184 Cutaneous Lymphomas: Morphology, Immunohistochemistry and Molecular Testing

David Cassarino MD, PhD
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AMERICAN SOCIETY FOR CLINICAL PATHOLOGY
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Chicago, IL 60603
Cutaneous lymphomas often cause significant consternation among pathologists because they are difficult to diagnose both clinically and histologically. Atypical-appearing lymphoid infiltrates may have a benign etiology, and bland-appearing infiltrates may be malignant. The medical literature regarding cutaneous lymphomas is often conflicting, also adding to the diagnostic uncertainty. Recently, the WHO has published the 2008 Classification of Haematopoietic and Lymphoid Tissues and the 2007 Pathology and Genetics of Skin Tumors, both of which deal with this topic. New entities have been described, and older entities have been reclassified. Many pathologists may have not yet incorporated these classifications into their daily practices. This session will examine the topic of cutaneous lymphomas, both from the perspective of a dermatopathologist and a hematopathologist. The above-mentioned WHO classification will be outlined and illustrative cases will be presented. Also presented will be the clinical findings helpful to make these diagnoses, and the presenters will examine the specific morphologic characteristics, as well as the immunophenotypic and molecular findings of these lymphomas. The focus will be on selected T-cell lymphomas, including mycosis fungoides, anaplastic large cell lymphoma, and systemic T-cell lymphomas with cutaneous involvement. The presentation will also include the classification of B-cell lymphomas, focusing on the differences compared to nodal B-cell lymphomas, and situations will be noted in which it is impossible to render a definitive diagnosis, and the approach to signing out such difficult and borderline cases.

- Classify difficult cutaneous lymphomas accurately.
- Recognize the most recent international guidelines for diagnosis and reporting of these challenging tumors.
- Recognize borderline or unclassifiable proliferations, and how to report them and guide clinical management.

FACULTY:

David Cassarino MD, PhD
Aaron Auerbach MD

Practicing Pathologists
Surgical Pathology
Surgical Pathology (Derm, Gyn, etc.)
2.0 CME/CMLE Credits

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Course 1357: Cutaneous Lymphomas: Morphology, Immunohistochemistry, and Molecular Testing

Aaron Auerbach, MD, MPH
David S. Cassarino, MD, PhD

Frustrations with Cutaneous Infiltrates

- Scant lymphoid infiltrates can be malignant
- Dense lymphoid infiltrates can be benign
- Many cases need clinicopathologic correlation, which the pathologist may not have access to
- Classification of these lesions changes

Approach to Cutaneous Lymphoma

- Clinical information can be critical to make diagnosis
  - Appearance of lesion
  - Lab values (HTLV1, EBV hypo/hypergammaglobulinemia)
- Ancillary testing is critical in diagnosis
  - IHC, Molecular testing
Primary cutaneous lymphomas are different from secondary lymphomas

- They have a different clinical behavior from nodal-based and other extranodal lymphomas
  - Often less aggressive clinical course
- They have a different prognosis
  - Often better prognosis
- They have a different treatment
  - Often do not need chemotherapy

Traditional Classification

Our Classification

We are going to present a classification based on the pathologist’s perspective looking at tumor location, tumor cell morphology, and tumor cell lineage
**Tumor location**

Is tumor in epidermis?

Is tumor in dermis?

Is tumor in subcutis?

**Lesions segregated by location in skin**

<table>
<thead>
<tr>
<th>Epidermis</th>
<th>Dermis</th>
<th>Subcutis</th>
</tr>
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<tbody>
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**Tumors with cells that are mostly small to medium in size**

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**All T-cells**

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**B-cells + T/NK-cells**

**All T-cells**
What about neoplasms with large, atypical cells?

<table>
<thead>
<tr>
<th>B-cell</th>
<th>T-cell</th>
<th>Other</th>
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<tbody>
<tr>
<td>Diffuse large B-cell lymphoma, leg type</td>
<td>Primary cutaneous CD30+ lymphoproliferative disorders (ALCL, LYP)</td>
<td>Blastic plasmacytoid dendritic-cell neoplasm</td>
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<td>Systemic large B-cell lymphomas involving skin</td>
<td>Some systemic T-cell lymphomas involving skin</td>
<td>Histiocytic sarcoma</td>
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<td>Plasmaablastic lymphoma</td>
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<td>Rosai-Dorfman disease</td>
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<td>Intravascular large B-cell lymphoma</td>
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<td>Leukemia cutis</td>
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<td>Primary cutaneous diffuse large B-cell lymphoma, NOS</td>
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<tr>
<td>Lymphomatoid granulomatosis</td>
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Is it that simple?

- Of course, we recognize that some hematopoietic neoplasms can involve more than one compartment of the skin (i.e., epidermis, dermis, and subcutis) in a single biopsy
- Some neoplasms can have small or large sized tumor cells

Part 1: Cutaneous infiltrates with a propensity to involve the epidermis
### Small to medium-sized cells

<table>
<thead>
<tr>
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<td>Dermis</td>
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</tr>
<tr>
<td></td>
<td>Primary cutaneous CD4+ cytotoxic T-cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Primary cutaneous organoid cell lymphoma</td>
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<td></td>
<td>Primary cutaneous mycosis fungoides T-cell lymphoma</td>
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### Large-sized cells

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<tr>
<td>Dermis</td>
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<td></td>
<td>Primary cutaneous plasmablastic lymphoma</td>
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<tr>
<td></td>
<td>Primary cutaneous extranodal marginal zone lymphoma</td>
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<td></td>
<td>Primary cutaneous mantle cell lymphoma</td>
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<td></td>
<td>Primary cutaneous marginal zone lymphoma</td>
</tr>
<tr>
<td></td>
<td>Plasmablastic lymphoma</td>
</tr>
<tr>
<td></td>
<td>Extranodal marginal zone lymphoma, nasal type</td>
</tr>
</tbody>
</table>

### Mycosis Fungoides

- A primary cutaneous epidermotropic T-cell lymphoma with cerebriform cells and indolent course
- A clinical sequential evolution
  - patches
  - plaques
  - tumors
- Extracutaneous dissemination in advanced disease

Disease has a long natural history, so patients may have non-specific infiltrates in the skin and rashes for years before diagnostic histology develops.
Mycosis Fungoides Morphology
- Epidermotropism
- Linear basilar lymphocytes
- Tips of rete ridges
- Haloed lymphocytes
- Intraepidermal lymphocytes larger than dermal lymphocytes
- Pautrier microabscesses
  - > Intraepidermal clusters of cerebriform T-cells
- Papillary dermal fibrosis

Patch Stage
- Pinkish-red circumscribed lesions, symmetrical irregular patches with little scaling
- Mostly covered areas
- Pruritus

