Mycosis Fungoides and Variants

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Classic mycosis fungoides

The most common cutaneous lymphoma is known historically as mycosis fungoides (MF), and represents about 50-60% of all cutaneous lymphomas. The broader term “cutaneous T-cell lymphoma” has also been applied to mycosis fungoides and related conditions such as Sézary syndrome, but it is important to recognize that there are several forms of T-cell lymphoma in the skin unrelated to mycosis fungoides, including CD30-positive large cell anaplastic lymphoma, subcutaneous panniculitic lymphoma, panniculitis T-cell lymphoma, and other miscellaneous peripheral T-cell lymphomas.

Clinically, MF typically presents as annular patches and plaques affecting sun-protected sites such as buttocks or axillae. Older adults are most commonly affected, but MF does occur in children as well. Disease progression is slow, with tumors developing in some patients as a late event. Transformation to large cell lymphoma is associated with a poor prognosis.

Histologically, the changes of MF are often subtle, requiring multiple biopsies over extended periods of time to secure a diagnosis. Various patterns of epidermotropism are useful criteria in the diagnosis of MF. “Disproportionate epidermotropism,” refers to significant numbers of intraepidermal lymphocytes disproportionate to the degree of spongiosis in the biopsy, and is helpful if not highly sensitive or specific criterion. Pantry’s microabscesses have been variably defined as clusters of few to several atypical lymphocytes in the epidermis, often in association with Langerhans cells. These cellular aggregates are nearly pathognomonic of MF; although they are typically seen in only a minority of early biopsies (with an incidence ranging for 3% to 30% depending on the study).

An important pattern of epidermotropism in MF is “linear basal epidermotropism.” For reasons unknown, the malignant lymphocytes in MF tend to line up along the basal layer of the epidermis like a “row of toy soldiers” or a “string of pearls.” This pattern is considered a highly sensitive, albeit less specific, feature of MF.

Another helpful histologic criterion is that of “bathed lymphocytes,” a term that reflects the tendency of malignant intraepidermal lymphocytes to show artifactual cytolytic retraction, giving the impression of halos around the nuclei. This feature has been reported in about 60% of MF, and 13% of inflammatory dermatoses, representing a fairly robust diagnostic criterion.

References:
Orbanza JG et al. Lymphomatoid contact dermatitis: a syndrome produced by epidermatous hypersensitivity with clinical features and histopathologic picture similar to that of mycosis fungoides. Contact Dermatitis 2, 139-143, 1976.

Drug-induced pseudolymphoma vs mycosis fungoides

There is ample attention in the literature to the problem of drug reactions mimicking MF. Drug induced pseudolymphoma, in particular due to Dilantin, exemplifies this phenomenon. In general, patients with this condition have a fever, generalized rash, and lymphadenopathy. However, there are also reports of cutaneous lesions resembling MF secondary to medications without systemic symptoms. Clearly, clinical history is essential in this differential diagnosis. Historically, it is difficult if not impossible to differentiate between drug induced pseudolymphoma and true MF. In addition, some drugs induced pseudolymphomas show clonal gene rearrangements, making a distinction by molecular methods suspect. Usually drug induced pseudolymphoma resolves with cessation of drug therapy and recovers with rechallenge.

Drugs mimicking MF

**CLINICAL MIMICS**
phenytoin
carbamazepine
flusoxetin

**HISTOLOGIC MIMICS**
phenytoin, carbamazepine
flusoxetin, enalapril, captoril, quinine
atenolol, phenobarbital
d-pensicillin
antihistaminic drugs

The finding of intraperidermal lymphocytes larger than dermal lymphocytes also strengthens the histologic diagnosis of MF. This feature reflects the fact that early in disease, a clonal malignant lymphoid population is present in the epidermis, while the dermal infiltrate typically is comprised of reactive CD8+ cytotoxic lymphocytes.

Finally, in a recent review by Santucci and colleagues, the finding of medium large cerebriform lymphocytes in the epidermis is reported to offer a higher degree of sensitivity and specificity in the diagnosis of MF. These cells are defined as lymphocytes with a nuclear diameter the same size or larger than neighboring keratinocytes (7-9 microns). Other studies question the helpfulness of this finding, either because such cells are infrequently present in MF, or because of the inherent interobserver variability in judging lymphocyte atypia.


Diagnostic pitfalls

Because so many inflammatory dermatoses mimic MF not only histologically but clinically as well, it has been suggested that the best way to rule out MF may be to make another diagnosis. Some of the common pitfalls are discussed briefly below.

**Spongiotic dermatitis vs mycosis fungoides**

Spongiotic dermatitis is one of the most common considerations in the clinical and histologic differential diagnosis of MF. Some forms of dermatitis in particular, such as allergic contact dermatitis, are notable for their close histologic similarity to MF (for which the term “lymphomatoid contact dermatitis” has been coined).

Histologically, the finding of nonlymphoid intraepidermal monocellular cell collections (pseudopancreatic microabscesses) favors the possibility of spongiotic dermatitis. These collections are distinguished by their classic shape in the epidermis, and by the presence of Langerhans cells and precursors (clinging CD1a+, S100+, CD68-, CD8+). However, since approximately 10% of cases of MF also feature spongiosis, the presence of pseudopapillar microabscesses alone does not confirm a benign diagnosis. In fact, in a study by Candiago, while pseudopapillary microabscesses were found in 43% of cases of spongiotic dermatitis, they were also observed in 13% of cases of MF. Subtle clues favoring the diagnosis of MF over spongiotic dermatitis in difficult cases include a spongiotic-pustuliform-lichenoid pattern, the presence of purpuric, epidermal atrophy and hypoplasia in a single silhouette, and a uniform laminated horn.

**References:**

**Lichenoid dermatitis (LP, LSA, PPE) vs mycosis fungoides**

The histologic distinction between some lichenomatous dermatoses and lichenoid presentations can be at times problematic. In a review of the distinction between early lichen sclerosis (LS) and lichen planus (LP), LeBoit et al noted that 100% of cases of early LSA show a pustuliform lichenoid pattern (also common in MF), 100% showed basal epidermotropism (as in MF), and 35% showed epidermal atrophy, also common in MF. While in that study, such features helped distinguish cases of LS from LP, the results underscore the potential similarities between LS and MF. Decreased elastic fibers and a thickened basement membrane favor LS, and are not typical in MF. Clearly, the clinical features should be helpful diagnostically as well.

Some cases of lichenoid MF closely resemble lichen planus (LP) histologically. Guitart et al published a series of cases of MF with lichenoid features bearing a close histologic resemblance to LP, but also showing plasma cells, eosinophils, lymphocyte atypia and prominent basal epidermotropism. Clinically, the cases were notable for intense pruritis and an accelerated course, suggesting that lichenoid MF may have a worse prognosis than other presentations of MF.

Examples of lichenoid pigmented purpura may share many histologic features with MF, and there is current debate whether this pigmented purpura dermatitis (PPPD) represent a simulans of MF, a precursor, or both. In a recent review of 56 patients with PPPD by Toro et al, 29 cases showed histologic patterns typical of MF. Further, clonal gene rearrangements were found in 8 of 12 specimens showing a lichenoid pattern of PPPD that resembled MF. There are also reports of PPPD preceding or occurring concurrently with MF, further suggesting a relationship between these processes. Interestingly, the first patient reported in the American literature as having lichen aureus later proved to have MF. Both PPPD and MF may show lymphocytes in the lower epidermis, linear epidermotropism, and papillary dermal infiltrate. Features favoring the diagnosis of MF include large collections of lymphocytes in the epidermis with many lymphocytes in the spinous layer, and lymphocytic atypia. The presence of edema of the papillary dermis favors the diagnosis of PPPD.

Another common entity which may closely mimic MF histologically is the benign lichenoid keratosis (BLK) or lichen planus-likes keratoses (LPK). Such cases are much less common, and are often difficult to distinguish from MF.

In general, clinical findings such as size and duration, and histologic findings such as epidermal destruction should enable a distinction between MF/LK and true solitary lesions of MF (see chart below).
unrelated to clinical parameters in any given case, and is not associated with the dramatic pendulous skin folds of... 138:191-198, 2002.


MFLK (1.LK, BLK, LPLK) Unilesional MF
trunk and extremities
small and scaly (< 1 cm)
short duration
clinically usually R/O CA
bx MF-like, epidermal destruction
polyclonal

References:

Further confusing our ability to make a definitive diagnosis of MF is the presence of many unusual clinical and histologic variants of this disease. The most common of these will be discussed below.

Woringer-Kolopp disease (pap gdyżt reticulosis)
In 1970, Woringer and Kolopp described a solitary cutaneous plaque on the foot of a 13-year-old child, characterized by intraepidermal lymphocytes. Since then, the term Woringer-Kolopp disease has been applied to solitary lesions of the skin with a histologic pattern typical of mycosis fungoides, analogous to Woringer-Kolopp disease, some of which do show gene rearrangements, and a few of which show progression to widespread MF. Clinically, lesions historically classified as Woringer-Kolopp disease favor acral sites; the term “mycosis fungoides palmaris et plantaris” has been applied to such lesions. In a recent report describing 20 lesions of solitary MF, Cerroni emphasized involvement of the trunk and extremities. All cases showed a band-like dermal infiltrate with epidermotropism, and moderate lymphocyte atypia. T cell receptor gene rearrangements were detected in half the cases tested. The authors concluded that cases of solitary MF exist, show a relatively indolent course, and can be treated conservatively, but should be followed for potential progression to more widespread disease.

