Published in final edited form as:

Hematol Oncol Clin North Am. 2019 February ; 33(1): 103–120. doi:10.1016/j.hoc.2018.09.001.

Mycosis Fungoides and Sézary Syndrome:

An Update

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Keywords

Mycosis fungoides; Sézary syndrome; Cutaneous T-cell lymphoma; Review; Diagnosis; Genetics; Therapy; Cause

INTRODUCTION

Cutaneous T-cell lymphomas (CTCLs) encompass a heterogeneous collection of non-Hodgkin lymphomas that arise from skin-tropic memory T lymphocytes. Among them, mycosis fungoides (MF) and Sézary syndrome (SS) are the most common malignancies. In its earliest stages, patients classically present with discrete skin lesions that resemble eczema or with widespread erythema. Patients with advanced disease may have fungating tumors or leukemic disease with eventual involvement of lymph nodes and viscera. Most patients with MF present with early stage disease and have an indolent disease course with a low risk of disease progression; however, cure is rarely achieved. The goal of treatment is to minimize symptomatic morbidity and limit disease progression. Increasingly, hematopoietic stem cell transplantation is being considered for patients with advanced stages, is the only therapy with curative intent.

EPIDEMIOLOGY

The overall incidence of CTCL is 10.2 per million persons.[1] More than half of these cases are MF, with an incidence of 5.6 per million persons.[1] The age-adjusted incidence rate for SS is 0.1 per million persons.[2] Men are more commonly affected than women (incidence rate ratio [IRR] 5 1.6).[2] The incidence increases with age, with the highest CTCL incidence at greater than 70 years of age. Blacks have a higher incidence rate than whites (IRR 5 1.57).[2] Black patients are diagnosed at an earlier age (median age of diagnosis of 53 years, compared with 63 years for whites) and have worse survival than white patients regardless of age and stage of presentation.[2]

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DIAGNOSIS

The diagnosis of MF/SS can be challenging and requires input from the clinical presentation, pathologic evaluation, and molecular studies. MF/SS can resemble benign inflammatory dermatoses, and characteristic histologic features of MF may be absent in early disease even after multiple biopsies. Moreover, traditional polymerase chain reaction (PCR) of the T-cell receptor (TCR) used to identify the presence of a T-cell clone in clinical samples has a significant false-negative rate in early stage disease.[3] An algorithm to assist in the diagnosis of early MF has been proposed, although not formally validated.[4] This algorithm emphasizes the importance of integrating the clinical presentation (persistent, progressive patches or plaques in non–sun-exposed location and morphology), histopathology (superficial lymphoid infiltrate, epidermotropism without spongiosis, lymphoid atypia), immunopathology (decreased expression of CD5, CD7 or epidermal-dermal discordance of CD2, CD3, CD5, CD7), and molecular evaluation of T-cell clonality.[4] Pathologic criteria to assist in the diagnosis have been put forth but are not often used in clinical practice.[5] To date there are no diagnostic molecular markers used clinically that can reliably identify malignant T-cell from benign T-cell. However, expression of TOX, a thymocyte selection-associated HMG box protein, may be a useful adjunct.[6–8]

There are 3 clinical morphologies in MF: patch, plaque, and tumor (Fig. 1–3).[9,10] Each is distinguished from the former by increasing thickness. There are 3 recognized subtypes of MF by the World Health Organization(WHO)/European Organization for Research and Treatment of Cancer (EORTC) with different clinical and histologic features (Table 1, Fig. 4).[11] Clinicians must also be aware of the several distinct clinicopathologic variants of MF (Box 1, Fig. 5).[12]

Patients with SS typically present with erythroderma, defined as diffuse erythema affecting at least 80% of the body surface area (Fig. 6).[11] These patients must be distinguished from other benign causes of erythroderma (Box 2).

The single greatest advancement to aid in the diagnosis of MF/SS is the advent of high-throughput sequencing (HTS) of the TCRB gene, which permits identification of a T-cell clone through the sequence of its CDR3 region with superior sensitivity compared with traditional *TCRG* PCR (Fig. 7).[3] It has also shown to be effective at discriminating between CTCL and benign inflammatory diseases when the frequency of the top T-cell clone is evaluated as the fraction of total nucleated cells.[3] This analysis, however, is being used in a limited number of cancer centers at this time.

Given these diagnostic challenges, referral of patients to specialized multidisciplinary cutaneous lymphoma cancer centers is advised.

STAGING AND PROGNOSIS

Staging of MF/SS was initially set forth by the MF Cooperative Group of the American Joint Committee on Cancer.[9] The International Society for Cutaneous Lymphomas (ISCL) and the EORTC in 2007 proposed a revision of the staging criteria, which was later validated in a single-center cohort of 1502 patients.[9] The National Comprehensive Cancer Network

(NCCN) has adapted the revised ISCL/EORTC recommendations for staging of MF/SS (Tables 2–4).