Early Patch Stage
- Dermal T-cell infiltrate
- T-cells in epidermal basal layer or epidermis
  - Singular or linear
  - Clear halos

Photo courtesy of Magda Tomaszewska
Late Patch Stage

Pautrier microabscess

Plaque Stage

- Plaques similar to patches but with induration (raised above skin surface)

Photos courtesy of Magda Tomaszewski

Plaque Stage

More epidermotropism
More Pautrier microabscesses
Tumor Stage

- Previous patch/plaque lesions and/or biopsy-proven MF
- Exophytic growth
- Irregularly shaped brownish-red nodules
- Ulceration usually

Tumor Stage

- Often loses epidermotropism
- Often ulceration and necrosis
- Diffuse dermal lymphocytic infiltrate
  - Variably sized T-cells (small, medium and large)
  - Large cell transformation
  - $\geq 25\%$ large T-cells
  - CD30+ or -
  - $\uparrow$ Ki-67

Photo courtesy of Magda Tomasewski
Large cell transformation

- Large atypical cells

**Immunohistochemistry**

- Usually helper T-cells
  - CD4+/CD8-
- Rarely, CD8+/CD4+, CD4+/CD8+
  - Low Ki-67 nuclear index/proliferation rate
  - Same clinical behavior as CD4+/CD8-
- Loss of T-cell antigens
  - CD7 most common (in all stages), may lose CD5
- CD30-, betaF1+
- Cytotoxic markers can be+ in late stage disease
Molecular testing

- Clonal T-cell receptor gamma or beta gene rearrangements
- Demonstration of dominant T-cell clone in borderline cases provides strong evidence of evolving CTCL
- Rarely, reactive conditions can have clonal TCR rearrangements (PLEVA, PLC, drug rxs)

Prognosis

Indolent clinical course
  - Slow progression can take years or decades
  - Depends on clinical stage

Variants

- Pagetoid reticulosis
- Folliculotropic MF
- Syringotropic MF
- Granulomatous slack skin
Pagetoid Reticulosis (PR)

- Aka, localized Woringer-Kolopp disease
- Single crusty plaque or patch on distal limb
- Recurrences common
- Doesn’t disseminate
- Prognosis good
- Local therapy sufficient

Morphology

- Marked epidermotropism of cerebriform T-cells
- Sponge-like disaggregation of epidermis
- CD4+/CD8- or CD4-/CD8+
- CD30+/-
- ↑Ki-67
### Differential Diagnosis

- Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma
  - Diagnosis if disseminated and not localized lesion
- Mycosis fungoides
  - Multiple lesions
  - PR has better prognosis than MF
  - Ki-67 > 30% in PR, Ki-67 < 10% in MF (patch/plaque)
- Malignant melanoma
  - S100+, Melan A+, tyrosinase+, HMB45+
- Paget’s disease
  - panCK+, CK7+, CEA+

### Folliculotropic Mycosis Fungoides

- Malignant T-cells around hair follicles, spare interfollicular areas
- Usually grouped papules with associated alopecia on head and neck
- Worse prognosis than plaque stage MF

### Folliculotropic Mycosis Fungoides

- AKA pilotropic MF
- Follicular T-cell infiltrate
  - Often spares epidermis
  - CD3+, CD4+, CD8-
  - In classic MF, follicles are involved over 50% of cases
- Dilation/plugging of follicles
- +/- follicular mucinosis
Granulomatous Slack Skin

- Pendulous folds of lax skin in major folds (groin, axilla)
- Dermal granulomatous infiltrate with clonal CD4+ T-cells
- Loss of elastic fibers
- Epidermotropism and psoriasiform epidermal hyperplasia
- CD163+, CD68+ histiocytes
- Clonal TCR gene rearrangements
- May coexist with MF and classic Hodgkin lymphoma

Photos courtesy of Magda Tomaszewski
Multinucleated giant cells

Photos courtesy of Magda Tomaszewski

Large Plaque Parapsoriasis

Epidermotropism

Dermal T-cell infiltrate

Photo courtesy of Magda Tomaszewski

Sezary Syndrome

- Erythroderma
- Sezary cells = clonal CD4+ cerebriform T-cells in blood, skin, LN, often spares BM
- Generalized lymphadenopathy
- Criteria (one or more)
  - 1000 cells per mm²
  - CD4:CD8 > 10:1
  - Loss of T-cell antigens

Photo courtesy of Magda Tomaszewski
Sezary Syndrome

- Circulating T-cells with cerebriform nuclei are diagnostic, but not sensitive
- Lesions in skin are nonspecific or MF-like
- Loss of epidermotropism
- LN effaced architecture
- Clonal TCR rearrangement is diagnostic in peripheral blood

Prognosis

- Poor (15% 5-year survival)
  - Prognosis depends on degree of LN and blood involvement
  - Death from infection secondary to immunosuppression

Atypical T-cells
Primary Cutaneous Aggressive Epidermotropic CD8+ Cytotoxic T-cell Lymphoma

- Epidermotropic (in diff'nt dx of MF)
- T-cell lymphoma of CD8+ cytotoxic αβ T-cells in the epidermis, exhibiting aggressive clinical behavior
- Provisional entity in 2008 WHO
- Previously included in PTCL-NOS
- Often separated from other CD8+ lymphomas based on clinical behavior

Presentation

- Skin lesions
  - Often tumors, nodules and papules
  - Less often patches or plaques
  - Ulceration and/or necrosis
  - Widespread disseminated lesions
- Rapid extracutaneous spread
  - Lungs, testes, brain and oral cavity
  - Usually spares LNs
- Poor prognosis
  - 32 month median survival
Morphology

- Epidermotropism
  - Pagetoid spread with linear colonization of basal epidermis
  - Small/medium-sized T-cells with moderate to marked atypia, coarse or blastic chromatin
- Epidermis
  - Ulceration/necrosis, acanthotic or atrophic, apoptotic keratinocytes
- Dermal T-cell infiltrate
  - Superficial or deeper tissues
  - Angiocentric, lichenoid, or adnexal

Ancillary Testing

- T-cell antigens+ (CD3, CD2, CD7)
- Cytotoxic T-cells (CD4-, CD8+)
- Cytotoxic markers+ (perforin, granzyme B, and TIA1)
- αβ T-cells (βF1+, TCRδ1-)
- EBER-, CD15 +/-, CD56 +/-
- High proliferative rate by MIB1 (>90% of tumor cells)
- Clonal for T-cell receptor gene gamma rearrangement
Differential Diagnosis

- Mycosis fungoides
  - Rarely is CD4-/CD8+
  - Slower disease progression (patch to plaque can take years)
  - Less necrosis by morphology