References:

Granulomatous slack skin
Granulomatous slack skin is a rare and clinically dramatic disease, featuring large pendulous folds of skin typically in the axilla and groin, with erythema and swelling. There is a female predominance. Histologically, there are sheets of granulomas and lymphocytes in the dermis. Numerous giant cells are present, and are notable for containing 30 to 40 nuclei per cell. Elastic tissue stains demonstrate complete loss of elastic fibers throughout the dermis. Fragments of elastic fibers as well as lymphocytes are identified in multinucleated giant cells. The superficial dermis may contain features more typical of MF, including papillary dermal fibrosis, a band-like lymphocytic infiltrate, and epidermotropism. Molecular studies have revealed T cell clonality, further supporting the diagnosis of lymphoma. Cases tend to be indolent or slowly progressive. It should be noted that otherwise typical cases of MF sometimes also show granulomatous inflammation, the etiology of which is unclear. This change seems

References:

Hypopigmented mycosis fungoides
Another rare variant of mycosis fungoides presents with hypopigmentation. Although this variant is more common in dark-skinned patients, it can be seen in Caucasians as well. Younger patients seem more often affected by this disorder, with a median age of 15 years, and a female predominance in cases reported to date. Typically, clonality of epidermotropic T cells can be detected. The malignant clone is often composed of CD8+ rather than CD4+ lymphocytes. Persistent or unusual hypopigmented lesions, particularly in younger age groups, should be biopsied to assess the possibility of mycosis fungoides and enable prompt treatment.


Sezary Syndrome
The triad of erythroderma, generalized lymphadenopathy, and neoplastic T lymphocytes (Sezary cells) in the skin and blood defines Sezary syndrome. Importantly for the histopathologist, the cutaneous infiltrates of Sezary syndrome may not show specific features of MF, and diagnosis must be established by immunophenotypic and genotypic studies of the circulating lymphocytes in these patients. The prognosis is generally poor, and patients are at risk of opportunistic infection due to immunosuppression.

Primary cutaneous CD30+ lymphoproliferative disorders (CD30+ LPDs) are relatively uncommon, comprising approximately 30% of lymphoid neoplasms in primary skin, and are second in frequency only to mycosis fungoides.1 Cutaneous CD30+ LPD represents a biologic and histologic spectrum with lymphomatoid papulosis (a benign disorder with spontaneous regression) at one end2 and primary cutaneous anaplastic large cell lymphoma (C-ALCL), an indolent CD30+ lymphoma usually treated with local therapy2 at the other end.2 In between these borderline lesions that may defy definitive classification until time passes and the lesion “declares itself.” The classification of CD30+ LPD is predominantly based on the number and size of lesions, number of large CD30+ cells, and the clinical evolution of the lesion (progression versus regression).3 It is extremely important to distinguish C-ALCL from secondary involvement of the skin by systemic ALCL, an aggressive disease that requires multisystem chemotherapy.

### Topics for Discussion:

- Clinical and pathological features of primary cutaneous ALCL
- Pathogenesis of primary cutaneous ALCL
- Distinguishing primary cutaneous ALCL from systemic ALCL
- Treatment of primary cutaneous ALCL
- Clinical and pathological features of LP
- Relationship of primary cutaneous ALCL to LP
- Other lymphomas and reactive processes in the differential diagnosis of CD30+ LPD

#### Primary Cutaneous ALCL

**Definition of primary cutaneous ALCL:**

- Skin involvement without evidence of systemic disease
- No antecedent history of LP, mycosis fungoides, Hodgkin lymphomas, or other cutaneous T-cell lymphoma

*Cases with regional (draining) node involvement are problematic; it is uncertain if they have a different prognosis or if they should be included as primary cutaneous ALCL.*

1 One recent study has shown only a slightly decreased overall 5-year survival for primary cutaneous ALCL, versus cutaneous ALCL with regional node involvement (85% vs. 78%, respectively); however, it should be noted that 82% of the patients with regional node involvement received multimodal chemotherapy.

**Clinical features of primary cutaneous ALCL:**

- Older age, median 40-67 yrs (range 2-95 yrs; most over 50 yrs); pediatric C-ALCL is rare (< 2% of cases of C-ALCL)1,2,3
- Male to female ratio of 2:3-1
- Nodule (1-2 cm) tumor (≤2 cm rapidly growing); papule (< 1 cm) or plaque (3-5 cm)
- Solitary/multifocal; regional/multifocalized; multifocal disease is seen in approximately 20% - 25%
- Larger lesions are often ulcerated

**Distinguishing Primary Cutaneous ALCL from Systemic ALCL**

#### Importance of distinguishing primary versus secondary ALCL:

Skin involvement is seen in approximately 15% - 25% of systemic ALCL.2,3 Primary cutaneous ALCL has an excellent prognosis (80% - 100% overall 5 year survival; disease related survival ≥ 90%), whereas the prognosis of systemic ALCL with associated skin involvement is much less favorable.1-3 (see Table 1).

**How to distinguish primary cutaneous ALCL from systemic disease:**

- Careful staging is imperative; there are no footpath markers to distinguish
- ALK expression correlates with systemic disease (but is rarely seen in primary cutaneous ALCL)
- Morphologic histology is more often seen in systemic disease
- C-ALCL more pleomorphic, more RS-like cells and acute inflammatory cells
- Chastanet was initially reported as being exclusively expressed in systemic ALCL; Wollman et al., 2000 reported 100% of systemic ALCL and no primary cutaneous ALCL were positive, however a small number of cases were tested. Recent larger studies have shown clustet expression in approximately 41% - 100% of cases of primary cutaneous ALCL.4,5
- Cutaneous lymphocyte antigen (CLA) is more frequent in C-ALCL than systemic ALCL (44% vs. 18%, respectively)
Lymphomatoid Papulosis

Overlapping clinical and pathologic features indicate LyP and some cutaneous ALCL represent a continuous spectrum.70-75

Clinical features of LyP:7-14
- Adults (median age 45 years; male:female ratio 1.5:1)
- May occur in children7,15
- Multiple papular, papulonodular, or nodular lesions, usually <1 cm
- Extremities and trunk/face, genitalia
- Lesions usually appear and heal with a scar in 3-12 weeks
- Chronic, recurrent lesions; duration of several months to more than 40 years

Treatment:70
- None if few lesions and little scarring
- Low dose methotrexate (5-30 mg/wk) helps suppress development of new lesions
- PUVA and topical chemotherapy (relapses generally occur after the discontinuation)
- 5% - 20% are associated with lymphoma (MF, ALCL, or HL) after, concurrent with, or before the diagnosis of LyP.15,16
- Lymphoma arising in LyP (ALCL and MF) do not appear to have a more aggressive course.17,18

Histologic features of LyP:8
- Large atypical cells mixed with small lymphocytes, acute inflammatory cells
- Variable appearance depending on the stage of evolution (i.e., age) of the lesion
- Three histologic types:15,17,18
  - Type A
    - Wedge-shaped infiltrate, perivascular
    - Scattered CD3+ large atypical cells
    - Dense background of inflammatory cells; neutrophils, and/or eosinophils may be particularly prominent
  - Type B (less common, <5%)
    - Band-like dermal distribution
    - Lymphocytes with convoluted “cerebriform” nuclei
    - Some epidermotropism may be present
    - Large CD3+ cells are rare or absent
  - Distinguishable from mycosis fungoides on clinical parameters; LyP remits spontaneously and does not have extensive plaques and plaques
- Type C (diffuse large cell type)
  - Indistinguishable from ALCL except invasion of the subcutis is minimal or absent
- History of regression is the most important distinguishing feature
- May have extracutaneous spread, or true “borderline” lesions
- Variants include: follicular,19-21 and granulomatous (see note).22

Immunophenotype of LyP:23
- Most series report predominance of CD4+ phenotype, but some report CD8+24,25
- EMA present in up to 35% of LyP
- CD15+ in up to 33% in frozen tissue81
- TIA-1 and/or granzyme B expressed in 74% - 100% of LyP36, 37, 72

Table 2. Clinical Features Useful in Distinguishing ALCL and LyP

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>LyP</th>
<th>ALCL</th>
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<tr>
<td>Skin thickness</td>
<td>Rare</td>
<td>Abnormal</td>
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<tr>
<td>Palmar/periungual</td>
<td>Absent</td>
<td>Present</td>
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<tr>
<td>Mycetoma</td>
<td>Rare</td>
<td>Absent</td>
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<tr>
<td>Mycobacterium</td>
<td>Rare</td>
<td>Absent</td>
</tr>
<tr>
<td>Erythema</td>
<td>Rare</td>
<td>Present</td>
</tr>
</tbody>
</table>