Clinical stage is an important determinant of the risk of disease progression (RDP) and overall survival (OS).[13] Patients with stage IA have a median survival of 35.5 years and a disease-specific survival (DSS) of 90% at 20 years, which is comparable with patients without MF. Although these patients have an indolent disease course, there is an 18% RDP at 20 years.[13] Patients with stage IB have a median survival of 21.5 years, a DSS of 67%, and an RDP of 47% at 20 years.[13] Patients with stage IIA have a median survival of 15.8 years, a DSS of 60%, and an RDP 41% at 20 years.[13] Patients with stage IIB have a median survival of 4.7 years and a DSS of 56% at 5 years and 29% at 20 years.[13] Their RDP is 48% by 5 years and 71% by 20 years.[13] Patients with IIIA and IIIB have a median survival of 4.7 and 3.4 years, respectively, and a 10-year DSS of 45%.[13] Their RDP is 53% and 82%, respectively.[13] Patients with stage IVA1 have a median survival of 3.8 years, a DSS of 41% at 5 years and 20% at 10 years.[13] Their RDP is 62% at 5 years.[13] Patients with stage IVA2 have a median survival of 2.1 years and a DSS of 23% at 5 years and 20% at 10 years.[13] Their RDP is 77% by 5 years.[13] Patients with stage IVB have a median survival of 1.4 years with a DSS of 18% at 5 years.[13]

In this patient cohort, several prognostic factors were identified.[13] Advanced age was associated with a higher RDP, poorer OS, and worse DSS. Skin (T) stage, B0b (compared with those with B0a), folliculotropic MF, large-cell transformation (LCT), and elevated lactate dehydrogenase (LDH) were independently associated with RDP, worse OS, and DSS. These prognostic factors gave rise to the prognostic index score, developed by the Cutaneous Lymphoma International Consortium study, for patients with advanced MF/SS.[14] Stage IV, age greater than 60 years, large-cell transformation, and increased LDH were combined into a 3-tier prognostic index model. These risk groups had significantly different 5-year survival rates regardless of patient stage (IIB–IV): low risk (68%), intermediate risk (44%), and high risk (28%).

One of the greatest challenges in the management of MF is the identification of which early stage patients are at risk for disease progression. A significant advancement in identify these patients comes from the work of de Masson and colleagues.[15] In this single-center retrospective study, the burden of malignant T-cell clone (tumor clone frequency [TCF]) in lesional skin predicted RDP and OS in early stage patients. A TCF of greater than 25% was significantly associated with progression-free survival (PFS) and OS. This measure was superior to predicting the PFS compared with stage (IB vs IA), presence of plaques, elevated LDH, age, and the presence of LCT. Furthermore, when patients at high risk of disease progression as determined by TCF were treated with radiation, a superior therapy capable of locally eliminating malignant disease, they had an improved OS (O'Malley and colleagues, submitted for publication).

Determination of malignant clonal burden by HTS has also been found important in determining outcomes following bone marrow transplantation.[16]

PATHOPHYSIOLOGY

Malignant T-Cell Origin

Although MF and SS have overlapping presentations and are not distinguished in the WHO/EORTC staging criteria, they are considered separate entities.[11] The WHO/EORTC and the ISCL consider SS to be a clinical syndrome presenting with erythrodermic skin and leukemic disease.[9] This consideration is in contrast to patients who initially present with classic skin lesions of MF and later meet the staging criteria for SS. The latter are referred to as leukemic MF, SS preceded by MF, or secondary SS. The NCCN considers patients with SS to be anyone who meets the criteria for a high blood burden of disease (B2 disease).

MF and SS classically arise from skin tropic memory CD41 T-cell (CD81 and CD4– CD8- subtypes may also be observed); but demonstration of different T-cell surface phenotypes and molecular profiles support the hypothesis that these malignancies originate from distinct memory T-cell subsets: the skin resident memory T-cell (T_{RM}) in MF and the skin-tropic central memory T-cell (T_{CM}) in SS.[17]

The average adult skin contains about 20 billion T-cell.[18] These T-cell are normally present in noninflamed human skin.[19] Most of these T-cell are memory T-cell; less than 5% are naïve.[18] Naïve T-cell reside in the blood or lymph nodes.[20] If naïve T-cell first encounter antigen in skin-draining lymph nodes, they proliferate clonally as effector T-cell and differentiate to express the skin homing addressin cutaneous lymphocyte antigen (CLA) and the C-C chemokine receptor 4 (CCR4) (Fig. 8).[20] Once these effector T-cell eliminate their cognate antigen, they differentiate into memory T-cell (Fig. 8).[20–22] Skin T_{CM} cells are CCR41/CCR71/L-selectin1, which allows for circulation in skin, blood, and lymph nodes.[22] Skin resident T_{RM} cells are CCR41/CLA1 and lack CCR7 and L-selectin. They rarely circulate out of the skin.[22] A subset of T-cell, termed the migratory memory T-cell (T_{MM}), express CCR7 but not L-selectin and perhaps represent an intermediate phenotype recirculating more slowly out of the skin to blood compared with the T_{CM}.[22,23]

Campbell and colleagues[17] showed that MF malignant T-cell are CCR41/CLA1/L-selectin-/CCR7-(T_{RM}), whereas SS malignant T-cell are CCR41/L-selectin1/CCR71 (T_{CM}). The molecular behavior of these T-cell types correlates with the clinical presentation of their malignant counterpart (Fig. 9). Skin T_{RM} are nonmigratory populations, and clinically patients with MF have fixed skin lesions with discrete borders.[20,24] In contrast, T_{CM} recirculate between skin, blood, and lymph node; clinically patients with SS have diffuse erythema and leukemic disease.[17,23] Patients with a T_{MM} phenotype have ill-defined but discrete skin lesions.[22,23] Interestingly, patients with a T_{MM} phenotype do not respond to alemtuzumab as well as patients with a T_{CM} phenotype. This therapy is effective only for leukemic disease; malignant T_{CM} cells seem to recirculate into frequently.[23]

