(Mycosis Fungoides) **no patient handout** Cutaneous T-cell lymphoma in Child/Adult

Contributors: Vivian Wong MD, PhD, Belinda Tan MD, PhD, Susan Burgin MD

Synopsis

Mycosis FungoidesPrimary cutaneous lymphomas may be either of T- or **B-cell** origin. Cutaneous T-cell lymphomas (CTCLs) account for 75%-80% of these lymphomas and are a heterogeneous group of neoplasms that vary considerably in their clinical presentation, histology, immunophenotype, genetics, and prognosis. CTCLs are seen most often in the elderly, but they can occur in patients of all ages. The definitive diagnosis of CTCL may require large or multiple biopsies as well as specialized testing of the biopsy specimens. Typing of the CTCL and staging are important to determine the extent of disease and treatment strategy.

Mycosis fungoides and its variants (folliculotropic mycosis fungoides, pagetoid reticulosis, and granulomatous slack skin), Sézary syndrome, **lymphomatoid papulosis**, and **cutaneous anaplastic large cell lymphoma** make up 90% of all CTCL cases.

This summary focuses on mycosis fungoides and variants and Sézary syndrome.

Other types of CTCL discussed separately include **subcutaneous panniculitis-like T-cell lymphoma**, **adult T-cell leukemia / lymphoma**, and **nasal type extranodal NK/T-cell lymphoma**.

Mycosis Fungoides

Mycosis fungoides (MF) is the most common type of CTCL, accounting for 50% of all primary CTCL cases. Erythematous patches and plaques with fine scale and tumors that anatomically favor the buttocks and sun-protected areas of the trunk and limbs characterize this subtype. The etiology remains unclear. Current hypotheses propose that persistent antigenic stimulation occurs and that CD8+ T-cells play a critical role. MF takes on an indolent course over years to decades. Associated features include pruritus, poikiloderma, and ulceration of tumors. Extracutaneous involvement correlates with generalized skin involvement and erythroderma. Neoplastic T-cells demonstrate a memory T-cell phenotype: CD3+, CD4+, CD45RO+. MF staging requires CTCL physician specialists. Some consider **large plaque parapsoriasis** to be early patch stage MF.

MF is approximately twice as common in men as in women, and sex differences in incidence increase with age. In the United States, individuals of African descent have twice the incidence of individuals of Northern European descent, though this difference decreases with age. MF is mostly seen in older adults (median age at presentation is 50-55 years), although any age group may be affected. Onset of disease may occur at an earlier age (before age 40), and this has especially been reported in people of African descent and US women of Hispanic descent. Although the clinical course of MF usually progresses slowly, US patients of African descent, especially women with early-onset disease, have a worse prognosis than other groups.

Hypopigmented MF – A hypopigmented variant of MF is seen primarily in individuals of African descent but has also been reported in those of Asian, Indian, and Latin American descent. This is the most common variant in children.

Folliculotropic MF – Folliculotropic MF (FMF, also known as follicular MF or pilotropic MF) is the most common variant of MF (6% of all CTCL), characterized by lesions on the head and neck clinically and follicular involvement ("folliculotropism") microscopically. Most cases are seen in adult males, but children and adolescents may also be affected. Early stage (IA, IB) disease with patches and plaques with follicular accentuation and keratosis pilaris-like or acneiform lesions may exhibit better prognosis with an indolent course. These lesions have a predilection for the trunk and extremities. On the other hand, advanced stage (IIB) disease with indurated or infiltrative alopecic plaques and tumors may be more aggressive with poorer prognosis. These lesions favor the head and neck and are more pruritic. 5-year survival rate approaches 80%.

Pagetoid reticulosis – Pagetoid reticulosis, also known as Woringer-Kolopp disease, represents approximately 1% of all cases of CTCL. It is a localized variant of MF, characterized by a solitary, slow-growing patch or plaque on a distal extremity clinically and striking epidermotropism microscopically. Pagetoid reticulosis has a predilection for middle-aged males but it can be seen in any age group. Prognosis is excellent with a 100% 5-year survival rate.

