
Akhyani *et al.* (2005)[34]	97	1.85:1	46.2	57.9	21.6	10.3	0	0	7.2
Rym *et al.* (2005)[35]	80	2.2:1	53.78	67.5	11.25	8.75	0	5	7.5
Kondo *et al.* (2006)[72]	58	1.76	56.89	56.89	18.97	0	0	0	24.14
Fernandes et al. (2008)[15]	170	1.2:1	53.5	58.23	21.77	10.58	0	0.4	9.4
Khaled et al. (2009)[14]	82	1:1	55.13	43.9	21.9	4.87	0	0	25.6
Yuan et al. (2010)[36]	82	4.7:1	53.4	72	17	3.7	1.2	0	6.1
Li et al. (2012)[28]	260	3:1	52.57	67.31	12.69	1.15	0.77	3.85	14.23
César et al. (2016)[17]	103	1.5:1	54.4	65.0	18.4	11.6	0	1	3.9
Present study	309	2.2:1	57	46.2	12.3	17.8	1.3	6.8	16.8

ERYTHRODERMIC DERMATOSES

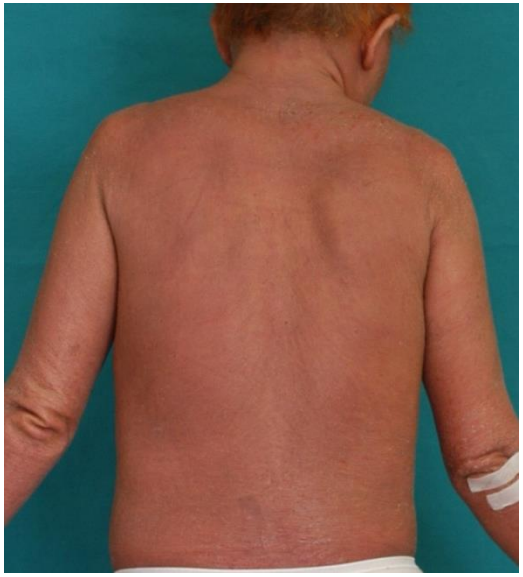
- Drug eruptions
- Contact dermatitis
- Fhyto-photo- dermatitis
- Lichen planus
- Pemphigus foliaceous
- Pityriasis rubra pilaris
- Pityriasis rubra pilaris
- Mastocytosis
- Seborrhoeic eczema
- Paraneoplastic
- Idiopathic erythroderma (red-man syndrome)



Psoriasis



DRESS



Atopic dermatitis

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Webinars
Cutaneous Lymphoma
EuroBloodNet Topic on Focus

CLINICAL AND LABORATORY INVESTIGATIONS

BJD
British Journal of Dermatology

Histopathological and immunophenotypical criteria for the diagnosis of Sézary syndrome in differentiation from other erythrodermic skin diseases: a European Organisation for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Task Force Study of 97 cases

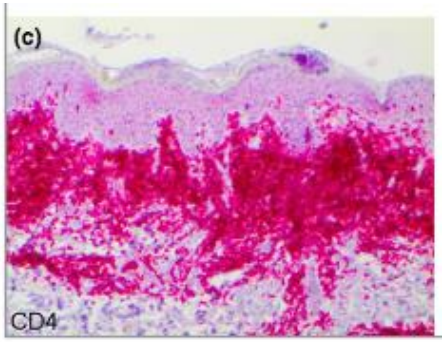
C.D. Klemke,[1] N. Booken,[1] C. Weiss,[2] J.P. Nicolay,[1] S. Goerdt,[1] M. Felcht,[1] C. Géraud,[1] W. Kempf,[3] C. Assaf,[4] N. Ortonne,[5] M. Battistella,[6] M. Bagot,[7] R. Knobler,[8] P. Quaglino,[9] B. Arheiliger,[10] M. Santucci,[11] P. Jansen,[12] M.H. Vermeer[12] and R. Willemze[12]

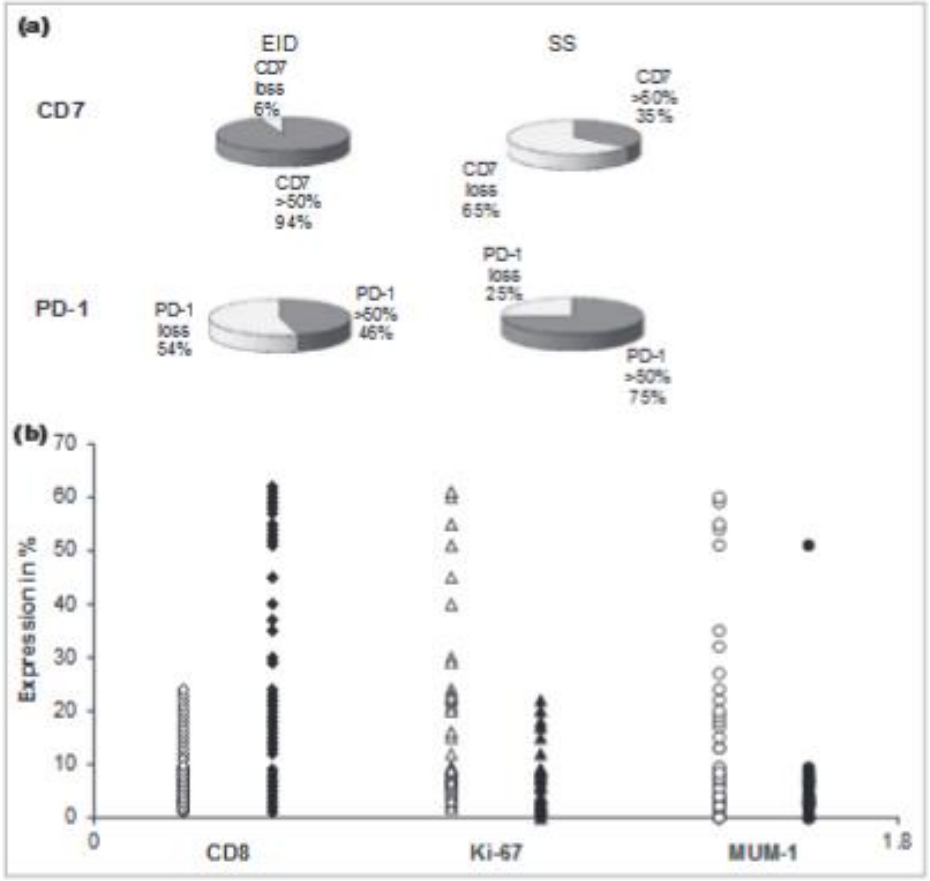
What does this study add?

- Histology of SS skin biopsies revealed a significantly increased degree of epidermotropism and more intraepidermal atypical lymphocytes compared with EID, and Pautrier microabscesses were seen only in SS samples.
- The lymphocytic infiltrate in SS skin samples was found significantly to express PD-1, MUM-1 and Ki-67, and showed less infiltration of $CD8^+$ lymphocytes.

SEZARY

PSORIASIS





European Reference Network
for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

EuroBloodNet Topic on Focus

ORIGINAL ARTICLE

See related commentary on pg 1313

Evaluation of Immunophenotypic and Molecular Biomarkers for Sézary Syndrome Using Standard Operating Procedures: A Multicenter Study of 59 Patients

Stephanie E. Boonk[1,10], Willem H. Zoutman[1,10], Anne Marie-Cardine[2,3], Leslie van der Fits[1], Jacoba J. Out-Luiting[1], Tracey J. Mitchell[4], Isabella Tosi[4], Stephen L. Morris[5], Blaithin Moriarty[4], Nina Booken[6], Moritz Felcht[6], Pietro Quaglino[7], Renata Ponti[7], Emanuela Barberio[7], Caroline Ram-Wolff[2,3,8], Kirsi Jäntti[9], Annamari Ranki[9], Maria Grazia Bernengo[7], Claus-Detlev Klemke[6], Armand Bensussan[2,3], Laurence Michel[2,3], Sean Whittaker[4], Martine Bagot[2,3,8], Cornelis P. Tensen[1], Rein Willemze[1] and Maarten H. Vermeer[1]

Differentiation between Sézary syndrome and erythrodermic inflammatory dermatoses can be challenging, and a number of studies have attempted to identify characteristic immunophenotypic changes and molecular biomarkers in Sézary cells that could be useful as additional diagnostic criteria. In this European

Table 3. Results of aberrant gene expression in all tested genes in 55 SS patients relative to 19 EID patients and 4 healthy control subjects[1]

Gene (Up-Regulation or Down-Regulation)	SS, n/total (n = 55)	Sensitivity, %
PLS3	36/55	66
DNM3	41/55	75
CDO1	20/55	36
TRAIL	4/55	7
CD1D	6/55	11
GATA3	2/55	4
MYC	0/55	0
JUNB	9/55	16
TWIST1	38/55	69
EPHA4	36/55	66
STAT4	50/55	91

Abbreviations: EID, erythrodermic inflammatory dermatoses; SS, Sézary syndrome.

