Atypical Lymphoid Infiltrates

IS IT LYMPHOMA, PSEUDOLYMPHOMA OR SOMETHING ELSE?

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BM, Lymph Nodes, Cutaneous Atypical Lymphoid Infiltrate consultation practice

Many infectious agents disseminate in blood and the lymphatic system, and many of these infections are also tropical diseases that affect a large segment of the world’s population, including travelers, immigrants, and refugees. The authors have carefully incorporated in this new book those diseases found in both Western and Eastern hemispheres, in order to assist pathologists and medical laboratory professionals all over the world to better diagnose and treat infections that may be expected, or indeed quite unusual for a given geographic region. The book features a wide range of non-neoplastic hematologic disorders, as well as reactive patterns of non-infectious and infectious agents, all thoroughly illustrated with photographs, tables and text. In addition to the comprehensive and state-of-the-art diagnostic materials, the epidemiology, pathobiology, clinical and pathologic manifestations in blood and lymphatic organs, as well as approaches to treatment, are also described.
Objectives

- To go over cutaneous atypical infiltrates work up in order to facilitate diagnosis by showing:
  - Exemplary cases seen in cutaneous hematopathology subspecialty practice
  - Using an approach to diagnosis based on appearance and cell markers
atypical cutaneous lymphoid infiltrate?
The CD3 CD20 negative phenotype

62 female, thigh patch

71 female forearm nodule

43 F with nevus and increased WBC

36 M HIV+ facial alveolus mass
- Perivascular lichenoid pattern with epidermotrophic collections
High power view of nests
## Histiocytic Disorders Immunophenotype by Cell Type

### Antigen presenting histiocytic cells

<table>
<thead>
<tr>
<th></th>
<th>CD45</th>
<th>CD1a</th>
<th>S100</th>
<th>CD21</th>
<th>CD35</th>
<th>FactorXIII</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Langerhans cell</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Follicular dendritic</strong></td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Interdigitating</strong></td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Dendrocyte (dermal)</strong></td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Indeterminate</strong></td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Source: Adapted from Onciu (2004).*
Langerhans cell hyperplasia

- The Langerhans cell is named after Paul Langerhans. Because of their dendritic appearance, he thought these cells part of the nervous system—close.

Skin sentinel cells—stratum spinosum = 2 to 4% scattered, seen as collections in:
- Scabies, atopic dermatitis, leprosy, tuberculosis.
- Neoplasms—MF

- LNs and extra nodal tissue

- Benign, may be mistaken for Pautrier’s abscess, may be associated with certain infections and tumors.
43 female
Myeloid sarcoma (chloroma)

- cd43
- ki67
- Virtual flow Ki67
- cd68
MS or Extramedullary myeloid tumor

- Common in skin
- Can happen before, during and after AML, CML or MDS
- Can be differentiated or Blastic
- May rarely show blasts cell markers CD34 or Tdt
- Clues: nests of single file, figurate tumor cells
- Subclassification is best done by work up of blood or bone marrow, NPM1 mutation in 1 of 6
- CD3 negative, CD43 positive phenotype
- Comprise about 13% of cases I see in referral
71 female scalp mass
Dendritic cell vs melanocytic neoplasm

- Cd68+
- s100
- cd43
- s100
- Cd68+
Plasmablastic Lymphoma

Epstein Barr virus in situ hybridization +
The CD3 CD20 negative phenotype

Langerhans cell hyperplasia

Dendritic cell neoplasm

Myeloid sarcoma (chloroma)

Plasmablastic Lymphoma
The CD3 (20)negative CD43 positive phenotype

- Langerhans cell hyperplasia
- Dendritic cell neoplasm
- Myeloid sarcoma (chloroma)
- Plasmablastic Lymphoma
### Case distribution

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous B cell lymphoma</td>
<td>24.6%</td>
</tr>
<tr>
<td>Cutaneous T cell lymphomas</td>
<td>18.2%</td>
</tr>
<tr>
<td>CD30 Lymphomas</td>
<td>5.1%</td>
</tr>
<tr>
<td>Myeloid sarcoma etc</td>
<td>12.7%</td>
</tr>
<tr>
<td>Cutaneous Pseudolymphoma</td>
<td>25%</td>
</tr>
<tr>
<td>Real atypical Clonal CLH</td>
<td>5.0%</td>
</tr>
<tr>
<td>Secondary lymphoma</td>
<td>1.2%</td>
</tr>
<tr>
<td>Others miscellaneous</td>
<td>7.0%</td>
</tr>
</tbody>
</table>
Primary Cutaneous B-cell lymphomas*28.5

