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 Sezary 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, pleomorphic 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 a helpful if not highly sensitive or specific criterion. Pautrier’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 basilar 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 early MF.

Another helpful histologic criterion is that of “haloed lymphocytes,” a term that reflects the tendency of malignant intraepidermal lymphocytes to show artifactual cytoplasmic retraction, giving the impression of haloes around the nuclei. This feature has been reported in about 60% of MF, and 13% of inflammatory dermatoses, representing a fairly robust diagnostic criterion.
The finding of intraepidermal lymphocytes larger than dermal lymphocytes also strengthens the histologic diagnosis of MF. This feature reflects the fact that early in disease, a clonal malignant lymphocyte population is present in the epidermis, while the dermal infiltrate typically is comprised of reactive CD8 positive 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 high 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 “lymphomatosid contact dermatitis” has been coined).

Histologically, the finding of nonlymphoid intraepidermal mononuclear cell collections (pseudopautrier microabscesses) favors the possibility of spongiotic dermatitis. These collections are distinguished by their flask shape in the epidermis, and by the presence of Langerhans cells and precursors (staining CD1a+, S100+, CD68+, CD83+). However, since approximately 10% of cases of MF also feature spongiosis, the presence of
pseudopautrier microabscesses alone does not confirm a benign diagnosis. In fact, in a study by Candiago, while pseudopautrier 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-psoriasiform-lichenoid pattern, the presence of purpura, epidermal atrophy and hyperplasia in a single silhouette, and a uniform laminated horn.

References:


Orbaneja JG et al. Lymphomatoid contact dermatitis: a syndrome produced by epicutaneous hypersensitivity with clinical features and a 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. Histologically, is can be difficult if not impossible to differentiate between drug induced pseudolymphoma and true MF. In addition, some drug-induced pseudolymphomas show clonal gene rearrangements, making a distinction by molecular methods suspect. Usually drug induced pseudolymphoma resolves with cessation of drug therapy and recurs with rechallenge.

Drugs mimicking MF

<table>
<thead>
<tr>
<th>CLINICAL MIMICS</th>
<th>HISTOLOGIC MIMICS</th>
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<tbody>
<tr>
<td>phenytoin</td>
<td>phenytoin, carbemazepine</td>
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<td>carbemazepine</td>
<td>fluoxetine</td>
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<td>fluoxetine</td>
<td>enalopril, captopril</td>
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<td>atenolol</td>
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<td>phenobarbital</td>
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<td></td>
<td>d-penicillamine</td>
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<td>antihistaminic drugs</td>
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References:


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

The histologic distinction between some lichenoid dermatoses and lichenoid presentations MF can at times be problematic. In a review of the distinction between early lichen sclerosus (LS) and lichen planus (LP), LeBoit et al noted that 100% of cases of early LSA show a psoriasiform lichenoid pattern (also common in MF), 100% showed basilar epidermotropism (as in MF), and 33% 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 basilar 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 cases of persistent pigmented purpuric dermatitis (PPPD) represent a simulant 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 fibrosis. Features favoring the diagnosis of MF include large collections of lymphocytes in the epidermis with many lymphocytes in the spinous layer, and lymphocyte 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-like keratosis (LPLK). Such cases have aptly been termed mycosis fungoides-like keratosis (MFLK) or lymphomatoid lichenoid keratosis (LLK). In general, clinical findings such as size and duration, and histologic findings such as epidermal destruction should enable a distinction between MFLK and true solitary lesions of MF (see chart below).
### MFLK (LLK, BLK, LPLK) vs. Unilesional MF

<table>
<thead>
<tr>
<th>MFLK (LLK, BLK, LPLK)</th>
<th>Unilesional MF</th>
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<tbody>
<tr>
<td>trunk and extremities</td>
<td>often acral</td>
</tr>
<tr>
<td>small and scaly (&lt; 1 cm)</td>
<td>usually &gt; 1 cm</td>
</tr>
<tr>
<td>short duration</td>
<td>usually longer duration</td>
</tr>
<tr>
<td>clinical usually R/O CA</td>
<td>clinical rash, dermatitis, MF</td>
</tr>
<tr>
<td>bx MF-like, epidermal destruction</td>
<td>bx MF</td>
</tr>
<tr>
<td>polyclonal</td>
<td>monoclonal</td>
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### References:


### Variants of MF

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

### Woringer Kolopp disease (pagetoid reticulosis)

In 1939, 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, featuring prominent lymphocytic epidermotropism, often with minimal dermal infiltrates. The lymphocytes tend to reside in the epidermis with small haloes, hence the resemblance to Paget’s disease for which the term “pagetoid reticulosis” was coined. Cases typically show an indolent clinical course. In the past, there has been considerable debate in the literature about the relationship between Woringer-Kolopp disease and mycosis fungoides. Despite the histologic similarity between Woringer Kolopp and classic MF, the lymphocytes of Woringer-Kolopp disease are as likely to show a T-suppressor phenotype (CD8 positive) as they are to be CD4 positive, and gene rearrangements have not been consistently identified in examined cases.

Nonetheless, reports are accumulating in the literature of solitary lesions 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 axillae and groin, with erythema and scale. 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
unrelated to clinical parameters in any given case, and is not associated with the dramatic pendulous skin folds of granulomatous slack skin.

References:


**Adnexotropic mycosis fungoides (folliculotropic and syringotropic patterns)**

A relationship between follicular mucinosis and MF is well documented, occurring primarily in the head and neck as pruritic plaques with concurrent alopecia, and lymphocytes invading follicles distorted by mucin deposition. Follicular involvement in MF may also occur as keratotic plaques and cysts comprised histologically of dense aggregates of lymphocytes invading follicular epithelium, without mucin in follicles or changes of MF in the overlying epidermis. Recognition of folliculotropic MF is important, whether or not there is accompanying follicular mucinosis, since folliculotropic lesions tend to be recalcitrant to superficial therapy such as photochemotherapy, and require alternative treatment such as with electron beam.

Cases have been reported in which lesions of MF are predominately syringotropic, again with minimal epidermal involvement. In the early 1990’s, this phenomenon was reported as “syringolymphoid hyperplasia with alopecia”. Clinically, this variant features plaques studded with papules. Histologically, the eccrine apparatus is hyperplastic and diffusely infiltrated with atypical lymphocytes. As with cases of folliculotropic MF, classification as lymphoma relies on the presence of cytologic atypia, T-cell gene rearrangements, and usually the presence of more classic lesions of MF elsewhere in the same patient. It is interesting to note that in classic lesions of MF, involvement of eccrine glands is visible in approximately one third of cases, and involvement of follicles can be seen in about half of cases, further demonstrating the tendency for adnexotropism of the malignant lymphocytes in this disease.

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 lymphoadenopathy, 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 immunopheotypic 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 (LPD) are relatively common, comprise approximately 30% of lymphoid neoplasms primary in the skin, and are second in frequency only to mycosis fungoides. Cutaneous CD30+ LPD represents a biologic and histologic spectrum with lymphomatoid papulosis (a benign disorder with spontaneous regression) at one end and primary cutaneous anaplastic large cell lymphoma (C-ALCL, an indolent CD30+ lymphoma usually treated with local therapy) at the other end. In between are 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). It is extremely important to distinguish C-ALCL from secondary involvement of the skin by systemic ALCL, an aggressive disease that requires multiagent, systemic chemotherapy.

**Topics for Discussion:**
- Clinical and pathologic features of primary cutaneous ALCL
- Pathogenesis of primary cutaneous ALCL
- Distinguishing primary cutaneous ALCL from systemic ALCL
- Treatment of primary cutaneous ALCL
- Clinical and pathologic features of LyP
- Relationship of primary cutaneous ALCL to LyP
- Other lymphomas and reactive processes in the differential diagnosis of CD30+ LPD

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**Primary Cutaneous ALCL**

**Definition of primary cutaneous ALCL:**
- Skin involvement without evidence of systemic disease *
- No antecedent history of LyP, mycosis fungoides, Hodgkin lymphoma, 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. One recent study has shown only a slightly decreased overall 5-year survival for primary cutaneous ALCL versus cutaneous ALCL with regional node involvement (83% vs. 76%, respectively); however, it should be noted that 82% of the patients with regional node involvement received multiagent 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)
- 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 > multiple; regional > generalized; multifocal disease is seen in approximately 20% - 25%
- Larger lesions are often ulcerated
• Extremities>head and neck>trunk>genitalia
• Rarely described in the post transplant setting\textsuperscript{16-19} and in HIV+ patients\textsuperscript{20-22}

\textbf{Note:} Localized disease refers to a few clustered lesions restricted to one anatomic area, and generally not exceeding 15 x 15 cm. Multifocal disease has skin involvement of two or more anatomic sites.\textsuperscript{6}

