Evaluation, Diagnosis, and Staging of Cutaneous Lymphoma

Elise A. Olsen, MD

KEYWORDS

• Primary cutaneous lymphoma (PCL) • Cutaneous T-cell lymphoma (CTCL)
• Cutaneous B-cell lymphoma (CBCL) • Mycosis fungoides • Sézary syndrome

KEY POINTS

- The unique features of the diagnosis, evaluation, classification and staging of mycosis fungoides and Sézary syndrome.
- The evaluation, classification and staging of the nonMF/nonSS CTCLs and the most common subtypes of CBCLs.
- The response criteria for evaluation of therapeutic efficacy for all subtypes of cutaneous lymphoma.

INTRODUCTION

Cutaneous lymphomas are an extremely heterogeneous group of non-Hodgkin lymphomas (NHLs) that manifest in the skin.[1,2] Although most patients do not have evidence by traditional screening methods of extracutaneous disease at the time of presentation (and, hence, fit the classic definition of primary cutaneous lymphoma [PCL]), those with certain clinical or histologic subtypes commonly have, or will, develop nodal, visceral, and/or blood involvement. The prognosis and survival of patients varies not only on the type of cutaneous lymphoma but the stage as well; each lymphoma has its own best treatments to date, which are primarily stage based. Because there is no cure for any of these cutaneous lymphomas, but treatment can be life saving and insure quality of life, the overall prognosis for any given patient begins with the correct diagnosis and staging. It is the purpose of this article to discuss the evaluation, diagnosis, and staging of the 3 main subcategories of cutaneous lymphoma.

SUBTYPES AND EPIDEMIOLOGY OF CUTANEOUS LYMPHOMA

The annual incidence of PCLs is estimated at 10.0 to 10.7 per million person-years,[3,4] and they account for 19% of cases of extranodal lymphomas.[4] The World Health Organization–European Organization for Research and Treatment of Cancer (WHO-EORTC) have classified the cutaneous lymphomas with primary cutaneous manifestations into cutaneous T-cell lymphomas (CTCLs) and cutaneous B-cell lymphomas (CBCLs) (**Box 1**).[5,6] The CBCLs are the least common of the PCLs, estimated at 3.1 per million person-years in an assessment of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry for 2001 to 2005 but making up 29% of all PCLs.[4] The annual incidence rate of CBCLs steadily increased to an annual rate of 3.92 between 2006 and 2010.[7] The age-adjusted incidence of all types of CTCLs, based on 2 different sets of SEER, ranged from 6.4 to 7.7 million person-years.[4,8] What is clear is that the incidence

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Department of Dermatology, Trent & Erwin Roads, Duke University Medical Center, Durham, NC 27710, USA
E-mail address: elise.olsen@dm.duke.edu

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Box 1
WHO/EORTC classification of cutaneous lymphomas

CTCLs and cutaneous NK-cell lymphomas

- Mycosis fungoides (MF)
- MF variants and subtypes
  - Folliculotropic MF
  - Pagetoid reticulosis
  - Granulomatous slack skin
- Sézary syndrome
- Adult T-cell leukemia/lymphoma
- Primary cutaneous CD30+ lymphoproliferative disorders
  - Primary cutaneous anaplastic large cell lymphoma
  - Lymphomatoid papulosis
- Subcutaneous panniculitis-like T-cell lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Primary cutaneous peripheral T-cell lymphoma, unspecified
  - Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)
- Cutaneous γ/δ T-cell lymphoma
- Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoproliferative disorder (provisional)
- Primary cutaneous acral CD8+ T cell lymphoma (provisional)

CBCLs

- Primary cutaneous marginal zone lymphoma
- Primary cutaneous follicle center lymphoma
- Primary cutaneous diffuse large B-cell lymphoma, leg type
- Primary cutaneous diffuse large B-cell lymphoma, other
  - Intravascular large B-cell lymphoma
  - EBV+diffuse large B-cell lymphoma of the elderly (provisional)

Precursor hematologic neoplasm

- Blastic plasmacytoid dendritic cell neoplasm

Abbreviations: MF, mycosis fungoides; NK, natural killer.

Adapted from Willemze R, Jaffe E, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3769; with permission.

of both CBCLs and CTCLs has continued to increase dramatically and consistently over the past 3 decades,[4] CTCL by 2.9 per million per decade.[8] Based on the numbers available, there are over 3000 new patients with the diagnosis of PCL each year.