[1]With the receiver operating characteristic curve analysis, a threshold was established at a specificity of 100% and an accuracy above 0.80. *PLS3*, *DNM3*, *TWIST1*, *EPHA4*, and *STAT4* were found to be useful diagnostic markers in SS.

Table 2. Overview of the tested flow cytometry markers in 59 SS and 19 EID patients at inclusion of the study

Markers for SS Described in the Literature	SS Patients, n/total (n = 59)	EID Patients, n/total (n = 19)	Sensitivity, %	Specificity, %
CD4/CD8 ratio ≥10	46/53	1/12	87	92
$CD4^+CD7^-$ ≥ 40%	32/59[1]	0/19	54	100
$CD4^+CD26^-$ ≥ 30%	51/59[2]	10/19	86	47
CD158a[3]	2/58	0/19	3	100
CD158b[3]	13/59	1/19	22	95
CD158k[3]	19/58	1/19	33	95

Accepted: 28 May 2018

DOI: 10.1111/exd.13701

REVIEW

WILEY Experimental Dermatology

Molecular pathogenesis of cutaneous lymphomas

Rudolf Stadler | René Stranzenbach

TABLE 2 Molecular changes in CTCL

First author	Genes
Almeida et al[37]	TP53, RB1, PTEN, DNMT3a, CDKN1B, TET2, CREBBP, KMT2D, KMT2C, BRD9, SMARCA4, CHD3, MAPK1, BRAF, CARD11, PRKG1
Choi et al[36]	TP53, ZEB1, ARID1A, DNMT3A, NFKB2, CD28, RHOA, PLCG1, STAT5B, BRAF, ATM, CTCF, TNFAIP3, PRKCQ, IRF4
Kiel et al[40]	PLCG1, JAK1, JAK3, STAT3, STAT5B, ARID1A
McGirt et al[41]	JAK3, TP53
Prasad et al[42]	ITPR1, ITPR2, DSC1, RIPK2, IL6, RAG2
Ungewickell et al[43]	TNFRSF1B, TNFR2
Vaque et al[44]	PLCG1
Wang et al[30]	TP53, CARD11, CCR4, PLCG1, CDKN2A, ARID1A, RP56KA1, ZEB1
Woollard et al[45]	POT1, TP53, DNMT3A, BRCA2, PRKCQ, ATM

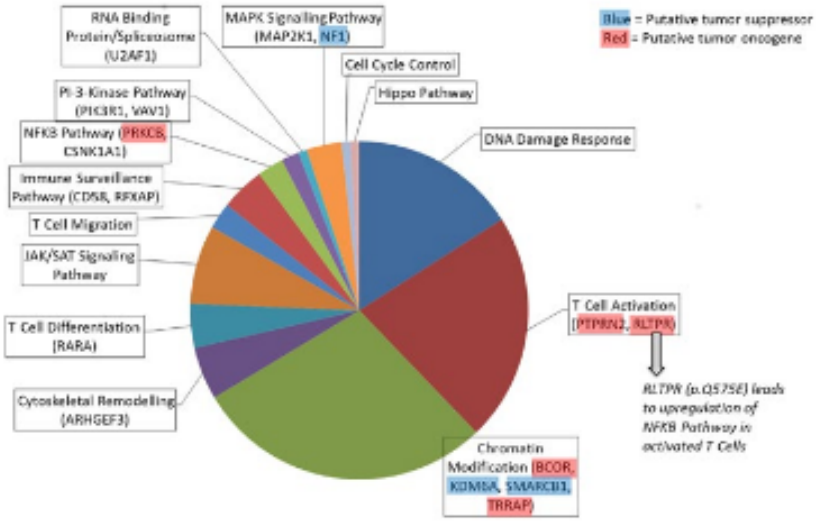


FIGURE 1 Affected pathways with driver genes in CTCL and 17 newly identified mutated genes by genomic analysis of 220 patients.[39] The size of each pie represents the number of mutations found in the corresponding pathway. Park et al further showed that RLTPR (p.Q575E) increases binding of RLTPR to downstream components of the NFkB signalling pathway and selectively upregulates the NFkB pathway in activated T cells

SS: The DIAGNOSTIC route

- **Clinical:** erythroderma. History of previous dermatoses, drug intake (antibiotics, NSADs, allopurinol), modality of presentation and timing

- **Pathology:** epidermotropic CD4+ infiltrate, usually CD7 negative. Loss of T cell markers in few cases

…IN AN APPROPRIATE CLINICO-PATHOLOGIC CONTEXT..

- **Molecular biology**: demonstration of clonal TCR beta and/or gamma rearrangement (Multiple sample approach)

TCRγ-Chain Gene Rearrangement by PCR-Based GeneScan: Diagnostic Accuracy Improvement and Clonal Heterogeneity Analysis in Multiple Cutaneous T-Cell Lymphoma Samples

J INVEST DERMATOL 2008

TCRγ-Chain Gene Rearrangement by GeneScan: Incidence and Significance of Clonal Heterogeneity in Sézary Syndrome

Maria T. Fierro[1], Renata Ponti[1], Stefano Titli[1], Lisa Bonello[2], Alessandra Comessatti[1], Mauro Novelli[1], Paolo Fava[1], Paola Francia di Celle[2], Pietro Quaglino[1] and Maria Grazia Bernengo[1]

J INVEST DERMATOL 2010

Learning objectives

SEZARY SYNDROME

- DISEASE DEFINITION AND EPIDEMIOLOGY/DEMOGRAPHICS
- CLINICAL ASPECTS
- HISTOLOGY & IMMUNOPHENOTYPE
- DIFFERENTIAL DIAGNOSIS
- STAGING & FOLLOW-UP

STAGING AND FOLLOW-UP

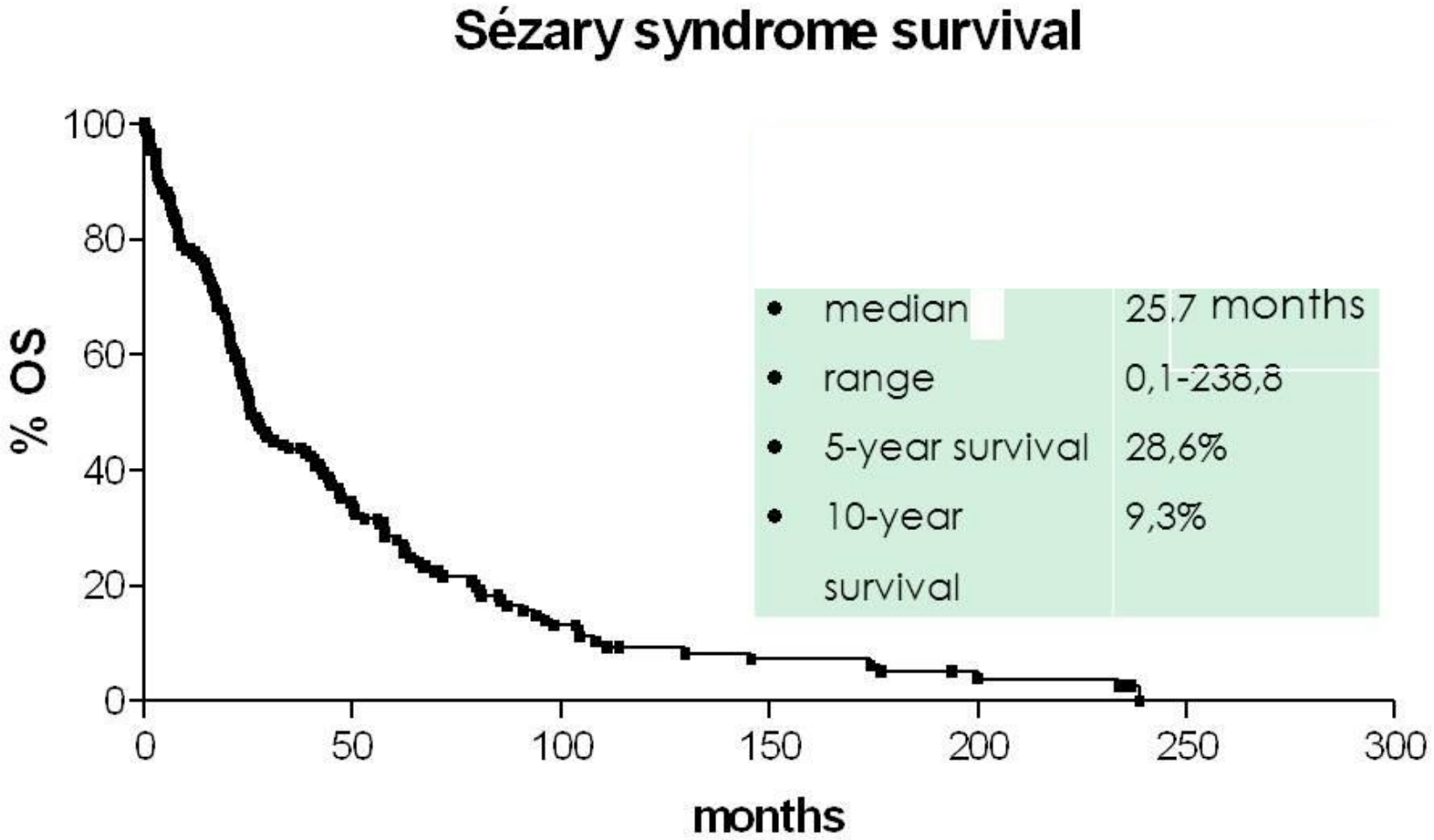
- SKIN BIOPSY to be repeated (infiltrated lesions, tumours, check for CD30 expr)
- NODE BIOPSY (try to perform)
- CT SCAN/PET (very low percentage of patients with visceral involvement demonstrated “in vivo”)
- Bone marrow biopsy = usually negative (perform in selected cases)
- FLOW-CYTOMETRY= VERY INFORMATIVE
- STAGE TNMB : T4 B2 per definition = IVA1 – IVA2 = not so useful
- DONOR if the patient is young and high B score