Table 3. Pathologic Features Useful in Distinguishing ALCL and LyP

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>Skin thickness</th>
<th>Palmar/periungual</th>
<th>Mycetoma</th>
<th>Mycobacterium</th>
<th>Erythema</th>
</tr>
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<tbody>
<tr>
<td>LyP</td>
<td>Rare</td>
<td>Absent</td>
<td>Rare</td>
<td>Absent</td>
<td>Present</td>
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<tr>
<td>ALCL</td>
<td>Abnormal</td>
<td>Present</td>
<td>Absent</td>
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Table 4. Pathologic Features Useful in the Differential Diagnosis of CD30+ Cutaneous Lymphomas/LyP

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>ALCL</th>
<th>C-ALCL</th>
<th>Non-Hodgkin Lymphoma</th>
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<tbody>
<tr>
<td>ALCL</td>
<td>CD30+</td>
<td>CD30+</td>
<td>CD30+</td>
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<tr>
<td>C-ALCL</td>
<td>CD30+</td>
<td>CD25+</td>
<td>CD30+</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>CD30+</td>
<td>CD30+</td>
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Summary

1. A diagnosis of primary cutaneous ALCL can only be made after careful staging. Regional node involvement is controversial and currently most cases are treated with systemic chemotherapy.
2. ALK expression is rarely present in primary cutaneous ALCL and usually indicates systemic disease.
3. Borderline lesions between ALCL and LyP should be diagnosed as LyP type C if there is a clinical history of regression and lack of involvement of the subcutaneous tissue.
4. If CD4+ cerebriform small lymphocytes are present, or if there is an antecedent history of patch or plaque lesions, transformation of mycosis fungoides to “secondary” ALCL should be considered.
5. The treatment of primary cutaneous ALCL is conservative and usually local (complete excision with or without local irradiation); systemic treatment may be indicated in multicentric disease.
6. Close clinical follow-up is recommended as 10% - 25% of C-ALCL (particularly multicentric disease) develop extracutaneous disease.
7. CD30+ large cells may be present in reactive conditions; the CD30+ cells are usually scattered and do not form large clusters.

Differential Diagnosis of CD30+ Lymphoproliferative Disorders

Primary Cutaneous ALCL versus Transformed Mycosis Fungoides (MF):

Transformed mycosis fungoides in large cell lymphoma:88-90
- Occurs in ~20-25% of cases of MF at a median of 12 months (range 0-128 months)
- Large cells form microscopic nodules or represent ≥25% of total cells
- Epidermotropism may be absent
- CD30+ in 25%-50% of cases
- Aggressive disease
  - Median survival 29-37 months from diagnosis compared to 163 months for MF without transformation
  - Median survival after transformation 12-19 months

Note: ALCL often involves the subcutaneous tissue, but the sheet-like growth of large tumor cells and strong CD30 expression distinguishes it from subcutaneous panniculitis-like T-cell lymphomas.

Primary Cutaneous ALCL versus Reactive Infiltrates:

Reactive cutaneous T-cell infiltrates often have CD30+ large cells and may mimic ALCL or LyP in the following circumstances:
- After multiagent chemotherapy for large cell lymphoma or leukemia
- Following narrow ablative therapy and growth factor administration at the time of lymphocyte recovery (eruption of lymphocyte recovery)

Note: These reactions often have the gross appearance of a rash and CD30+ cells are often scattered rather than sheet-like; however, some may have a perivascular distribution with clustering of CD30+ cells.

Note: See Table 2 for differential diagnosis.
References

4. Marzola M, Carpenter J, and classification into subtypes A, B, and C
"Unusual Types of Cutaneous T-cell, NK-cell, and Precursor Lymphomas and their Relationship to the Invasive Immune System"

Dan Jones, MD, PhD
M. D. Anderson Cancer Center

This lecture covers several rare types of lymphomas that present in skin, including T-cell lymphomas of gamma-delta origin, natural killer (NK) cell lymphomas and blastic tumors of putative plasmacytoid dendritic lineage. The histogenetic relationship of these tumors to the cell types of the innate immune system is emphasized.

Historical Perspectives and Current Classification

Table I summarizes the current EORTC/WHO classification of cutaneous T-cell and NK T-cell malignancies. The recognition and classification of the rarer types of cutaneous lymphomas (indicated, in bold) has been a slow process. Most were recognized as more clinically aggressive than mycosis fungoides (MF) before their exact lineage was delineated.3

Table I. WHO-EORTC 2005 Classification of Cutaneous Lymphomas.4,5

<table>
<thead>
<tr>
<th>Cutaneous T-cell and NK-cell lymphomas</th>
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<tbody>
<tr>
<td>Mycosis fungoides</td>
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<tr>
<td>MF variants and subtypes</td>
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<tr>
<td>Folliculotrophic MF</td>
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<tr>
<td>Pagetoid reticulosis</td>
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<td>Granulomatous slack skin</td>
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<td>Sézary syndrome</td>
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<tr>
<td>Adult T-cell leukemia/myeloma</td>
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<tr>
<td>Primary cutaneous CD30+ lymphoproiferative disorders</td>
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<td>Primary cutaneous anaplastic large cell lymphoma</td>
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<td>Lymphomatoid pappulosis</td>
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Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)

Extranodal NK/T-cell lymphoma, nasal type (NK/T-L)

Primary cutaneous peripheral T-cell lymphoma, unspecified

Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)

Cutaneous gamma/delta T-cell lymphoma (provisional) (g/d TCL)

Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)

Precursor hematologic neoplasm (BT)

CD4/CD56+ hematodermic neoplasm (blastic NK-cell lymphoma)

Summary of helpful pathological and immunophenotypic features

Cutaneous gamma/delta T-cell lymphoma

Cutaneous γTCL was often grouped in the past with SPTCL prior to its recognition as a highly aggressive tumor, with distinct pathological features.4

Clinical appearance of lesions: Multiple, rapidly appearing nodules on extremities, often up to 10 cm in size, frequently with fungation/ulceration.4

Pattern of infiltration: Early stage: Mid-dermal, perivascular. Later stage: Dense infiltrates confluent in mid-dermis, with variable extension into epidermis and into subcutaneous tissue.4

Cytomorphology: Often deceptively small size, but with blastoid nuclear features.

Immunophenotypy: See Table II. Absence of CD4, CD8 and TCR-beta expression can be used in parallelized material as putative evidence of gamma-delta origin, although transformed MF can also be negative for all 3 markers.4 With subcutaneous infiltration, γTCL may show large numbers of admixed reactive lymphocytes and mononuclear cells.

Clinical behavior: Multiple cutaneous recurrences, with minimal spread outside skin until late in disease course. Hematopoietic syndrome (HPS) seen in up to 75%.4 Poor response to conventional chemotherapy, some are radiosensitive, transplantation may be an option.

Differential diagnosis: Dermatoses (early stage lesions), SPTCL and transformed MF.

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)

The distinction of cutaneous γTCL from SPTCL has highlighted the indolent behavior of a subset of these tumors.5

Clinical appearance of lesions: Slowly spreading subcutaneous masses or non-specific appearing rash that may wax and wane. May show association with connective tissue diseases.

Pattern of infiltration: Largely confined to subcutis, with rimming of fat, necrosis, karyorrhexis and lymphomatoid morphology.

Cytopathology: Variable size, often prominent nuclear irregularities in a subset of tumor.

Immunophenotypy: See Table II. Most infiltrates are common, but CD8 expression in tumor cells is usually apparent.6 CD4+ tumors with otherwise typical SPTCL features are reported.

Clinical behavior: Local, expandable growth until time of transformation when extensive extracutaneous dissemination may occur.

Differential diagnosis: Panniculitis (focus on atyia and diffuse growth), systemic PTCL, NOS

Cutaneous immune surveillance and the innate immune system

The skin and mucous membranes are a major portal of entry for infectious organisms and have therefore developed a highly effective but non-specific immune surveillance program that complements the specific immunity provided by antibody-expressing B-cells and TCR-a/-expressing helper and cytotoxic T-cells.7

This "innate" portion of the immune system, in contrast to adaptive acquired immunity, is focused on immediate (minutes to hours) detection and control of pathogens based on non-specific features. These immune targets include non-human glycoproteins, glycoproteins and genomic material complexed with novel antigen presenting molecules.

Key cellular players in the innate immune response are dendritic cells (particularly the DC2 subset which produces interferon-alpha), NK cells and gamma-delta T-cells.

Antigen receptors on γT-cells7 and cognate receptors on NK cells8 have relatively limited diversity consistent with their role in recognizing common microbial antigens. Dendritic cell maturation mediated by group of TLR-like receptors is also tuned to recognize broad antigenic patterns.9 This generalized microbial recognition system is in contrast to the high level of specificity encoded by the TCR-a/-β, which recognizes predominantly protein antigens with high affinity in the context of the highly polymorphic HLA class I and class II molecules.