Mycosis fungoides (MF) is the most common type of CTCL, comprising 53–54%[4,9] to 73%[8] of cases of CTCL in various SEER reviews. Sézary syndrome (SS) is classified as a separate entity from MF by the WHO-EORTC[10] but shares the same histologic criteria and staging as MF and often evolves from MF.[1] SS accounted for 2.5% of the cases of CTCL in the report by Criscione and Weinstock.[8] The prevalence of MF is likely more than 50,000 based on survival curves, but this number is unsubstantiated without a formal registry. The 10-year survival of patients with MF with tumor or nodal involvement is compromised (42% and 20% respectively),[5] and the 5-year survival of patients with SS (who have blood and may also have node involvement) is 24% in one report.[5] Although these patients with tumor or node stage MF or leukemic blood involvement are the minority of patients with MF, they represent the potential progression for which treatments used in those with lesser disease strive to prevent. There is no current cure for MF or SS; patients living with MF or SS endure the chronic symptoms and signs of their disease and the constant time, cost, and potential side effects of treatment to prevent progression. Although there are general clinical characteristics, such as skin (T) stage, or histologic features, such as large cell transformation (LCT), that are able to identify those with a worse prognosis in certain situations, there is great heterogeneity in these subclasses of PCL and no treatment available that targets the trigger for the final unremitting growth of the lymphoma that occurs in some patients. In addition, no genetic markers are currently available that would help identify subsets of patients more likely to respond to certain treatments.

Short of a long-term national registry of patients with cutaneous lymphoma and clear documentation of the effect on overall prognosis and survival of the various treatments used and the potential for clinical, histologic, and genetic factors to influence the outcome or choice of treatment, physicians are unable to make the kind of advances necessary to move toward a curative treatment of MF and SS. The same issues are present in the other types of CTCLs and CBCLs, none of which currently have curative treatment and, because of their relative small numbers, would benefit greatly from a national registry.

What follows in this article is the consensus approach of the International Society for Cutaneous Lymphomas (ISCLC), the EORTC Cutaneous Lymphoma Taskforce, and the United States Cutaneous Lymphoma Consortium (USCLC) on the diagnosis and staging of both the CTCLs and CBCLs. Given that there are certain nuances of MF and SS, including type of skin lesions, node histology, and potential blood involvement, that separates these cancers from the other cutaneous lymphomas, a separate and distinct staging system exists for MF and SS from that of the non-MF/non-SS CTCLs and the CBCLs.

MYCOSIS FUNGOIDES AND SÉZARY SYNDROME

Diagnosis

Classically, the lesions of MF are described as patches, plaques, or tumors.[1] Patches are flat but may be scaly or have textural change. Plaques are defined as slightly raised lesions and can be smooth, scaly, crusted, or ulcerated. A tumor is defined as a lesion at least 1 cm in diameter that has vertical growth or depth. Most of these lesion subtypes are erythematous on presentation but can be hyperpigmented. When the presentation involves diffuse scaling or confluence of patch or plaque lesions and covers 80% or greater body surface area (BSA), this meets the criteria for the term erythroderma.[1] There are other clinical presentations of MF including poikiloderma (a relatively specific finding for MF), hypopigmented macules and patches, follicular plugging, alopecia, keratoderma, blisters, and redundant skin within the axillary or inguinal folds.

The diagnosis of MF or SS is one that requires clinicopathologic correlation but starts with a representative skin biopsy suggestive of MF. Because the type of lesion may affect both the hematoxylin and eosin (H&E) and immunophenotyping results and the potential to find a clone of the T-cell receptor (TCR) gene rearrangement (GR), the choice of skin lesion for biopsy is critical. The most indurated lesion should be biopsied and if various types of lesions are present, a biopsy of each type of lesion should be taken: this is important to help identify clinical and histologic prognostic factors as well as to help differentiate between the types of CTCL. For example, a biopsy of a patch of alopecia may indicate that a patient has a folliculotropic form of MF in which the base of the abnormal lymphocytic infiltrate is far deeper than one would expect with a typical patch lesion. In general, H&E as well as immunophenotyping with various T-cell surface markers, including at a minimum CD3, CD4, CD8, CD7, and CD30, and one B-cell marker, such as CD20, are used to assess the infiltrate. The lymphocytic infiltrate may be affected by topical steroids or other topical or systemic immunosuppressive agents, so it is important for patients to be off of these, if possible, for at least the 2 weeks before the skin biopsy; this is especially true for patch stage lesions. The specifics of the histologic criteria for the diagnosis of MF/SS are covered in Dr Kempf's article in this issue.

The evaluation for a clonal TCR GR in the skin is a necessary part of the evaluation as the presence of a positive clone is supportive evidence of MF: both gamma and beta testing should be explored before making a final conclusion as to whether positive. However, it is important to keep in mind that a TCR GR clone may be present in benign skin conditions as well, so the presence of a clone is not a *sine qua non* of malignancy. The specifics of testing for clonality are key, with the BIOMED-2 method currently favored. A biopsy collected on saline is preferred for clonality testing as the yield will be increased; but it is clear that, with thick plaques and tumors, this clonality testing can be performed on formalin fixed tissue.