Genomic Alterations

MF/SS have diverse and complex genomic abnormalities, which have been best studied in SS. Striking findings include the discovery of many chromosomal abnormalities; somatic copy number variations (SCNVs) are favored over single nucleotide variants (SNVs) with 92% of all driver mutations arising from SCNVs.[25] Chromosomal aberrations most often

occur on chromosomes 8, 10, and 17.[25–27] There is a high incidence of complex chromosomal structural rearrangements with more than 65% of patient samples exhibiting at least one chromothripsis-like rearrangement.[25] Chromosomal instability may be favored because of abnormal DNA repair machinery, activation of RAG endonucleases, impaired cell cycle control, and widespread DNA hypomethylation.[25,28,29] Most (74%) point mutations are C > T because of age-related and UVB-related mutagenesis.[25]

A meta-analysis of 220 genetically profiled patients with CTCL identified 55 driver mutations and implicated 14 biologically relevant pathways.[28] Affected pathways broadly include those involved in T-cell activation, function, migration, and differentiation; chromatin modification; cell cycle, survival and proliferation; and DNA damage response (Table 5).[25–28,30] Most genes are affected because of SCNV.[25,30] Mutations within genes are comparably much less common across CTCL cohorts (Table 6).[27,31] It is not surprising given the recurrent alterations of epigenetic modifiers that patients with SS exhibit marked hypomethylation and hypermethylation of CpG islands across the genome compared with patients with benign inflammatory dermatoses and solid tumor malignancies.[29] Overall the SS methylome is most comparable with that of regulatory T-cell.[29] Evaluation of open chromatin sites used to predict transcription factor binding sites in CTCL samples, using assay of transposase-accessible chromatin with sequencing, showed unique regulomes and chromatin dynamics in CTCL cells compared with benign host T-cell and healthy donor T-cell.[32] Notable findings include decreased interferon gamma, interleukin (IL)-2, NFAT, and PIK3R1 (regulatory subunit of PI3K) expression in leukemic cells and gain of expression of HDAC9 and natural killer–kB in all samples with activation of 1 of 3 transcription factor motif patterns due to chromatin modification: Jun-AP1; CTCF; or EGR, SMAD, MYC, and KLF.[32] Interestingly, differences in the chromatin accessibility landscape among leukemic cells predicted responses to HDAC inhibitors.[32]

Immunopathogenesis

Patients with MF/SS are at increased risk of bacterial infection, especially in advanced stages, because of the disruption of the skin barrier by ulcerated tumors as well as depressed local and systemic immune response to pathogens.[33] Immunosuppression is directly correlated with the malignant T-cell burden and is driven in part by abnormalities in the JAK/STAT signaling pathway (Fig. 10).[27,34,35] The tumor microenvironment becomes skewed from a T-helper 1 to a T-helper 2 phenotype with advancing stages.[34,36–38] These effects are reversible with depletion of malignant T-cell.[39]

Cause

Although the cause of MF is unknown, the leading therapy is the chronic antigen stimulation theory first described in 1974 by Tan and colleagues.[40] Chronic antigen or superantigen stimulation is thought to lead to clonal expansion of T-cell and malignant transformation. Several lines of observation support this theory. MF/SS is largely a malignancy of memory T-cell.[17] Malignant T-cell depend on dendritic cells for survival and proliferation.[41] The most frequent clonally expanded TCR vb gene is TRBV20 to 1, which is associated with recognition of *Staphylococcus aureus*.[27] *S aureus*, in a series of patients with MF/SS, was able to act as a superantigen and stimulate proliferation of malignant T-cell.[42] As yet, no

heritable germ-line mutations have been identified. However, patients with psoriasis and atopic dermatitis, which has a known familial inheritance, are at a somewhat higher risk for MF/SS.[43,44] Most patients with CTCL, however, have no antecedent T-cell–mediated skin disease. Many infectious agents have been investigated for putative roles in the cause of MF/SS. However, the data are limited and studies have yielded contradictory results to reliably implicate any single infectious agent, including HTLV-1 in CTCL.[45,46] Recently, a more sophisticated genomic analysis of SS samples using VirCapSeq-VERT revealed no functional coding sequences for viral pathogens or unknown viruses or evidence for active infection.[47] Interestingly, partially coding proviral sequences of human endogenous retroviruses (HERVs) were detected.[47] Although these particles may play a pathogenic role in disease, given that HERVs are normally present in the human genome, demonstrating a causal role in CTCL will be challenging.[48]

TREATMENT

Treatment is often multidisciplinary, as it combines skin-directed (Table 7) and systemic therapies (Table 8). Although there are several therapies recognized by the NCCN for the treatment of MF/SS, there is a paucity of effective therapies providing durable responses. Targeted therapies have variable response rates ranging from 30% to 67%, with complete responses no higher than 41%.[49–61]

Furthermore, although traditional chemotherapy may have a higher response rate, these gains are short-lived and associated with worse overall outcomes.[62–64] Traditional nonmyeloablative allogeneic stem cell transplantation, the only potential cure for CTCL, has a 46% OS at 5 years.[65] Recently, the Stanford transplantation regimen showed an overall response rate of 90% with a 2-year OS and PFS of 76% and 50%, respectively.[66] There was a low incidence of graft-versus-host disease (GVHD) (23% grade II–IV acute GVHD and 23% with chronic GVHD at 2 years). Nonrelapse mortality due to GVHD or secondary malignancy at 1 year was 3%.[66] An important predictor of successful transplantation is the degree of remission achieved before transplant. Because CR is more readily achieve in SS than in advanced MF, most successful transplants have been performed in patients with SS.