Differential diagnosis

- Localized Pagetoid reticulosis (PR)
  - Woringer-Kolopp disease
  - Different clinical picture with less aggressive disease and less necrosis than AECTCL
  - Sponge-like epidermal disaggregation, unlike AECTCL
- Disseminated PR
  - Ketron-Goodman disease
  - Considered a form of AECTCL, and not separately classified
Small to medium-sized cells

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Adult T-cell Leukemia/Lymphoma (ATLL)

- T-cell lymphoma/leukemia of regulatory T-cells (CD4+CD25+FoxP3+) caused by human T-cell leukemia virus type-1 (HTLV1)
- Serologic testing: HTLV1+
- Epidermotropic
- Endemic to southwest Japan, Caribbean islands, South America, Central Africa

HTLV1

- Leads to leukemia/lymphoma in <5% of infected individuals
- Long latency period
  - Most exposed as infants/children
  - Tumor often after 20 yrs of exposure
- Transmitted through blood + breast milk
- Encodes Tax
  - A viral oncoprotein
  - Plays a role in development of ATLL
  - Activates transcription factors for T-cell proliferating genes
Presentation

- Skin lesions
  - 50%
  - Usually multiple nodules, papules, plaques
- Lymph nodes
  - Most have generalized lymphadenopathy
- Bone
  - Hypercalcemia from ↑ osteoblast bone resorption
- Peripheral blood, lung, liver, CNS

Skin Morphology

- T-cell infiltrate in epidermis, dermis, and/or subcutis
  - Frequent epidermotropism and/or Pautrier microabscesses
  - Eosinophils
- Medium to large-sized pleomorphic T-cells with marked atypia
- Multilobated T-cells
  - Flower cells (more easily seen in PB)
Lymph node with ATLL

Effaced LN

CD25+

Atypical T-cells

Immunohistochemistry

- T-cell antigens+, but one or more lost
- Usually CD4+/CD8-
  - Rarely CD4+/CD8+ or CD4+/CD8-
- Regulatory T-cells (CD25+, FOXP3+, CCR4+)
- ATLL-assoc antigen+ (a specific antibody to HTLV-1)
- Cytotoxic markers-
- CD30 often+, but CD15-

Subtypes

<table>
<thead>
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<th>Clinical and Path Findings</th>
<th>Acute</th>
<th>Chronic</th>
<th>Smoldering</th>
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<tr>
<td>Abnormal T-cells PB</td>
<td>Yes</td>
<td>Little</td>
<td>&gt;5%</td>
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<td>Bone marrow tumor</td>
<td>Sometimes</td>
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<td>Calcium</td>
<td>Sometimes ↑</td>
<td>Normal</td>
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<td>HSM</td>
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<tr>
<td>Lymphocytosis</td>
<td>Increased</td>
<td>Sometimes ↑</td>
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<tr>
<td>Skin lesions</td>
<td>Sometimes</td>
<td>Sometimes ↑</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Poor (&lt;10% 5 yr surv)</td>
<td>Better</td>
<td>Better</td>
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Lymphomatous subtype: lymphadenopathy, no PB involvement
- Little hypercalcemia and skin usually involved
Chronic subtype: lymphocytosis, but ↓WBC than acute subtype
Smoldering subtype: >5% tumor cells in PB, even though normal WBC
Differential Diagnosis

- MF
  - Both have T-cell infiltrate with epidermotropism
  - ATLL flower cells have outward nuclear projections, MF cerebriform nuclei have inward infoldings
  - Both CD4+/CD8-, but only ATLL CD25+, FOXP3+, CD30+

- ALC
  - Both CD30+ medium/large T-cells
  - FOXP3-, CCR4-, HTLV1-

Part 2: Cutaneous Infiltrates with a Propensity to Involve the Dermis: B-cells
Primary Cutaneous Follicle Center Lymphoma

- Mature B-cell lymphoma of follicle center cells, primary to skin/not originating in another site
  - Confined to skin for 6 months after dx
- Different disease than lymph node follicular lymphoma
  - Better prognosis
  - Different treatment
  - Less BCL-2 gene rearrangements

PCFCL

- Usually single, plaque/nodule/tumor
- Mostly head/neck
- Recurrence (often proximal) ~35%
  - Extracutaneous spread ~10%
  - Dissemination
- Treatment
  - Observation, local radiation or excision
  - Chemotherapy restricted for extensive disease and extracutaneous

Morphology

- Dermal B-cell infiltrate, ± subcutis, no epidermotropism
- Growth pattern
  - Nodular, diffuse, or nodular and diffuse
- Follicles
  - Often not well-defined
  - Lack mantle zones
  - Lack tingible body macrophages
  - Follicular dendritic cells
- Mostly centrocytes
  - Small to medium-sized, cleaved
- Variable numbers of centroblasts
  - Larger in size

Grading

- Not of prognostic value

Not recommended for PCFCL necessary for systemic follicular lymphoma

Single raised red nodule on scalp
Nodular growth pattern

Diffuse growth pattern

Ancillary Testing

**Phenotype**
- B-cell markers +
  - CD20+, PAX-5+
  - often MUM-1(-) unlike DLBCL, leg type
- Follicle center markers +
  - Bcl-6+
  - CD10 +/- (usually - in diffuse areas)
  - Bcl-2 /-
  - Often dim, and + in follicular areas
- Follicular dendritic cell meshwork
  - CD23, CD21, and CD35+

**Molecular**
- T(14;18) only ~30% of cases
  - More common in nodal follicular lymphoma
- Clonal IgH gene rearrangement
  - ~45% by PCR
- Gene expression profiling
  - Findings akin to germinal center-like large B-cell lymphoma
Marginal Zone Lymphoma

• Recapitulates architecture of Peyers patches
• 3 types:
  – Extranodal (Gastric, skin), LN, spleen
• Plaque or nodule, rarely ulcerates
  – Multiple nodules in secondary cutaneous MZL
• Excellent prognosis
  – But tendency to recur
• Treatment
  – Excision or radiation if single nodule or few lesions
Morphology

- Malignant B-cells expanding marginal zones surrounding reactive follicles and colonizing them
- If tissue is small, may not see the follicles

Two Components

1. Reactive
   -- Reactive follicles

2. Malignant
   -- Expanded/confluent marginal zones
   -- Monocytoid and plasmacytoid cells
   -- Dutcher bodies
   -- Lymphoepithelial lesions

Low power, lymphocytes forming a mass

MZL forms a mass lesion and invades the subcutis
Nodular to diffuse growth pattern
Marginal zone cells surround reactive follicles

Heterogeneous infiltrate

Monocytoïd change
Plasmacytoïd change

Intranuclear inclusions

Normal nucleus
Dutcher body
Follicular colonization

Lymphoepithelial Lesion

- 3 or more lymphocytes entering an epithelial structure (usually a gland) and destroying it
- Rare in skin

Immunophenotype

- Non-specific
- B-cell predominance
- CD43+, BCL-2+ coexpression
- Expanded dendritic network by CD21
- Light chain restriction sometimes
B-cell predominance

- Sheets of B-cells with few T-cells is concerning for B-cell lymphoma
- If there is a mix of B- and T-cells, then look for other features (IHC, clonality) to diagnose lymphoma

Coexpression of CD43 and BCL2

Feature of B-cell lymphomas, not specific to MZL
Bcl2 is normally expressed on reactive mantle zone cells

CD21

- Tight follicular meshworks
- Loose or irregular follicular meshworks
- Reactive or follicular lymphoma
- PCMZL
Marginal zone lymphoma may be difficult to diagnose morphologically because of the non-specificity of many of the morphologic features, the absence of one or more classic features, and the nature of the small biopsies!