Multiple skin biopsies may be necessary for the diagnosis in cases of erythroderma where the percentage of inflammatory cells is high and the tumor cells low; in such cases in which the skin biopsy remains suggestive but not diagnostic of lymphoma, a lymph node biopsy or blood studies indicative of lymphoma may enable a diagnosis of MF or SS to be made. One must also keep in mind that a MF-like histology in the skin can be a manifestation of a drug reaction: most of these cases typically do not demonstrate clonality of the TCR GR. When suspected, the potentially offending drug should be discontinued for at least 2 to 3 months before ascribing the condition to lymphoma.

A useful algorithm focusing on clinicopathologic correlation was developed by the ISCL in 2005 for the diagnosis of early MF (**Table 1**).[11] This algorithm is a point scoring system that includes points for clinical, histologic, molecular, and clonality findings with an overall point score of 4 indicating probable MF. This point scoring was not meant to be used for the diagnosis of hypopigmented MF (although it seems to have validity) or for SS.

Evaluation and Staging

Clinical assessment

A full physical examination is important for evaluation with emphasis on the skin and lymph nodes.

Table 1
Clinicopathologic algorithm for the diagnosis of early MF

Criteria	Major (2 Points)	Minor (1 Point Each)
Clinical Persistent and/or progressive patches/thin plaques plus 1. Non–sun-exposed location 2. Size/shape variation 3. Poikiloderma	Any two	Any one
Histopathologic Superficial lymphoid infiltrate plus 1. Epidermotropism 2. Atypia	Both	Either
Molecular/biological Clonal TCR gene rearrangement	—	Any
Immunopathologic 1. <50% $CD2^+$, 3^+, 5^+ T cells 2. <10% $CD7^+$ T cells 3. Epidermal/dermal discordance of CD2, CD3, CD5 or CD7	—	Any one

Adapted from Pimpinelli N, Olsen EA, Santucci M, et al. Defining early mycosis fungoides. J Am Acad Dermatol 2005;53:1054.

The type of skin lesions and percent BSA covered by the skin lesions should be noted and will establish the T stage (**Table 2**). The T stage has independent prognostic significance[12,13] as does patch versus plaque lesions.[14] All peripheral or central lymph node groups should be assessed for any that are enlarged or abnormal (firm or fixed), and any lymph node 1.5 cm or greater on examination should be further assessed by imaging and biopsy.

Blood work

The basic blood tests to perform in suspected MF/SS include a complete blood count (CBC) with differential, complete metabolic panel and lactate dehydrogenase (LDH). In addition, there are several disease-specific tests to help determine whether there is any significant blood tumor burden. A Sézary cell prep includes determining the percentage of Sézary cells in the buffy coat of the CBC. Sézary cells are lymphocytes with hyperconvoluted nuclei that may also be larger than normal lymphocytes; they are not specific to MF or SS and can be seen in small numbers in healthy individuals or patients with inflammatory skin disease.[15,16] Although a subjective test, the Sézary cell prep is, nonetheless, useful as there are situations where the typical cell surface markers are lacking on the malignant lymphocytes and the abnormal cell population would otherwise be missed on flow cytometry. Flow cytometry offers an objective test of potential blood involvement and is particularly useful when focused on those parameters that have been found to be associated with blood involvement in MF and SS (ie, CD4/CD8 ratio, CD4+CD26− and CD4+CD7− lymphocytes).

The percentage and absolute numbers of both Sézary cells and abnormal cells by flow cytometry are used to determine blood staging, which is divided into B_0, B_1, and B_2 (**Table 2**). B_0 is essentially normal, and B_2 indicates a significant blood tumor burden that moves a patient to a stage equal to nodal lymphoma. The absolute number of abnormal lymphocytes is a mathematical computation of the absolute number of lymphocytes multiplied by either the percent of Sézary cells/100 or the percent abnormal cells by flow cytometry/100.

A blood TCR GR clonality study is important to perform to help assess B status. B_2 blood involvement, according to the ISCL/EORTC consensus criteria, must also include a clone of the TCR GR in the blood. Although the guidelines did not specifically require the clone in the blood to match that of the skin, this is more or less understood that it should. Left unsaid is what to do when a patient has a high Sézary cell count or abnormal cells on flow cytometry but a different clone in the blood than in the skin. There are T-cell clones seen in the blood that increase with age and would not be expected to match the malignant clone in the skin. The author's personal approach is to note B_0-B_2 based on the total abnormal lymphocyte number and separate notation for clonality for all B ratings including +/+ for a positive clone in the blood that matches the same clone as in skin, +/− for a positive clone in the blood but a different or absent clone in the skin, −/+ for no clone in the blood and a positive clone in the skin, and −/− for no clone in either blood or skin. The same method of testing for clonality in the blood should be done as that performed in the skin.