Learning objectives

SEZARY SYNDROME

- DISEASE DEFINITION AND EPIDEMIOLOGY/DEMOGRAPHICS
- CLINICAL ASPECTS
- HISTOLOGY & IMMUNOPHENOTYPE
- DIFFERENTIAL DIAGNOSIS
- STAGING & FOLLOW-UP
- SURVIVAL & PROGNOSIS

SURVIVAL



EORTC 2018 ST GALLEN, EUR J CANCER 2018 abstract

VOLUME 28 · NUMBER 31 · NOVEMBER 1 2010

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Survival Outcomes and Prognostic Factors in Mycosis Fungoides/Sézary Syndrome: Validation of the Revised International Society for Cutaneous Lymphomas/ European Organisation for Research and Treatment of Cancer Staging Proposal

Nita Sally Agar, Emma Wedgeworth, Siobhan Crichton, Tracey J. Mitchell, Michael Cox, Silvia Ferreira, Alistair Robson, Eduardo Calonje, Catherine M. Stefanato, Elizabeth Mary Wain, Bridget Wilkins, Paul A. Fields, Alan Dean, Katherine Webb, Julia Scarisbrick, Stephen Morris, and Sean J. Whittaker

Table 1. Summary of Demographic and Clinical Staging Characteristics According to ISCL/EORTC Classification (continued)

Characteristic	No.	%	Median Survival (years)	OS (%)			DSS (%)			RDP (%)		
				5 Years	10 Years	20 Years	5 Years	10 Years	20 Years	5 Years	10 Years	20 Years
Clinical stage												
IA	438	29.2	35.5	94	88	73	98	95	90	8	12	18
IB	583	38.8	21.5	84	70	52	89	77	67	21	38	47
IIA	40	2.7	15.8	78	52	47	89	67	60	17	33	41
IIB	167	11.1	4.7	47	34	21	56	42	29	48	58	71
IIIA	100	6.7	4.7	47	37	25	54	45	31	53	62	74
IIIB	56	3.7	3.4	40	25	NR	48	45	NR	82	73	NR
IVA1	67	4.5	3.8	37	18	15	41	20	17	62	83	86
IVA2	37	2.5	2.1	18	15	3	23	20	6	77	80	94
IVB	14	0.9	1.4	18	NR	NR	18	NR	NR	82	NR	NR

Abbreviations: ISCL, International Society for Cutaneous Lymphomas; EORTC, European Organisation for Research and Treatment of Cancer; OS, overall survival; DSS, disease-specific survival; RDP, risk of disease progression; NR, not reached; MF, mycosis fungoides; SS, Sézary syndrome; LyP, lymphomatoid papulosis; LDH, lactate dehydrogenase.

*LDH results based on subset of 435 patients.

†Stage T3 and T4(T3) only.

‡B0 represents those patients without *TCR* data.

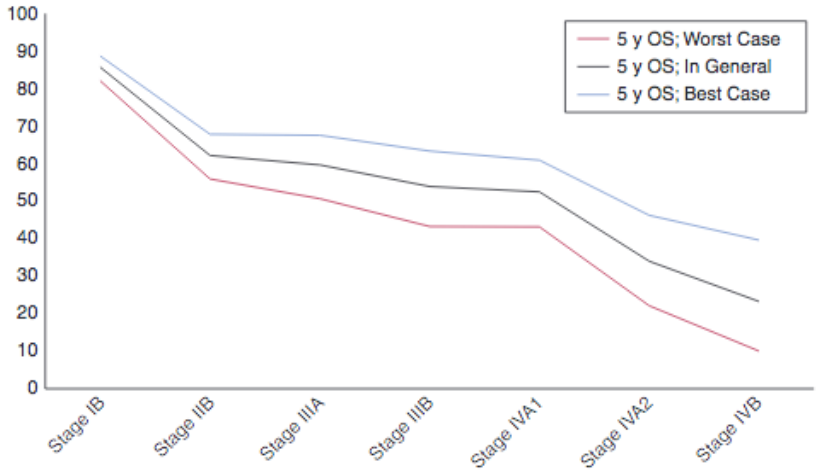
§B1 represents combined data on B1 + B1a + B1b in view of small numbers.

Overall Survival in Mycosis Fungoides: A Systematic Review and Meta-Analysis

Journal of Investigative Dermatology (2019) ■, ■–■; doi:10.1016/j.jid.2019.07.712

TO THE EDITOR

Mycosis fungoides (MF) is the most common cutaneous T-cell lymphoma that confers significant mortality in advanced-stage disease (Suzuki et al., 2010; Vollmer, 2014). Although stage-specific survival data are available from different cohorts, there have been no attempts to combine existing overall survival (OS) data in this disease (Suzuki et al., 2010). Moreover, the hitherto published OS data are presented as Kaplan-Meier curves and mortality risks, which are of limited utility for the patients who prefer to have an estimate of their chances of survival (Kiely et al., 2011). The patients prefer prognostic information in terms of survival, not mortality, for example, "the chance to live 5 years" or "the longest (best-case) survival" (Hagerty et al., 2004; Kiely et al., 2011).



	Stage IB	Stage IIB	Stage IIIA	Stage IIIB	Stage IVA1	Stage IVA2	Stage IVB
5 y OS, In General (%)	85.8	62.2	59.7	54.0	52.5	34.0	23.3
5 y OS, Best Case	88.8	67.9	67.6	63.4	61.0	46.3	39.7
5 y OS; Worst Case	82.1	56.0	50.7	43.3	43.2	22.1	10.0

Figure 1. Pooled 5-year OS in different stages of MF. The fraction of survivors was estimated from the pooled HRs for each stage. HR, hazard ratio; MF, mycosis fungoides; OS, overall survival.

PROGNOSTIC FACTORS IN SS: WORSE SURVIVAL

- **Advanced age** (Agar et al., 2010;Diamandidou et al., 1999; Foulcet al., 2003; Kim et al., 2003; Kubicaet al., 2012; Talpur et al., 2012)
- **Short duration of skin lesions before diagnosis of SS** (Foulc et al., 2003)
- **Previous history of mycosis fungoides** (Bernengo et al., 1998; Kubica et al., 2012)
- **Elevated serum lactate dehydrogenase levels** (Agar et al., 2010; Bernengo et al., 1998; Diamandidou et al.,1999; Foulc et al., 2003; Kubica et al.,2012; Talpur et al., 2012)
- **Degree of nodal involvement** (Diamandidou et al., 1999; Kim et al., 2003)
- **Factors reflecting blood tumor burden such as increased leukocyte counts** (Bernengo et al., 1998; Talpur et al.,2012; Vidulich et al., 2009) **or high Sézary cell counts** (Bernengo et al., 1998).