\textbf{Histologic features of primary cutaneous ALCL}:\textsuperscript{8, 9, 11}
• Dense and diffuse dermal infiltrate often extending into subcutaneous tissue
• Epidermal ulceration in 30%-50%; no significant epidermotropism
• Pseudoepitheliomatous epidermal hyperplasia may mimic carcinoma\textsuperscript{23, 24}
• Tumor cells are present in sheets or large clusters
• Most cases are anaplastic with large cells having folded or indented nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm
• 10% -25% have non-anaplastic morphology (pleomorphic folded nuclei with denser chromatin or an immunoblastic appearance)
• Vascular invasion or perivascular cuffing, but not destruction, by tumor cells can be seen\textsuperscript{11, 25, 26}
• Variable numbers of multinucleated, Reed-Sternberg-like giant cells
• Neutrophils and/or eosinophils may be prominent and a pyogenic form of C-ALCL has been described\textsuperscript{5, 20, 27}
• Reactive lymphocytes are often present at the periphery of the lesion
• Large numbers of eosinophils may be predictive of subsequent lymph node disease\textsuperscript{8}

\textbf{Note:} Regressing atypical histiocytosis is now considered as ALCL\textsuperscript{8, 28-30}

\textbf{Immunophenotype of primary cutaneous ALCL:}
• Strong CD30 expression in virtually all (>75%) tumor cells
• CD4+>> CD8+ (< 5%); variable loss of pan T-cell antigens CD2, CD3, CD5
• EMA+ in \textless 32% of cases; CD15+ in \textless 10%\textsuperscript{9, 31} \textsuperscript{†}
• CD56+ in 12% - 75%; does not appear associated with a worse prognosis as seen in ALCL at other extranodal sites or in systemic ALCL\textsuperscript{32-35}
• Roughly 75% express at least one cytotoxic protein (TIA-1, granzyme B, perforin)\textsuperscript{36, 37}
• ALK protein expression is uncommon, but is seen in rare cases of primary cutaneous ALCL,\textsuperscript{38-40}
• In most cases ALK positivity suggests systemic disease\textsuperscript{41}
• EBV- in > 90%\textsuperscript{42-44}
• Clusterin + (41% - 100%)\textsuperscript{45-47}
• Fascin+ in 64% of C-ALCL\textsuperscript{48}
• C-ALCL has higher expression of apoptosis signaling molecules than systemic ALCL\textsuperscript{49}
• Cutaneous lymphocyte antigen (CLA) expression as detected by antibody HECA-452 is reported in 44% C-ALCL in most tumor cells\textsuperscript{7}

\textsuperscript{†} Cytoplasmic (not membrane) CD15 expression has been reported in up to 40% of cases

\textbf{Note:} Two molecules have been identified as important in predicting whether cutaneous lesions may or may not regress. BCL-2 expression correlates with non-regression; \textsuperscript{50} CD30L (ligand) correlates with regression.\textsuperscript{51}

\textbf{Pathogenesis of primary cutaneous ALCL:}
As primary cutaneous ALCL is ALK negative, the pathogenesis is different from the usual systemic ALCL. HOX homeobox gene \textit{HOXC5} is preferentially expressed in primary cutaneous ALCL and
MALT lymphoma. HOX genes are important in regulating trafficking, as their target is genes encoding adhesion molecules.\textsuperscript{52} JunB is expressed in virtually all CD30+ tumors including Hodgkin lymphoma, ALK+ and ALK-ALCL, C-ALCL, and LyP.\textsuperscript{6,53,54} Amplification of \textit{JunB} has been reported in 70\% of primary cutaneous ALCL and JunB protein expression has been detected in 100\% of C-ALCL in the small number of cases tested.\textsuperscript{53,55} JunB is a component of the AP-1 transcription factor complex that binds to an AP-1 site within the microsatellite region (that is normally repressive) in the CD30 promoter thus allowing transcription of the CD30 gene. In addition, CD30 signaling activates the ERK1/2 MAPK pathway that increases JunB creating an autocrine loop.\textsuperscript{56} It is interesting that this “amplifying loop” is not present in normal cells where expression of CD30 is too weak to transduce self-activating signals. Recent studies have also shown polymorphisms in the CD30 promoter microsatellite repressive element (30M377 in LyP and 30M362 in ALCL or HL arising in LyP) suggesting a possible predisposition in these patients to develop a CD30+ LPD.\textsuperscript{57}

**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.\textsuperscript{58,59} Primary cutaneous ALCL has an excellent prognosis (83\% - 100\% overall 5 year survival; disease related survival is > 90\%), whereas the prognosis of systemic ALCL with associated skin involvement is much less favorable\textsuperscript{8,10} (see Table 1).

<table>
<thead>
<tr>
<th>Clinical type of ALCL</th>
<th>5-year cumulative survival (%)</th>
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<tbody>
<tr>
<td>Primary cutaneous</td>
<td>83% - 100%</td>
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<tr>
<td>Skin involvement in systemic disease</td>
<td>24% - 44%</td>
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<tr>
<td>Simultaneous presentation of skin and extracutaneous lesions</td>
<td>15%</td>
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<tr>
<td>Cutaneous ALCL following LyP/MF/Hodgkin lymphoma</td>
<td>65% - 85%*</td>
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*ALCL developing in LyP appears to have a good prognosis\textsuperscript{6}

**Note:** Most series report overall 5-year survival for systemic ALCL (includes adults and children, all clinical types) as 65\% - 85\%.

**How to distinguish primary cutaneous ALCL from systemic disease:**
- Careful staging is imperative; there are no foolproof markers to distinguish
- ALK expression correlates with systemic disease (but is rarely seen in primary cutaneous ALCL)\textsuperscript{39-41}
- Monomorphic histology is more often seen in systemic disease
- C-ALCL more pleomorphic, more RS-like cells and acute inflammatory cells
- Clusterin was initially reported as being exclusively expressed in systemic ALCL; Wellman et al., 2000\textsuperscript{60} 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 clusterin expression in approximately 41\% - 100\% of cases of primary cutaneous ALCL.\textsuperscript{45-47}
- Cutaneous lymphocyte antigen (CLA) is more frequent in C-ALCL than systemic ALCL (44\% vs. 18\%, respectively)\textsuperscript{7}
• Rashes are rare in ALCL overall and are more often seen in reactive CD30+ infiltrates (see below); but, if present in lymphoma suggest systemic disease

Note: EMA expression is not useful in distinguishing primary cutaneous disease versus systemic ALCL as it has been reported in 54% of simultaneous cutaneous and systemic ALCL, 100% of secondary skin involvement, and up to one third of primary cutaneous ALCL.31

Note: Remember primary cutaneous ALCL is uncommon in children; careful staging and follow-up to rule out systemic disease are important.

Outcome in Primary Cutaneous ALCL

Disease course, prognosis, and treatment:
• Spontaneous regression (partial or complete) in up to 23% - 44%6,8,31
• Indolent course7,8,13,31,61
  - Overall 5 year survival (83% - 100%) with a disease related survival > 90% versus ~65% - 85% in nodal (systemic) ALCL6,62
  - Cutaneous relapse common (32% - 44%)6,8,63, particularly with multifocal disease and in the pediatric population14,64
• Overall, 10% - 25% (17% - > 40% in patients with multifocal disease) develop nodal (or other extracutaneous) disease6,9,64
  - Median of 24 months (range 2-117 mos.) after initial diagnosis
  - Aggressive disease appears associated with early spread to nodes other than regional nodes; approximately 50% with disseminated disease die

Note: In the new WHO-EORTC classification of C-ALCL, the requirement for disease to be limited to the skin for six months has been dropped; however, as a subset of patients develop nodal involvement close clinical follow-up is indicated.

• Sentinel lymphadenectomy for staging of C-ALCL has been described65
• Treatment varies with extent of disease:
  - Excision, with or without radiation in localized lesions is usual
  - Imiquimod (Aldara) an immune response modifier may be helpful66
  - Generalized cutaneous disease appears to be more aggressive and at greater risk to develop extracutaneous disease; low dose methotrexate, systemic retinoids w/ or w/o interferon alpha; monoclonal anti-CD30 therapy may be used with muticentric disease; combination chemotherapy and bone marrow transplant have not been shown to prevent relapse; at relapse the disease may remain indolent6,62,64,67,68
  - Photodynamic therapy with topical 5-aminolevulinic acid has been used for debulking69
  - Development of extracutaneous disease or rapid progression is currently treated with doxorubicin-based multiagent chemotherapy1

Remember: Patients with systemic ALCL and secondary skin lesions require aggressive multi-agent chemotherapy.

Note: Primary cutaneous ALCL in children has a high relapse rate despite systemic chemotherapy; however there is no systemic spread and the course is still favorable.14 Optimal therapy is not known.12

Note: No prognostic difference is seen in anaplastic vs. pleomorphic vs. immunoblastic morphology
Overlapping clinical and pathologic features indicate LyP and some cutaneous ALCL represent a continuous spectrum.

**Clinical features of LyP:**
- Adults (median age 45 years; male: female ratio 1.5:1)
- May occur in children
- Multiple papular, papulonecrotic, or nodular lesions, usually <1 cm
- Extremities and trunk
- Lesions usually ulcerate and heal with a scar in 3-12 weeks
- Chronic, recurrent lesions; duration of several months to more than 40 years
- Treatment:
  - None if few lesions and little scarring
  - Low dose methotrexate (5-20 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
- Lymphomas arising in LyP (ALCL and MF) do not appear to have a more aggressive course.