The specific designation of SS, as noted by the ISCL and USCLC,[17] implies that a patient has erythroderma and B_2 blood involvement with a positive clone.

Radiology

In cases when the skin examination would be characterized as T_1, there are no abnormal

Table 2
ISCL/EORTC/USCLC revisions to the TNMB classification of MF/SS

TNMB Classification	Description of TNMB
Skin	
T_1	Limited patches, papules, and/or plaques covering <10% of the skin surface; may further stratify into T_{1a} (patch only) vs T_{1b} (plaque +/− patch)
T_2	Patches, papules, or plaques covering ≥10% of the skin surface; may further stratify into T_{2a} (patch only) vs T_{2b} (plaque +/− patch)
T_3	One or more tumors (≥1 cm diameter)
T_4	Confluence of erythema covering ≥80% BSA
Node	
N_0	No clinically abnormal peripheral or central lymph nodes; biopsy not required
N_1	Clinically abnormal peripheral or central lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2}
N_{1a}	Clone negative
N_{1b}	Clone positive
N_2	Clinically abnormal peripheral or central lymph nodes; histopathology Dutch grade 2 or NCI LN_3
N_{2a}	Clone negative
N_{2b}	Clone positive
N_3	Clinically abnormal peripheral or central lymph nodes; histopathology Dutch grade 3–4 or NCI LN_4 Clone positive or negative
N_x	Clinically abnormal peripheral or central lymph nodes, no histologic confirmation
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation, and organ involved should be specified)
Blood	
B_0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sézary cells); <15% CD4+CD7− or CD4+CD26− cells; or <250/ul Sézary cells, CD4+CD7− or CD4+CD26− cells
B_{0a}	Clone negative
B_{0b}	Clone positive
B_1	Low blood tumor burden: >5% of peripheral blood lymphocytes are atypical (Sézary) cells greater than B_0 criteria but does not meet the criteria of B_2
B_{1a}	Clone negative
B_{1b}	Clone positive
B_2	High blood tumor burden: >1000/uL Sézary cells, CD4+CD7− or CD4+CD26− cells; or >40% CD4+CD7-cells; or >30% CD4+CD26- cells; or CD4/CD8 >10; with positive clone

Adapted from Olsen EA, Whittaker S, Kim YH, et al. Clinical endpoints and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC), and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). J Clin Oncol 2011;29:2598–607; and *From* Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions of the staging and classification of mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:1715.

nodes on physical examination and the blood staging is B_0, only a chest radiograph is recommended to screen for visceral disease. For all other cases, imaging is recommended to complete staging. Computed tomography (CT) scans of the chest, abdomen, and pelvis +/− neck are recommended to assess visceral and nodal disease: contrast enhances the ability to size the nodes and is preferred unless there is renal impairment or contrast allergy. PET scans

are not specifically recommended in MF/SS, although some reports suggest they add staging accuracy.[18] MRI may be used instead of CT but is usually reserved for cases where there is a history of contrast allergy.

Biopsies

Liver and spleen involvement can usually be designated as lymphoma by imaging studies alone, but other solid organs require a biopsy for confirmation. Bone marrow (BM) biopsy in MF is not generally recommended unless there is an unexplained hematologic abnormality exclusive of the abnormal lymphocytic population; if performed, a positive BM biopsy would not be considered visceral involvement if B_2 blood involvement already exists.

Any lymph node that is 1.5 cm or greater in the short axis would be considered suspicious of lymphoma and an excisional biopsy versus a core biopsy or fine-needle aspirate (FNA) recommended. In contradistinction to the other cutaneous lymphomas, there is a gradation of involvement histologically in the lymph node of MF or SS that falls short of lymphoma (so-called dermatopathic lymph node, LN1–LN3), which depends on the architectural features of the lymph node, features that cannot be discriminated from frank lymphoma by core biopsy or FNA. The lymph node or N staging is detailed in **Table 2**. The exception to an excisional biopsy is if the only lymph node that is enlarged is a central one that would require significant surgical risk to remove or if there is only a need to establish a similar process to that in the skin or blood; in that case, a core biopsy with flow cytometry and clonal TCR GR studies may suffice. If any enlarged nodes are not biopsied, the designation in staging should be Nx.

Table 3
ISCL/EORTC revisions to the staging of MF/SS

Stage	T	N	M	B
IA	1	0	0	0, 1
IB	2	0	0	0, 1
IIA	1–2	1, 2	0	0, 1
IIB	3	0–2	0	0, 1
IIIA	4	0–2	0	0
IIIB	4	0–2	0	1
IVA_1	1–4	0–2	0	2
IVA_2	1–4	3	0	0–2
IVB	1–4	0–3	1	0–2

From Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:1719.