VOLUME 33 · NUMBER 32 · NOVEMBER 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sézary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model

Julia J. Scarisbrick, H. Miles Prince, Maarten H. Vermeer, Pietro Quaglino, Steven Horwitz, Pierluigi Porcu, Rudolf Stadler, Gary S. Wood, Marie Beylot-Barry, Anne Pham-Ledard, Francine Foss, Michael Girardi, Martine Bagot, Laurence Michel, Maxime Battistella, Joan Guitart, Timothy M. Kuzel, Maria Estela Martinez-Escala, Teresa Estrach, Evangelia Papadavid, Christina Antoniou, Dimitris Rigopoulos, Vassiliki Nikolaou, Makoto Sugaya, Tomomitsu Miyagaki, Robert Gniadecki, José Antonio Sanches, Jade Cury-Martins, Denis Miyashiro, Octavio Servitje, Cristina Muniesa, Emilio Berti, Francesco Onida, Laura Corti, Emilia Hodak, Iris Amitay-Laish, Pablo L. Ortiz-Romero, Jose L. Rodriguez-Peralto, Robert Knobler, Stefanie Porkert, Wolfgang Bauer, Nicola Pimpinelli, Vieri Grandi, Richard Cowan, Alain Rook, Ellen Kim, Alessandro Pileri, Annalisa Patrizi, Ramon M. Pujol, Henry Wong, Kelly Tyler, Rene Serranzenbach, Christiane Querfeld, Paolo Fava, Milena Maule, Rein Willemze, Felicity Evison, Stephen Morris, Robert Twigger, Rakhshandra Talpur, Jinah Kim, Grant Ogunbiyi, Shufeng Li, Mahkam Tavallaee, Richard T. Hoppe, Madeleine Duvic, Sean J. Whittaker, and Youn H. Kim

Listen to the podcast by Dr Pinter-Brown at www.jco.org/podcasts

Table 1. Participating International Centers

Center No.	Principal Investigator	Address	No. of Patients
E 001	Julia Scarisbrick	University Hospital Birmingham, Birmingham, United Kingdom	35
E 002	Pietro Quaglino	University of Turin, Turin, Italy	50
E 004	Sean Whittaker	St Thomas' Hospital, London, United Kingdom	215
E 005	Maarten Vermeer	Leiden University Medical Centre, Leiden, the Netherlands	55
E 006	Richard Cowan	Christie Hospital, Manchester, United Kingdom	11
E 007	Evangelina Papadavid	Athens University Medical School, Athens, Greece	40
E 008	Pablo Ortiz-Romero	Hospital 12 de Octubre, Madrid, Spain	23
E 009	Martine Bagot	Hospital St Louis, Paris, France	50
E 010	Rudolf Stadler	Johannes Wesling Medical Centre, Minden, Germany	10
E 011	Robert Gniadecki	Bispebjerg Hospital, Copenhagen University, Copenhagen, Denmark	33
E 012	Robert Knobler, Stefanie Pokert	University of Vienna Medical School, Vienna, Austria	7
E 018	Nicola Pimpinelli	University of Florence, Florence, Italy	22
E 019	Octavio Servietje	Hospital Universitari de Bellvitge, Barcelona, Spain	14
E 020	Emilia Hodak	Rabin Medical, Tel Aviv, Israel	30
E 021	Alessandro Pileri	University of Bologna, Bologna, Italy	14
E 022	Marie Beylot-Barry	Centre Hospitalier Universitaire Hospital de Bordeaux, Bordeaux, France	50
E 023	Teresa Estrach	Hospital Clinico, University of Barcelona, Barcelona, Spain	13
E 024	Emilio Berti	University of Milano, Milano, Italy	29
E 025	Ramon Pujol	Hospital del Mar Barcelona, Barcelona, Spain	12
NA 001	Youn Kim	Stanford University, Stanford, CA	121
NA 003	Steven Horwitz	Memorial Sloan-Kettering Cancer Center, New York, NY	46
NA 004	Joan Guitart	Northwestern University, Chicago, IL	46
NA 005	Madeleine Duvic	The University of Texas MD Anderson Cancer Center, Houston, TX	164
NA 006	Pierlugi Porcu	Ohio State University, Columbus, OH	11
NA 010	Francine Foss	Yale University, New Haven, CT	40
NA 011	Alain Rook	University of Pennsylvania, Philadelphia, PA	16
OC 001	Miles Prince	Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia	56
AS 001	Makoto Sugaya	Faculty of Medicine, University of Tokyo, Tokyo, Japan	29
SA 001	José Antonio Sanches	University of Sao Paulo Medical School, Sao Paulo, Brazil	33

Abbreviations: AS, Asia; E, Europe; NA, North America; OC, Oceania; SA, South America.

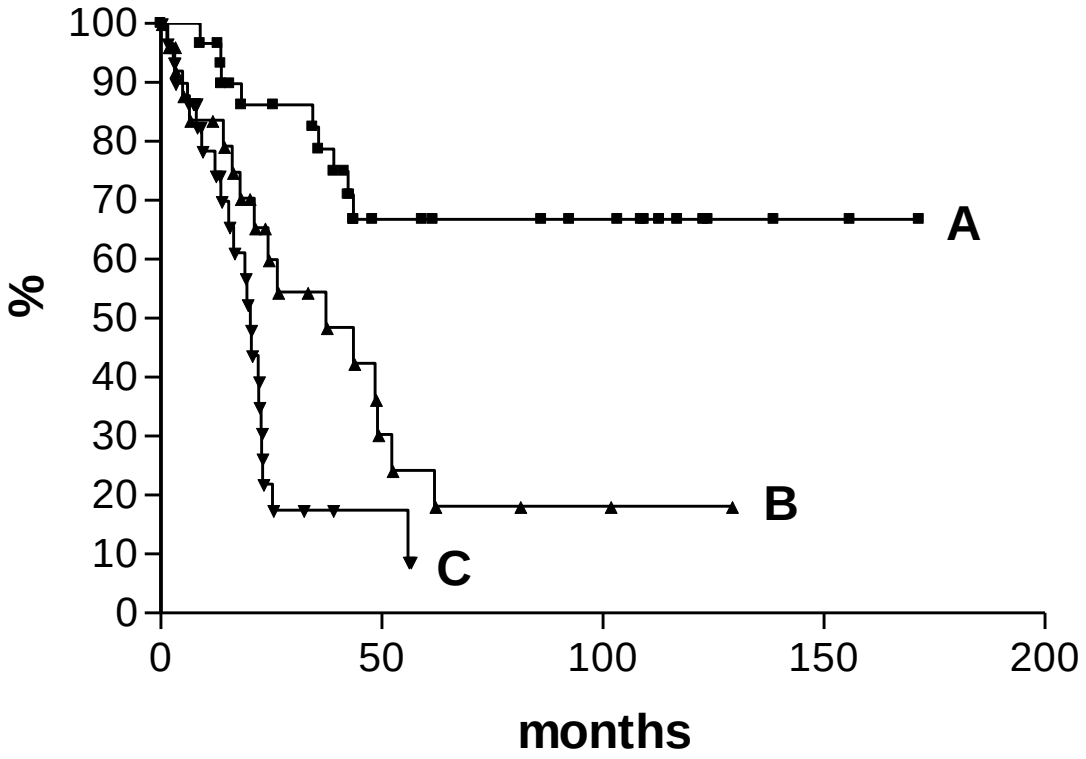
In multivariable analysis, stage IV disease (P<0.009), age greater than 60 years (P<.001), LCT in the skin (P<.001), and elevated serum LDH (P<.001) were all independent prognostic variables for worse survival.

Table 4. Prognostic Index Model Using Four Risk Factors (stage IV, age > 60 years, elevated LDH, and LCT in skin)

Risk of Poor Survival	No. of Patients	No. of Deaths	Stage (No. of patients)			1-Year Survival (months)	2-Year Survival (months)	5-Year Survival (months)	Median OS (months)	Hazard Ratio	95% CI	P
			IIB	III	IV							
Low (0-1 risk factor)	327	100	166	134	27	94.0	86.6	67.8	NR	1		
Intermediate (2 risk factors)	329	123	91	82	156	83.9	71.9	43.5	46.4	2.09	1.56 to 2.80	< .001
High (3-4 risk factors)	201	100	20	4	177	84.7	62.2	27.6	34.2	2.91	2.15 to 3.96	< .001

Abbreviations: LCT, large-cell transformation; LDH, lactate dehydrogenase; NR, not reached; OS, overall survival.

Sézary sd: Survival based on the tumour burden in the blood



A <1000
B >=1000 and >3000
C >=3000

A vs B p = 0.0024
A vs C p = 0.0001
B vs C p = 0.0449

B-SCORE

European Reference Network
for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

AJCP / Original Article

Blood Flow Cytometry in Sézary Syndrome

New Insights on Prognostic Relevance and Immunophenotypic Changes During Follow-up

Mauro Novelli, MSc,[1] Paolo Fava, MD,[1] Cristina Sarda, MD,[1] Renata Ponti, MSc,[1] Simona Osella-Abate, MSc,[1] Paola Savoia, MD,[1] Massimiliano Bergallo, MSc,[2] Francesco Lisa, MSc,[1] Maria Teresa Fierro, MD,[1] and Pietro Quaglino, MD[1]

From the [1]Dermatologic Clinic, Department of Medical Sciences, and [2]Department of Public Health and Pediatrics, University of Torino, Torino, Italy.