Given the limited efficacy of existing therapies, patients with advanced disease are encouraged to participate in clinical trials. Several agents are in clinical development for the treatment of MF/SS (Table 9).

SUMMARY

This is an exciting time in cutaneous oncology. The advent of HTS for TCR has enhanced our ability to diagnose MF/SS earlier, to predict which patients are at risk for disease progression, and to predict the treatment response to bone marrow transplantation. Major insights into disease biology have been made through genomic and epigenomic studies of MF/SS. There are increasing numbers of clinical trials for novel therapies for MF/SS.

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KEY POINTS

- Mycosis fungoides and Sézary syndrome are the most common non-Hodgkin lymphomas to arise from skin-tropic clonal T lymphocytes.
- Significant advances have been made in understanding the genetic and epigenetic aberrations in mycosis fungoides and Sézary syndrome.
- Diagnosis requires a combination of clinical, pathologic, and molecular features.
- Several prognostic factors have been recognized to identify patients with poor prognosis.
- Treatment is intended to minimize morbidity and limit disease progression, as cure is rarely achieved.

Box 1

Clinicopathologic variants of mycosis fungoides

MF clinical variants
Bullous
Hypopigmented (see Fig. 5)
Ichthyosiform
MF palmaris et plantaris (keratoderma-like)
Pigmented purpuric dermatosis-like
Papular
Poikilodermatous
Psoriasiform
Pustular
Solitary/unilesional
Syringotropic
Verrucoid

Box 2

Causes of erythroderma

Differential diagnosis of erythroderma
Idiopathic
Atopic dermatitis
Psoriasis
Pityriasis rubra pilaris
SS
Systemic allergic contact dermatitis

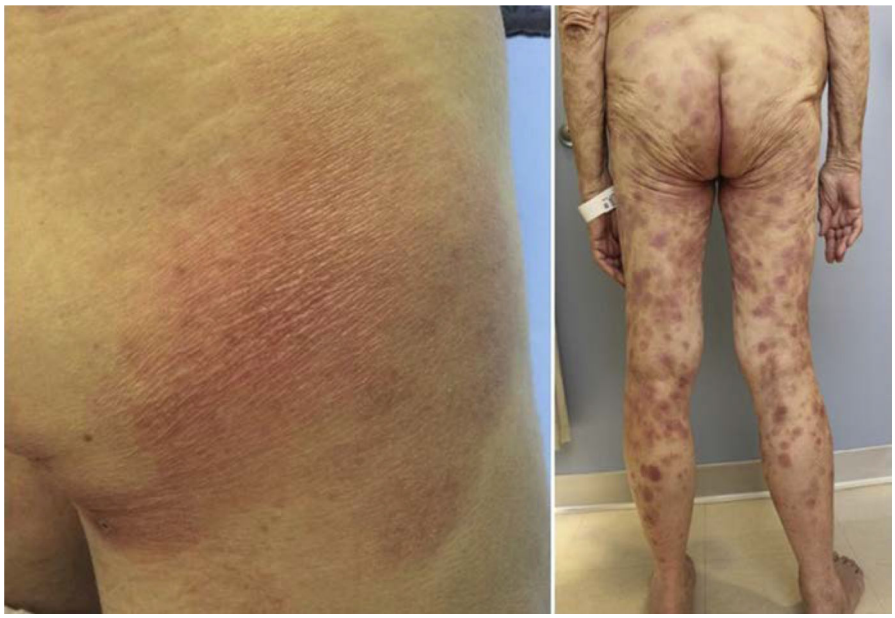

Fig. 1.

Patch-stage MF. Patches are flat to atrophic lesions, usually erythematous with variable amounts of scale, and may resemble eczema. Atrophic lesions have a cigarette-paper, wrinkled appearance. (*Courtesy of* J. O'Malley, MD, PhD, Boston, MA.)

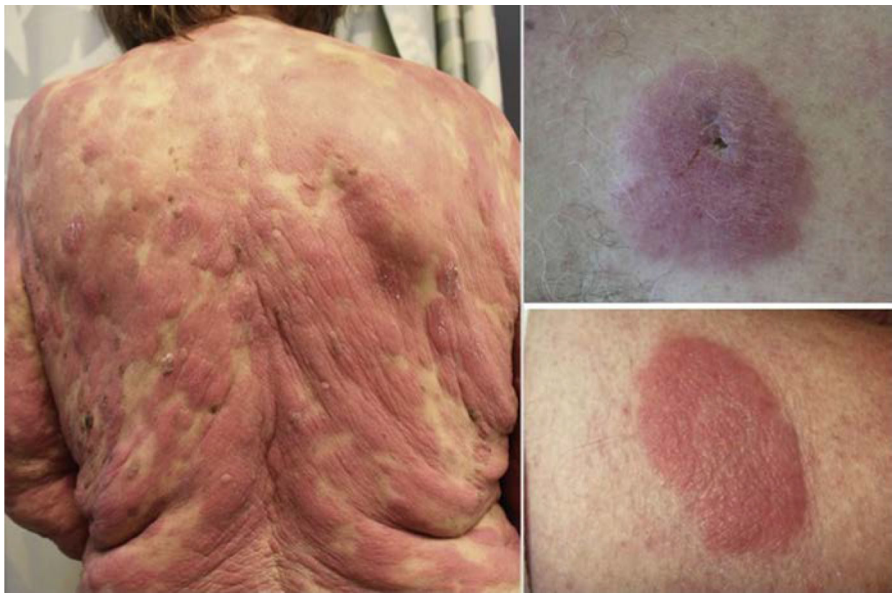

Fig. 2.
Plaque-stage MF. Plaques are raised or indurated lesions. Affected acral sites are considered plaques.