Table 4
Modified severity weighted assessment tool

Body Region (% BSA)	Patch[a]	Plaque[b]	Tumor[c]
Head (7%)			
Neck (2%)			
Anterior trunk (13%)			
Arms (8%)			
Forearms (6%)			
Hands (5%)			
Posterior trunk (13%)			
Buttocks (5%)			
Thighs (19%)			
Legs (14%)			
Feet (7%)			
Groin (1%)			
Subtotal of lesion BSA			
Weighting factor	1	2	4
Subtotal lesion BSA × weighting factor			
mSWAT score = summation of each column line in final row above			

[a] Patch = any size lesion without significant elevation above the surrounding uninvolved skin or induration;
[b] plaque = any size lesion that is elevated or indurated;
[c] tumor = any solid or nodular lesion ≥1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

From Olsen EA, Whittaker S, Kim YH, et al. Clinical endpoints and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC), and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). J Clin Oncol 2011;29:2598–607.

Staging

Once the individual classification of TNMB has been determined, then these can be rolled into the staging system for MF and SS (**Table 3**). In a departure from how the term staging is used with other NHLs, the TNMB characterization of stage

in MF/SS can be noted as initial as well as maximum and current stage. It is not uncommon for patients with MF to present with $T_2N_0M_0B_0$ (stage IB) disease, progress to $T_3N_0M_0B_0$ (stage IIB) disease, be treated, and then currently have $T_1N_0M_0B_0$ (stage IA) disease. Without the communication of all these TNMB classifications (stages), especially in consideration of a clinical trial, a given patient's risk for progressive disease would not be fully communicated or information generated to help determine best treatments.

Response Assessment

It is important to note how the response to a given treatment is assessed as most papers in this issue relate to treatment. The methods in clinical trials of MF/SS since 2001 have used either the Severity Weighted Assessment Tool (SWAT) or modified SWAT (mSWAT) score, which involves determining the percentage BSA covered by patch, plaque, or tumor of MF/SS, then multiplying each lesion BSA by a factor that gives gradations of weight to patch versus plaque versus tumor and summing these scores (**Table 4**).[19,20] The change in SWAT or mSWAT from the beginning of treatment can be used to assess overall response. Complete response (CR) in the skin is defined as complete clinical clearing, partial response (PR) as 50% to 99% clearing, and objective response (OR) as the combination of CR and PR (**Table 5**).[20] There are scoring systems to assess local response in the skin to agents applied to limited BSAs, but agents used in this manner are not able to prevent new lesions from occurring outside the treated areas. There is a global scoring system that addresses the entire TMNB spectrum (**Table 6**) which is heavily weighted to the response in skin[20]; this has only recently been developed, and most treatment studies in the past have only addressed the response in the skin.

Table 5
Response in skin in MF and SS

Complete response	100% clearance of skin lesions. If there is any question of postinflammatory changes or xerotic skin vs residual disease, confirmation of clearing is also necessary in a representative biopsy or biopsies. If a biopsy of questionable residual disease is positive (meets the criteria of early MF[9]), then the response should be labeled as partial response.
Partial response	50%–99% clearance of skin disease from baseline without new tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease.
Stable disease	<25% increase to <50% clearance in skin disease from baseline without new tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease.
Progressive disease	≥25% increase in skin disease from baseline or new tumors (T_3) in patients with T_1, T_2, or T_4 only skin disease.
Relapse	Any disease recurrence in those with complete response

From Olsen EA, Whittaker S, Kim YH, et al. Clinical endpoints and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC), and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). J Clin Oncol 2011;29:2598–607.

Table 6
Global response score for MF and SS

Global	Skin	Nodes	Blood	Viscera
CR	CR	All categories have CR/NI.		
PR	CR	All categories do not have a CR/NI, and no category has a PD.		
PR	PR	No category has a PD and if any category is involved at baseline, at least one has a CR or PR.		
SD	PR	No category has a PD and if any category is involved at baseline, no CR or PR in any.		
SD	SD	CR, PR, SD in any category and no category has a PD.		
PD	PD in any category.			
Relapse	Relapse in any category.			

Abbreviations: NI, noninvolved; PD, progressive disease; SD, stable disease.

From Olsen EA, Whittaker S, Kim YH, et al. Clinical endpoints and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC), and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). J Clin Oncol 2011;29:2598–607.