Key Words: Sézary syndrome; CTCL; CD26; Flow cytometry; Hypermethylation; Immunophenotypic changes

Am J Clin Pathol January 2015;143:57-69

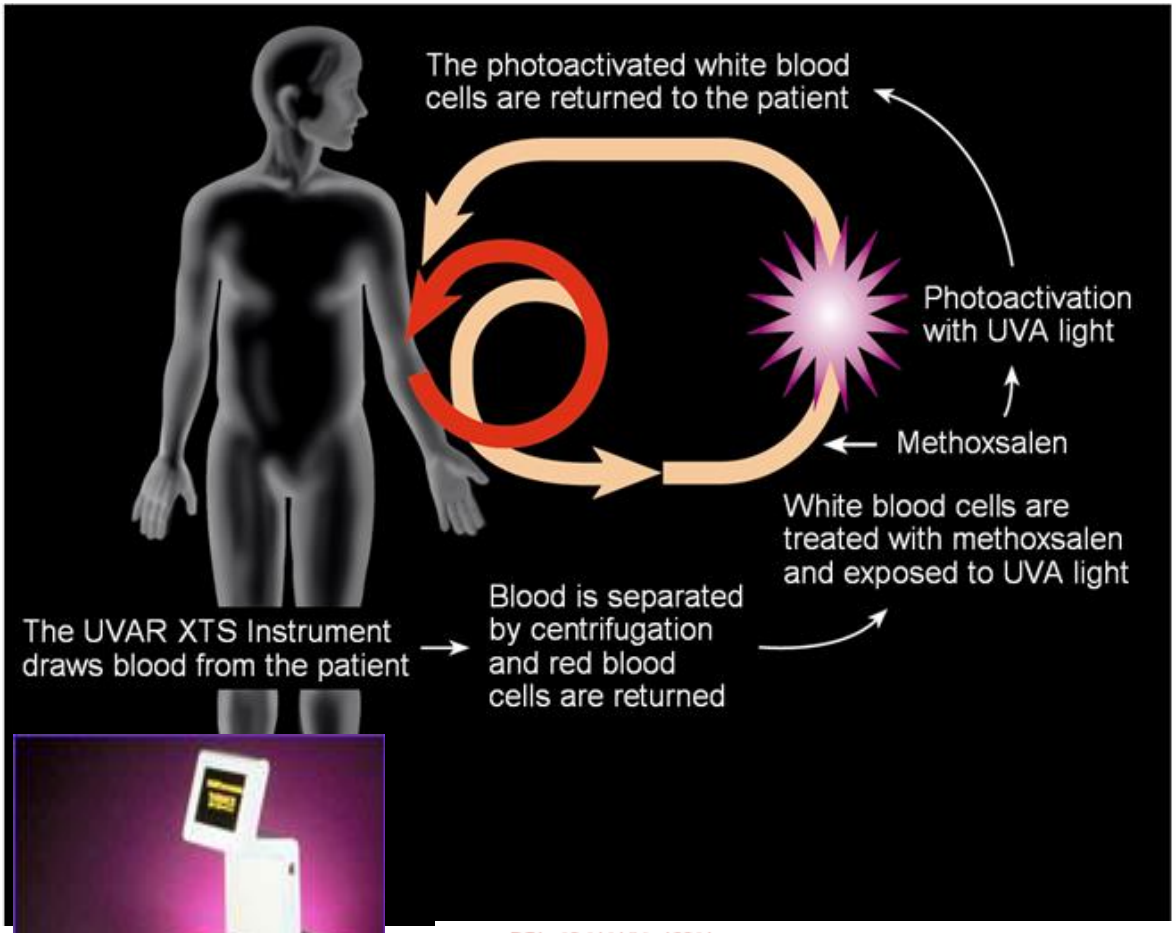
DOI: 10.1309/AJCP1NA3YCHCDEIG

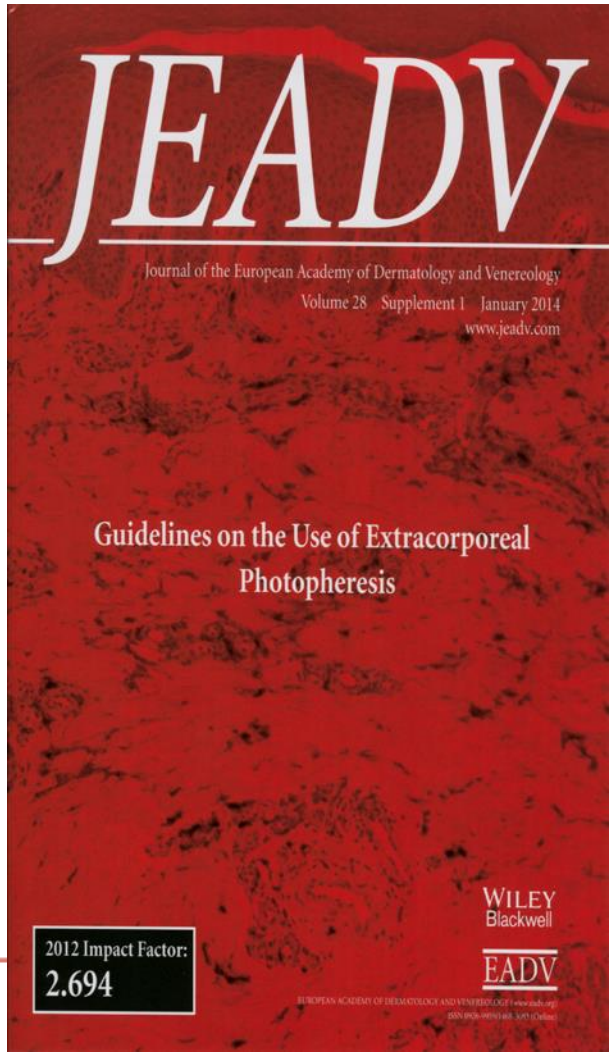
Learning objectives

SEZARY SYNDROME

- DISEASE DEFINITION AND EPIDEMIOLOGY/DEMOGRAPHICS
- CLINICAL ASPECTS
- HISTOLOGY & IMMUNOPHENOTYPE
- DIFFERENTIAL DIAGNOSIS
- STAGING & FOLLOW-UP
- SURVIVAL & PROGNOSIS
- TREATMENT

EXTRACORPOREAL PHOTO CHEMOTHERAPY





DOI: 10.1111/jdv.12311

ORIGINAL ARTICLE

Guidelines on the use of extracorporeal photopheresis

R. Knobler,[1,*] G. Berlin,[2] P. Calzavara-Pinton,[3] H. Greinix,[4] P. Jaksch,[5] L. Laroche,[6] J. Ludvigsson,[7] P. Quaglino,[8] W. Reinisch,[9] J. Scarisbrick,[10] T. Schwarz,[11] P. Wolf,[12] P. Arenberger,[13] C. Assaf,[14] M. Bagot,[15] M. Barr,[16] A. Bohbot,[17] L. Bruckner-Tuderman,[18] B. Dreno,[19] A. Enk,[20] L. French,[21] R. Gniadecki,[22] H. Gollnick,[23] M. Hertl,[24] C. Jantschitsch,[1] A. Jung,[25] U. Just,[1] C.-D. Klemke,[26] U. Lippert,[25] T. Luger,[27] E. Papadavid,[28] H. Pehamberger,[1] A. Ranki,[29] R. Stadler,[30] W. Sterry,[31] I.H. Wolf,[12] M. Worm,[32] J. Zic,[33] C.C. Zouboulis,[25] U. Hillen[34]