**Histologic features of LyP:**
- 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:
  - Type A
    - Wedge shaped infiltrate, perivascular
    - Scattered CD30+ large atypical cells
    - Dense background of inflammatory cells; neutrophils, and/or eosinophils may be particularly prominent
  - Type B (less common, <10%)
    - Band-like dermal distribution
    - Lymphocytes with convoluted “cerebriform” nuclei
    - Some epidermotropism may be present
    - Large CD30+ cells are rare or absent
    - Distinguished from mycosis fungoides on clinical parameters; LyP remits spontaneously and does not have extensive patches 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, so true “borderline” lesion
- Variants include: follicular and granulomatous eccrinotropic

**Immunophenotype of LyP:**
- Most series report predominance of CD4+ phenotype, but some report CD8+  
- EMA present in up to 31% of LyP
- CD15+ in up to 33% in frozen tissue
- TIA-1 and/or granzyme B expressed in 74% - 100% of LyP
- CD56 in 0% - 50% \textsuperscript{72, 82}
- Fascin+ in 24% LyP, but is present in 60% of LyP associated with systemic lymphoma and may be a predictor of disease progression\textsuperscript{98}
- Cutaneous lymphocyte antigen (CLA) is present on most large cells in LyP (82% +/- 6%) as compared to weaker expression in C-ALCL (13% +/- 7\%)\textsuperscript{83}

**Molecular findings in LyP:**
- Clonal T-cell populations have been demonstrated in 38% - 100% of LyP\textsuperscript{76, 84, 85} and the same clone is present in LyP and the lymphomas that develop in some cases.\textsuperscript{76, 86} Other studies report polytypic large CD30+ T-cells in LyP with a clonal population of small CD3+ T-cells.\textsuperscript{87}

**Clinical (Table 2) and pathologic (Table 3) features are used to distinguish ALCL and LyP:**

### Table 2. Clinical Features Useful in Distinguishing ALCL and LyP

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>LyP</th>
<th>ALCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of lesion</td>
<td>Papules, nodules</td>
<td>Nodules, tumors, rarely rash</td>
</tr>
<tr>
<td>Number</td>
<td>Multiple</td>
<td>Single or grouped</td>
</tr>
<tr>
<td>Size</td>
<td>Usually &lt; 1 cm*</td>
<td>&gt; 2 cm*</td>
</tr>
<tr>
<td>Sites</td>
<td>Extremities, trunk</td>
<td>Extremities, head and neck</td>
</tr>
<tr>
<td>Regression</td>
<td>Yes, usually with scar</td>
<td>~ 25% of cases</td>
</tr>
</tbody>
</table>

* > 3 cm more predictive of lymphoma; borderline lesions are usually intermediate in size, 1-2 cm.

### Table 3. Pathologic Features Useful in Distinguishing ALCL and LyP

<table>
<thead>
<tr>
<th>Histology/Immunophenotype</th>
<th>LyP</th>
<th>ALCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pattern of infiltration</td>
<td>Wedge-shaped perivascular/periadnexal</td>
<td>More diffuse</td>
</tr>
<tr>
<td>Subcutaneous involvement</td>
<td>Absent (or minimal)</td>
<td>Present</td>
</tr>
<tr>
<td>Mixed inflammatory cells</td>
<td>Many</td>
<td>Few to many</td>
</tr>
<tr>
<td>CD30+Cells</td>
<td>Scattered single or small clusters</td>
<td>Large groups or sheets</td>
</tr>
<tr>
<td>EMA</td>
<td>Present in 10% to 30% of cases</td>
<td>Present in 10% to 30% of cases</td>
</tr>
<tr>
<td>ALK</td>
<td>Usually negative</td>
<td>Usually negative</td>
</tr>
<tr>
<td>Fascin</td>
<td>Present in 25%*</td>
<td>Present in 50% - 75%</td>
</tr>
</tbody>
</table>

EMA = epithelial membrane antigen
* 60% of LyP that progress to ALCL are fascin+

**Differential Diagnosis of CD30+ Lymphoproliferative Disorders**

**Primary Cutaneous ALCL versus Transformed Mycosis Fungoides (MF):**

*Transformation of mycosis fungoides to large cell lymphoma:*\textsuperscript{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
**Features useful in distinguishing transformed mycosis fungoides (MF) and primary cutaneous ALCL:**

- Antecedent or coexistent patch or plaque stage lesions
- Small residual cerebriform lymphocytes usually present

**Remember:** Do immunohistochemistry for CD4 and CD8; Small, reactive CD8+ lymphocytes with irregular, sometimes “cerebriform appearing”, nuclei may surround and infiltrate primary cutaneous ALCL.

**Primary Cutaneous ALCL versus Primary Cutaneous Hodgkin Lymphoma:**

Hodgkin lymphoma (0.5%-3.4%) may secondarily involve the skin as secondary retrograde lymphatic spread from involved lymph nodes or infiltration of soft tissue in advanced (terminal) disease; primary cutaneous Hodgkin lymphoma is very rare.

**Primary cutaneous Hodgkin lymphoma:**

- Very rare
- Clinical course is variable; usually indolent; can develop nodal involvement 2 mos-46 years; rare cases with aggressive course
- Extremities >> trunk
- Tumor cells are scattered, not sheet-like
- Diagnostic, multinucleate RS cells present
- CD45-, CD30+, CD15+, EBV+/-

**Table 4. Pathologic Features Useful in the Differential Diagnosis of CD30+ Cutaneous lymphomas/LyP**

<table>
<thead>
<tr>
<th>Type of lesion</th>
<th># of Tumor Cells</th>
<th>RS-cells</th>
<th>CD15</th>
<th>CD30</th>
<th>EMA</th>
<th>CD45</th>
<th>EBV</th>
<th>T cell Antigens</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALCL</td>
<td>Many</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>+</td>
<td>Multiple papules with regression</td>
</tr>
<tr>
<td>LyP</td>
<td>Few</td>
<td>Rare</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transformed Mycosis Fungoides</td>
<td>Many</td>
<td>Rare</td>
<td>-/+</td>
<td>+/±</td>
<td>NT</td>
<td>+</td>
<td>NT</td>
<td>-</td>
<td>Admixed cerebriform lymphocytes; history of patches and plaques</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>Few</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>Very rare</td>
<td></td>
</tr>
</tbody>
</table>

+ = >50% of cases; +/- = 25% - 49%; -/+ = 5% - 24%; - < 5%

* frozen tissue

**Beware:** CD30 expression has been reported in granulocytic sarcoma, which can occur in the skin; CD30 can be weakly expressed in malignant melanoma; CD30 expression in these other tumors is usually weak and more diffuse.

**Primary Cutaneous ALCL versus Cutaneous Nasal Type NK/T Cell Lymphoma:**

- ALCL may show vascular invasion (angiocentricity) but lacks angiodestruction
- Zonal necrosis is rare or absent
- EBV expression is uncommon in ALCL
- The immunophenotype is not definitive; CD56 is present in some cases of ALCL and CD30 expression is seen in ~20% of nasal type NK/T cell lymphoma
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 lymphoma.

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 marrow ablative therapy and growth factor administration at the time of lymphocyte recovery (eruption of lymphocyte recovery)
- Hypersensitivity reaction to carbamazepine Rare C-ALCL have been described in patients on carbamazepine
- Herpesvirus or parapoxvirus infection
- Reactive cutaneous infiltrates that contain a prominent neutrophilic or eosinophilic component including insect and spider bites, hidradenitis suppurativa, Sweet syndrome

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

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.
References

“Unusual Types of Cutaneous T-cell, NK-cell, and Precursor Lymphomas and their Relationship to the Innate Immune System”

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

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

Historical Perspectives and Current Classification

Table 1 summarizes the current EORTC/WHO classification of cutaneous T-cell and NK 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.¹

Table I. WHO-EORTC 2005 Classification of Cutaneous Lymphomas.²,³
Cutaneous T-cell and NK-cell lymphomas
- Mycosis fungoides
- MF variants and subtypes
  - Folliculotrophic MF
  - Pagetoid reticulosis
  - Granulomatous slack skin
- Sézary syndrome
- Adult T-cell leukemia/lymphoma
- Primary cutaneous CD30+ lymphoproliferative disorders
  - Primary cutaneous anaplastic large cell lymphoma
  - Lymphomatoid papulosis
- Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)
- Extracutaneous 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 $\gamma\delta$TCL 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.\(^5\)

**Pattern of infiltration:** Early stage: Mid-dermal, periadnexal and perivasculare. Later stage: Dense infiltrates centered in mid-dermis, with variable extension into epidermis and into subcutaneous tissue.\(^5,6\)

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

**Immunophenotype:** See Table II. Absence of CD4, CD8 and TCR-beta expression can be used in paraffin-fixed material as putative evidence of gamma-delta origin, although transformed MF can also be negative for all 3 markers.\(^\)\(^6\) With subcutaneous infiltration, $\gamma\delta$TCL may show large numbers of admixed reactive lymphocytes and monodendritic cells.