NON-MYCOSIS FUNGOIDES AND NON-SÉZARY SYNDROME CUTANEOUS T-CELL LYMPHOMAS

Incidence and Prognosis

The most common types of the non-MF/non-SS CTCLs are the two CD30+ lymphoproliferative disorders (LPDs) (ie, primary cutaneous anaplastic large cell lymphoma [PCALCL] and lymphomatoid papulosis [LyP]). These CD30+ LPDs represent the most common differential diagnosis for MF. The prognosis for PCALCL, which, by its definition, excludes any extracutaneous disease at diagnosis, is excellent with treatment but like MF/SS, there is no cure currently, and continued treatment and vigilance must be used to prevent internal spread. The prognosis for LyP is excellent, with the potential for any internal spread being extremely rare.[21] LyP not uncommonly occurs with MF/SS and is discriminated from MF by its presentation (usually papules of a self-remitting nature) and biopsy findings consistent with one of 5 subtypes (see the article by Kempf in this issue).

The other types of non-MF/non-SS CTCLs are rare and also much more concerning in their prognosis compared with the CD30+ LPDs. Many present with tumors with the main differential being other primary CTCLs, primary CBCLs, systemic T- or B-cell lymphomas with skin metastasis, or even pseudolymphomas. Histologic methods for assessing these other subtypes are discussed further in Dr Kempf's article in this issue. Readers are directed to publications on each of these cutaneous T-cell tumor subtypes for further specifics on prognosis and treatment.

Diagnosis

Like MF/SS, diagnosis of the CD30+ LPDs begins with a skin biopsy; but even more importantly than in MF, the clinical history is key to the final diagnosis. Both PCALCL and LyP are characterized histologically by CD30+ T cells (typically CD4+) that have at least 25% of the lymphocyte population defined as large cells.[21] The latter may also be seen in patients with MF with so-called LCT, usually in patients with tumor stage disease. In this case, the diagnosis of MF with LCT versus PCALCL is made by the type of other lesions present: patients with MF typically also have patches/plaques that have classic histology for MF, which is absent in PCALCL. LyP lesions are small and self-remitting, whereas MF does not spontaneously improve; PCALC lesions are generally larger than Lyp lesions and more persistent. However, when the percentage of large cells exceeds 75%, the diagnosis is more likely PCALCL than MF.[21] The histologic findings and clinical parameters of PCALCL and LyP are discussed further in articles by Drs Kempf and Hughey in this issue.

Evaluation

Clinical assessment

Like MF and SS, a full physical examination of patients with possible non-MF/non-SS CTCL is important at baseline. Unlike MF/SS, any lymph node that is 1 cm or greater would be of concern in these patients. Peripheral or central lymph nodes can be further evaluated by core biopsy or FNA with flow and TCR GR clonality studies, because, in contradistinction to that in MF and SS, there is no equivalent to dermatopathic nodes in these other CTCLs which would require an excisional biopsy to differentiate from frank lymphoma.

Blood work

The basic blood tests to perform in suspected non-MF/non-SS CTCL include a CBC with differential, complete metabolic panel, and LDH. Because there is no blood tumor burden with these conditions, the only reason to do a Sézary cell prep or blood flow cytometry would be to exclude MF/SS in cases where the diagnosis is hazy. BM biopsy is not recommended in LyP, and guidelines on its use in the other CTCLs are not clear.

Radiology

PET/CT is recommended for the assessment of the non-MF and non-SS CTCLs and all CBCLs.

Biopsies

Any abnormality noted on imaging should be further assessed, and either a core biopsy or FNA of lymph nodes or visceral organs suspected of lymphoma should suffice. If there is any confirmation of extracutaneous disease, these CTCLs would no longer be classified as primary cutaneous but rather as a systemic lymphoma. However, in a confusing area, the literature allows for patients with PCALCL and a single regional lymph node to remain characterized as PCALCL.