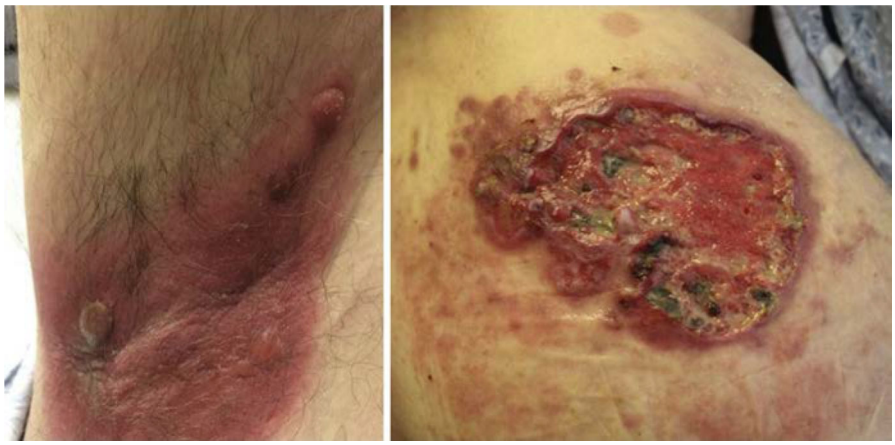

Fig. 3.

Tumor-stage MF. Tumors exhibit a significant vertical growth phase and must measure at least 1 cm in diameter. They are often ulcerated.

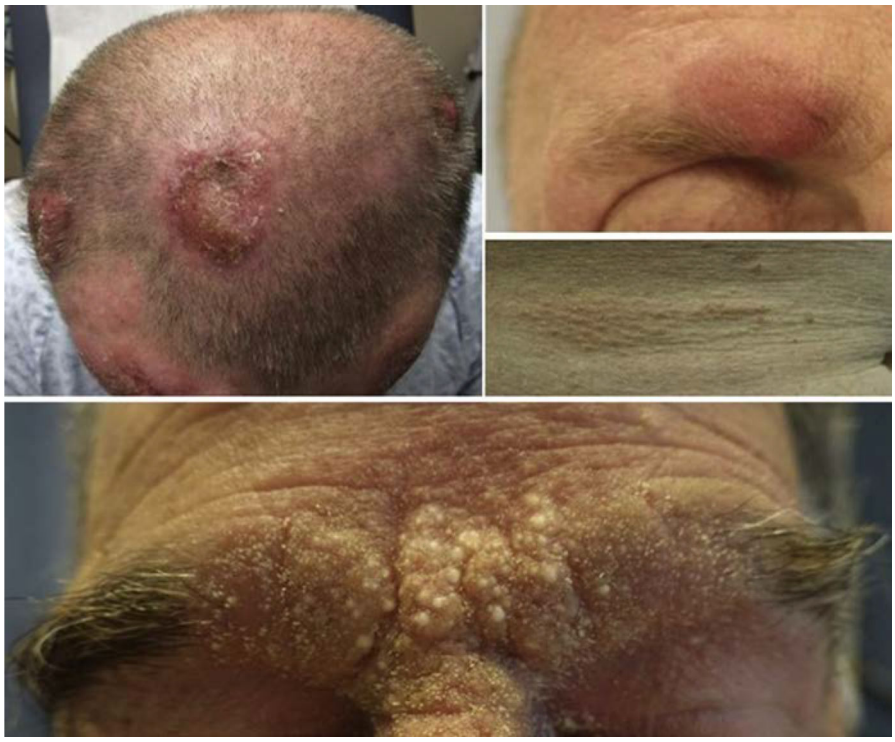

Fig. 4.

Folliculotropic MF. Lesions preferentially affect the head and neck area. When located within hair-bearing areas, it may cause alopecia. Patches or plaques may be composed of cyst-like or follicular-based papules.

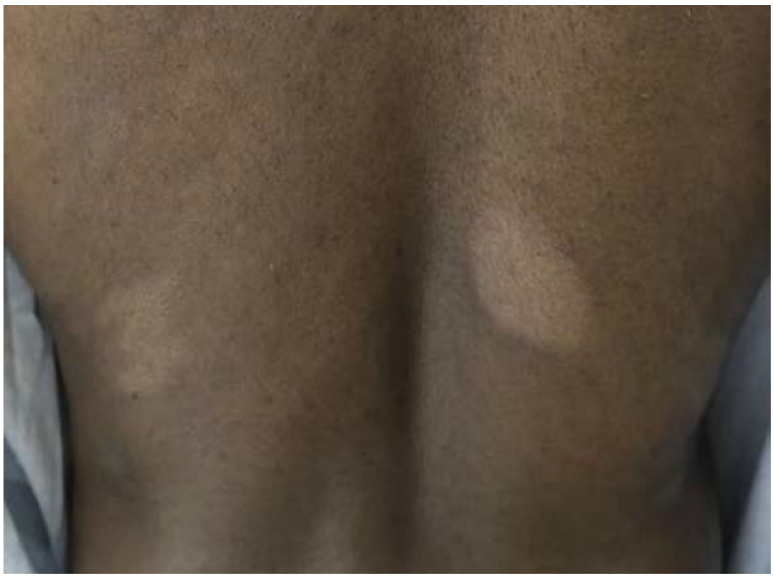

Fig. 5.