Ketron-Goodman disease is a disseminated and aggressive variant of pagetoid reticulosis with a potential for systemic involvement.

Granulomatous slack skin – Granulomatous slack skin, also known as granulomatous dermohypodermitis, is a rare variant of CTCL (<1% of all cases). It is characterized by asymptomatic pendulous loose skin masses in the body folds clinically, and granulomatous T-cell infiltration microscopically. The disease may be associated with a lymphoproliferative disorder, such as MF, **Hodgkin lymphoma**, and **non-Hodgkin lymphoma**. Males in the third and fourth decades are more commonly affected. Overall, prognosis is good with a 100% 5-year survival rate.

Sézary Syndrome
Sézary syndrome accounts for less than 5% of all primary CTCL cases. Erythroderma, generalized lymphadenopathy, and neoplastic T-cells (Sézary cells) in the skin and peripheral lymph nodes classically characterize Sézary syndrome. Associated features include severe pruritus, palmoplantar hyperkeratosis, lichenification, edema, and exfoliation. The etiology remains largely unknown. Immunophenotyping demonstrating a CD4:CD8 ratio of >10, an absolute count of >1000 Sézary cells per μL, and demonstration of T-cell clonality in the peripheral blood are diagnostic criteria. The prognosis is poor, with a 24% 5-year survival.

Codes

ICD10CM:
C84.00 – Mycosis fungoides, unspecified site

SNOMEDCT:
118618005 – Mycosis fungoides

Look For

MF
Patch and plaque stage MF presents as patches or thin plaques with fine scale that measure 2-20 cm and favor the sun-protected areas of the body, including buttocks and posterior axillary folds. A classic feature of patches is a wrinkled surface that resembles "cigarette-paper." A poikilodermatous variant of patch stage MF comprises atrophy, telangiectasias, and hyper- and hypopigmentation. Annular, serpiginous, horseshoe-shaped and bizarrely shaped plaques are frequently seen in plaque stage disease. Tumor stage MF presents with violaceous, exophytic tumors that predominantly affect the face and body folds. Tumors often undergo ulceration or necrosis and secondary infection. Pruritus may be severe.

Hypopigmented MF – In this variant, hypopigmented patches predominate. Fine scales may be seen.

Folliculotropic MF – This variant presents as patches and plaques with follicular prominence, or with keratosis pilaris-like or acneiform lesions, that favor the trunk and extremities. Later, indurated or infiltrative alopecic plaques and tumors are seen, favoring the head and neck, especially the scalp and face. Lesions are typically more pruritic.

Pagetoid reticulosis – This presents as large localized erythematous patches or plaques on the distal extremities of a middle-aged male. The lesions are slow-growing and indolent. Verrucous and hyperkeratotic plaques may also be found. In the generalized form, there are disseminated plaques on the neck, trunk and extremities.

Granulomatous slack skin – This presents as asymptomatic red or violet infiltrated patches and plaques with poikilodermatous surfaces in body folds, particularly on the axillae and groin. The plaques can become bulky with pendulous masses resembling cutis laxa. There may be mild pruritus.

Sézary Syndrome
Look for erythroderma and generalized lymphadenopathy. Associated features include extreme pruritus, palmoplantar hyperkeratosis, lichenification, edema, and exfoliation. Often, there are alternating bands of pigment and erythema with uninvolved skin around flexural areas known as the "deck chair" sign or "folded luggage" sign. Infiltrative plaques occurring on the face may result in exaggeration of normal skin folds, known as a lion-like face, or leonine facies.

Diagnostic Pearls

Many patients have a long history of generalized eczematous or psoriasiform dermatitis before being diagnosed with MF.

Previous treatment with phototherapy, topical steroids, and immunosuppressants can profoundly change the histology of the lesion and make diagnosis difficult. Repeat biopsies after suspension of any treatment may be required to make a diagnosis.