**Clinical behavior:** Multiple cutaneous recurrences, with minimal spread outside skin until late in disease course. Hemophagocytic syndrome (HPS) seen in up to 75%.\(^7\) 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 $\gamma\delta$TCL from SPTCL has highlighted the indolent behavior of a subset of these tumors.\(^7,8\)

**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 lymphohistiophagocytosis.

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

**Immunophenotype:** See Table II. Mixed infiltrates are common, but CD8 expression in tumor cells is usually apparent.\(^9\) CD4+ tumors with otherwise typical SPTCL features are reported.

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

**Differential diagnosis:** Panniculitis (focus on atypia and diffuse growth), systemic PTCL, NOS
Extranodal NK/T-cell lymphoma, nasal type

The boundaries of this entity are still being established, with both highly aggressive and more indolent variants seen. Whether EBV-negative cases should be separately classified is unclear.

Clinical appearance of lesions: Multiple, ulcerating nodules, may mimic MF plaques.

Pattern of infiltration: Dermis, often extending to subcutis.

Cytomorphology: Highly variable from small cells with minimal cytologic atypia to large cell morphology.10

Immunophenotype: See Table II. EBV+ positivity is most helpful since it is extremely rare in other cutaneous lymphomas.10 Strong CD30 expression may be seen in transformed cases.11

Clinical behavior: Highly variable, some cases may be largely restricted to skin for years;12 others may be show frequent metastases to oropharynx, testes, GI tract, and lung.13 A subset of tumors will overlap with aggressive NK-cell leukemia, with extensive marrow infiltration and rapidly fatal course.14 Many tumors are radiosensitive.

Differential diagnosis: Cutaneous anaplastic large cell lymphoma and cutaneous presentations of peripheral T-cell lymphoma, especially CD8+ tumors expressing cytotoxic markers,15,16 including aggressive epidermotropic CD8+ T-cell lymphoma.17

CD4+/CD56+ hematodermic blastic tumor (BT)

This CD4+CD56+ agranular hematodermic neoplasm was classified provisionally as blastic NK lymphoma in the 2001 WHO scheme. Most recent evidence has suggested that it is related to plasmacytoid dendritic cells (DC2)18-20 or to immature hematopoietic precursors with multilineage potential.21 Cytogenetic changes are similar to acute leukemias.22 This tumor is awaiting a definitive name due to uncertainties about its histogenesis.

Clinical appearance of lesions: Solitary nodules, to rapidly progressing tumors.

Pattern of infiltration: Dermis and subcutis, perivascular aggregates or single-file infiltration in early stages.

Cytomorphology: Medium-sized, with blastoid chromatin. Some cases have abundant cytoplasm. Nucleoli are variably prominent.

Immunophenotype: Positive for CD56, CD4 (can be weak) as well as CD43, CD45RA (4KB5), CD123 (IL3R-alpha) and TCL1.23 The DC2 marker BDCA-224 is positive in subset, as is TdT.21,25 Negative for CD3, CD20, and most T-cell markers.26 Variable CD2, CD10, and CD33 expression seen.20

Clinical behavior: Highly aggressive, with marrow and peripheral blood dissemination within 12-18 months. A small number of indolent cases have now been described. Myeloid or myelomonocytic recurrences following chemotherapy are well-documented.21

Differential diagnosis: Myeloid leukemia (if MPO+), monocytic leukemia (if lysozyme or butyrate esterase+), lymphoblastic leukemia.
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-α/β-expressing helper and cytotoxic T-cells. 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 glycoplipids, 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 γδ T-cells and cognate receptors on NK cells have relatively limited diversity consistent with their role in recognizing common microbial antigens. Dendritic cell maturation mediated by group of Toll-like receptors is also tuned to recognize broad antigenic patterns. This generalized microbial recognition system is in contrast to the high level of specificity encoded by the TCR-α/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 adnexal structures and dermal vascular beds 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.

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 early MF might thus be achieved by achieving by identifying and treating specific inciting agents.

In contrast, the factors driving expansions in the early stages of the innate-immunity group of cutaneous tumors is unknown but would likely be distinct. Given the highly dynamic nature of innate responses, immunotherapy may prove useful in treatment of these aggressive neoplasms.
<table>
<thead>
<tr>
<th></th>
<th>surface CD3</th>
<th>CD4</th>
<th>CD8</th>
<th>CD5</th>
<th>CD56</th>
<th>CD30</th>
<th>Cytotoxic proteins</th>
<th>EBV</th>
<th>TCR usage</th>
<th>TCR genes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SPTCL</strong></td>
<td>+</td>
<td>-/+</td>
<td>+</td>
<td>+</td>
<td>-/+</td>
<td>+</td>
<td>rare</td>
<td></td>
<td>αβ</td>
<td>Rearranged</td>
</tr>
<tr>
<td><strong>γδ-TCL</strong></td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-/+</td>
<td>+ (&gt;90%)</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>γδ</td>
<td>R</td>
</tr>
<tr>
<td><strong>NK/T nasal</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+ (90%)</td>
<td>-/+ (15%)</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>NKR</td>
<td>- /+ (20%)</td>
</tr>
<tr>
<td><strong>MFt</strong></td>
<td>+/-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-/+ (5%)</td>
<td>-/+ (35%)</td>
<td>+/- (50%)</td>
<td>-</td>
<td>αβ&gt;&gt;γδ</td>
<td>R</td>
</tr>
<tr>
<td><strong>ALCL</strong></td>
<td>+/-</td>
<td>-</td>
<td>+/-</td>
<td>-/+</td>
<td>-/+ (10%)</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>- (50%)</td>
<td>R</td>
</tr>
<tr>
<td><strong>BT</strong></td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>- (10%, pre-TCR)</td>
<td></td>
</tr>
</tbody>
</table>

Marker expression frequencies are those seen in archival tumors from M. D. Anderson Cancer Center, and will vary widely in different geographical areas due to differences in EBV infection patterns and other etiologic causes.33-35
References


Cutaneous B-cell Lymphomas
Lyn M. Duncan, M.D.
Associate Professor of Pathology, Harvard Medical School
Dermatopathology Unit, Massachusetts General Hospital, Boston, MA

Cutaneous B-cell lymphomas
- Primary cutaneous marginal zone B-cell lymphoma (pcMZL)
- Primary cutaneous Follicle center lymphoma (pcFCL)
- Primary cutaneous Diffuse large B-cell lymphoma, leg-type (pcDLBCL, leg)
- Primary cutaneous Diffuse large B-cell lymphoma, other (pcDLBCL, other)

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 effecting one cutaneous region and rarely ulcerate. There is some regional predilection for various sub-types 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 epidermotropism, the tumor cells in cutaneous B-cell lymphomas spare the epidermis and are usually separated from it by a grenz zone of uninvolved dermis.

Immunophenotype
Some observers have proposed that a 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 borrelia infection and tattoo. 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 responder 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 >75% 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 lymphoma; in some cases of B-cell lymphoma the neoplastic B cells may represent only a minor component of the dermal lymphocytic infiltrate. An immunohistochemical panel including CD20, CD3, CD21, CD10, bcl-2, and bcl-6 is often useful in distinguishing follicle center lymphoma from marginal zone B-cell lymphoma.

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 lymphoma but only 50% of cutaneous B-cell lymphomas. As with any diagnostic tool, the interpretation of the genetic results should be in the context of the clinical, histologic and immunophenotypic findings of the case.

Treatment and Prognosis

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 lymphoma are usually treated with chemotherapy; single agent chemotherapy is given to patients with the more indolent tumors, multiagent 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 (pcMZL) and follicle center types (pcFCL) usually remain localized to the skin and are often cured by local therapy. Whereas primary cutaneous diffuse large B-cell lymphoma (pcDLBCL) of the leg is more often associated with eventual extracutaneous lymphoma. 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 Program 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 (Willemze 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 skin. The current most broadly accepted definition of primary cutaneous lymphoma is: lymphoma arising in the skin without evidence of extra-cutaneous lymphoma for six months following initial presentation and staging including bone marrow biopsy and radiological examination.

B-CELL LYMPHOMAS OF THE SKIN
Of all cutaneous lymphomas approximately 25% have been estimated to be of B-cell lineage. The estimated annual incidence of primary cutaneous B-cell lymphomas in Europe is 0.2/100,000 per year. The vast majority of these patients have cutaneous B-cell lymphomas of follicle center and marginal zone B-cell type, with a minor cohort of patients with large B-cell lymphomas. Other forms of cutaneous B-cell lymphoma represent rare but distinct clinical entities.