Staging

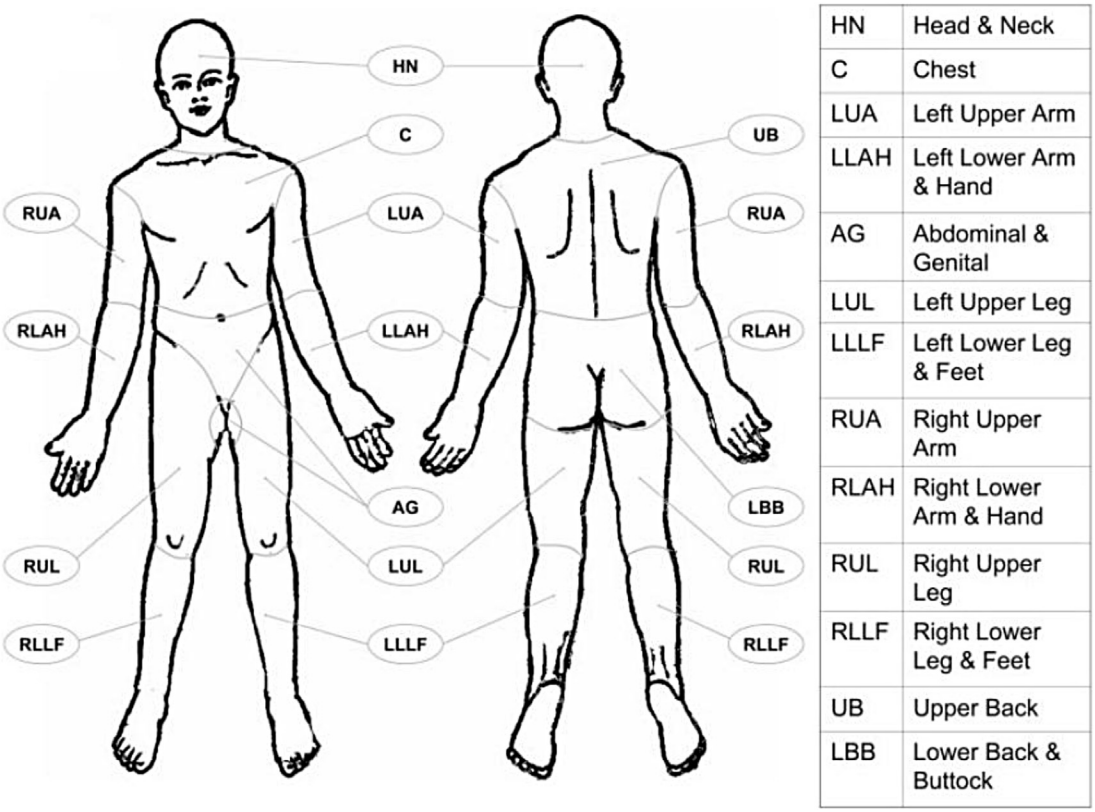
The staging of non-MF/non-SS CTCLs is different than MF and SS and is the same as the primary CBCLs (**Table 7**, **Fig. 1**). The major difference from MF/SS relates to the characterization of the skin lesions according to size and location relative to lymph node drainage regions versus the type of skin lesions and percentage BSA covered used to classify MF/SS. The staging of LyP defies capture by current staging systems as the lesions are in a constant state of flux and occur diffusely over the body surface.

Table 7
ISCL/EORTC TNM classification of cutaneous lymphomas other than MF/SS

Classification		Description
Skin (T)	T1	Solitary skin involvement
	T1a	Solitary lesion <5 cm diameter
	T1b	Solitary lesion ≥5 cm diameter
	T2	Regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions
	T2a	All disease encompassing a <15 cm diameter circular area
	T2b	All disease encompassing a 15 to ≤30 cm diameter circular area
	T2c	All disease encompassing a ≥30 cm diameter circular area
	T3	Generalized skin involvement
	T3a	Multiple lesions involving 2 noncontiguous body regions
	T3b	Multiple lesions involving ≥3 body regions
Lymph nodes (N)	N0	No clinical or pathologic lymph node involvement
	N1	Involvement of one peripheral or central lymph node region that drains an area of current or prior skin involvement
	N2	Involvement of ≥2 peripheral or central lymph node regions or involvement of any lymph node region that does not drain in an area of current or prior skin involvement
	N3	Involvement of central lymph nodes
Viscera (M)	M0	No evidence of extracutaneous non–lymph node disease
	M1	Extracutaneous non–lymph node disease present

T= any type of skin lesion.

Adapted from Kim YH, Willemze R, Pimpinelli N, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110(2):480.



HN	Head & Neck
C	Chest
LUA	Left Upper Arm
LLAH	Left Lower Arm & Hand
AG	Abdominal & Genital
LUL	Left Upper Leg
LLLF	Left Lower Leg & Feet
RUA	Right Upper Arm
RLAH	Right Lower Arm & Hand
RUL	Right Upper Leg
RLLF	Right Lower Leg & Feet
UB	Upper Back
LBB	Lower Back & Buttock

Fig. 1. Body regions defined in the TNM designation of skin involvement (T designation). These body areas are based on regional lymph node drainage patterns. (*From* Kim YH, Willemze R, Pimpinelli N, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110(2):479–84.)

Response Assessment

There is no mSWAT equivalent for the non-MF/non-SS CTCLs, although in many cases, the mSWAT for skin would suffice. CR, PR, and OR in the skin are as defined for MF/SS. A global scoring system has been published for LyP (**Table 8**) and PCALCL (**Table 9**) with potential for the latter to be used for other non-MF/non-SS PCLs.