Systemic B-cell Lymphomas Involving Skin

- Often multiple lesions, usually tumor or nodules
- Skin involvement may present at initial diagnosis or develop later
- Higher stage than primary cutaneous lymphoma (PCL)
  - Worse prognosis than PCL
  - Treated with chemotherapy, unlike most PCL

Phenotype of Secondary Cutaneous B-cell Lymphomas

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>CD10</th>
<th>CD19</th>
<th>CD20</th>
<th>CD43</th>
<th>BCL1</th>
<th>BCL6</th>
<th>MUM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkitt lymphoma</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-+</td>
</tr>
<tr>
<td>CLL/PLL</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>@</td>
</tr>
<tr>
<td>DLBCL</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-+</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

@ = positive in proliferation centers
* = positive in activated B-cell type
### Molecular Findings

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Abnormality</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL/SLL</td>
<td>Del(11q); del(13q); +12;</td>
<td>Many</td>
</tr>
<tr>
<td></td>
<td>del(17p)</td>
<td></td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>T(14;18)(q32;q21)</td>
<td>BCL-2, IgH</td>
</tr>
<tr>
<td>Lymphoplasmacytic</td>
<td>Del(6q21)</td>
<td></td>
</tr>
<tr>
<td>lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>T(11;14)(q13;q32)</td>
<td>CCND1, IgH</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>T(11;18)(p13;q21)</td>
<td>+3, +8, +18</td>
</tr>
<tr>
<td></td>
<td>T(14;18)(q32;q21)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T(11;14)(p22;q32)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>T(8;14)(q24;q32)</td>
<td>IgH, C-myc</td>
</tr>
<tr>
<td></td>
<td>T(2;8)</td>
<td>C-myc, kappa</td>
</tr>
<tr>
<td></td>
<td>T(6;22)</td>
<td>C-myc, lambda</td>
</tr>
</tbody>
</table>

### Follicular Lymphoma Involving Skin

- BCL2+ or t(14;18) should raise suspicion for a systemic lymphoma involving skin.
Cutaneous Follicular Hyperplasia

Can be caused by infection, drugs, or folliculitis
- Polarized follicles
- Tingible body macrophages
- Mantle zones
- CD10+, BCL6+, BCL2-
- No clonal IgH gene rearrangement
- Negative for t(14;18)
### Differential Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>PCFCL</th>
<th>Secondary FL of skin</th>
<th>MZL</th>
<th>PCFCL/FL, leg type</th>
<th>Follicular hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gross</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nodular</td>
<td>Plaque or isolate</td>
<td></td>
<td>Multiple dome-shaped nodules</td>
<td>Papules/histoides</td>
</tr>
<tr>
<td><strong>Clinical stage</strong></td>
<td>Stage I</td>
<td>High stage</td>
<td></td>
<td>Stage I with rapid progression to T(14;18)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Growth pattern</strong></td>
<td>Follicular or diffuse</td>
<td>Follicular or diffuse</td>
<td></td>
<td>Follicular or diffuse</td>
<td>Diffuse</td>
</tr>
<tr>
<td><strong>Follicles</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malignant</td>
<td>Malignant</td>
<td></td>
<td>Malignant</td>
<td>Colloidized</td>
</tr>
<tr>
<td><strong>Cell type</strong></td>
<td>centrocyte &amp; centroblast</td>
<td>centrocyte &amp; centroblast</td>
<td></td>
<td>centrocyte &amp; centroblast</td>
<td>centrocyte &amp; centroblast</td>
</tr>
<tr>
<td><strong>Molecular studies</strong></td>
<td>Monoclonal T(14;18) subset</td>
<td>Monoclonal T(14;18) subset</td>
<td></td>
<td>Monoclonal T(14;18) subset</td>
<td>Monoclonal T(14;18) subset</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Usually no chemo</td>
<td>Chemo</td>
<td></td>
<td>No chemo</td>
<td>Chemo</td>
</tr>
</tbody>
</table>

### Part 3: Cutaneous infiltrates with a propensity to involve the dermis - T/NK-cells

- Part 3: Cutaneous infiltrates with a propensity to involve the dermis - T/NK-cells
### Small to medium-sized cells

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycosis fungoides</td>
<td>Primary cutaneous T-cell lymphoma</td>
</tr>
<tr>
<td>Primary cutaneous aggressive epidermotropic</td>
<td>Primary cutaneous epithelial lymphoma</td>
</tr>
<tr>
<td>CD8+ cytotoxic T-cell lymphoma</td>
<td>Plasmacytoma</td>
</tr>
<tr>
<td>Lymphomatoid pseudolymphoma with T-cell</td>
<td>Blastic transformation sarcoma</td>
</tr>
<tr>
<td>Large T cell lesion/plaque</td>
<td>Extravasation of T cells in subcutaneous tissue</td>
</tr>
</tbody>
</table>

### Large-sized cells

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>Primary cutaneous diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>Systemic large B-cell lymphoma</td>
<td>Blastic plasmacytoid dendritic cell neoplasm</td>
</tr>
<tr>
<td>Systemic large T-cell lymphoma</td>
<td>Leukemia cutis</td>
</tr>
<tr>
<td>Primary cutaneous large B-cell lymphoma</td>
<td>Histiocytic sarcoma</td>
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<td>Blastic transformation sarcoma</td>
</tr>
<tr>
<td>Large T cell lesion/plaque</td>
<td>Extravasation of T cells in subcutaneous tissue</td>
</tr>
</tbody>
</table>

### CD4+ Small/Medium Pleomorphic T-cell Lymphoma (PC-SMPTCL)

- T-cell lymphoma of skin with small to medium-sized CD4+ T-cells and usually indolent clinical course
  - Without typical patches/plaques of mycosis fungoides
- A provisional entity in 2008 WHO
  - Non-aggressive natural history, but worrisome histologic and molecular features