- Marginal zone B-cell lymphoma of (pcMZL)
- Follicle center lymphoma (pcFCL)
- Diffuse large B-cell lymphoma, leg-type (pcDLBCL, leg)
- Diffuse large B-cell lymphoma, other (pcDLBCL, other)

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue

WHO-EORTC: Primary cutaneous marginal zone lymphoma B-cell lymphoma (pcMZL)

Primary cutaneous marginal zone lymphoma B-cell lymphoma (pcMZL) is defined as a neoplastic proliferation of small B cells including marginal zone (centrocyte-like) cells, monocytoid B cells and, in most cutaneous tumors, lymphoplasmacytoid cells and plasma cells. Primary cutaneous marginal zone lymphoma (pcMZL) shares features with extranodal lymphomas of Mucosa Associated Lymphoid Tissue (MALT). Primary cutaneous immunocytoma and cutaneous lymphoid hyperplasia with monotypic plasma cells are considered to be variants of marginal zone lymphoma.

- Epidemiology
Cutaneous MZL affects both men and women, with a median age of 50 years and a range of 24-77 years. pcMZL shows a predilection for the trunk and upper extremities. Because of the predominance of T-cell lymphomas in the skin, pcMZL are rare among all cutaneous lymphomas. MZL is estimated to comprise approximately 35% of primary cutaneous B-cell lymphomas, second only to follicular lymphoma.

- Etiology
The etiology of most pcMZL 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 H. Pylori story for gastric MALToma, in Europe, Borrelia burgdorferi has been proposed as an etiological agent in the development of pcMZL. A few case reports even describe resolution of lesions following antibiotic therapy. Interestingly, no association between borrelia and pcMZL has been identified in reports from the United States and Asia. Other settings in which pcMZL have been described include tattoo, vaccination site, and insect bite (not related to tick borne illness).

- Clinical features
pcMZL usually presents as a solitary deep 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 pcMZL do not have B symptoms and have normal serum levels of LDH and β3 microglobulins. A rare association of pcMZL is Waldenstrom macroglobulinemia with resulting hyperviscosity syndrome; serum protein electrophoresis is a reasonable part of the laboratory evaluation of patients with extranodal MZL.

- Morphology
The histologic features of pcMZL, as in other sites, include reactive germinal centers with a proliferation of marginal zone cells with sheets of interfollicular plasma cells, and surrounding reactive T lymphocytes, with or without lymphoepithelial lesions. The mid-dermal and occasionally subcutaneous proliferation of marginal zone B cells surround reactive germinal centers and occasionally fill the interfollicular dermis. The neoplastic B cells are centrocyte-like cells with small–cleaved nuclei and amphophilic cytoplasm. The foci with plasmacytic differentiation may contain plasma cells with intranuclear pseudo-inclusions of immunoglobulin, termed Dutcher bodies. Follicular colonization, e.g. the infiltration of reactive lymphoid follicles by neoplastic B cells, may be present. Invariably there is a reactive T-cell infiltrate admixed among the neoplastic B cells. The T-cell infiltrate may be sparse or extremely dense; in some cases the T cells out-number the neoplastic B cells.

Marginal zone lymphomas that arise at other sites characteristically display infiltration of glandular epithelium termed “lymphoepithelial lesions”. This finding is less commonly observed in pcMZL and when present is observed in the epithelium of the hair follicles. The
epidermis is usually free of lymphocytes and is separated from the underlying dermal tumor by a grenz zone of uninvolved papillary dermis.

- **Immunophenotype**

In cases with plasmacytic differentiation, light chain restriction is identified in 70%. The plasma cells express CD138 and CD79a but not CD20. The neoplastic marginal zone cells usually have a CD20+, CD79a+, CD22+, CD5-, CD10-, CD23-, bcl-6- immunophenotype. Scattered rare large CD30+ activated T lymphocytes have also been reported in some cases of pcMZL. Notably, the staining pattern when B and T cell stains are compared is deceptively benign with central zones of B cells and surrounding T cells. In cases with colonized follicles the bcl6- bcl2+, CD10- neoplastic cells are observed admixed with bcl6+, bcl2+, CD10+ follicle center cells sometimes with splayed or dispersed CD21+ follicular dendritic cell meshworks.

- **Genetics**

Clonal rearrangement of immunoglobulin heavy chain genes has been detected using PCR based techniques in 70% of pcMZL. Bcl-2 protein expression is commonly observed in pcMZL. A proportion of pcMZL have displayed the presence of t(14:18)(q32:q21) involving the IGH gene on chromosome 14 and the MLT gene on chromosome 18.

- **Clinical course**

MZL is defined as a primary cutaneous tumor only when staging, including thoracoabdominal CT scan and bone marrow biopsy studies, has not revealed extracutaneous disease for 6 months after the diagnosis of the cutaneous lymphoma. pcMZL are usually clinically indolent, however, up to 30% of patients diagnosed with pcMZL will experience extracutaneous relapse, most commonly in other extranodal 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 pcMZL have been effectively treated with electron beam irradiation, radiotherapy, intralesional interferon alpha, chroambucil and/or local injection of steroids. Patients with disseminated disease receive more aggressive treatment including rituximab and combination chemotherapy.

- **Differential Diagnosis**

The differential diagnosis of pcMZL always includes cutaneous lymphoid hyperplasia (CLH) and primary cutaneous follicle center lymphoma (pcFCL). Cutaneous lymphoid hyperplasia (CLH) is a benign reactive proliferation in the skin that probably arises secondary to continued antigenic stimulation (e.g. arthropod bite, autoimmune disease, drugs, tattoos, or infectious agents). Synonyms for CLH include pseudolymphoma, lymphocytoma cutis, lymphadenosis benigna cutis, pseudolymphoma of Speigler-Fendt, and lymphadenoma granulosa. Because of overlap in the clinical presentation and histological features, it is likely that cutaneous low-grade B-cell lymphomas were diagnosed as CLH in past decades.

Clinically, CLH and pcMZL 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 grenz zone, reactive follicles, and admixed inflammatory cells (Table 3). Marginal zone cells and confluent sheets or zones of plasma cells in the interfollicular regions and around the superficial vascular plexus support a diagnosis of pcMZL. In contrast, epidermal atrophy or hyperplasia, exocytosis, spongiosis, or hyperkeratosis, are seen in the majority of cases of CLH, and only rarely in pcMZL. The more common occurrence of epidermal changes in CLH may be the result of an ongoing local inflammatory response to external antigen. Recognition of pcMZL and the finding that reactive lymphoid
Follicles are more commonly observed in pcMZL than CLH has led to a revision of the historical dictum that the presence of lymphoid follicles favors a benign diagnosis. In cases with inconspicuous follicles on hematoxylin-eosin stain, stains for bcl-2 and CD21 are useful in identifying focal non-staining areas and aggregates of follicular dendritic cells, respectively. The presence of a bottom-heavy infiltrate, although traditionally thought to favor a diagnosis of lymphoma is not diagnostic. A superficial dermal or "top-heavy" infiltrate may be observed in cutaneous B-cell lymphomas, whereas hypersensitivity reactions to injected antigens and lymphomatoid drug reactions may both show deep dermal, bottom-heavy, lymphoid infiltrates. While the presence of a grenz zone, eosinophils, or neutrophils, are not statistically significant distinguishing features, aggregates of eosinophils or abundant neutrophils with nuclear dust should lead one to carefully consider a diagnosis other than pcMZL.

PCR detects clonal rearrangement of immunoglobulin heavy chain genes in only 30 – 50% of B-cell lymphomas. More often, Immunohistochemistry demonstrates monotypic cytoplasmic expression of light chains by plasma cells in pcMZL. An infiltrate of ≥ 75% B cells and co-expression of CD43 and CD20 also support a diagnosis of B-cell lymphoma.

In pcMZL the proliferation of marginal zone B cells may be minimal and inconspicuous; 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 pcFCL and pcMZL. A predominantly nodular or follicular pattern is observed in most pcFCL, and the presence of diffuse areas is present in all pcMZL. However, pcFCL may be entirely diffuse or display diffuse areas, and the majority of pcMZL have at least a partially nodular pattern. A predominance of small cells with irregular, somewhat cleaved nuclei characterizes both tumors. Moreover, anti-CD21 immunostaining highlights follicular dendritic cell meshworks, indicating true follicular structures in both pcFCL and pcMZL.

A combination of immunostaining for bcl-6, CD10 and bcl-2, yields distinct patterns of staining in the follicular and extra-follicular regions of FL and MZL. Distinguishing neoplastic follicles of FL from reactive or colonized follicles of pcMZL 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 pcFCL. In cases of pcMZL with colonized follicles, bcl-6, CD10, bcl-2 and CD21 may allow the distinction of expanded or colonized meshworks of follicular dendritic cells from neoplastic follicles. The colonized follicles, which typically correspond to nodular areas on H&E sections, display tight, 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- germinal center cells. The other pattern observed in pcMZL is that of expanded, colonized meshworks of follicular dendritic cells corresponding to areas that appear diffuse or 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 cell meshworks of pcMZL represent residual follicle center cells or blast transformation. Neoplastic follicles in pcFCL, on the other hand, contain a uniform population of neoplastic bcl-6+ cells, and in those cases expressing bcl-2, it is also uniformly expressed by cells within the follicles. In contrast to pcFCL, bcl-6+ and CD10+ cells are never seen in interfollicular and diffuse areas devoid of CD21+ cells in pcMZL.
Primary cutaneous follicle center lymphoma (pcFCL)

**WHO/EORTC:** Primary cutaneous follicle center lymphoma*

**WHO Classification:** Follicular lymphoma

**REAL Classification:** Follicle center lymphoma

* These tumors may have a follicular, follicular and diffuse, or diffuse growth pattern.