Differences between MF and cutaneous tumors of the innate immune system

Most of the cutaneous tumors discussed here have putative histogenetic origin from cell types of the innate immune system. The remarkable tropism of these tumors for adherent structures and dermal vascular bed mimics the normal sites of innate immune surveillance.

The aggressive clinical behavior of these tumors may be partly related to their retained functional capacity to participate in uncontrolled cytokine-mediated innate responses. Such sequelae would include hemophagocytic syndromes, cytokine release syndromes and tissue necrosis/angiodestruction. The demonstrable immunophenotypic plasticity of the CD4+CD56+ BT may also be evidence of retained functional differentiation capacity.10,11

The majority of patients with mycosis fungoides have long precedent histories of chronic dermatitis, and their tumors develop out of oligoclonal phases in many cases. This suggests that MF (and perhaps lymphomatoid papulosis) can be regarded as T-cell (MALT) like tumors, with specific antigens driving early stages of proliferation. Long-term control of MF might thus be achieved by achieved by identifying and treating specific inciting agents.

In contrast, the factors driving extrusions in the early stages of the innate-immune-morbid tumors are unknown but would likely be distinct. Given the highly dynamic nature of innate responses, immunotherapy may prove useful in treatment of these aggressive neoplasms.
Ile II. Immunophenotypic features of dermal and subcutaneous NK, T-cell and blastoid malignancies.

<table>
<thead>
<tr>
<th>surface CD3</th>
<th>CD4</th>
<th>CD8</th>
<th>CD5</th>
<th>CD56</th>
<th>CD30</th>
<th>Cytoplasmic proteins</th>
<th>EBV</th>
<th>TCR usage</th>
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Table II.

*References* and expression frequencies are those seen in archival tumors from M. D. Anderson Cancer Center, and will vary widely inrent geographical areas due to differences in EBV infection patterns and other etiologic factors.


Cutaneous B-cell Lymphomas
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Primary cutaneous marginal zone B-cell lymphoma (pcMZL) [previously reported as PC-1 or MALT lymphoma]

- Neoplastic proliferation of small B cells involving mainly skin and subcutaneous tissue
- Often associated with chronic inflammatory conditions
- Usually low-grade, low-malignant potential

Primary cutaneous Diffuse large B-cell lymphoma, leg-type (pcDLBCL, leg)

- High-grade lymphoma
- Can involve extracutaneous sites
- May have aggressive clinical course

Primary cutaneous B-cell lymphoma, other (pcDLBCL, other)

- Includes various subtypes
- Clinical presentation and behavior may vary

Clinical features and history

Cutaneous B-cell lymphomas usually present as one or more erythematous papules or nodules that may coalesce to form plaques. They are usually localized tumors affecting one cutaneous region and rarely systemic. There is some regional predilection for various subtypes of tumors: follicle center lymphoma more commonly arises on the scalp, marginal zone B-cell lymphomas usually occur on the trunk or extremities, and the more aggressive diffuse large B-cell lymphoma usually arises on the lower leg.

Histomorphology

In contrast to malignancies of T lymphocytes which frequently show epimorphosis, the tumor cells in cutaneous B-cell lymphomas spare the epidermis and are usually separated from it by a gene zone of uninvolved dermis.

Immunophenotype

Some observers have reported that cutaneous lymphomas develop in the setting of a persistent inflammatory reaction or immune dysregulation. This hypothesis has been applied not only to T-cell proliferations in the setting of connective tissue disease, chronic actinic dermatitis (actinic reticuloid), and lymphomatoid drug eruptions, but also has been used to explain the development of cutaneous B-cell lymphomas in the setting of bowel infections and tumors. As with T-cell lymphomas, an aberrant B-cell immunophenotype supports the diagnosis of lymphoma, as may be seen in light chain restriction or co-expression of CD43 and CD20. Because the responding cell in cutaneous inflammatory processes is usually a T cell, most non-neoplastic cutaneous infiltrates are composed almost exclusively of T cells. Thus, when B cells comprise ≥50% of the dermal infiltrate a diagnosis of cutaneous B-cell lymphoma is favored. On the other hand, dense reactive T-cell infiltrates are frequently present in cutaneous lymphomas; in some cases of cutaneous lymphomas the neoplastic B cells may represent only a component of the dense lymphocytic infiltrate. An immunohistochemical panel including CD20, CD3, CD21, CD10, and CD22 is often useful in distinguishing follicle center lymphomas from marginal zone B-cell lymphomas.

Gene Rearrangements

The southern blot method of detecting T-cell receptor and immunoglobulin gene rearrangements may yield negative results if the tumor cells represent less than 5% of the sample. PCR-based techniques are reported to be positive in most cases of cutaneous T-cell lymphomas but only 50% of cutaneous B-cell lymphomas. As with any diagnostic test, interpretation of the genetic results should be in the context of the clinical, histologic and immunophenotypic findings of the case.


REAL: Extramodal marginal zone B-cell lymphoma (low grade B-cell lymphoma of MALT-type)

Primary cutaneous marginal zone B-cell lymphoma (pcMALT) is defined as a neoplastic proliferation of small B cells involving mainly skin (cutaneous type) and, in most cases, lymphatic tissue. This lymphoma is characterized by the production of monoclonal immunoglobulins and plasma cells and plasma cells are considered to be of marginal zone lymphomas.

- Epidemiology
  - Cutaneous MALT affects mostly men and women, with a median age of 50 years and a range of 24-77 years. pcMALT is characterized by a predilection for the trunk and upper extremities.
  - Because of the predominance of T cell lymphomas in the skin, pcMALT constitutes most all cutaneous lymphomas. Involvement of cutaneous lymphomas. MALT is estimated to comprise approximately 35% of primary cutaneous B-cell lymphomas, second only to follicular lymphomas.

- Etiology
  - The etiology of most pcMALT remains unclear. Several authors have proposed the existence of a skin associated lymphoid tissue (SALT) that with persistent antigenic stimulation may give rise to neoplastic proliferations of marginal zone B cells. Similar to the B. Pylori story for gastric MALToma, in mice, B cell neoplasms have been recognized in experimental models in the development of pcMALT. A few cases report evidence of lesions following anti-inflammatory therapy. Interestingly, an association between boralmia and pcMALT has been identified in reports from the United States and Asia. Other settings in which pcMALT has been described include tattoo, vaccination site, and insect bite (not related to tick borne illness).

- Clinical features
  - pcMALT usually presents as a solitary red or violaceous infiltrated nodule, usually on the upper arm or trunk. Occasionally tumors are multiple, or present as a confluent plaque of erythematous papules. Patients with pcMALT do not have B symptoms and have normal serum levels of LDH and β2-microglobulin.

- Treatment and Prognosis

- Immunophenotype
  - In cases with plasmacytic differentiation, light chain restriction is identified in 70%. The plasma cells express CD138 and CD38 and express a single light chain. The plasma cells are usually associated with a marked increase in the number of marginal zone B cells and plasma cells.

- Genetics
  - Extramodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)-type: Primary cutaneous marginal zone B-cell lymphoma (pcMALT)


Patients with solitary or localized tumors are usually treated with excision and/or radiation therapy, solitary low-grade tumors may also be treated with injection of high dose steroids. Patients with multifocal or disseminated cutaneous lymphomas are usually treated with chemotherapy: single agent chemotherapy given to patients with the more indolent tumors, multagent chemotherapy is instituted for those with biologically aggressive lymphomas. In general, cutaneous lymphomas are more indolent than their nodal counterparts. Primary cutaneous B-cell lymphomas of marginal zone (pcMALT) and follicle center type (pcFCL) usually remain localized to the skin and are often cured by local therapy. Whereas primary cutaneous diffuse large B-cell lymphomas (pcDLBCL, leg) is more often associated with eventual extranodal lymphomas. Even the pcDLBCL of the leg has a better disease free survival than does nodal diffuse large B-cell lymphoma (Table 1).

CLASSIFICATION OF PRIMARY CUTANEOUS LYMPHOMA

It is now widely recognized that there are many distinct B-cell and T-cell lymphomas that occur as primary tumors of the skin. In 1994 the Revised European-American Lymphoma Classification (REAL) scheme was published and shortly thereafter, the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Project Group published a classification scheme specifically for primary cutaneous lymphoma. One of the aims of the EORTC report was to define primary cutaneous tumors and draw attention to those lymphomas that have a clinical behavior that would not be predicted using classification schemes designed for nodal lymphomas. Since then, the WHO International Agency for Research and Cancer has published the Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues (Table 2). Additionally, but certainly not finally, a group of pathologist and dermatologist representatives of the WHO and have proposed the WHO/EORTC classification for cutaneous lymphomas (Willeumier et al. Blood 2005).