Hypopigmented MF. Predominately affects African Americans. It has an indolent disease course. Immunophenotype is classically of atypical CD81 T-cell.

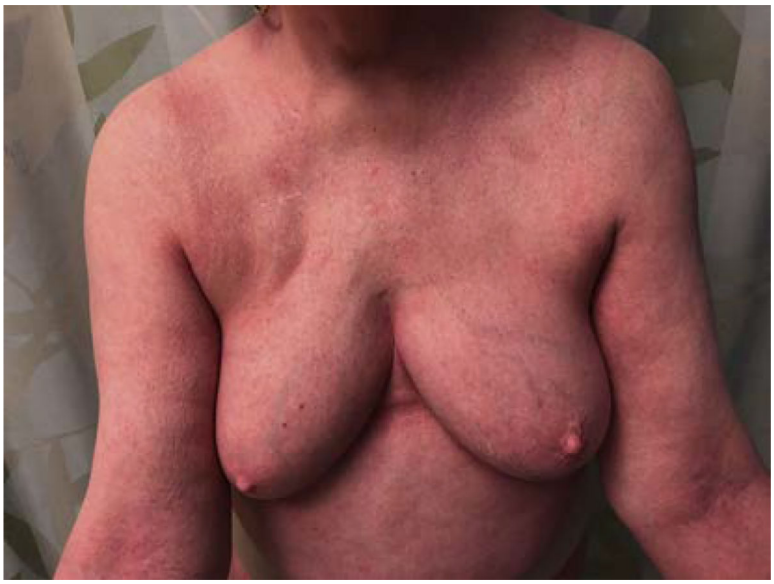

Fig. 6.

Erythroderma. Erythroderma is defined as diffuse erythema affecting 80% or greater body surface areas. It often appears eczematous with a variable amount of scale. Erythroderma is often a sign of leukemic disease.

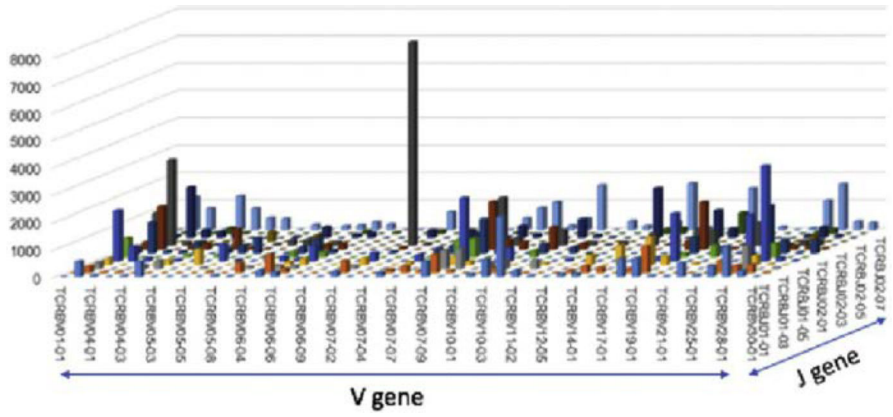

Fig. 7.

HTS of the TCR. TCR sequencing identifying expanded population of clonal malignant T-cell in a patient with patch-stage CTCL. The V versus J gene usages of T-cell from a patch MF lesion are shown. The gray peak includes the clonal malignant T-cell population and other benign T-cell that share the same V and J usage. (Image *courtesy of* Dr. John O'Malley.)

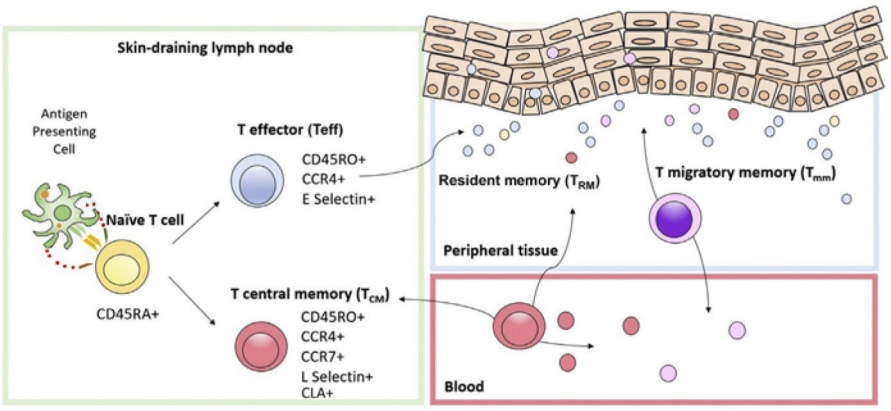

Fig. 8.

Skin-tropic T-cell subtypes. Naïve T-cell differentiate into effector memory and central memory T-cell after binding to their cognate antigen on antigen presenting cells in skin-draining lymph nodes. Expression of surface ligand CCR4 determines their skin homing ability. Expression of CCR7/L-selectin determines their ability to re-circulate between blood and lymph node.