### PC-SMPTCL

- Typically, single plaque or nodule
  - Can be >1 lesion
  - No progression typical of MF
- No lymphadenopathy or systemic dz
- Does not usually disseminate
  - Rare local recurrence
- Treatment
  - Usually excision or radiation
- Good prognosis
  - Better than PCTCL or secondary cutaneous T-cell lymphomas
Morphology

• Dense dermal infiltrate
  – ± Subcutis
  – Usually no epidermotropism
  – Diffuse or nodular growth pattern
• Variably sized T-cells
  – Usually small or medium
  – Large cells, when present, should be < 30% of total cells
• Pleomorphic cells
• Other features
  – Often reactive background infiltrate
  – ↑ reactive B-cells present
  – Granulomatous inflammation

IHC

• T-cell antigens positive
  – Rarely loss of one or more T-cell antigens
  – CD4+/CD8-
• Expresses follicular helper T-cell markers
  – PD1+, CXCL13+, BCL6+
• Negative for:
  – Cytotoxic markers
  – CD30, LMP

Ancillary Testing

• Epstein-Barr virus small-encoded RNA (EBER) negative
• Clonal T-cell receptor gene rearrangement, 60%
• Polyclonal IgH immunoglobulin gene rearrangements
Diffuse & vaguely nodular infiltrate involves subcutis.

Small/medium cells vs large cells.

Granulomatous inflammation.

CD3+, CD7-, CD20-, PD1+, CD4+, CD8-.
Differential Diagnosis: Reactive Lymphoid Hyperplasia/“Pseudolymphoma”

- Similar morphology to PC-SMPTCL
- Loss of T-cell antigens favors SMP-TCL
- More CD8+ T-cells in pseudolymphoma
- Polyclonal TCR gene rearrangement favors pseudolymphoma
- Pseudolymphoma may resolve w/o txmt

Drug-Related Pseudolymphoma

Peripheral T-cell Lymphoma (PTCL), NOS

- Diagnosis of exclusion
  - Does not fit into any better defined subtypes
- One or more nodules or tumors
- Small to large pleomorphic cells
- IHC
  - Expresses T-cell antigens
    - Often loses CD7
  - CD30- or + in rare cells
  - CD56 -/+ 
- Prognosis
  - Poor, <20% 5-year survival
Angioimmunoblastic T-cell Lymphoma (AITL)

- T-cell lymphoma of follicular helper T-cells
- Skin is most frequent extranodal site
  - 50% of cases
  - Can be 1st site of disease
  - Pruritic rash, most commonly maculopapular eruption
  - It is debated whether skin represents tumor or secondary reaction to cytokines
- Lymph node involved in nearly all cases
- Also involves spleen, liver, BM

Morphology

- Dermal infiltrate, sometimes perivascular, may be sheet-like
- With or without atypia
- High endothelial venules
- Eosinophils
- Follicular dendritic cell meshworks

Ancillary testing

- T-cell antigens +
- Helper T-cells (usually CD4+, CD8-, βF1+)
- Follicular helper T-cell phenotype
  - CD10+, BCL-6+, PD1+, CD20-
  - CXCL13+ and CD10- in cutaneous AITL
- Follicular dendritic T-cell meshworks
- CD21+, CD23, CD35 and clusterin +
- EBER+
  - 80% of LNs, usually negative in skin
- ↑ reactive B-cells CD20+
  - can develop into B-cell lymphoma
Extranodal NK/T-cell Lymphoma, Nasal type

- Lymphoma of NK-cells or T-cells characterized by necrosis, EBV infection, and angioinvasion
- Common in Asia and South America
- Primary or secondary skin involvement with nodular/ulcerated lesions
- Poor prognosis outside nasal cavity
ENNKTCL, Nasal Type

- Angiocentric/angiodestructive growth of pleomorphic lymphocytes with necrosis
- Often ulcerated epithelium
- Phenotype:
  - EBER+
  - IHC
    - NK-cell markers (75%)
      - βF1+, CD2+, cytoplasmic CD3ε+, surface CD3-, CD4-, CD5-, CD8-, CD56 +/-, cytotoxic markers+
    - T-cell markers (25%)
      - βF1+, CD2+, cytoplasmic CD3ε+, CD5+, CD8 +/-, CD43+, CD56 +/-, cytotoxic markers+
- TCR gene rearrangement in T-cell tumors not NK-cell tumors

Ulcerated epidermis is common

Angiocentric

Necrosis
Part 4: Cutaneous Infiltrates With a Propensity to Involve the Subcutis

Small to medium-sized cells

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycosis fungoides</td>
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</tr>
<tr>
<td>Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Lymphohistiocytic, type B</td>
<td></td>
</tr>
<tr>
<td>Adult T-cell leukemia/lymphoma</td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous follicle center lymphoma</td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous marginal zone lymphoma</td>
<td></td>
</tr>
<tr>
<td>Plasmacytoma</td>
<td></td>
</tr>
<tr>
<td>Most systemic B-cell lymphomas</td>
<td></td>
</tr>
<tr>
<td>CD4 small/medium pleomorphic T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>PTCL, NOS</td>
<td></td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Most systemic T-cell lymphomas</td>
<td></td>
</tr>
<tr>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Cutaneous gamma delta T-cell lymphoma</td>
<td></td>
</tr>
</tbody>
</table>

Large-sized cells

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse large B-cell lymphoma, leg type</td>
<td>Primary cutaneous diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>Primary cutaneous diffuse large B-cell lymphoma, leg type</td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous diffuse large B-cell lymphoma, NOS</td>
<td></td>
</tr>
<tr>
<td>Pharyngeal lymphoma</td>
<td></td>
</tr>
<tr>
<td>Lymphomas with monocytoid B-cells</td>
<td></td>
</tr>
<tr>
<td>Cutaneous B-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Cutaneous gamma delta T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Cutaneous plasmacytoma</td>
<td></td>
</tr>
<tr>
<td>Cutaneous plasmacytoid dendritic cell neoplasm</td>
<td></td>
</tr>
<tr>
<td>Leukemia cutis</td>
<td></td>
</tr>
<tr>
<td>Histiocytic sarcoma</td>
<td></td>
</tr>
<tr>
<td>Large-sized cells</td>
<td></td>
</tr>
</tbody>
</table>

Other

Non-Hodgkin lymphoma with dermatitis, NOS | |
| Lymphomatoid granulomatosis | |
| Intravascular large B-cell lymphoma | |
| Primary cutaneous CD30+ lymphoproliferative disorders (ALCL, LYP) | |
| Some systemic T-cell lymphomas involving skin | |
| Blastic plasmacytoid dendritic cell neoplasm | |
| Leukemia cutis | |
| Histiocytic sarcoma | |
Subcutaneous Panniculitis-like TCL (SPTCL)