Table 8
LyP response in skin

CR	100% clearance of skin lesions
PR	50%–99% clearance of skin disease from baseline without new larger and persistent nodules/tumors[b] in those with papular disease only
SD	<50% increase to <50% clearance in skin disease from baseline without new larger and persistent nodules/tumors in those with papular disease only
IDA[a]	>50% increase in skin disease from baseline without larger and persistent nodules/tumors[b]
PD[c]	1. Occurrence of larger and persistent nodules/tumors if not present before 2. Extracutaneous spread
Relapse	Any disease recurrence in those with CR

Persistent lesions are defined as lesions that do not show spontaneous regression after 12 weeks.
Abbreviations: IDA, increased disease activity; PD, progressive disease; SD, stable disease.
[a] The term *increased disease activity* indicates an increased number of papulonodular lesions (<2 cm), which do not imply impaired prognosis.
[b] Larger lesions are defined as greater than 2 cm in diameter.
[c] Whichever criterion appears first.
Adapted from Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood 2011;118(15):4024–35.

Table 9
Global disease response score in PCALCL

Global Score	Definition	Skin	Nodes	Viscera
CR	Complete disappearance of all clinical evidence of disease	CR	Both categories have CR or NI.	
PR	Partial response of measurable disease	CR	Both categories do not have a CR/NI, and neither category has a PD.	
		PR	No category has a PD; if either category is involved at baseline, at least one has a CR or PR.	
SD	Failure to attain CR, PR, or PD representative of all disease	PR	No category has a PD and if either involved at baseline, no CR or PR in either.	
		SD	There is CR/NI, PR, or SD in any category and neither category has a PD.	
PD	Progressive disease	PD in any category		
Relapse	Recurrence of disease in prior CR	Relapse in any category		

Abbreviation: NI, noninvolved.
Adapted from Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood 2011;118(15):4024–35.

CUTANEOUS B-CELL LYMPHOMAS

Incidence

There are 3 main types of primary CBCL (ie, primary cutaneous marginal zone lymphoma [MZL], follicular center cell lymphoma (FCCL), and diffuse large B-cell lymphoma, leg type). Each usually presents with infiltrated plaques, nodules, or tumors but each subtype has its own histology, typical location, potential for progression, and current treatment algorithm. This is discussed in greater detail in the articles by Drs Kempf and Pinter-Brown elsewhere in this issue.

Diagnosis

Like the CTCLs, the CBCLs can be diagnosed by a combination of H&E, immunophenotyping, and B-cell clonality studies (immunoglobulin heavy or light chain rearrangement) performed on representative skin lesions. The diagnosis hinges much more on positive clonality than the T-cell lymphomas, and there may be difficulty in distinguishing these from pseudolymphomas, which also typically present clinically with thick plaques or tumors. The presence of an abnormal lymph node may lead to a final diagnosis: however if positive for lymphoma, patients would be viewed as having a systemic lymphoma with skin manifestations versus a PCL.

Evaluation

Clinical assessment

A full physical examination is necessary with any lymph node that is 1 cm or greater in diameter considered abnormal.

Blood work

The basic blood tests to perform in primary CBCL include a CBC with differential, complete metabolic panel, and LDH. There is no leukemic counterpart to the CBCLs as there is with MF/SS. An evaluation for paraprotein may be done in PCMZL.

Radiology

PET/CT is recommended for assessment of all CBCLs.

Biopsies

Any abnormality should be further assessed and either a core biopsy or FNA for suspected lymph nodes or visceral involvement would suffice. BM biopsy is required in diffuse large B-cell lymphoma, leg type, should be considered in PCFCCL and is not required in PCMZL. If there is any confirmation of extracutaneous disease, patients would no longer be classified as having a primary CBCL but rather as having a systemic B-cell lymphoma.

Staging

The staging of CBCLs is as with the non-MF/non-SS CTCLs (see **Table 7**) with emphasis on the characterization of the skin lesions according to size and location relative to the lymph node drainage regions.

Response Assessment

CR, PR, and OR in the skin are as previously noted. A global scoring system has been devised but not yet published although the one used for PCALCL could be utilized in the interim.

SUMMARY

The cutaneous lymphomas are a heterogeneous group of NHLs that are concerning for multiple reasons: (1) the incidence is on the rise, (2) there is no cure with current existing therapies, (3) they often require life-long treatment with systemic medications in order to prevent progression and to maintain quality of life and (4) some types and some stages of all types of cutaneous lymphoma have a very poor prognosis. The prognosis may be best related to maximum TNM or TNMB classification and treatment ideally planned based on both maximum and current TNM(B) classification; this is not currently considered in treatment algorithms and is something a registry will be able to sort out. The collective efforts of investigators in the clinical and basic research realm and a national registry of all patients with cutaneous lymphoma give patients the best chance of finding a cure for these rare and uncommon cancers.

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