- Ideal biopsy: one or more broad shave biopsies in previously untreated skin for patches or thin plaques. For tumor stage MF, a 5-8 mm punch biopsy should be performed.
- Early patch stage disease may have nondiagnostic histopathology and repeated biopsies may be necessary to clinch the diagnosis.
- Immunophenotyping utilizes fluorescently tagged antibodies that recognize cell surface markers. For example, loss of CD3, CD4, or CD5 surface expression in neoplastic T-cells assists in making the diagnosis.
- T-cell gene rearrangement analysis: This should be used in conjunction with the overlying clinical, histological, and immunophenotyping findings. Note that clonal T-cells can be found in benign inflammatory conditions such as lichen sclerosus, lichen planus, and pityriasis lichenoides et varioliformis acuta, and hence they support but never exclusively confirm a diagnosis of CTCL.

Differential Diagnosis & Pitfalls

MF:

- **Psoriasis** – Look for erythematous silver-scaled plaques, nail oil-drop changes, and nail pitting. A family history of psoriasis is often noted. Psoriasis and CTCL are histologically different, and a biopsy will aid in the diagnosis.
- **Atopic dermatitis** – Patients are often aware of their atopic history, which commonly starts in childhood. Mild to moderate spongiosis is seen on histology. Look for lichenified plaques on the flexural surfaces and neck.
- Superficial fungal infections (eg, **tinea corporis**) – Erythematous plaques with a raised, red scaling border. Central clearing is more common in tinea corporis. Check KOH.
- **Seborrheic dermatitis** – Sebaceous distribution of erythematous scaling plaques. Chronic history of mesiolabial, glabellar, auricular pruritus, erythema, scale.
- Chronic contact dermatitis (**allergic**, **irritant**) – Bright red erythematous or vesiculating plaques.
- **Small plaque parapsoriasis**
- **Pityriasis rubra pilaris** (PRP) – Look for orange-red, waxy-like keratoderma of the palms and soles. Islands of normal skin within larger plaques are characteristically seen in PRP. PRP and MF are histologically different, and a biopsy will aid in the diagnosis.
- **Pityriasis lichenoides et varioliformis acuta** – Papules and nodules in various stages of healing. Central necrosis can be noted in some papules, like lymphomatoid papulosis.

- **Secondary syphilis** – Generalized scaling papules and plaques. Can involve the palms and soles. Check rapid plasma reagin (RPR), history of chancre.
- **Pityriasis rosea** – Herald patch, scaly papules / plaques on trunk. Crusts / vesicles / bullae not a common finding.
- **Lichen planus** – Very pruritic, flat-topped violaceous papules with fine scale. Associated with hepatitis C.
- **Lepromatous leprosy**
- **Sarcoidosis**
- Leishmaniasis (**Old World** or **New World**)

MF hypopigmented variant:

- **Vitiligo**
- **Pityriasis alba**
- **Tinea versicolor**
- **Sarcoidosis**
- **Postinflammatory hypopigmentation**

MF tumor stage:

- **Leukemia cutis**
- **B-cell lymphoma**
- **Pseudolymphoma**

Folliculotropic MF:

- **Acne vulgaris**
- **Folliculitis**
- **Keratosis pilaris**
- **Lymphomatoid papulosis**
- **Drug eruption**

Pagetoid reticulosis:

- **Eczema**
- **Psoriasis**
- **Paget disease**
- **Cutaneous tuberculosis**
- **Lupus erythematosus**
- **Adult T-cell lymphoma / leukemia**
- **Cutaneous B-cell lymphoma**
- **Leukemia cutis**
- **Pseudolymphoma**
- **Verruca vulgaris**

Granulomatous slack skin:

- **Cutis laxa**
- **Psoriasis**
- **Sarcoidosis**
- **Paget disease**
- **Granuloma annulare**
- Infectious granuloma
- Reticulohistiocytoma
- **Rosai-Dorfman disease**

Best Tests

Skin biopsy for basic histology, immunophenotyping, and T-cell receptor (TCR) gene analysis. Peripheral blood can be sent for TCR gene analysis.