- A T-cell lymphoma of αβ cells involving the subcutaneous tissue with karyorrhexis and cytotoxic phenotype
- Cases of γδ cells are re-classified as cutaneous γδ T-cell lymphoma in the 2008 WHO

Presentation

- Single or multiple subcutaneous nodules or plaques
- Extremities, trunk most common
- Painless mass, rarely ulcerates
- Symptoms due to mass effects

Presentation

- Rarely involves lymph nodes (not at time of diagnosis)
- B-symptoms
  - Can be months to years before diagnosis
- Cytopenias, ↑ESR, ↑C-reactive protein
Morphology

• T-cell infiltrate in subcutaneous fat
  – Mimics panniculitis
  – Involves lobules, usually spares septae
  – Uncommon septal pattern represents spilling of T-cells from lobules to septa
  – No tumor in overlying dermis or epidermis
• T-cells rim individual adipocytes
  – Characteristic but not specific for SPTCL

No tumor in epidermis
No tumor in dermis
Tumor in subcutis

Inflamed lobules
Septae mostly spared

Courtesy of Magda Tomaszewska
SPTCL: High Power

- Atypical T-cells
  - Range from small to large in size
  - Irregular nuclear contours
  - Hyperchromatic nuclei
  - Pale clear cytoplasm
- Karyorrhexis and fat necrosis
- Histiocytes
  - Vacuolated/foamy cytoplasm from imbibed fat
  - Erythrophagocytosis
  - Sometimes poorly formed granulomas and multinucleated giant cells
  - Usually lacks plasma cells, eos, pmns

Histiocytes in SPTCL

Atypical T-cells rim fat

Histiocytes with apoptotic debris

Courtesy of Magda Tomaszewski
Immunohistochemistry

- Mature cytotoxic T-cell phenotype
  - T-cell antigens + (CD3, CD2, CD5, CD7)
    - May have loss of one or more T-cell antigens
  - 95% CD4-/CD8+
    - Rare CD4-/CD8- or CD4+/CD8-
  - Cytotoxic markers + (TIA-1, granzymeB, perforin)
    - βF1+ TCRδ1-
  - CD56- CD30-
Molecular

- Monoclonal TCR gene rearrangement
- EBER usually negative
  - Rare EBER+ assoc with immunocompromised patients (PTLD)
Prognosis

• Indolent disease
  – ~80% 5-year survival
  – Mostly stage I (confined to skin)
• Rare dissemination
  – Often years after diagnosis (LN)
• Hemophagocytic syndrome
  – ~20% of patients
  – May occur 5 years after dx
  – Medium survival ~2 years

Cutaneous γδ T-cell lymphoma

• A T-cell lymphoma of skin composed of cytotoxic γδ T-cells
• Separated from SPTCL
• 3 patterns of disease: epidermotropic, dermal, and subcutaneous
  – More than one pattern of disease often seen in a patient

<table>
<thead>
<tr>
<th>CGDTCI</th>
<th>SPTCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median 50s</td>
</tr>
<tr>
<td>Ulceration</td>
<td>Usually yes</td>
</tr>
<tr>
<td>Clinical</td>
<td>More B symptoms and HPS</td>
</tr>
<tr>
<td>Epidermis + dermis</td>
<td>Often yes</td>
</tr>
<tr>
<td>IHC</td>
<td>CD8-, CD56+, βF-1-</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Poor</td>
</tr>
<tr>
<td>5 yr survival</td>
<td>~11%</td>
</tr>
<tr>
<td>Treatment</td>
<td>Multagent chemotherapy ± stem cell transplant</td>
</tr>
</tbody>
</table>
Ulcerated nodule w/satellite lesions

Tumor in dermis and subcutis

Ulcer and epidermal T-cell infiltrate

Panniculitis infiltrate

Karyorrhexis

Tumor cells rim fat

More pleomorphism than reactive panniculitis

CGDTCL is CD4-/CD8-/βF1-, whereas SPTCL is CD4-/CD8+/βF1+
Differential Diagnosis

- Reactive conditions
  - Lupus profundus panniculitis
  - Atypical lymphocytic lobular panniculitis
  - Histiocytic cytophagic panniculitis

Lupus Profundus Panniculitis

- Plasma cells and germinal centers
  - B-cell aggregates
- Less atypia, no rimming by T-cells
- Vacuolar epidermal change and interstitial mucin
- Other features of systemic and cutaneous lupus
- Cytotoxic markers –
  - CD4+ > CD8+ T-cells
Lupus Profundus Panniculitis

Lobular panniculitis

Plasma cells (not seen in SPTCL)

CD4

CD8

Mix of CD4+ and CD8+ T-cells

CD20

Clusters of B-cells

Atypical Lymphocytic Lobular Panniculitis

- A clonal lymphoid infiltrate without histologic criteria for lymphoma
- Chronic condition that spontaneously regresses
- Lobular T-cell infiltrate small to medium cells without prominent atypia
  - Less rimming of fat than SPTCL
  - No karyorrhexis
  - CD4+ T-cells
  - ↑ histiocytes
  - Can develop into SPTCL
Interstitial and panniculitic infiltrate

No atypia, karyorrhexis or rimming

**Histiocytic Cytophagic Panniculitis (HCP)**

- Most cases now reclassified as SPTCL
- FEW HCP cases still remain
- Rarely if ever progresses to SPTCL
- ↑d histiocytes
- No clonal T-cell receptor gene rearrangement

Bilateral thigh plaques/nodules
Panniculitic-like infiltrate w histiocytes
CD68+
Rim fat
Perforin- 
Granzyme-B+
Part 5: Cutaneous Infiltrates with Larger, More Atypical Cells

Small to medium-sized cells

- Mycosis fungoides
- Primary cutaneous aggressive CD8+ lymphoma
- Lymphomatoid panniculitis, type B
- Adult T cell leukemia/lymphoma
- Primary cutaneous follicle center lymphoma
- Primary cutaneous marginal zone lymphoma
- Plasmacytoma
- Most systemic B-cell lymphomas
- CD4 small/medium pleomorphic T-cell lymphoma
- PTCL, NOS
- Angioimmunoblastic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Cutaneous gamma delta T-cell lymphoma

Large-sized cells

- Diffuse large B-cell lymphoma, leg type
- Systemic large B-cell lymphoma involving skin
- Primary cutaneous diffuse large B-cell lymphoma, NSB
- Plasma-cell lymphoma
- Lymphomatoid granulomatosis
- Lymphoma in situ, large B-cell lymphoma