Primary cutaneous follicle center lymphoma (pcFCL) is likely the most common B-cell lymphoma to occur as a primary lymphoma of the skin. This tumor is characterized by the proliferation of a mixture of centrocytes and centroblasts often in a follicular pattern. Rarely, pcFCL displays diffuse areas or, even less commonly, an entirely diffuse pattern.

- **Epidemiology**

  pcFCL is a tumor of adults with a median age of 65 years, affecting slightly more men than women. pcFCL are most commonly located in the head and neck region and occasionally present on the trunk, or other cutaneous site.

- **Clinical features**

  Follicular lymphoma presents as solitary or grouped erythematous cutaneous papules, nodules or plaques. Tumors on the back may be associated with indurated plaques (so-called historically ‘reticulohistiocytoma of the dorsum’ or ‘Crosti’s lymphoma’).

- **Morphology**

  pcFCL is characterized by a mid-dermal and subcuticular admixed proliferation of centrocytes and centroblasts in either a follicular, follicular and diffuse, or diffuse pattern. Usually the centrocytes are more plentiful than the centroblasts and there is an admixed benign T-cell infiltrate of variable density. The centrocytes have small cleaved nuclei with inconspicuous nucleoli, or large cleaved nuclei with scant cytoplasm. Large centrocytes are generally more plentiful in diffuse pcFCL. Centroblasts have large round nuclei with peripherally located basophilic nucleoli and a rim with basophilic or amphophilic cytoplasm. Although centroblasts may be present they do not form confluent sheets in pcFCL.

  This neoplasm often appears as expanded, irregularly shaped, lymphoid follicles in the dermis. Occasionally, the neoplastic cells appear to spill-out of the follicles and surround aggregates of benign small lymphocytes, termed “inside-out follicles” by some observers. Sclerosis, manifest as an increase in fibrous tissue within the tumor, may also be observed.

- **Grading**

  Although grading is usually not reported with pcFCL, for comparison’s sake, pcFCL is on a morphological continuum up to FL grade 3b and diffuse FL grade 3a. In this way, the cutaneous classification of pcFCL and pcDLBCL is site specific, in as much as a grade 3 follicular lymphoma would be termed large B-cell lymphoma in a lymph node.

- **Immunophenotype**

  Immunohistochemical stains for kappa and lambda light chains reveal light chain restriction of the neoplastic centrocytes and centroblasts and a CD20+, CD79a+, CD10+/-, CD5-, CD43-, bcl-6+ immunophenotype. Diffuse pcFCL more often have a CD10- immunophenotype. In contrast to nodal follicular lymphomas, which are almost all bcl-2+, fewer than 30% of pcFCL have been reported to express the bcl-2 protein. Because bcl-2 protein is normally present on most T cells and B cells, except for the B cells in reactive follicle centers, and because the neoplastic cells in pcFCL are often bcl-2 negative, a negative bcl-2 staining pattern of follicles with the remaining lymphocytes staining positively for bcl-2 does not allow for distinction between a reactive and neoplastic process in the skin. Staining for MUM-1/IRF4 is negative.

In reactive B cells, expression of the bcl-6 transcription factor and of the membrane metalloproteinase CD10 is restricted to germinal center cells. Among nodal small B-cell neoplasms, anti-bcl-6 and anti-CD10 have been shown to react exclusively with follicular lymphomas. The non-lymphoid CD21+, CD35+ follicular dendritic cells have elongated processes, and form nodular meshworks within germinal centers. In addition to their function in B-cell maturation following exposure to antigen, follicular dendritic cell meshworks are helpful in defining the presence of lymphoid follicles.

- Genetics

Primary cutaneous follicle center lymphomas have the gene expression profile of germinal center-like large B-cell lymphomas. pcFCL typically does not have the association of t(14;18) observed in nodal follicular lymphoma. Faint bcl-2 expression and/or the t(14;18) translocation has been reported in a minority of pcFCL. PCR techniques detect clonal rearrangement of immunoglobulin genes in only 50% of cases.

- Clinical course

PcFCL rarely spread to lymph nodes, spleen or bone marrow, unlike the majority of nodal follicular lymphoma. The estimated 5 year survival for patients with pcFCL is > 97%. Excision and radiation therapy is effective for localized lesions, disseminated disease may be treated with anthracycline-based chemotherapy. Systemic or intralesional rituximab may also be effective. Therapy is not linked to grade in contrast to extracutaneous follicular lymphoma. In tumors with a follicular growth pattern the presence or absence of bcl-2 protein is not associated with a difference in clinical presentation or behavior.

- Differential Diagnosis

From a histological viewpoint, when pcFCL has a prominently follicular architecture, the differential diagnosis includes pcMZL and cutaneous lymphoid hyperplasia. Whereas, when pcFCL has a diffuse pattern of growth the differential diagnosis includes pcDLBCL.

Both pcMZL and pcFCL are predominantly localized to the head, trunk or upper extremities both tend to be localized to the skin at diagnosis and to have a low risk of dissemination to lymph nodes or bone marrow.

pcFCL and pcMZL also have overlapping morphologic features. pcFCL typically has a partially follicular pattern. pcMZL typically contains reactive or colonized follicles, and thus B-cell follicles can be found in both lymphomas. Factors that create difficulties in distinguishing the neoplastic follicles in pcFCL from the reactive follicles in pcMZL include the lack of bcl-2 protein expression and BCL-2 gene rearrangement in the majority of pcFCL and the occasional presence follicular colonization in pcMZL.

Immunostaining for CD21, bcl-6, CD10 and bcl-2 often yields distinct patterns of staining in pcFCL and pcMZL. In both follicular and interfollicular/diffuse areas of pcFCL the neoplastic cells are bcl-6+, CD10+ and occasionally bcl-2+. In pcMZL, the neoplastic B cells are bcl-6-, CD10-, and bcl-2+. Three patterns of CD21+ follicles may be identified in pcMZL: 1. reactive germinal centers: uniformly bcl-6+, CD10+, bcl-2-; 2. colonized follicles: both bcl-6-, bcl-2+, CD20+ cells and bcl-6+, bcl-2- cells; 3. expanded or colonized follicular dendritic cell meshworks: bcl-6-, bcl-2+ B cells with rare residual bcl-6+, bcl-2- cells.
The presence of a CD21 follicular dendritic cell meshwork containing two immunophenotypically distinct populations of B cells (bcl6+, CD10+, CD5-, bcl-2+/ follicle center cells and bcl6-, CD10-, CD5-, bcl-2+ neoplastic marginal zone cells) supports the presence of colonized follicles in pcMZL. Whereas, expanded irregularly shaped aggregates of bcl-6+, CD10+ B cells are supportive of the diagnosis of follicular lymphoma.

In summary, the immunophenotype of pcFCL is distinct from that of pcMZL 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 addition to the difficulty in distinguishing pcFCL from pcMZL, there is also overlap in some features between follicle center lymphoma and large B-cell lymphoma (Table 4). For the purposes of this presentation, pcFCL is defined as a neoplastic proliferation of large and small centrocytes and centroblasts usually with a bcl-6+, CD10+ immunophenotype, supported by a meshwork of CD21+ follicular dendritic cells. Although usually displaying a follicular growth pattern, occasionally pcFCL may diffusely efface the dermis. A bcl-2-, MUM-1+ immunophenotype in diffuse cases supports the diagnosis of pcFCL. Tumors that are composed of a uniform proliferation of centroblasts are designated as large B-cell lymphoma and are discussed later. Notably this definition excludes diffuse large B-cell lymphoma whether occurring on the lower extremity or other cutaneous sites.

**Primary cutaneous, diffuse large B-cell lymphoma of the leg**

*WHO/EORTC Classification (2004):* Primary cutaneous diffuse large B-cell lymphoma, leg type.

*WHO Classification:* Large B-cell lymphoma

*REAL Classification:* Diffuse large B-cell lymphoma

Primary cutaneous diffuse large B-cell lymphoma (pcDLBCL) is defined morphologically as a dense, often diffuse, proliferation of confluent sheets of large transformed B cells resembling centroblasts and immunoblasts, with effacement of the dermis and the absence of lymphoid follicles (Table 5).

When presenting on the leg, these tumors are categorized as a distinct diagnostic entity (pcDLBCL, of the leg) because of the associated increased risk of recurrence and dissemination. Other defined variants of diffuse large B-cell lymphoma that occur in the skin include T-cell rich B-cell lymphoma, pcDLBCL of sites other than the leg (pcDLBCL, other), and intravascular B-cell lymphoma (pcDLBCL, intravascular).