CBC with differential and buffy coat smear with Sézary cell count. Also obtain CD4 and CD8 T-cell counts.

Consider obtaining human T-lymphotropic virus type-1 (HTLV-1) serology, as this virus can cause lesions that appear similar to MF.

Patients with clinically abnormal lymph nodes should have them biopsied, and the biopsy specimens should be examined by the same methods as the skin specimen(s).

CT imaging, chemistry panel and a bone marrow biopsy should all be considered, depending on clinical manifestations, for accurate staging.

Histopathology Findings:
MF – Common features

- Epidermotropism of neoplastic lymphocytes: lymphocytes aligned along the basal layer; lymphocytes within the epidermis but without associated spongiosis
- Pautrier microabscesses (epidermal collections of neoplastic lymphocytes)
- Atypical lymphocyte morphology: convoluted and "cerebriform" nuclei; epidermal lymphocytes larger than dermal
- Epidermis may be normal, atrophic, or show psoriasiform epidermal hyperplasia.
- Papillary dermal fibrosis
- Immunostains: neoplastic lymphocytes are often CD3/CD4 positive, less often CD3/CD8 positive.

MF – Occasional features

- Interface change
- Spongiosis
- Eosinophils and plasma cells in the dermis

Folliculotropic MF

- Folliculotropism, with perifollicular and intrafollicular atypical lymphocytic infiltrates and relative sparing of the epidermis. Follicular mucinosis may be noted. Advanced stage lesions may exhibit more perifollicular infiltrates with deeper infiltrate depth and eosinophils.

Pagetoid reticulosis

- Variable acanthosis and mild spongiosis with superficial dermal atypical lymphocytic infiltrate with remarkable epidermotropism.

Granulomatous slack skin

- Granulomatous proliferation of atypical T-lymphocytes with numerous multinucleated giant cells and elastophagocytosis and occasional emperipolesis
- Elastic stains can be used to demonstrate elastophagocytosis.
- The epidermis may be hyperkeratotic and psoriasiform with interstitial and perivascular inflammation.

Management Pearls

Patients should be staged. Staging for MF:

- Stage 1: Patches and plaques on less (1A) or more (1B) than 10% of the skin surface
- Stage 2: Lesions as with stage 1, plus nonmalignant lymphadenopathy (2A) or cutaneous tumors (2B)
- Stage 3: Erythroderma
- Stage 4: Malignant infiltration of lymph nodes (4A) or visceral organs (4B)

Patients, especially those with stage 1B disease or higher, should be managed in a multidisciplinary setting with consultations by dermatologists with expertise in cutaneous lymphoma and medical and radiation oncologists.

Therapy

MF

Stage 1 disease – Skin-directed therapies

Total body phototherapy – Ultraviolet B or psoralen with ultraviolet A (PUVA)

Topical corticosteroids may be used on limited lesions.

Superpotent corticosteroids (class 1) – Use cautiously, on lesional skin only:

- Clobetasol propionate – Apply every 12 hours (30, 60 gm), or
- Betamethasone dipropionate – Apply every 12 hours (30, 60 gm), or

- Halobetasol – Apply every 12 hours (20, 50 gm), or
- Diflorasone diacetate – Apply every 12 hours (15, 30, 60 gm).

High-potency topical corticosteroids (class 2):

- Fluocinonide cream, ointment – Apply every 12 hours (15, 30, 60, 120 gm), or
- Desoximetasone cream, ointment – Apply every 12 hours (15, 60, 120 gm), or
- Halcinonide cream, ointment – Apply every 12 hours (15, 60, 240 gm), or
- Amcinonide ointment – Apply every 12 hours (15, 30, 60 gm).