2014

phoma

on Focus

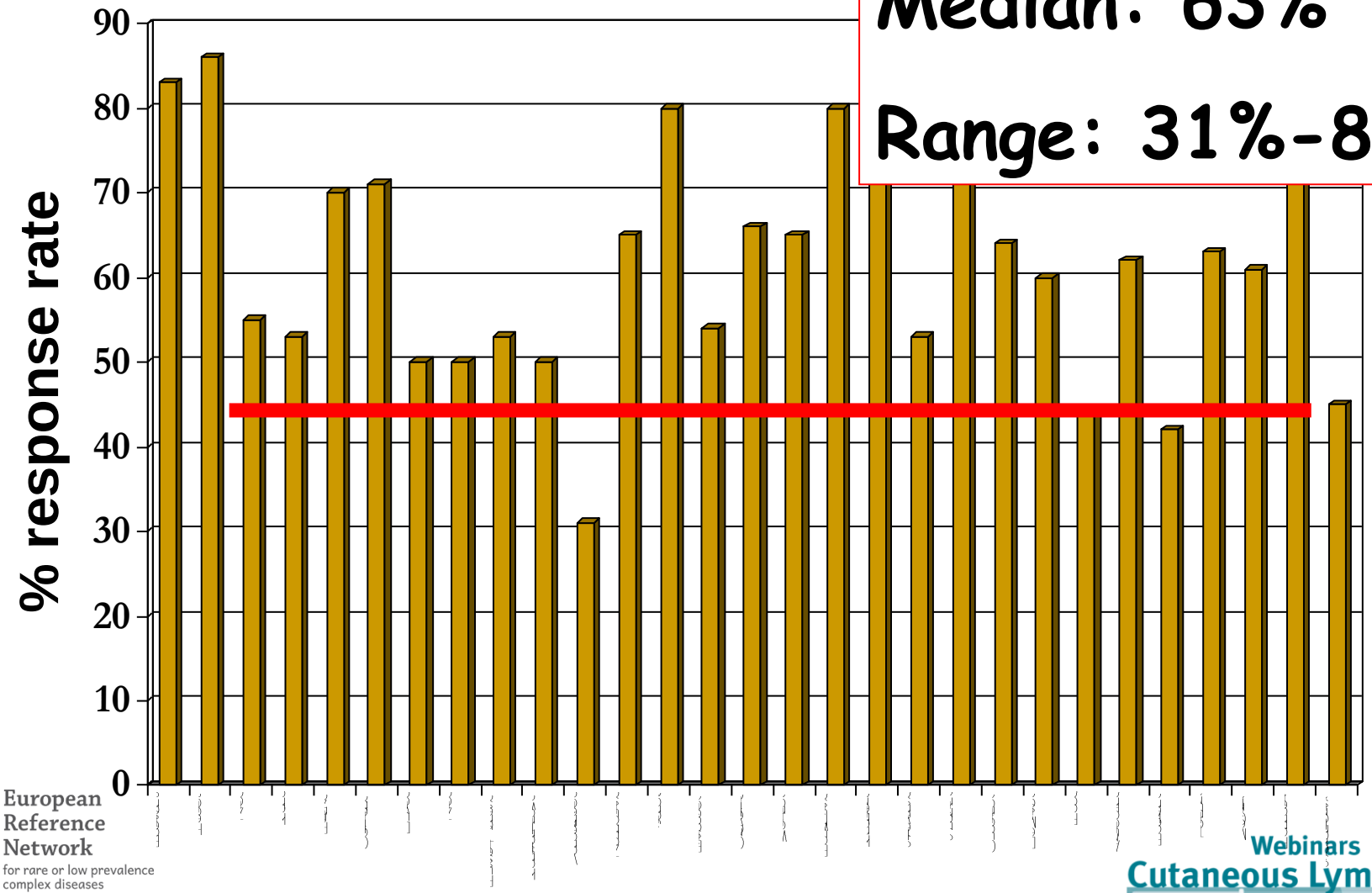
Summary of literature data

Response rate in erythrodermic CTCL

* Studies including > 10 CTCL patients

Median: 63%

Range: 31%-86%



Quaglino, Int J Dermatol 2013

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

Webinars Cutaneous Lymphoma

EuroBloodNet Topic on Focus

SS THERAPY AT A GLANCE: FIRST & SECOND LINE

European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2017.

F. Trautinger, J. Eder, C. Assaf, M. Bagot, A. Cozzio, R. Dummer, R. Gniadecki, C.D. Klemke, P.L. Ortiz-Romero, E. Papadavid, N. Pimpinelli, P Quaglino, A. Ranki, J. Scarisbrick, R. Stadler, L. Väkevä, M.H. Vermeer, S. Whittaker, R. Willemze, R. Knobler

European Journal of Cancer (2017) 77: pp57-74

EORTC
European Organisation for Research and Treatment of Cancer

	Wait & see	Topical steroids	Photo therapy	TSET	Interferon	Bexarotene	Mono-CT	MTX	PoliCT	ECP	ASCT
FIRST LINE											
SECOND LINE											

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Webinars
Cutaneous Lymphoma
EuroBloodNet Topic on Focus

ESMO
CLINICAL PRACTICE GUIDELINES
Annals of Oncology 29 (Supplement 4): iv30–iv40, 2018
doi:10.1093/annonc/mdy133
Published online 6 June 2018

Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

R. Willemze[1], E. Hodak[2], P. L. Zinzani[3], L. Specht[4] & M. Ladetto[5], on behalf of the ESMO Guidelines Committee*

[1]Department of Dermatology, Leiden University Medical Centre, Leiden, The Netherlands; [2]Department of Dermatology, Rabin Medical Centre, Beilinson Hospital, Petach Tikva, Israel; [3]Institute of Hematology and Medical Oncology, University of Bologna, Bologna, Italy; [4]Department of Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [5]Divisione di Ematologia, Azienda Ospedaliera Sant' Antonio e Biagio e Cesare Arrigo, Alessandria, Italy

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, 6900 Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Committee: December 2006, last update January 2018. This publication supersedes the previously published version—Ann Oncol 2013; 24 (Suppl. 6): vi149–vi154.

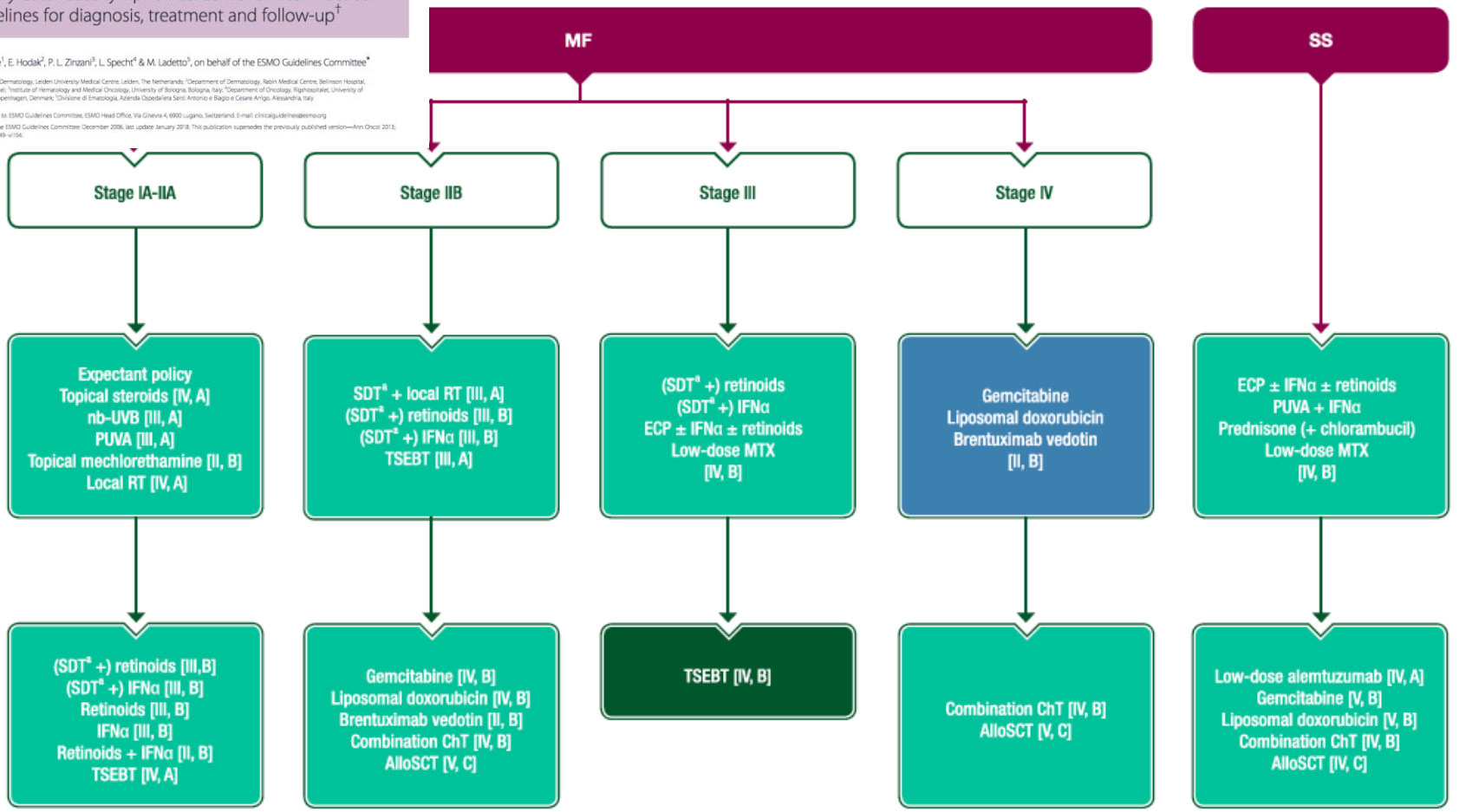


Figure 1. Recommendations for the treatment of MF/SS.
[a]Most commonly PUVA.
AlloSCT, allogeneic stem cell transplantation; ChT, chemotherapy; ECP, extracorporeal photopheresis; IFNα, interferon alpha; MF, mycosis fungoides; MTX, methotrexate; nb-UVB, narrow-band ultraviolet B; PUVA, psoralens plus ultraviolet A; RT, radiotherapy; SS, Sézary syndrome; SDT, skin-directed therapy; TSEBT, total skin electron beam therapy.