Diffuse Large B-cell Lymphoma (DLBCL), Leg Type

- Often on lower legs, but can arise in other sites
  - Can have DLBCL, leg type that is NOT on the leg
- ≥ 1 plaque/ nodules ± ulceration
- More aggressive than most PTCLs
  - Disseminates to other sites, ~40% 5-year survival
  - Treatment:
    • R-CHOP or radiotherapy if single lesion

(Courtesy of Magda Tomaszewski)
Diffuse dermal B-cell infiltrate
Sheets of large cells
Centroblasts or immunoblasts (often round nuclei)
No centrocytes (or small B-cells)
No epidermotropism

Ancillary Testing

- B-cell antigens +
- Bcl-2+ (90%) MUM-1/IRF-4+, FoxP1+
- BCL6+, CD10-
- No follicular dendritic cell meshworks
  - CD21, CD23, CD35 negative
- MYC, BCL6 and IgH translocations
- No t(14;18) translocation
  - seen in systemic large B-cell lymphomas
**Differential Diagnosis:**

**PCFCL with Diffuse Pattern and Large Cells**

- Predominance of large cells
- Diffuse pattern
- Focal follicular areas
- Perivascular areas
- Cleaved tumor cells, not round cells of DLBCL-LT
- Admixed with small lymphs

**Phenotype**:
- BCL-6+  
- CD10-  
- BCL-2+, Mum1+, FoxP1+  
- T(14;18)

**Location**
- 85% on legs
- 5% survival
- 5-year survival

**Treatment**
- Usually R-CHOP
- Radiation or surgery if one lesion

**Morphology**
- Diffuse pattern
- Focal follicular areas
- Perivascular areas
- Round cell morphology
- Cleaved irregular nuclei
- No centrocytes (small B cells)
- Often admixed small centrocytes
- No stromal fibrosis

**Phenotype**
- BCL-6+  
- CD10-  
- BCL-2+ (or focal/weak), Mum1-, FoxP1-  
- T(14;18) Absent

**Phenotype**
- BCL-6+  
- CD10-  
- BCL-2+ (or focal/weak), Mum1+, FoxP1+  
- T(14;18) Present (10-40%)
Systemic DLBCL Involving Skin vs. DLBCL-LT
- Similar morphology and immunophenotype
- Must differentiate by clinical findings
  - History of systemic disease is key for diagnosis
  - If patient has systemic and skin involvement at time of presentation
    - Tumors of lower legs support PCDLBCL-LT

Primary Cutaneous Diffuse Large B-cell Lymphoma, Other
- No typical features of DLBCL-LT or PCFCL, diffuse pattern
Plasmablastic Lymphoma Involving Skin

- Immunoblasts, plasmacytic B-cells, but no plasma cells
- Sheets of large B-cells look similar to DLBCL-LT

CLASSIC PRESENTATION
- Oral cavity/GI tract
- HIV+
- 50% EBV+, HHV8-

REALITY
- Any site in skin
- Immunocompetent
- Variable EBV and HHV8

![Immunoblasts and PlasmacytoidDifferentiation](image)

- Positive
  - CD138+, CD38+, MUM-1+, CD79+, EBER+
- Negative
  - CD45-, CD20-, PAX5-
- EBV+ DLBCL of Elderly can look very similar
  - but has no history of immunodeficiency

![CD138, CD20, CD45, PAX5, EBER](image)

Lymphomatoid Granulomatosis (LyG)

- An extranodal EBV+ B-cell lymphoma that is angiocentric with numerous reactive T-cells
  - Lung most common, skin 2nd
- Morphology
  - B-cells often scattered
  - Angiocentric/angiodestructive
  - Fibrinoid necrosis
- Grading based on # of EBV+ cells
  - Grade 1 <5 EBER+ per hpf
  - Grade 2 5-20 EBER+ per hpf
  - Grade 3 >50 EBER+ per hpf

![CD45, CD20, CD10, PAX5, EBER](image)
- Diff dx:
  - DLBCL-LT
    - EBER-, sheets, not scattered cells, not angiocentric
  - Vasculitis
    - usually not EBER (+), no clonal IgH gene rearrangement

Small to medium-sized cells

<table>
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<tr>
<th>Subtypes</th>
<th>Causes</th>
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<td>Primary cutaneous NK/T-cell lymphoma</td>
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- CD20
- EBER
- T-cells in blood vessel
- Large atypical cells
Primary Cutaneous CD30+ Lymphoproliferative Disorders

- Represent 30% of CTCL
- Spectrum from Lymphomatoid Papulosis (LyP) to Anaplastic Large Cell Lymphoma (ALCL)
- Common phenotype: CD4+, CD30+
- Regression often observed

Primary Cutaneous Anaplastic Large Cell Lymphoma (ALCL)

- Solitary or few, localized lesions
- Tumors or nodules ± ulceration
- May regress, but recur
- Good prognosis
  - surgical excision and/or local radiotherapy
  - Chemotherapy if extracutaneous dissemination

Morphology

- Diffuse/nodular large T-cells, in the dermis ± subcutis
- Large, anaplastic, pleomorphic or immunoblastic appearance
  - Hallmark cells with multiple nuclei (horseshoe-shaped)
- Involve lymphatics/sinusoids
- Usually less of a polymorphic infiltrate (eos and plasma cells, more in LyP)
Phenotype

- **CD30+ (> 75% of tumor cells), CD15-**
- T-cell antigens+ with some loss of expression
- **CD4+/CD8-**
  - (CD4-/CD8+ and CD4-/CD8- rare)
- Cytotoxic markers positive
- Negative EMA and ALK in PC-ALCL
  - EMA and ALK+/- in systemic ALCL
  - ALK+ skin lesion usually indicates secondary cutaneous ALCL
- CLA+ and HOX5+ in PC-ALCL
  - But CLA- in systemic ALCL
- PAX5+ rarely, but - for other B-cell markers
**Therapy:**
- PC-ALCL: surgical excision and/or local radiotherapy
- Systemic ALCL: chemotherapy

**Molecular Testing**
- ALK gene translocation on chr2 is absent in PC-ALCL
- ALK translocation+ in systemic ALCL
- Break apart FISH probe for 2p23 (ALK) in systemic ALCL
  - Blue signal 5' region of ALK
  - Red signal 3' region of ALK
  - Two signals indicates there has been a rearrangement

**Lymphomatoid Papulosis (LyP)**
- Indolent end of spectrum of CD30+ LPDs with self-healing lesions
- CD30+ T-cells in wedge-shaped pattern, and polymorphous inflammatory background
- Multiple erythematous papules or nodules
  - At different stages of development
  - New lesions develop as old lesions regress
  - Self-healing w/ hyper- or hypopigmented scars

Photo courtesy of Rein Willemze
4 Subtypes

- **Type A**
  - Scattered large atypical cells
  - Abundant reactive polymorphous inflammatory cells