An understanding of how the terms "primary" and "secondary" have been applied to cutaneous lymphomas is critical to understanding the classification schemes. Most observers use the term "secondary cutaneous lymphoma" to describe lymphomas that develop in the skin as a secondary manifestation of a lymphoma primarily arising at a site other than the skin. The current most broadly accepted definition of primary cutaneous lymphomas is: lymphoma arising in the skin without evidence of extra-cutaneous disease for 6 months. Patients with circulating lymphoma cells (PC-CLL) are usually clinically asymptomatic, however, up to 30% of patients diagnosed with pcMALT will experience extracutaneous relapse, most commonly in other extracutaneous sites including breast, salivary glands and orbit. This clinical behavior is similar to marginal zone lymphoma reported at other sites and is associated with an excellent prognosis. Although, rare transformation to large cell lymphoma has been reported and may be lethal.

Patients with pcMALT have been effectively treated with certain immunosuppressive agents and/or chemotherapy. Clinical response to various regimens has been reported, including chlorambucil, cyclophosphamide, prednisolone, and rituximab. Recurrence is common, and the lymphomas may be refractory to subsequent therapy.

- Clinical course
  - MALT is defined as a primary cutaneous tumor only when staging, including thoracodorsal CT scan and bone marrow biopsy studies, has not revealed extracutaneous disease for 6 months after the diagnosis of the cutaneous lymphoma. pcMALT are usually clinically indolent, however, up to 30% of patients diagnosed with pcMALT will experience extracutaneous relapse, most commonly in other extracutaneous sites including breast, salivary glands and orbit. This clinical behavior is similar to marginal zone lymphoma reported at other sites and is associated with an excellent prognosis. Although, rare transformation to large cell lymphoma has been reported and may be lethal.

Clinically, CLH and pcMALT affect females more often than males, and present with single or multiple, slow-growing cutaneous nodules on the face, arms, or trunk. Both entities are characterized by a dermal lymphocytic infiltrate, a germinal follicle, reactive follicles, and admixed inflammatory cells (Table 3). Marajozone marginal zone cells and follicle center cells in the interfollicular regions and around the superficial vascular plexus support a diagnosis of pcMALT. In contrast, epidermal anoma and hyperplasia, epidermotropism, or epidermotropism, are seen in the majority of cases of CLH, and only rarely in pcMALT. The molecular basis of these differences is not yet understood.

Clinically, CLH and pcMALT usually respond to systemic therapy (prednisolone, chlorambucil, rituximab, and others) with complete or partial responses. Adjuvant therapy with chemotherapy or radiotherapy may be used in some cases. The prognosis for CLH is generally good, with a 5-year survival rate of approximately 90%. The prognosis for pcMALT is also favorable, with a 5-year survival rate of approximately 85%.
In reactive B cells, expression of the bcl-6 transcription factor and of the membrane bcl-2+ cells. In pmZL, the proliferation of marginal zone B cells may be minimal and incomparable, it is possible that the cases reported by others as reactive lymphoid hyperplasia with monotypic plasma cells represent cutaneous marginal zone lymphomas with inconspicuous marginal zone B cells. There is also considerable overlap in the histological appearance of pmFCL and pmZL. A predominantly nodular or follicular pattern is observed in most pmFCL, and the presence of diffuse areas is present in all pmZL. However, pmFCL may be entirely diffuse or display diffuse areas, and the majority of pmZL have at least a partially nodular pattern. A predominance of small cells with irregular, somewhat cleaved nuclei characterizes both tumors. Moreover, anti-bcl-2 immunostaining highlights follicular dendritic cell meshworks, indicating true follicular structures in both pmFCL and pmZL.

A combination of immunostaining for bcl-1, bcl-2, bcl-6, and bcl-10, yields distinct patterns of staining in the follicular and extranodal regions of FL and MCL. Distinctive neoplastic follicles of FL are revealed with expanded or coexpression of CD43 and CD30 also support a diagnosis of B-cell lymphoma. 

In pmZL, the proliferation of marginal zone B cells may be minimal and incomparable, it is possible that the cases reported by others as reactive lymphoid hyperplasia with monotypic plasma cells represent cutaneous marginal zone lymphomas with inconspicuous marginal zone B cells. There is also considerable overlap in the histological appearance of pmFCL and pmZL. A predominantly nodular or follicular pattern is observed in most pmFCL, and the presence of diffuse areas is present in all pmZL. However, pmFCL may be entirely diffuse or display diffuse areas, and the majority of pmZL have at least a partially nodular pattern. A predominance of small cells with irregular, somewhat cleaved nuclei characterizes both tumors. Moreover, anti-bcl-2 immunostaining highlights follicular dendritic cell meshworks, indicating true follicular structures in both pmFCL and pmZL.

In reactive B cells, expression of the bcl-6 transcription factor and of the membrane bcl-6, bcl-2- cells. Distinguishing neoplastic follicles of FL from reactive or colonized follicles of pmZL may be difficult because bcl-6 and CD10 are expressed by both reactive and neoplastic follicles, and bcl-2 is not expressed in all neoplastic follicles of pmZL. In cases of pmZL, with colonized follicles, bcl-6, CD10, bcl-2 and CD21 may allow the distinction of expanded or colonized follicles of follicular dendritic cells from neoplastic follicles. The colonized follicles, which typically correspond to nodular areas on H&E sections, display bright, nodular aggregates of CD21+ follicular dendritic cells, similar to neoplastic follicles or reactive germinal centers, but contain distinct clusters of bcl-6, bcl-2+ neoplastic B cells, in addition to clusters of bcl-6, bcl-2-, follicular center cells. The other pattern observed in pmZL is that of expanded, colonized meshworks of follicular dendritic cells corresponding to areas that appear diffuse to only vaguely nodular on routine sections with only scattered bcl-6+ cells; most cells are bcl-6-. It remains unclear whether the bcl-6+ cells in the dispersed dendritic meshworks of pmZL represent residual follicular center cells or blast transformation. Neoplastic follicular dendritic cells can be seen in pmFCL, on the other hand, contain a uniform population of neoplastic bcl-6-, and in these cases expressing bcl-2, it is also uniformly expressed by cells in the follicles. In contrast to pmFCL, bcl-6+ and bcl-2+ cells are never seen in interfollicular and diffuse areas devoid of CD1+ cells in pmZL.

In summary, the immunophenotype of pmFCL is distinct from that of pmZL and consistent with a germinal center-derived tumor. Its unique clinical behavior may reflect a derivation from extranodal B-cell follicles rather than nodal lymphoid follicles in lymph nodes. In contrast to the difficulty in distinguishing pmFCL from pmZL, there is also overlap in some features between follicle center lymphomas and large B-cell lymphoma (pmFCL). For the purposes of the present presentation, pmFCL is defined as a neoplastic proliferation of large and small centrocytes and centroblasts usually with bcl-6+, CD10- immunophenotype, supported by a meshwork of CD21+ follicular dendritic cells. pmFCL is often bcl-2 negative, a negative bcl-2 staining pattern of follicles with the remaining lymphocytes are inconspicuous for bcl-2 does not allow for distinction between a reactive and neoplastic process in the skin. Staining for MUM-1/IRF-4 is negative.

The presence of a CD21 follicular dendritic cell meshwork containing two immunophenotypically distinct populations of B cells (bcl-6+, CD10+, CD5-, CD24-, CD1a- follicular center cells and bcl-6-, CD10+, CD5-, CD24+ neoplastic marginal zone cells) supports the presence of colonized follicles in pmZL. Whereas, expanded irregularly shaped aggregates of bcl-6-, CD10+ cells are supportive of the diagnosis of follicular lymphoma.

In summary, the immunophenotype of pmFCL is distinct from that of pmZL and consistent with a germinal center-derived tumor. Its unique clinical behavior may reflect a derivation from extranodal B-cell follicles rather than nodal lymphoid follicles in lymph nodes. In contrast to the difficulty in distinguishing pmFCL from pmZL, there is also overlap in some features between follicle center lymphomas and large B-cell lymphoma (pmFCL). For the purposes of the present presentation, pmFCL is defined as a neoplastic proliferation of large and small centrocytes and centroblasts usually with bcl-6+, CD10- immunophenotype, supported by a meshwork of CD21+ follicular dendritic cells. pmFCL is often bcl-2 negative, a negative bcl-2 staining pattern of follicles with the remaining lymphocytes are inconspicuous for bcl-2 does not allow for distinction between a reactive and neoplastic process in the skin. Staining for MUM-1/IRF-4 is negative.
extend to the dermoepidermal junction. Although the growth pattern is diffuse, some cases have an overall multi-nodular appearance at scanning magnification. There is variation in the proportion of centroblast-like and immunoblast-like cells in large B-cell lymphoma and the density of large B cells with round cell morphology has been reported to be of prognostic significance.

- **Grading**: B-cell lymphomas of the skin are characteristically not graded with a grade. For comparison's sake though, the pcDLBCL is comparable to diffuse grade 3b nodal LBCL.

- **Immunophenotype**: Monotypic surface immunoglobulin is identified along with CD20+, CD20a, CD22a, CD79a+, bcl-2+, bcl-6+, CD10−/+, CD5−/+, CD138− immunophenotype. The intensity of bcl-2 stain may exceed that of the non-neoplastic T cells. The MIR-1/κl6% fraction is high, ranging from 60 to 95%. Whether arising on the leg or other sites, these tumors have been demonstrated to occasionally express both bcl-6 and MUM1/IRF4 (multiple myeloma / interferon regulatory factor 4) proteins. In this series the tumors did not have associated CD21+ follicular dendritic cells.