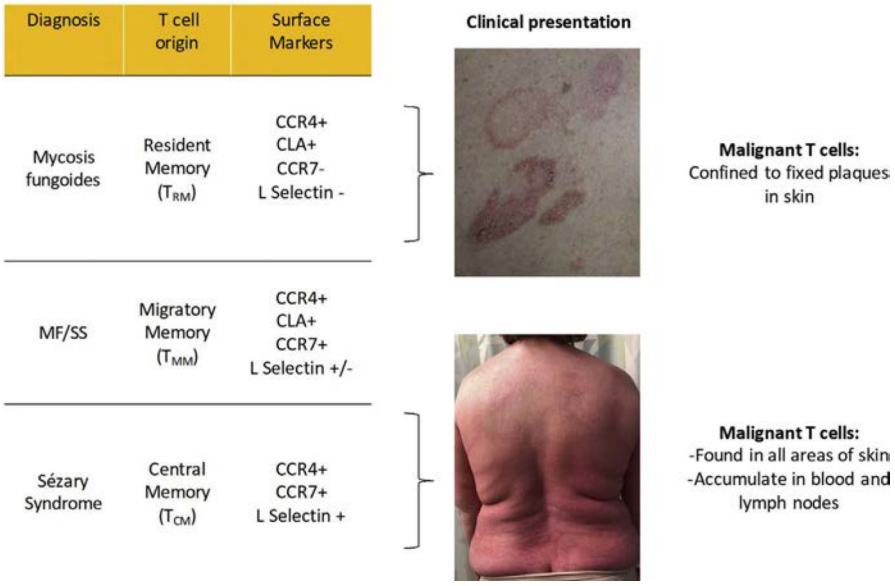

Fig. 9.

Distinct T-cell origins of MF and SS. Surface molecular phenotype correlates with clinical presentation and morphology of skin disease. T_{MM}, migratory memory T-cell.

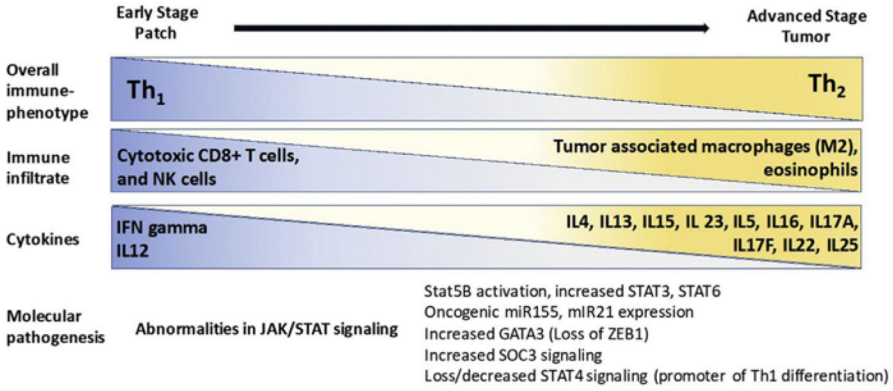

Fig. 10.
Immunopathogenesis of MF/SS.

Table 1

Mycosis fungoides variants recognized by the World Health Organization/European Organization for Research and Treatment of Cancer

MF Subtype	Clinical Presentation	Immunophenotype	Histology
Folliculotropic MF	Predilection for head/neck Alopecic skin lesions Follicular papules; Acneiform/ comedonal-like papules or nodules (see Fig. 4)	CD41CD31 T-cell Admixed CD30 1 blasts	Perivascular and periadenexal lymphocytic infiltrates with infiltration of follicular epithelium (folliculotropism); variable infiltration of eccrine sweat glands by atypical lymphocytes with sparing of epidermis; follicular mucinosis
Pagetoid reticulosis	Predilection for extremities Localized psoriasiform patch or plaque Indolent clinical behavior	CD41CD31 T-cell or CD81CD31 T-cell CD30 often positive	Hyperplastic epithelium with marked pagetoid-like atypical lymphocytes; dermis with mixed reactive lymphocytes and histiocytes
Granulomatous slack skin	Predilection from axillae and groin Lax pendulous skin Indolent clinical behavior	CD41CD31 T-cell	Dense granulomatous dermal infiltrates of atypical lymphocytes, macrophages, many multinucleated giants cells; destruction of elastic tissue

Data from Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105(10):3768–85.

Table 2

International Society for Cutaneous Lymphomas/European Organization for Research and Treatment of Cancer classification of mycosis fungoides/Sézary syndrome

TNMB Stages	Definition
T (Skin)	
T1	Patches, papules, and/or plaques covering <10% BSA T1a patch only T1b plaque ± patch
T2	Patches, papules, and/or plaques covering 2:10% BSA T2a patch only T2bplaque±patch
T3	One or more tumors (at least one 1-cm-diameter solid or nodular lesion with evidence of depth and/or vertical growth
T4	Confluence of erythema covering 2:80%BSA
N (Node)	
N0	No clinically abnormal peripheral lymph nodes, biopsy not required
N1	Clinically abnormal peripheral lymph nodes, histopathology Dutch grade 1 or NCI $LN_{0–2}$ N1a clone negative N1b clone positive
N2	Clinically abnormal peripheral lymph nodes, histopathology Dutch grade 2 or NCI LN_3 N2a clone negative N2b clone positive
N3	Clinically abnormal peripheral lymph nodes, histopathology Dutch grade 3–4 or NCI LN_4, clone positive or negative
Nx	Clinically abnormal peripheral lymph nodes, no histopathologic confirmation
Visceral (M)	
M0	No visceral organ involvement
M1	Visceral involvement (must have pathology, and organ is to be specified)
Blood	
_____	B0 Absence of significant blood involvement: s5% of blood lymphocytes are Sézary cells B0a clone negative B0b clone positive
B1	Low blood tumor burden: >5% of peripheral blood lymphocytes are Sézary cells but does not meet criteria for B2 disease B1a clone negative B1 b clone positive
B2*	High blood tumor burden: 2:100/uL Sézary cells with positive clone in blood (matching clone in skin) or positive clone and one of the following: 1. CD4/CD8 ratio of 10 or more 2. 2:40% CD41CD7- cells of total lymphocytes
	3. 2:30% CD41CD26- cells of total lymphocytes

Abbreviation: BSA, body surface area.