- **Type B**
  - Epidermotropism by small T-cells, resembles MF
  - Not separated from MF by histology or IHC
  - Type B LyP spontaneously regresses, unlike MF

- **Type C**
  - Monotonous sheets of large atypical cells, like ALCL
  - Scant polymorphous background infiltrate

- **Type D**
  - Marked epidermotropism and CD8+
**Type C**

↑ large cells
↓ inflammatory cells

Courtesy of M. Tomaszewski

**Ancillary Testing**

- CD30+ (± in type B), ALK-, CD15-
- CD4+/CD8- (rarely CD8+, i.e. type D)
- No ALK rearrangements

**LYP vs ALCL**

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<tr>
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<th>ALCL</th>
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<tr>
<td>Lesions</td>
<td>Multiple papules/nodules</td>
<td>Often 1, less often several nodules &gt; papules</td>
</tr>
<tr>
<td>Natural history</td>
<td>Regress</td>
<td>Regress, but may recur</td>
</tr>
<tr>
<td>Eos, pmns</td>
<td>Prominent</td>
<td>Not prominent</td>
</tr>
<tr>
<td>CD30</td>
<td>+, but in lower % of cells</td>
<td>+ in higher % of cells</td>
</tr>
<tr>
<td>ALK</td>
<td>Negative</td>
<td>PC -, systemic type can be +</td>
</tr>
<tr>
<td>CD4</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cytotoxic markers</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>T(2;5)(p23;q35)</td>
<td>Absent</td>
<td>+ in primary skin, + in some systemic cases</td>
</tr>
<tr>
<td>Treatment</td>
<td>Usually no treatment</td>
<td>Skin targeted therapy for low stage dz; chemo for systemic dz</td>
</tr>
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Differential Diagnosis

- MF with large cell transformation vs. ALCL:
  - Differentiate based on clinical, patches to plaques to tumors in MF
  - ± CD30, same phenotype as ALCL
  - Epidermotropism lost in LC transformation
- MF vs. type B LyP:
  - Epidermotropism in both, MF lacks regressing lesions
- Infection vs. LyP:
  - Dense dermal infiltrate w/CD30+ T-cells
  - Viral inclusions, scabies, or fungal organisms
- PLEVA vs. type A LyP:
  - Children/young adults, scaly/hemorrhagic lesions, interface dermatitis, necrotic keratinocytes, CD8+, CD30- (usually)

Small to medium-sized cells

- Mycosis fungoides
  - Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma
- Lymphomatoid papulosis, type B
  - Primary cutaneous follicle center lymphoma
- Primary cutaneous marginal zone lymphoma
- Plasmacytoma
- Most systemic B-cell lymphomas
- CD4 small/medium pleomorphic T-cell lymphoma
- PTCL, NOS
- Angioimmunoblastic T-cell lymphoma
- Lymphoepithelioid T-cell lymphoma
- ENKTL, nasal type
- Subcutaneous panniculitis-like T-cell lymphoma
- Cutaneous gamma delta T-cell lymphoma

Large-sized cells

- Diffuse large B-cell lymphoma, leg type
- Systemic large B-cell lymphoma
- Primary cutaneous diffuse large B-cell lymphoma, NOS
- Primary cutaneous angiocentric large B-cell lymphoma
- Primary cutaneous T-cell lymphoma
- Primary cutaneousMarginal zone B-cell lymphoma
- Blastic plasmacytoid dendritic cell neoplasm

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)

- Tumor of precursor plasmacytoid dendritic cells (pDC), often involves the skin and frequently culminates in leukemia
  - 2008 WHO Hematopoietic Neoplasms categorizes it under AML and related precursor neoplasms
  - 2006 WHO, Skin Tumors includes it within T-cell/NK-cell section even though it is a pDC tumor
- AKA:
  - Blastic NK-cell lymphoma
  - CD4+CD56+ hematodermic neoplasm
  - Agranular CD4+ natural killer cell leukemia
  - CD4+CD56+ blastic tumor of skin
BPDCN

- Skin
  - First manifestation of disease
  - Skin involvement in nearly all patients
- Natural history
  - Involves multiple organ systems
  - Culminates in leukemia (PB or BM)
    - Often monocytic differentiation
    - Presents more like leukemia than lymphoma
  - Rare leukemia variants without skin involvement
- Treatment
  - Leukemia protocols
  - Intrathecal chemotherapy followed by allogeneic BMT
  
Phenotype

- pDC markers
  - CD123+, BDCA-2+
  - Most specific pDC markers
- CD56+
  - Rare CD56-, does not exclude the dx
- TCL1+
  - Also + in some B- and T-cell lymphomas
- Cutaneous lymphocyte Antigen+
- Negative for blast markers
  - CD34-, CD117-
  - TdT+, 50% of cases, only some cells
- Most myeloid markers negative
  - CD13-, CD15-, lysozyme-, CD163-, MPO-
  - But CD33 & CD43 can be +
- Most B-cell markers are negative
  - CD19, CD20, CD79a-
  - PAX5 & mum1 can be +
- Most T-cell markers negative
  - CD3-, CD5-
  - CD2, CD45RA and CD7 (+/-)
  - CD4+ (may be weak+)
BPDCT vs Leukemia Cutis (AML)

- **Similarities**
  - Especially AML with monocytic differentiation, appears similar to BPDCN
  - Both can be CD123+, CD56+, CD4+, TdT+ and CD33+

- **Differences**
  - Multiple myeloid markers favors AML
    - MPO and lysozyme+ in AML, but - in BPDCN
  - Multiple pDC markers favors BPDCN
    - CD123 is only weak+ in AML
  - TCL1+ in BPDCN, but - in AML

Histiocytic Sarcoma

- Malignant tumor of mature histiocytes
- Dermal infiltrate with large pleomorphic cells with ↑ cytoplasm
- Must prove lineage with phenotyping
  - Histiocyte markers positive
    - CD163, CD68 (KP1 & PGM1), lysozyme
    - CD4 +/
  - Other positive markers
    - LCA+, HLA-DR+, CD15 (+/−, weak)
    - S100 (+/−, partial and weak)
## Diagnosis of Exclusion

- B-cell markers negative
- Melanoma markers negative
- Carcinoma markers negative
- Myeloid cell markers negative
- Langerhans cell markers negative
  - CD1a, langerin
- Follicular dendritic cell markers negative
  - CD21, CD23, CD35

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## Summary

- 2008 WHO/EORTC classification is an international consensus on primary cutaneous lymphomas
- Primary cutaneous lymphomas are recognized as specific entities
- Diagnosis requires clinicopathologic correlation, phenotypic and molecular studies
- Primary cutaneous lymphoma differs in prognosis and treatment from secondary cutaneous lymphoma and from extracutaneous lymphoma