Mid-potency topical corticosteroids (class 3-4):

- Triamcinolone cream, ointment – Apply every 12 hours (15, 30, 60, 120, 240 gm), or
- Mometasone cream, ointment – Apply every 12 hours (15, 45 gm), or
- Fluocinolone ointment, cream – Apply every 12 hours (15, 30, 60 gm).

For localized disease unresponsive to the above treatments or more extensive disease, try one of the following topical therapies:

- Topical nitrogen mustard (mechlorethamine) – As an aqueous solution or in an ointment base, apply every 12 hours; or
- Valchlor* (mechlorethamine 0.016% gel), apply once daily, or
- Topical carmustine (BCNU) – As an aqueous solution or in an ointment base; apply every 12 hours, or
- Topical bexarotene gel – Apply every 12 hours, or
- Imiquimod 5% cream 3-5 times per week.

*FDA approved for topical treatment of stage IA and IB MF-type CTCL in adult patients who have received prior skin-directed therapy; contraindicated in pregnancy.

Additional treatments:

- Total skin electron-beam radiotherapy

- Interferon alpha – Start at 3 MU 3 times per week and increase up to 12 MU 3 times per week, as tolerated

Stage 2 disease

Therapies as for stage 1 disease (give more consideration to using interferon alpha or total skin electron beam therapy), plus local radiotherapy or low-dose methotrexate (5-12.5 mg p.o. weekly).

Combination therapy with PUVA and interferon alpha, or PUVA and acitretin or bexarotene can be used in relapsed or resistant cases. Denileukin diftitox and a histone deacetylase inhibitor (vorinostat, romidepsin) can be considered as second line therapy.

Stage 3 disease (erythroderma)

- Interferon alpha (as above)
- Low-dose methotrexate (as above)
- Low-dose chlorambucil and prednisone
- Oral bexarotene (as above)
- Extracorporeal photopheresis
- Denileukin diftitox and a histone deacetylase inhibitor (vorinostat, romidepsin) (as above)
- PUVA
- Total skin electron beam therapy
- Radiation to lymph nodes
- Some oncologists may recommend single agent or reduced-dose combination chemotherapy such as etoposide 100 mg/m2 IV for days 1-5.

Stage 4 disease

In addition to the treatments used for stage 2 and 3 disease, as above, stage 4 disease is often treated with combination chemotherapy. Agents that have had some treatment success include purine analogues (ie, fludarabine), bleomycin, vincristine, etoposide, and cisplatin.

Oral bexarotene, denileukin diftitox and allogeneic bone marrow transplantation have also been used for stage 4 disease.

Folliculotropic MF

There is no standard therapy. Oral bexarotene and PUVA have demonstrated success in case reports.

Pagetoid reticulosis
There is no standard therapy. The following therapies have been tried with moderate success:

- Oral bexarotene
- Topical bexarotene
- Radiation
- Photodynamic therapy
- Phototherapy
- Nitrogen mustard
- Excision
- Topical or intralesional steroids
- Imiquimod

Ketron-Goodman disease should be managed more aggressively given risk for systemic involvement.

Granulomatous slack skin
There is no standard treatment. It is typically treated using treatment modalities for MF.

Sézary syndrome
Systemic treatment is required.

- Interferon alpha (as above)
- Methotrexate (as above)
- Oral bexarotene (as above)
- Vorinostat
- Depsipeptide
- Extracorporeal photopheresis and PUVA as adjuvants
- Some oncologists may recommend single agent or combination chemotherapy.

Pruritus

- Hydroxyzine 25-50 mg every 6-8 hours, or
- Gabapentin 100-300 mg every 8 hours, or
- Aprepitant 80 mg daily.

Drug Reaction Data

Below is a list of drugs with literature evidence indicating an adverse association with this diagnosis. The list is continually updated through ongoing research and new medication approvals. Click on Citations to sort by number of citations or click on Medication to sort the medications alphabetically.

Medication	Citations
Calcineurin inhibitor	2
cyclosporine	2
etanercept	2
glatiramer acetate	1
infliximab	4
lithium	1