- **Genetics**: Immunoglobulin genes have detectable clonal rearrangements and (14;18) is usually absent although bcl-2 protein expression is often strong. Translocation involving myc, bcl-6 and IgH genes have been reported.

- **Clinical course**: Irradiation is the most effective therapy for localized tumors, anthracycline-based chemotherapy is used to treat disseminated disease. pcDLBCL, of the leg is the form of cutaneous B-cell lymphoma that is associated with the worst prognosis. In the following description of the clinical behavior reported for these tumors one should bear in mind that like other forms of cutaneous lymphoma, pcDLBCL has a more favorable overall prognosis than does large B-cell lymphoma arising in lymph nodes. Grange et al. reported the five-year disease-specific survival rate for DLBCL of the leg as 50% in 2001. An increased risk of recurrence and a reduced survival is associated with multiple tumors at presentation, location on the leg, and bcl-2 expression.

**Primary cutaneous, diffuse large B-cell lymphoma, other type**

**WHO/UITC Classification**: Primary cutaneous diffuse large B-cell lymphoma, other.

**REAL Classification**: Diffuse large B-cell lymphoma

Variants of pcDLBCL also include tumors composed of confluent sheets of large B cells with intense staining for bcl-2 protein occurring at sites other than the leg (pcDLBCL, other). In addition, tumors comprised purely of centroblasts or immunoblasts, which weakly express bcl-2 protein are included in this category (pcDLBCL, other). These rare cases of large B-cell lymphomas arising in the skin do not belong to the leg type group of DLBCL or the group of pcFL.

Included in the group of diffuse large B-cell lymphoma, other is intravascular large B-cell lymphoma (pcDLBCL, intravascular). This tumor is characterized by a dermal intravascular accumulation of large neoplastic B cells that express monotypic immunoglobulin and pan-B-cell antigens (CD19+, CD20+, CD22+, CD79a+). The tumors appear as violaceous plaques on the trunk and lower extremities, and may disseminate to involve extranodal sites. CNS involvement is not infrequently observed and is associated with a poor outcome. Patients with this disease have a poor prognosis with less than 50% survival at 5 years. Treatment is with combination chemotherapy.

Another rare histological variant of cutaneous diffuse large B-cell lymphoma is T-cell rich B-cell lymphoma. In these tumors there is a dominant reactive infiltrate of T cells with large neoplastic B cells comprising <15% of infiltrate.

### Table 1. General Features of Primary Cutaneous B-cell Lymphoma

<table>
<thead>
<tr>
<th>Clinical</th>
<th>- significant similarity in cutaneous morphology between sub-types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological</td>
<td>- epidermotropism absent, minimal if any epidermal changes</td>
</tr>
<tr>
<td></td>
<td>- germinal center present</td>
</tr>
<tr>
<td></td>
<td>- often with lymphoid follicles</td>
</tr>
<tr>
<td>Immunophenotype classification is linked to phenotype in most tumors</td>
<td>MZL: CD10−, CD5−, CD10+, bcl-2−, bcl-6−</td>
</tr>
<tr>
<td></td>
<td>FCL: CD20+, CD5+, CD10+, bcl-2+, bcl-6−</td>
</tr>
<tr>
<td></td>
<td>DLBCL, leg: CD20+, CD5+, CD10+, bcl-2+, bcl-6+</td>
</tr>
<tr>
<td>Also helpful:</td>
<td>- CD24+ follicular architecture may be distinctive</td>
</tr>
<tr>
<td></td>
<td>- Light chain restricted plasma cells in 70% of MZL</td>
</tr>
<tr>
<td></td>
<td>- Co-expression of CD20 and CD43 favor CBCL</td>
</tr>
<tr>
<td></td>
<td>- 75% B cells supports the diagnosis of CBCL</td>
</tr>
<tr>
<td>Gene rearrangements</td>
<td>Ig gene rearrangement detected in only 50% of CBCL</td>
</tr>
<tr>
<td>Treatment</td>
<td>False positives exceedingly rare</td>
</tr>
<tr>
<td>Treatment</td>
<td>Treatment most dependent on tumor location and number of lesions.</td>
</tr>
</tbody>
</table>

### Table 2. WHO/UITC schema for primary cutaneous follicle center lymphoma (pcFCL) and diffuse large B-cell lymphoma of the leg (pcDLBCL of the leg)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>pcFCL</th>
<th>pcDLBCL of the leg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphology</strong></td>
<td>Predominance of centrocytes that are often large, especially in diffuse lesions. Centroblasts may be present, but not in confluent sheets.</td>
<td>Predominance of large to medium sized B cells with mild nuclei, prominent nucleoli, and coarse chromatin. Cells may resemble centroblasts and immunoblasts.</td>
</tr>
<tr>
<td></td>
<td>Pattern may be follicular, follicular and diffuse, or diffuse (a continuum without distinct categories or grades).</td>
<td>Diffuse growth pattern</td>
</tr>
<tr>
<td></td>
<td>Sclerosis may be present</td>
<td>Little stromal reaction, confluence destructive growth pattern</td>
</tr>
<tr>
<td><strong>Phenotype</strong></td>
<td>Bcl-2: → Staining is weak, when present</td>
<td>Bcl-2: → Staining is typically strong and in most neoplastic cells</td>
</tr>
<tr>
<td></td>
<td>Bcl-6: +/−</td>
<td>Bcl-6: +/−</td>
</tr>
<tr>
<td></td>
<td>CD10: +/−</td>
<td>CD10: +/− Usually negative</td>
</tr>
<tr>
<td></td>
<td>MUM-1: +/− usually negative</td>
<td>MUM-1: +/− usually positive</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td>Middle aged adults</td>
<td>More commonly in elderly, especially females</td>
</tr>
<tr>
<td></td>
<td>Most cases localized lesions on the head or trunk</td>
<td>Lesions localized on the leg, most often below the knee</td>
</tr>
<tr>
<td></td>
<td>Tumor nodules, sometimes with satellite lesions</td>
<td>Rarely multifocal lesions</td>
</tr>
</tbody>
</table>
SECONDARY LYMPHOMAS OF THE SKIN

Daniel A. Arber, MD
Stanford University

Malignant lymphomas that secondarily involve the skin are relatively common and may be difficult to distinguish from primary skin lymphomas. While the morphologic features of primary and secondary lymphomas of the skin are often very similar, the clinical behavior of primary and secondary cutaneous lymphomas is often dramatically different.1 Although large series of secondary cutaneous lymphomas are uncommon, secondary lymphomas or lymphocytic lymphomas that secondarily involve the skin and the skin in presentation appear to represent approximately 25% of all cutaneous lymphomas and up to 50% of cutaneous lymphomas other than mycosis fungoides.2 In a recent survey of cutaneous lymphomas diagnosed at Stanford University, 24% were considered secondary based on a prior or simultaneous diagnosis of non-cutaneous lymphoma. The frequency of each lymphoma type among secondary cutaneous lymphomas at Stanford is given in parentheses after each disease type below.

In contrast to primary cutaneous lymphoma, secondary cutaneous lymphomas show a B cell predominance. Similar to other sites of lymphoma, the diffuse large B cell lymphoma and follicular lymphoma secondarily involving the skin are relatively common. However, secondary cutaneous involvement by T and NK cell proliferations is still more common in the skin than the frequency of primary nodal NK and T cell lymphomas.

B cell lymphomas (65.8%)

Diffuse large B cell lymphoma (26.96)

It is not surprising that diffuse large B cell lymphoma, the most common type of nodal non-Hodgkin lymphoma, is also one of the most common lymphoma types to secondarily involve the skin. The main differential diagnosis of this lymphoma is with diffuse large B cell lymphoma of cutaneous lymphoma lymphoma, the cell type in lymphomas the lymph node and most of the skin. Both primary and diffuse diffuse large B cell lymphomas commonly involve the head and neck region or the extremities, but skin involvement may be much more common. While the morphologic features of these entities are similar, both clinical behavior and gene expression profiling find clear differences in primary and secondary types.3 Other than clinical features, there are few clues to secondary cutaneous lymphomas. The most common primary skin lymphomas of small cell, neoplasms of the skin are usually CD10 negative and lack t(4;14). Therefore, expression of CD10 or t(4;14) common finding in a diffuse large cell lymphoma, should warn further investigation for systemic disease. However, both CD10 expression and t(4;14) may occur in primary disease and these features should not be considered as evidence of a secondary lymphoma.