Primary Cutaneous Lymphomas, Version 2.2020

Featured Updates to the NCCN Guidelines

Neha Mehta-Shah, MD[1,*]; Steven M. Horwitz, MD[2,*]; Stephen Ansell, MD, PhD[3]; Weiyun Z. Ai, MD, PhD[4]; Jeffrey Barnes, MD, PhD[5]; Stefan K. Barta, MD, MRCP, MS[6]; Mark W. Clemens, MD[7]; Ahmet Dogan, MD, PhD[2]; Kristopher Fisher, MD[8,*]; Aaron M. Goodman, MD[9,*]; Gaurav Goyal, MD[10,*]; Joan Guitart, MD[11,*]; Ahmad Halwani, MD[12]; Bradley M. Haverkos, MD, MPH, MS[13,*]; Richard T. Hoppe, MD[14,*]; Eric Jacobsen, MD[15]; Deepa Jagadeesh, MD, MP[16,*]; Matthew A. Lunning, DO[17]; Amitkumar Mehta, MD[10]; Elise A. Olsen, MD[18,*]; Barbara Pro, MD[11]; Saurabh A. Rajguru, MD[19]; Satish Shanbhag, MBBS, MPH[20]; Aaron Shaver, MD, PhD[21]; Andrei Shustov, MD[22,*]; Lubomir Sokol, MD, PhD[23]; Pallawi Torka, MD[24]; Carlos Torres-Cabala, MD[7]; Ryan Wilcox, MD, PhD[25]; Basem M. William, MD[26,*]; Jasmine Zain, MD[27]; Mary A. Dwyer, MS, CGC[28,*]; Hema Sundar, PhD[28,*]; and Youn H. Kim, MD[14,*]

SUGGESTED TREATMENT REGIMENS[a,b]

SYSTEMIC THERAPIES		
	Preferred Regimens (alphabetical order)	**Other Recommended Regimens**
SYST-CAT A	• Brentuximab vedotin[i,j,k] • Bexarotene[h] • Extracorporeal photopheresis (ECP)[l] • Interferons (IFN-alfa-2b[m] or IFN-gamma 1b) • Methotrexate (≤50 mg q week) • Mogamulizumab[n] • Romidepsin[h] • Vorinostat[h]	• Acitretin[h] • All-trans retinoic acid[h] • Isotretinoin [13-cis-retinoic acid][h]
SYST-CAT B	• Brentuximab vedotin[i,j,k] • Gemcitabine • Liposomal doxorubicin • Pralatrexate (low-dose or standard dose)	

COMBINATION THERAPIES (alphabetical order)	
Skin-directed + systemic	• Phototherapy + ECP[l] • Phototherapy + Interferon (IFN-alfa-2b[m] or IFN-gamma 1b) • Phototherapy + retinoid • TSEBT + ECP[l]
Systemic + systemic	• ECP[l] + Interferon (IFN-alfa-2b[m] or IFN-gamma 1b) • ECP[l] + retinoid • ECP[l] + retinoid + Interferon (IFN-alfa-2b[m] or IFN-gamma 1b) • Retinoid + Interferon (IFN-alfa-2b[m] or IFN-gamma 1b)

ERYTHRODERMIC DISEASE/SÉZARY SYNDROME		
	Preferred Regimens	**Other Recommended Regimens**
Low-intermediate burden (eg, absolute Sézary cell [ASC] count <5 K/mm³)	• Combination therapies (see above) • SYST-CAT A ± skin-directed therapies (skin-generalized) (See MFSS-A 2 of 6)	• SYST-CAT B ± skin-directed therapies (skin-generalized) (See MFSS-A 2 of 6) • Alemtuzumab[k,p] • Pembrolizumab[q,r]
Higher burden (eg, ASC >5 K/mm³)	• Combination therapies (see above) • Mogamulizumab ± skin-directed therapies (skin-generalized)[h] • Romidepsin ± skin-directed therapies (skin-generalized)[h]	• SYST-CAT A (options not listed under preferred regimens) (See MFSS-A 2 of 6) • SYST-CAT B (See MFSS-A 2 of 6) • Alemtuzumab[k,p] • Pembrolizumab[q,r]

SEZARY SYNDROME
ITALIAN GROUP FOR CUTANEOUS LYMPHOMAS

LOW TUMOUR BURDEN BLOOD	HIGH TUMOUR BURDEN BLOOD	RELAPSED/ REFRACTORY
ECP	CHEMO (gemcitabine, pegylated doxorubicin)	ALLOGENEIC STEM CELL TRANSPLANTATION
Low-dose IFN		
bexarotene		
CLINICAL TRIAL	CLINICAL TRIAL	CLINICAL TRIAL

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Original Article

Time Course, Clinical Pathways, and Long-Term Hazards Risk Trends of Disease Progression in Patients With Classic Mycosis Fungoides

A Multicenter, Retrospective Follow-Up Study From the Italian Group of Cutaneous Lymphomas

Pietro Quaglino, MD[1]; Nicola Pimpinelli, MD[2]; Emilio Berti, MD[3]; Piergiacomo Calzavara-Pinton, MD[4]; Giuseppe Alfonso Lombardo, MD[5]; Serena Rupoli, MD[6]; Mauro Alaibac, MD[7]; Ugo Bottoni, MD[8,9]; Angelo Carbone, MD[10]; Paolo Fava, MD[1]; Michele Fimiani, MD[11]; Angela Maria Mamusa, MD[12]; Stefano Titli, MD[1]; Pier Luigi Zinzani, MD[13]; Maria Grazia Bernengo, MD[1]; and On behalf of the Gruppo Italiano Linfomi Cutanei (GILC)

BACKGROUND: Mycosis fungoides (MF) is an indolent primary cutaneous T-cell lymphoma. To the authors' knowledge, no data currently are available regarding the evolution over time of the risk of developing specific pathways of disease progression. **METHODS:** This retrospective study analyzed 1422 patients with MF who were diagnosed and followed from 1975 through 2010 in 27 Italian Study Group for Cutaneous Lymphoma centers. The primary objectives were to ascertain the time course, pathways, and hazards risk trends of cutaneous/extracutaneous disease progression; to evaluate whether different tumor-lymph node-metastasis-blood (TNMB) stages have different pathways of disease progression; and to analyze differences between tumor-stage and erythrodermic MF with regard to clinical onset, disease evolution, and prognosis. The secondary objective was to provide a further validation for the revised International Society for Cutaneous Lymphomas and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (ISCL/EORTC) classification. **RESULTS:** The median follow-up was 14.5 years; stage progression occurred in 29.7% of patients and blood involvement was the most frequent extracutaneous site of disease progression. Patients with stage IA to stage IB disease demonstrated a steady low annual incidence of disease progression to tumor-stage (1%-2%); patients with stage IIA disease had a higher risk within the first years (up to 9.4%). Erythroderma evolved with a significantly higher frequency from patches/plaques (13.9%-28.2%) than tumors ($P = .028$ and $P = .013$, respectively). Hazards rates of extracutaneous involvement were low (< 1%). T classification was found to be associated with extracutaneous involvement site, tumor-stage disease with lymph node/

AQ7

	Stage I	Stage II	Stage III	Stage IV
	13.8%	-	-	-
Topical steroids	16.7%	3.3%	9.3%	-
Phototherapy alone	43.2%	24.2%	9.2%	2.6%
Phototherapy + IFN	9.7%	3.3%	2.1%	-
Phototherapy + retinoids	0.9%	3.3%	2.8%	3.1%
Acitretin	2.5%	2.6%	-	-
Bexarotene	0.2%	4.4%	9.2%	4.2%
IFN	8.9%	12.1%	23.4%	10%
Local RT	2.3%	16.5%	2.1%	6.7%
TSET	0.1%	1.8%	-	3.3%
Monochemotherapy[a]	1.7%	15.7%	22%	30%
ECP	-	7.7%	13.3%	16.7%
Polichemotherapy[b]	-	5.1%	6.4%	23.3%