- **Epidemiology**
  
  Diffuse large B-cell lymphoma more commonly involves the lower extremities of women than men and occurs late in life with more than 80% of tumors occurring in patients older than 70 years.

- **Clinical features**
  
  pcDLBCL of the leg presents as erythematous or violaceous nodules on one or both lower legs, often with ulceration. These tumors more often disseminate to non-cutaneous sites than pcDLBCL of non-leg type.

- **Morphology**
  
  The dermis is diffusely infiltrated by a proliferation of mostly round, monomorphic large transformed B cells with prominent nucleoli and clumped chromatin, resembling centroblasts and immunoblasts. Epidermotropism is absent, however in ulcerated cases, the tumor cells may
extend to the dermal epidermal 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 recently
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 reported with a grade. For comparison’s
sake though, the pcDLBCL are comparable to diffuse grade 3b nodal LBCL.

- Immunophenotype

Monotypic surface immunoglobulin is identified along with a CD19+, CD20+, CD22+, CD79a+,
bcl-2+/-, bcl6 -/+ , CD10/-+, CD5/-+, CD138- immunophenotype. The intensity of bcl-2 stain
may exceed that of the non-neoplastic T cells. The MIB-1/Ki-67+ 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 1/ 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 t(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/EORTC Classification: Primary cutaneous diffuse large B-cell lymphoma, other.
WHO Classification: Large B-cell lymphoma
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
lymphoma arising in the skin do not belong to the leg type group of DLBCL or the group of
pcFCL.

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 extracutaneous 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>
<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>- grenz zone 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>- CD21^+ 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></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 1. General Features of Primary Cutaneous B-cell Lymphoma
Table 2. WHO/EORTC 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>pc FCL</th>
<th>pcDLBCL of the leg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphology</td>
<td>Predominance of centrocytes that are often large, especially in diffuse lesions</td>
<td>Predominance of large to medium sized B cells with round nuclei, prominent nucleoli, and coarse chromatic, cells may resemble centroblasts and immunoblasts</td>
</tr>
<tr>
<td></td>
<td>Centroblasts may be present, but not in confluent sheets</td>
<td>Diffuse growth pattern</td>
</tr>
<tr>
<td></td>
<td>Pattern may be follicular, follicular and diffuse, or diffuse (a continuum without distinct categories or grades)</td>
<td>Little stromal reaction, confluent destructive growth pattern</td>
</tr>
<tr>
<td></td>
<td>Sclerosis may be present</td>
<td></td>
</tr>
<tr>
<td>Phenotype</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: +/- Diffuse lesions more often 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>Clinical features</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></td>
</tr>
<tr>
<td></td>
<td>Rarely multifocal lesions</td>
<td></td>
</tr>
</tbody>
</table>

References


34. Crosti A. Micosi fungoide e reticuloistiociti cutanei maligni. Minerva Dermat. 1951;26:3-11


SECONDARY LYMPHOMAS OF THE SKIN
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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 disease is often dramatically different.\(^1\) Although large series of secondary cutaneous lymphomas are uncommon, secondary lymphomas or lymphomas that involve both nodal sites and the skin at presentation appear to represent approximately 25% of all cutaneous lymphomas and up to 50% of cutaneous lymphomas other than mycosis fungoides.\(^2,3\) In a recent survey of cutaneous lymphomas diagnosed at Stanford University, 24.6% 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, 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 (26.8%)**

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 primary follicular center cell lymphoma of the skin and primary cutaneous diffuse large B-cell lymphoma of the leg type. Both primary and secondary diffuse large B cell lymphomas commonly involve the head and neck regions or the extremities, but trunk involvement may be more characteristic of secondary disease. While the morphologic features of these entities are similar, both clinical behavior and gene expression profiling find clear differences in primary and secondary types.\(^4\) Other than clinical features, there are few clues to secondary cutaneous disease. The most common primary large B cell neoplasms of the skin are usually CD10 negative and lack t(14;18).\(^5\) Therefore, expression of CD10 or t(14;18), common findings in a subset of nodal diffuse large B cell lymphomas, should warrant further investigation for systemic disease. However, both CD10 expression and t(14;18) may occur in primary disease and these features should not be considered as definitive evidence of a secondary lesion.\(^6,7\)

**Follicular lymphoma (21.4%)**

Both primary and secondary cutaneous follicular lymphomas frequently involve the head and neck region.\(^8\) Both show the presence of large centrocytes 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
genetic differences between primary and secondary follicular lymphoma, these are more striking in European studies than in series of patients from North America, suggesting a possible geographic difference in the primary diseases.\textsuperscript{8-11} BCL6 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 any one of these markers as a discriminator of primary versus secondary disease unreliable. The combined expression of BCL6, BCL2 and CD10 appears to a much stronger predictor of secondary disease than any one alone.\textsuperscript{12}

Detection of t(14;18) has also been reported to be fairly specific for secondary disease, but this is also controversial.\textsuperscript{8-11,13} 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. These t(14;18) positive primary cases are less frequent in European studies than in North American studies.

Marginal zone 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 lymphoma of the skin would include primary marginal zone lymphoma, follicular lymphomas and reactive proliferations. In one series, primary or concurrent tumors involving the ocular adnexa or salivary glands seemed to occur more commonly with skin disease than gastric primaries.\textsuperscript{14} 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.\textsuperscript{15} The molecular genetics of primary cutaneous marginal zone lymphoma appears to differ from other extranodal marginal zone lymphomas, in that the t(14;18)(q32;q21) of the $\text{IGH/MALT1}$ fusion is relatively common, but the t(11;18)(q21;q21) of $\text{API/MALT1}$ or the t(1;14)(p22;q32) of $\text{IGH/BCL10}$ are uncommon in the skin.\textsuperscript{16,17} This might suggest that the detection of the later translocations would support secondary disease, but this hypothesis has not been adequately tested.

Small lymphocytic lymphoma/chronic lymphocytic leukemia (5.5%)

Small lymphocytic lymphoma/chronic lymphocytic leukemia 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.\textsuperscript{18} 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.\textsuperscript{18,19} Virtually any pattern of infiltration of the dermis may be seen, including patchy, nodular, diffuse or band-like. Proliferation centers are often not seen, but the infiltrate has the characteristic CD20 (weak), CD5, CD43 and CD23 expression profile of CLL. Cutaneous involvement by CLL does not appear to impact prognosis.

T and NK cell lymphomas (34.2%)

Peripheral T cell lymphoma, unspecified (14.1%)
Peripheral T cell lymphomas (PTCLs) in the “unspecified” group of the WHO secondarily involve the skin or have cutaneous involvement at the time of diagnosis in 19-55% of cases. Essentially all subtypes of peripheral T cell lymphoma can present with skin involvement. The clinical appearance of the lesions can be quite variable, ranging from erythematous plaques to distinct tumor nodules. Because of the variable presentation and heterogeneous morphologic features, cases may mimic other conditions including granulomatous infections, granuloma annulare, dermatomyositis, panniculitis, vasculitis and eczema. Non-cutaneous peripheral T cell lymphomas with either simultaneous or secondary skin involvement are clinically aggressive when compared to primary cutaneous T cell neoplasms.

**Anaplastic large cell lymphoma (9.1%)**

Secondary cutaneous involvement by nodal anaplastic large cell lymphoma (ALCL) is distinct from primary cutaneous anaplastic large cell lymphoma and is important to recognize. While both show dermal involvement by CD30-positive large cells, the primary cutaneous disease is relatively indolent compared to the worse prognosis of skin involvement by ALK-positive anaplastic large cell lymphoma and the even more aggressive behavior of ALK-negative, non-cutaneous anaplastic large cell lymphoma. Nodal ALCL shows a bimodal age distribution that includes children, while primary cutaneous disease is primarily a disease of adults. Although rare exceptions are reported, the vast majority of primary cutaneous ALCLs are ALK-negative and lack the t(2;5) or variant ALK translocations. The detection of ALK expression in a skin lymphoma should warrant extensive evaluation for extracutaneous ALCL. Skin involvement by nodal ALCL occurs in approximately 30% of children with the disease, and most of these are ALK positive. The lack of ALK in a cutaneous, CD30-positive lymphoma, however, cannot be used as sufficient support for a primary cutaneous ALCL. A significant number of nodal ALCL cases, particularly in adults, will be ALK negative, and other CD30-positive proliferations, such as transformed mycosis fungoides and rare cases of Hodgkin’s disease in the skin may occur. Initial studies of clusterin expression in ALCL suggested that it was restricted to the non-cutaneous ALCL cases, but this was not confirmed in later studies.