Follicular lymphoma (21.4%)

Both primary and secondary cutaneous follicular lymphomas frequently involve the head and neck region. Both show the presence of large centrocyte cells as well as cells with irregular nuclear contours. Either type may have a diffuse or nodular appearance in the skin. While some studies have found distinctive immunophenotypic and molecular

Peripheral T cell lymphoma (PTCLs) in the "unspecified" group of the WHO classification scheme. BCL2 expression is common in both primary and secondary disease, but expression of BCL2 and CD10 tends to correlate more with secondary disease. Expression of BCL2 and CD10 in primary disease, however, is frequent enough to make use of one of these markers as a discriminator of primary versus secondary disease unreliable. The combined expression of BCL2 and CD10 appears to a much stronger predictor of secondary disease than any one clone.12 Detection of t(14;18) has also been reported to be fairly specific for secondary disease, but this data is also controversial.12,13 While most studies show a clear increase in the frequency of this translocation in secondary cutaneous follicular lymphoma, it is well documented in some primary cases. Therefore, positive primary cases are less frequent in European studies than in North American studies.

Malignant lymphoma (6.8%)

Marginal zone lymphomas are often primary cutaneous lymphomas, but may also be secondary. Distinct morphologic differences between primary and secondary cases are not well described, and the differential diagnosis of secondary marginal zone lymphomas of the skin would include primary nodal marginal zone lymphomas and secondary marginal zone lymphomas. In one series, primary or concurrent tumors involving the cutaneous disease or skin glands seemed to occur more commonly than skin disease of gastric primary. Secondary disease appears to be more commonly associated with multifocal skin disease when compared to primary marginal zone lymphomas, and the age of development of skin lesions was later in secondary versus primary disease (64 vs. 54 years) in one series.13 The molecular genetics of primary cutaneous marginal zone lymphomas appear to differ from other extranodal marginal zone lymphomas, in that the t(14;18)(q32;q21) of REL/NFκB translocation is relatively common, but the t(11;18)(q21;q11) of ABL/NFκB or the t(1;14)(q23;q32) of RCH/FOXO are uncommon in this skin.13 This might suggest that the detection of the latter translocations would support secondary disease, but this hypothesis has not been adequately tested.

Small lymphocytic lymphomas (chronic lymphocytic leukemia) (5.5%)

Small lymphocytic lymphomas of the skin may present as a skin lesion, but is not considered a primary cutaneous lymphoma. Patients may present with erythematous papules, plaques, nodules or large tumors which are usually not ulcerated. The lesions may be generalized or localized and virtually any site may be involved. A predilection for prior sites of herpes infection has been suggested in some cases.14 Virtually any site of the body may be involved, patchy, nodular, diffuse or band like. We have observed primary cutaneous cases, and several rare cases have been reported. In contrast, secondary involvement is much more common, with associated cutaneous features, cases of patchy, nodular, diffuse or dermal disease. In one series, the history of the lesion was not a factor in determining whether a lesion was primary cutaneous or secondary skin disease. In one series, the history of the lesion was not a factor in determining whether a lesion was primary cutaneous or secondary skin disease. In one series, the history of the lesion was not a factor in determining whether a lesion was primary cutaneous or secondary skin disease. In one series, the history of the lesion was not a factor in determining whether a lesion was primary cutaneous or secondary skin disease. In one series, the history of the lesion was not a factor in determining whether a lesion was primary cutaneous or secondary skin disease. In one series, the history of the lesion was not a factor in determining whether a lesion was primary cutaneous or secondary skin disease.

Skin lesions are present in patients with angioimmunoblastic T cell lymphoma (AITL, present in approximately half of cases. Based on one large series, the majority of skin lesions in this disorder demonstrate T cell clonality, although the histologic changes in the skin may be subtle. A maculopapular eruption involving the trunk or extremities is the most common presentation, and may be confused with a drug or viral eruption; however, plaque-like and nodular lesions may also occur. Several histologic patterns of AITL in the skin have been described. The infiltrate may be sparse with nonspecific follicular lymphoid infiltrates and rounded lymphocytes associated with epidermal capillary hyperplasia, with or without obvious abnormalities of the lymphocytes. In most cases, however, enlarged, atypical lymphocytes, sometimes including cells with a Hodgkin-like appearance, are present and rare cases show a dense superficial dermal lymphoid infiltrate with vascular proliferation similar to nodal AITL. The large atypical cells may show aberrant loss of T cell antigens. EBV has been found in a small number of cutaneous cases and is usually absent or present in a small percentage of cells, but one reported case had a large number of EBV-positive cells in a recurrent skin lesion following only sparse EBV positive cells in an initial skin biopsy.15

Many primary and secondary cutaneous lymphomas have similar names and morphologic features, and in some cases, such as NKT cell lymphoma, AITL and CCL, they represent different stages of the same disease. For other entities, however, it is important to recognize the clinical difference between the primary cutaneous disease and systemic disease. This is particularly true for primary cutaneous AITL, follicular lymphoma and the cutaneous lymphocytic lymphoma, in these cases, correlation with more detailed immunophenotypic studies and complete clinical evaluation is essential for proper classification.

Acknowledgment: I would like to thank Drs. Wendell Price, Chris Lai and Uma Sindram for their help in tabulating the Stanford University incidence data for secondary cutaneous lymphomas.

References
5. Kim BK, Sohn U, Pandya AG et al. Primary and secondary cutaneous diffuse large B cell lymphomas: a multivariate analysis of 25 cases including

NK T cell lymphoma (5.5%)

Nodal type NK T cell lymphoma may occur as primary cutaneous disease, may be secondary, or may occur simultaneously with disease at other sites. From 8 to 30% of NK T cell lymphomas of the nodal type have skin involvement.5 Some patients with apparent primary cutaneous disease have developed nasal masses within one to seven months of diagnosis, and the disease is aggressive in most cases. While some cases have presented as erythematous eruptions, most form ulcerated tumor nodules that may occur at any cutaneous site. The infiltrate is usually dense, surrounding adnexal structures and vessels and often extending from the dermis into subcutaneous adipose tissue. As in other sites, angioimmunoblastic disease may occur and the tumor infiltrate is composed of medium to large lymphocytes with intermediate chromatin that is similar to a blastic infiltrate. Similar to other sites, the cells usually express CD2, CD5, CD95 and are EBV positive.


spongiosis with a prominent scale or scale crust. Sometimes one may see endothelial swelling and extravasation of red blood cells. The histology of the superficial infiltrate is more associated with activation of endothelial cells than with a deeper infiltrate, in our experience. The differential diagnosis includes erythema chronium in which one finds an infiltrate superficial and deep of lymphocytes admixed with plasma cells and often distinct zones of the vessel wall by the infiltrate as well as a perivascular neutrophil may be observed. The changes in the epidermis are minimal. The presence of positive serology for Borrelia is rare cases. In other instances it is associated with the mononuclear ichthyosis type of reaction. Erythema gyratum repens, which can resemble both the superficial and deep and finally clinically has the distinctive picture, a so-called tree bark-like appearance to the skin caused by the infiltrate.


Polymorphous Light Eruption

Polymorphous light eruption represents an idopathic response to ultraviolet light. It combines features of a photosensitization reaction with those of a hypersensitivity reaction to ultraviolet light, which may be caused by either UVA, UVB or both wavelengths in some patients. The lesions present as papules or plaques in a light exposed area. They are erythematous and are sometimes associated with itching. Characteristically the history is appearance of these lesions 30 to 45 minutes to several days after exposure to either sun or ultraviolet light. Resolution in one to two weeks is common. The lesions are present normally on the sun-exposed areas of the body that after recurrences of the eruption, they may extend to non-sun-exposed areas as well. Because these lesions are commonly in a light exposed area they raise often the diagnosis of lupus erythematosus and one study has shown that approximately half of lupus patients had symptoms consistent with polymorphous light eruption sometimes for years before they developed the autoimmune disease. Histopathologically there are a group of changes that allow for correct diagnosis. First, in the epidermis there may be focal perilesional, spongiosis occurs to a mild degree in many cases but in some there is spongiosis vesiculosis. Disseminated keratinocytes or apoptotic cells are scattered in the epidermis of the affected skin. There is vasculopathy of the dermal/epidermal junction in most cases. Approximately 50-60% of the plaque like light rashes show vacuolopathy resembling the vacuolization of the lupus erythematosus. There is no thickening of the basement membrane zone and no epidermal atrophy. While papillary dermal edema of marked degree is characteristic. Some cases, in fact do not show marked edema of the papillary dermis but rather a more diffuse edema of the dermis. Characteristically, the infiltrate on low power shows a gradual tapering with a predominance of lymphocytes above tapering to lymphocytes of very few in number even around vessels as deep as subcutaneous fat.  Superficial vessels show characteristic vasculitis of the endothelial cells and the endothelial basement membrane zone they are associated not only with a perivascular lymphocytic infiltrate but also an edematous perivascular change that gives one the impression that the cells are present in an edematous background. Rare neutrophilic debris is present as well as an extravasation of red blood cells superficially. The changes of endothelial vaculization and activation are most superficial that do not affect the deeper dermis. Focal blood and mucin may be observed in some reactions. Direct immunofluorescence examination will show focal IgM and C3 deposition in some blood vessels with occasional IgM at the dermal/epidermal junction.