ECP: extracorporeal photochemotherapy; IFN: interferon; RT: radiotherapy; TSET: Total Skin Electron beam Therapy

[a]: includes methotrexate, fludarabine, gemcitabine, liposomal pegylated doxorubicin

[b] : CHOP or CHOP-like regimens were performed in the majority of patients

(n=1422)

Quaglino P, et al., Cancer 2012

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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ORIGINAL ARTICLE

Global patterns of care in advanced stage mycosis fungoides/Sezary syndrome: a multicenter retrospective follow-up study from the Cutaneous Lymphoma International Consortium

P. Quaglino[1*†], M. Maule[2†], H. M. Prince[3,4], P. Porcu[5], S. Horwitz[6], M. Duvic[7], R. Talpur[7], M. Vermeer[8], M. Bagot[9], J. Guitart[10], E. Papadavid[11], J. A. Sanches[12], E. Hodak[13,14], M. Sugaya[15], E. Berti[16], P. Ortiz-Romero[17], N. Pimpinelli[18], O. Servitje[19], A. Pileri[20], P. L. Zinzani[21], T. Estrach[22], R. Knobler[23], R. Stadler[24], M. T. Fierro[1], S. Alberti Violetti[16], I. Amitay-Laish[13,14], C. Antoniou[11], C. Astrua[1], S. Chaganti[25], F. Child[26], A. Combalia[22], S. Fabbro[5], P. Fava[1], V. Grandi[18], C. Jonak[23], E. Martinez-Escala[10], M. Kheterpal[6], E. J. Kim[27], C. McCormack[3,4], T. Miyagaki[15], D. Miyashiro[12], S. Morris[26], C. Muniesa[19], V. Nikolaou[11], G. Ognibene[28], F. Onida[16], S. Osella-Abate[1], S. Porkert[23], C. Postigo-Llorente[17], C. Ram-Wolff[9], S. Ribero[1], K. Rogers[28], M. Sanlorenzo[1], R. Stranzenbach[24], N. Spaccarelli[27], A. Stevens[25], D. Zugna[2], A. H. Rook[27], L. J. Geskin[28], R. Willemze[8], S. Whittaker[26], R. Hoppe[29], J. Scarisbrick[25†] & Y. Kim[29†]

Therapy	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
ECP (alone or in combination)	36.6	29.7	9.9	3.8	11.5	2.5	4.3	11.1	9.1	
Interferon	9.8	9.0	9.9	7.6	3.3	5.0		5.6		
Chlorambucil	8.5	5.8	4.5	5.1	1.6					
Phototherapy (alone or in combination)	7.6	3.2	1.8	2.5	1.6					
Methotrexate	7.1	3.9	9.9	6.3	3.3	10.0	13.0	11.1	9.1	20.0

IVA1

Polychemotherapy	14.9	21.4	15.4	17.2	22.2		14.3		33.3	33.3
ECP (alone or in combination)	12.2	8.9	12.8	13.8	11.1	20.0				
Bexarotene	10.8	12.5	15.4	6.9	16.7	40.0	14.3			
Interferon	10.8	8.9	5.1	3.4	11.1					
Methotrexate	8.1	5.4	2.6	3.4				16.7		

IVA2-IVB

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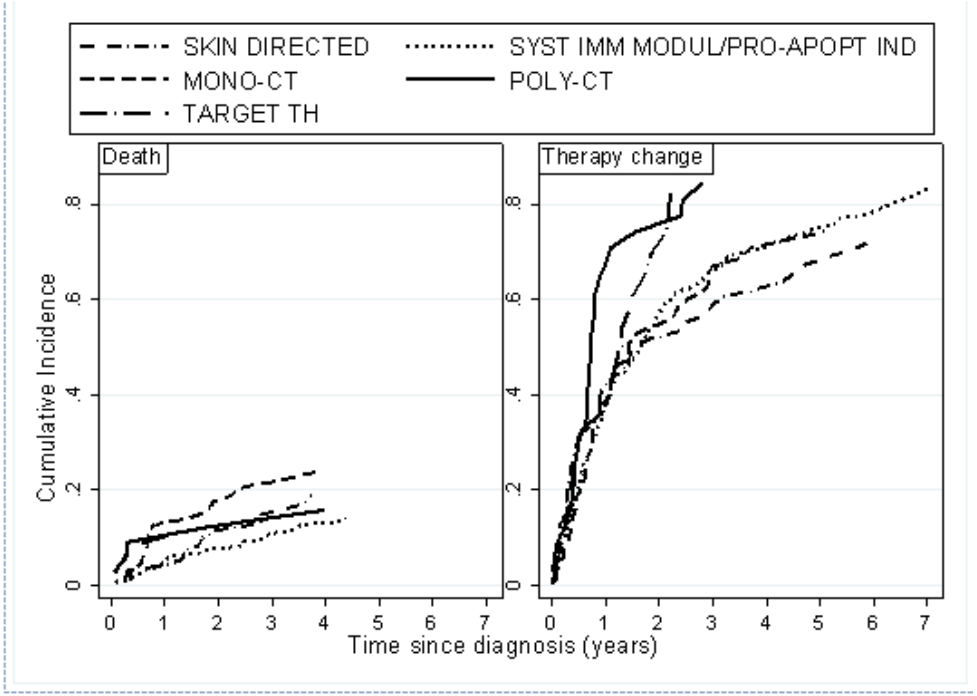
Cumulative incidence curves for death and change of therapy considered as competing risk events by first treatment line



Fine and Gray's test
p=0.1492

p=0.118

first-line treatment was selected as independent prognostic variable (p=0.008), both mono- and poly-chemotherapy being associated with higher mortality.

Table V. Principles of therapy for Sézary syndrome

- Use disease burden and rapidity of progression as determinants of approach to therapy
- Preserve immune response whenever possible
- Use immunomodulatory therapy before chemotherapy unless burden of disease or failure of prior such therapies warrants otherwise
- Always consider combination therapy, particularly systemic immunomodulatory plus skin-directed treatments, which in general has greater efficacy than monotherapy
- Consider potential *Staphylococcus* infection as cause of worsening disease and maintain low threshold for use of systemic antibiotics to prevent life-threatening sepsis
- Preserve quality of life by aggressive treatment of pruritus

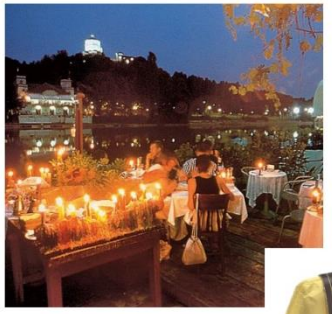
Sézary syndrome: Immunopathogenesis, literature review of therapeutic options, and recommendations for therapy by the United States Cutaneous Lymphoma Consortium (USCLC)

Elise A. Olsen, MD,[a] Alain H. Rook, MD,[b] John Zic, MD,[c] Youn Kim, MD,[d] Pierluigi Porcu, MD,[e] Christiane Querfeld, MD,[f] Gary Wood, MD,[g] Marie-France Demierre, MD,[h] Mark Pittelkow, MD,[i] Lynn D. Wilson, MD, MPH,[j] Lauren Pinter-Brown, MD,[k] Ranjana Advani, MD,[d] Sareeta Parker, MD,[j] Ellen J. Kim, MD,[b] Jacqueline M. Junkins-Hopkins, MD,[m] Francine Foss, MD,[j] Patrick Cacchio, BS,[a] and Madeleine Duvic, MD[n]

Durham, North Carolina; Philadelphia, Pennsylvania; Nashville, Tennessee; Palo Alto and Los Angeles, California; Columbus, Ohio; Chicago, Illinois; Madison, Wisconsin; Boston, Massachusetts; Rochester, Minnesota; New Haven, Connecticut; Atlanta, Georgia; Baltimore, Maryland; and Houston, Texas

Sézary syndrome (SS) has a poor prognosis and few guidelines for optimizing therapy. The US Cutaneous Lymphoma Consortium, to improve clinical care of patients with SS and encourage controlled clinical trials of promising treatments, undertook a review of the published literature on therapeutic options for SS. An overview of the immunopathogenesis and standardized review of potential current treatment options for SS including metabolism, mechanism of action, overall efficacy in mycosis fungoides and SS, and common or concerning adverse effects is first discussed. The specific efficacy of each treatment for SS, both as monotherapy and combination therapy, is then reported using standardized criteria for both SS and response to therapy with the type of study defined by a modification of the US Preventive Services guidelines for evidence-based medicine. Finally, guidelines for the treatment of SS and suggestions for adjuvant treatment are noted. (J Am Acad Dermatol 2011;64:352-404.)

Key word: Sézary syndrome.



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