**NK/T cell lymphoma (5.9%)**

Nasal 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 20% of NK/T cell lymphomas of the nasal type have skin involvement. Some patients with apparent primary cutaneous disease have developed nasal masses within one to seven months of diagnosis, and the disease is aggressive no matter what the presentation. 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, angioinvasion and necrosis may occur and the infiltrate is composed of medium to large irregular cells. The cells may have intermediate chromatin that is similar to a blastic infiltrate. Similar to other sites, the cells usually express CD2, cytoplasmic CD3, CD56 and are EBV positive.
Angioimmunoblastic T cell lymphoma (3.2%)

Skin lesions are common in patients with angioimmunoblastic T cell lymphoma (AILT), present in approximately half of cases. Based on one small 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 reaction; however, plaque-like and nodular lesions may also occur. Several histologic patterns of AILT in the skin have been described. The infiltrate may be sparse with fairly nonspecific perivascular lymphocytes and eosinophils with associated capillary hyperplasia, with or without obvious abnormalities of the lymphocytes. In most cases, however, enlarged, atypical lymphoid cells, 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 AILT. The large atypical cells may show aberrant loss of T cell antigens. EBV has been studied in a small number of cutaneous cases and is usually absent or only 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. Many primary and secondary cutaneous lymphomas have similar names and similar morphologic features, and in some cases, such as NK/T cell lymphoma, AILT and CLL, they represent differing presentations 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 ALCL, follicular lymphoma and the cutaneous diffuse large B cell lymphomas. In these settings, correlation with more detailed immunophenotyping studies and complete clinical evaluation is essential for proper classification.

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Benign Cutaneous Lymphoid Infiltrates

Introduction

The skin represents one of the organs in which the vast majority of diseases are associated with some manner of cutaneous lymphoid infiltration, or infiltration by other inflammatory cells. Just as benign processes can result in inflammatory disorders, so also atypical and malignant infiltrates of the skin can present a variety of different clinical manifestations. In addition to the classic inflammatory diseases of the skin such as psoriasis, seborrheic dermatitis, lichen planus, among others there is a definite group of diseases in which the presence of lymphocytic infiltrates occur with minimal epidermal involvement. These have been listed as the benign cutaneous lymphocytic infiltrates. They can be perivascular, nodular or diffuse in their presentation and some of them are so uniformly characteristic as they present that they are designated by specific names that allow not only for their diagnosis but often even for their causation. We will refer to a group of disorders, first which have classic names and very distinctive patterns of infiltration and then will discuss some of the more diffuse infiltrative lesions such as the so-called pseudolymphoma cutis or lymphocytoma cutis. For the sake of understanding and convenience of both clinical and pathologic manifestations, we will begin with a discussion of the superficial and then the superficial and deep cutaneous disorders and then the diffuse infiltrative lesions.

Superficial Cutaneous Lymphocytic Infiltration

Superficial Erythema Annulare Centrifugum

Superficial erythema annulare centrifugum is one of the first disorders to be designated as a gyrate or figurate erythema. This designation implies that there is an unusual pattern rather than a round lesion but one, which has some type of figurate appearance forming, for example, a C-shaped, or unusual S-shaped lesion or one with a highly irregular semilunar or serpiginous character. In erythema annulare centrifugum (EAC) there is a trailing scale behind the advancing edge of the lesion. These lesions occur at any age in life but are most common in early adulthood. The very initial lesions are small, pink, papule that eventually enlarges and forms an archiform pattern or semilunar pattern. The lesion can be present for days to months, or even rarely in some patients for years. The lesions do advance and can disappear and recur. The lesions may reach a diameter as great as 8 or 10 cm. There are different etiologic agents that result in EAC, approximately one-third of the lesions are associated with as an “id” reaction to superficial fungal infections at distant sites. In some patients the ingestion of bread molds will result in the presence of these lesions, they have also been described occasionally in association with drug reactions. Histopathology includes a prominent “sleeve-like” cuff of lymphocytes around superficial to mid-dermal vessels. In some cases there is a deep infiltrate. This type of so-called deep EAC is not associated with a scale but rather simply an irregularly shaped group of papules or plaque. The more superficial variant, that which is associated with the trailing scale characteristically affects the superficial vessels predominantly associated with mild exocytosis and
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 the deeper infiltrate, in our experience. The differential diagnosis includes erythema chronicum in which one finds an infiltrate superficial and deep of lymphocytes admixed with plasma cells and often dissection of the vessel wall by the infiltrate as well a plasma cellular neuritis may be observed. The changes in the epidermis are minimal. The presence of positive serology for Borrelia in some cases. In other instances it is associated with tick bite reaction. Erythema marginatum can resemble the early phase of EAC that is associated with the neutrophil-rich urticatal type of reaction. Erythema gyratum repens, which can resemble both the superficial and deep infiltrate 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 idiopathic response to ultraviolet light. It combines features of a phototoxic 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 usually 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 common 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 parakeratosis, spongiosis occurs to a mild degree in many cases but in some there is spongiotic vesiculation. Dyskeratotic cells or apoptotic cells are scattered in the epidermis of the effected skin. There is vasculopathy of the dermal/epidermal junction in most cases. Approximately 50-60% of the plaque like light eruptions show vaculopathy resembling the vaculopathy 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 papillary reticular 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 characteristically vacuolization 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 rare extravasation of red blood cells superficially. The changes of endothelial vacuolization 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 of very weak intensity. 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 so the same degree that is associated with the extensive dermal/epidermal necrosis. A mild perivascular lymphocytic infiltrate may be present superficially but the overwhelming changes are those of the epidermal change. Photoallergic reactions are very similar to contact dermatitis. The presence of occasional dyskeratotic cells and endometrial 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. First in acute lupus erythematosus there is massive mucinosis and debris along the dermal/epidermal junction with attenuation of the epidermis. In the more chronic lesions there is base membrane zone thickening with atrophy of the epidermis.

Chronic Photo Dermatitis

Chronic photo dermatitis also known as actinic reticuloid is associated with a very prominent perivascular lymphoid infiltrate with a mixture of histiocytes. The cells in perivascular array show activation of the lymphocytes and are associated with obvious cytoplasms in cells with immunoblastic-like changes. There is fibrosis of the papillary dermis with hyperkeratosis and usually increased granular cell layer. In the papillary dermis there are very activated appearing histiocytes with almost dendritic-like forms with the dendrites frequently arrayed pointing in a direction perpendicular to the long axis of the epidermis.


Jessner’s Lymphocytic Infiltrate of the Skin

Jessner’s lymphocytic infiltrate presents either as group papules or a plaque or plaques that are usually confined to 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 Jessner’s lymphocytic infiltrate usually are pink papules or plaques, often non-symptomatic that is with no pruritus or 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 array.

Histopathologically there is a quite extensive superficial and deep perivascular and periadnexal 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 infiltrate characteristically tapers as the lesion infiltrates the dermis There is 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 infiltrate. In some of the lesions with a more dense inflammation one may observe foci of B cell infiltration. In other lesions, one can observe CD68 positive cells admixed with lymphocytes around the vessels. The lupus band test is negative. One features of Jessner’s lymphocytic infiltrate that is helpful to distinguish it from lupus is that there are occasionally B cells admixed as indicated above. This presence of B cells rules out the diagnosis of 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 is Jessner’s and non-scarring DLE to antimalarials. Jessner’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
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 wax and wane and will respond both to Plaquenil systemically and intralesional 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 Jessner’s lymphocytic infiltrate. The angiocentric and periadnexal infiltrate of Jessner’s is associated with mucinosis but in non-scarring discoid erythematosus there is interface dermatitis predominately of the intrafollicular 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 C5B9 or IgG at the dermal/epidermal junction.


Deep Gyrate Erythemas

The deep gyrate erythemas represent a group of lesions that are associated with very dense lymphoid infiltrate in perivascular and periappendiceal array with no evidence of activation of the endothelial cells in the classic deep gyrate erythema that is a lymphocytic infiltrate. The group of disorders also includes erythema chronic migrans, erythema gyratum repens as well as erythema marginatum as a peculiar neutrophil mediated lesion.

Erythema chronica migrans

This disorder is a hallmark cutaneous manifestation of LYME disease. It presents as a lesion around a bite site that migrates gradually and forms rings clinically. It is a very characteristic lesion. Histologically the lesion shows a prominent perivascular lympho-eosinophilic infiltrate but with admixed plasma cells. The characteristic features include prominent endothelial cell activation with swelling as well as the infiltration of the lymphoid cell and plasma cells into the vessels of both the small veins, the medium size veins dissecting apart the area with edema. There can be focal mucin deposition. There is a plasma cell neuritis.
Erythema gyratum repens

Erythema gyratum repens is a rare manifestation of a neoplastic 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 extirpation 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-eosinophilic infiltration of the dermis 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 rheumatoid carditis. However, it also occurs spontaneous 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 intraepithelial 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.


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 pseudolymphomatous areas 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, indeed, 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. Tingle body macrophages 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 multinucleate giant cells are present and even often 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 infiltrate 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 CD21 positive or CD19 positive. The pathogenesis of this lesion is very interesting in that these lesions can occur as a result,
for example, repeated contact dermatitis. Therefore, these lesions are clonal for T cells. They can also follow tattooing, vaccination, repeated arthropod reactions, or even a hyposensitization to injection of antigen for hyposensitization. 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.