The differential diagnosis includes phototoxic reactions. Phototoxic reactions usually show extensive apoptosis and dyskeratosis. There is a neutrophilic infiltrate at the dermal/epidermal junction with the same degree that is associated with the extensive dermal/epidermal necrosis. A mild perivascular lymphocytic infiltrate may be present superficially but the overlying changes are those of the epidermal change. Photosensitizing reactions are very similar to contact dermatitis. The presence of occasional dyskeratotic cells and enz겔ent cell changes which occur also in this type of reaction are distinguishing features are the occasional neutrophilic debris. Also, the reactions of contact dermatitis have intense very closely applied lymphocytes without the edema of the perivascular adventitia that is seen in association with the polymorphous light eruption. The reactions of lupus erythematosus can be distinguished on the following basis. In acute lupus erythematosus there is massive mucinosis and debris along the dermal/epidermal junction with atrophy of the epidermis. The more chronic lesions there is base membrane zone thickening with atrophy of the epidermis.

Chronic Polymorphous Light Eruption

This group of patients presents with quite prominent plaques in photosensitized areas of the skin, especially head and neck, anterior chest, and the upper back. These lesions were and were and will respond both to Plaqueen systemically and intranasal injections to steroids. The patients have negative serologies. The band test may show focal staining with IgM and C3 at the dermal/epidermal junction. This lesion is considered to be a variant of discoid lupus erythematosus. Histopathologically, the most important differential diagnosis of this lesion is Leigners’ lymphocytic infiltrate. The angiocentric and perivascular infiltrate of Leszner’s is associated with mucinosis but in non-scarring discoid erythematosus there is interface dermatitis predominantly of the infiltrative infiltrate, the epidermis and of the follicular epidermis. These changes are associated with degenerative epithelial changes. There is no evidence of abnormal serologies nor do the patients have evidence of CSF89 or IgS at the dermal/epidermal junction.


Jesner’s Lympocytic Infiltrate of the Skin

Jesner’s lymphocytic infiltrate presents either as group papules or a plaque that is confined to some sun-exposed area, predominantly on the head and neck and upper trunk. Most patients with this disorder are in the age range of adult life from 30 to 60 years of age, however, it may be observed in childhood, and even later in life. The lesions of Jesner’s lymphocytic infiltrate are red papules or plaques, often non-symptomatic that is without or with other sensations. The lesions do tend to resolve. There is an overlap between this entity and the so-called non-scarring discoid lupus erythematosus. In patients with these reactions there is no evidence of collagen vascular disease. Direct immunofluorescence of these lesions fails to reveal changes other than occasional IgM or C3 scattered with weak intensity in perivascular area. Histopathologically there is a quite extensive superficial and deep perivascular and perianitial infiltrate of fully formed mature lymphocytes. In some cases there is even extension into the subcutaneous fat. Eosinophils may be observed in the infiltrate. The lymphocytic infiltrates of the lesions is there no evidence of interface dermatitis at the epidermal junction or along follicles, which helps to differentiate this lesion from variants of lupus erythematosus. Although there may be focal infiltrate of the external root sheath, there is no destruction of the external root sheath. Focal mucinosis occurs in approximately 40% of cases. The changes are associated predominantly with a T-cell shift. In some of the lesions with an acute dense inflammation one may observe foci of B cell infiltration. In other lesions, one can observe CD8 positive cells admixed with lymphocytes around the vessels. The lupus band test is negative. One features of Jesner’s lymphocytic infiltrate is that he is able to distinguish it from lupus in that there are occasionally B cells admixed as indicated above. This presence of B cells rules out the diagnosis lupus erythematosus (virtually exclusively). The differential diagnosis includes non-scarring DLE. In lupus erythematosus there is definitely interface dermatitis yet there may be more dermal mucinosis. It is interesting that both disorders do respond, that Jesner’s and non-scarring DLE to antimalarials. Jesner’s infiltrate can be distinguished from polymorphous light eruption by the presence of marked edema in the papillary dermis, by the presence of spongiosis in the epidermis and also by the presence of occasional eosinophils admixed with the infiltrate in polymorphous light eruption.

Non-Scarring Discoid Lupus Erythematosus/TUMID Lupus Erythematosus

Clinical
for example, repeated contact dermatitis. Therefore, these lesions are clouded for T cells. They can also follow tattooing, vaccination, repeated arthropod reactions, or even a hypoesthesia to injection of antigen for hypoesthesia. Indeed, in Europe, and also less so in the United States, these lesions have been shown to be associated with Borrelia-burgdorferi infection. In Europe they have reported that lesions of pseudolymphoma caused by Borrelia can give rise to cutaneous B cell lymphoma. This finding has been very rare in the United States.


Cutaneous B-cell Pseudolymphoma

(Lymphocytoma Cutis, Benign Cutaneous lymphoid Hyperplasia)

Introduction

With the appearance of an appreciation of a marginal zone lymphoma and follicular lymphoma in the skin, the entity of cutaneous B cell lymphoma has assumed a greater importance in diagnosis because of the fact that it is not a lymphoma but in some instances with recurrence can lead to lymphoma. As noted, by Philip McKee, the realization that germinal center formation does not mean necessarily a benign reactive process has changed our approach to these lesions and we must be extremely careful in diagnosis of the pseudolymphomatous lesion.

Clinical features

A prominent erythematous to plum colored nodule or plaque is characteristic of this lesion. The pseudolymphomatosus auras occur in the same sites often as the well-differentiated B cell lymphoma such as marginal zone lymphoma. The most common sites are face, head and neck, chest and upper extremities. The lesion are usually singular but in some patients they can be multiple. Women are more affected than men and mostly patients are under 40 years of age. The Borrelia associated pseudolymphoma that is more common in Europe than in the United States, affects the areas of the head but also the nipple of the areola and the scrotum. These lesions are more commonly noted in children. It is interesting that when lymphocytoma cutis is present on the trunk, it is associated with multiple lesions often. Histopathologically, the lesion has been described to show a so-called top-heavy infiltrate. However, in others, it can be seen as a diffuse infiltrate or it can be bottom-heavy as well that is affecting the subcutaneous fat predominantly. Lymphoid follicles with germinal centers are usually present and they often have a clear-cut mantle zone. Tightly packed lymphocytes are common and the germinal center shows the zonation that is characteristic of the germinal center in lymph nodes. The interfollicular population includes lymphocytes, plasma cells, histiocytes and eosinophils. Occasionally multilaminate giant cells are present and even present granulomatous elements. Blood vessels are associated with very prominent endothelial cell hypertrophy and swelling in some instances. Immunohistochemically these lesions are composed of B cells and T cells but the latter usually are equal to the B cells or can predominate. The germinal centers can be highlighted with CD21. There are polyclonal light chains, evidence of polyclonality in light chain examination for kappa and lambda. One very important differential diagnostic feature that we have found to be very useful is that the hair follicles can be infiltrated by B cells in lymphoma whereas this infiltration does not occur in for example, marginal zone lymphoma, where as this infiltration does not occur in B cell lymphoma. The B cells may be CD20 positive or CD23 positive. The pathogenesis of this lesion is very interesting in that these lesions can occur as a result,

Erythema gyratum repens

Erythema gyratum repens is a rare manifestation of a neoplasic disease, usually carcinoma of the lung but it has also been associated with other malignancies with tuberculosis with pityriasis rubra pilaris in a few patients and rarely with the CREST syndrome. The lesion is represented by broad irregularly shaped patches that resemble the bark of a tree as they are separated by clear skin. What is so fascinating in this disorder is that it may be associated with carcinoma of the lung, and on excision of the tumor, the lesions of erythema gyratum repens will disappear but then recur if the malignancy recurs. In the histopathology, this shows usually a prominent perivascular lymphoid infiltrate with variable edema and admixed eosinophils superficial and deep. In some instances it presents as a diffuse lympho-cosinophilic infiltration of the demis admixed with histiocytes. Clinical correlation is extremely important in this disorder.

Erythema marginatum

Erythema marginatum is a disorder that is associated with rheumatic fever and it may be associated with rheumatic carditis. However, it also occurs spontaneously and may be associated with strep infection. The lesions clinically are small, round, semilunar shaped lesions or irregular shaped papules and plaques that are very evident and occurring rapidly and resolving with sometimes 30 to 50 minutes. They typically involve the trunk. In the histopathology, there is a prominent vascular lymphoid infiltrate but most strikingly there are numerous neutrophils in perivascular and intervascular array with debris. The neutrophilic debris is scattered throughout the entire dermis and thus differs from other types of lesions that would be associated with vasculitis, for example. There is no evidence of fibrinoid necrosis nor is there any evidence of extravasation of red blood cells but simply neutrophils with debris. Occasionally the epidermis will show a dyskeratotic cell and there may be intravascular neutrophils. The main differential diagnosis of this lesion is leukocytoclastic vasculitis but there is minimal or no fibrin distribution in this lesion as one finds in urticarial vasculitis also there is not the diffuse debris but rather a rare neutrophil scattered through the dermis and to some debris around the vessels with or without fibrinoid necrosis.