Table 3

Histopathologic staging of lymph nodes

Classification	Dutch System	NCI Classification
N1	Grade 1 : Dermatopathic lymphadenopathy	LN0: No atypical lymphocytes LN1: Occasional, Isolated atypical lymphocytes LN2: many atypical lymphocytes In 3–6cellclusters
N2	Grade2: Dermatopathic lymphadenopathy, early involvement of MF	LN3: Aggregates of atypical lymphocytes; nodal architecture preserved
N3	Grade 3: Partial effacement of LN architecture; many atypical cells Grade 4: Complete effacement	LN4: Partial to complete effacement of nodal architecture by atypical lymphocytes

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Table 4

World Health Organization/European Organization for Research and Treatment of Cancer staging of mycosis fungoides/Sézary syndrome

Stage	T	N	M	B
IA	1.0	0	0	0.1
IB	2.0	0	0	0.1
II	1.2	1.2	0	0.1
IIB	3.0	0–2	0	0.1
IIIA	4.0	0–2	0	0
IIIB	4.0	0–2	0	1.0
IVA1	1–4	0–2	0	2.0
IVA2	1–4	3.0	0	0–2
IVB	1–4	0–3	1	0–2

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Table 5

Pathways affected in mycosis fungoldes/Sézary syndrome

Biological Pathway	Affected Gene/Pathway
T-cell function, cytokine signaling	CD28, CARD11, PDCD1, PLCG1, RLTPR, PTPRN2, PRKCB, PRKCQ, CSNK1A1, CCR4, ZEB4, JAK1/2/3, STAT3/5B, TNFRSF1B, NFKB2, IRF4
Chromatin modification	ARID1A, DNMT3A, KMT2C, KMT2D, SETDB2, TRRAP, TET1/2, KDM6A, NCOR1, BCOR, SMARCB1, CTCF
Cell cycle, survival, and proliferation	CDKN2A, CDKN1A, CDK4, MYC, RB1, RPSKA1, FAS, MAPK, and PI3K-Akt Dathwavs
DNA damage response	TP53, ATM

Table 6

Recurrently affected genes in mycosis fungoides/Sézary syndrome

Affected by CNV (% of CTCL Samples)	Affected by SNV (% of CTCL Samples)
TP53 (92.5%)	MLL3 (4%–57%)
ZEB1 (65%)	TP53 (16%–43%)
STAT5B (63%)	ZEB1 (4%–27%)
ARID1A (58%)	STAT5B (2.77%–26.0%)
CDKN2A (40%)	ARID1A (8%–25%)
FAS (40%)	CARD11 (7%–22%)
DNMT3A (38%)	FAS (3%–19%)
ATM (30%)	PLCG1 (18%)
PRKCQ (30%)	CDKN2A (4%–17%)
TNFAIP3 (25%)	

Table 7

Skin-directed therapies for the treatment of mycosis fungoides/Sézary syndrome

Skin-Directed Therapies	Overall Response Rate (%)
Topical superpotent corticosteroids	75–95
Bexarotene gel	50–75
Nitrogen mustard/mechlorethamine HCl gel	50–90
Imiquimod cream	50
Tazarotene cream	58
Narrow-band UVB	54–90
PUVA	85–100
Radiation therapy (local external electron beam, brachytherapy, total skin electron beam therapy)	—

Abbreviations: HCl, hydrochloride; PUVA, psoralen UVA.

Table 8

Systemic therapies used to treat mycosis fungoides/Sézary syndrome

Systemic Therapies	Overall Response Rate
Bexarotene	ORR 45%, CR 13%[14]
IFN a	ORR 64%; CR 27% in stage IA–IVA[15]
Romidepsin	ORR 38%, CR 6%[16]
Methotrexate	ORR 58%, CR 41% in erythrodermic MF[17] ORR 33%, CR 12% in plaque-stage MF[18]
Brentuximab vedotin	ORR 65%, CR 10%[10]
Pralatrexate	ORR 41%, CR <1%[19]
Doxorubicin	ORR 30% to 80%, CR 20% to 60%[20,21]
Gemcitabine	ORR 51.0%–70.5%, CR 11.5%–23.0%[22,23]
Pembrolizumab	ORR 38%, 1 CR[24]
Bortezomib	ORR 67%, CR 17%[25]

Abbreviations: IFN, interferon; ORR, overall response rate.

Table 9

Therapies in clinical development for cutaneous T-cell lymphoma

Investigational Agent	Clinical Development
Mogamulizumab (anti-CCR4 antibody)	Phase III (NCT01728805)
E7777 (cytotoxic IL-2 fusion protein)	Phase II (NCT01871727)
MRG-106 (miR-155 antagonist)	Phase II (NCT02580552)
Duvelisib (PI3K inhibitor)	Phase II (NCT02783625)
Ruxolitinib (JAK 1/2 inhibitor)	Phase II (NCT02974647)
TTI-621 (SIRPaFc IgG4, anti-CD47)	Phase I (NCT02663518)