Follicle center cell lymphoma 8.5 %
Marginal zone B-cell lymphoma 7.1
Diffuse large B-cell lymphomas, leg-type 2.6
Diffuse large B-cell lymphomas, other 8.8
Intravascular large B-cell lymphoma
Plasmablastic lymphoma
T cell rich B cell lymphomas
other rare types

*SEER USA data 2009, Blood 113:5064, 3884 cases (100%)
### CUTANEOUS B CELL LYMPHOMA

<table>
<thead>
<tr>
<th>Type</th>
<th>5 yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Prim Cut Follicle center cell lymphoma</td>
<td>95%</td>
</tr>
<tr>
<td>b. Prim Cut Marginal Zone lymphoma*</td>
<td>77%</td>
</tr>
<tr>
<td>c. Diffuse large B-cell lymphoma, leg type**</td>
<td>41%</td>
</tr>
<tr>
<td>d. Diffuse large B-cell lymphoma, other</td>
<td>50%</td>
</tr>
<tr>
<td>e. PC Intravascular large B-cell lymphoma</td>
<td>56%</td>
</tr>
</tbody>
</table>

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*ArchDerm 2005: 141, 1139 Clin Therapy Features of 50 cases, Relapse free SR after complete remission Solitary 77%, Multifocal 39%; ** Arch Derm 2007, 143:1144
ALL other data: WHO-EORTC 2005
CD20 predominant phenotype

- **Cutaneous B cell lymphoma 24.6%**
  - Marginal zone lymphoma 5.0%
  - Follicle center cell, F/D 5.0%
  - DLBCL Leg type 1.2%
  - DLBCL, Other 5.0%
  - Immunocytoma 2.5%
  - SECONDARY, ie, CLL 2.5%

- **Cutaneous B cell Pseudolymphoma 3.8%**
Diffuse FCCL
Primary Cut Follicle center cell, diffuse pattern

- CD20
- CD3
- CD10
- CD5
DLBC, LEG TYPE
>80% CENTROBLASTS AND IMMUNOBLASTS
Cutaneous Pseudo-B & T cell lymphoma

- Pseudolymphoma-benign infiltrate that simulate cutaneous lymphoma histologically or clinically, some may harbor small clones by molecular test.
  - Synonyms: cutaneous lymphoid hyperplasia, lymphadenoma benigna cutis, lymphocytoma cutis, Spiegler-Fendt sarcoid
  - Classic division- Pseudo T and Pseudo-B
  - Pseudo-B more or less uniform in appearance with germinal center like reactions- Borrelia, L drug eruption, vaccine, tattoo, infections- Syphilis, Herpes Zoster
  - Pseudo- T are heterogeneous
    - With MF-like pattern- Actinic, contact derm, L drug eruption, Lichenoid keratosis, L aureus, L sclerosis
    - With nodular pattern- CD30 pseudolymphomas, L drug eruption, arthropod bites
PSEUDOLYMPHOMAS 25% of cases

- **B CELL PSEUDOLYMPHOMA** 3.8%
  - Germinal centers or > 70% nodules of B cells

- **T CELL PSEUDOLYMPHOMA** 9.0%
  - Band or nodular, >90% T cells

- **MIXED B CELL AND T CELL PSEUDOLYMPHOMA** 12.9%
  - Dermal nodules or perivascular, about equal number of B and T cells (40 to 60%)

- **CLONAL CLH** 5.0%
  - Features of pseudolymphoma that has clonal T or B
CD20 CD3 (with CD30) mixed phenotype

- Cutaneous Mixed Pseudolymphoma 12.9%
  - Majority unknown etiology

- Clonal atypical Cutaneous Pseudolymphoma 5%
  - Usually solitary, mostly in mixed pseudolymphoma category or one with exuberant granulomas, observed in patients with previous cutaneous B cell pseudolymphoma that recurred—now with atypical germinal centers, increased transformed cells, increased B: T cell ratio — Continuum REF: Kulow, Cualing et al.. Progression of cPseudoB to CBCL.

- Clonal Tumor of Uncertain Significance
  - Similar to the terms: MGUS, MLUS, thyroid or prostate microcarcinomas, melanocytic lesions of uncertain significance
Cutaneous Lymphoid Hyperplasia or Pseudo- B cell lymphoma with defined etiology
CLH SECONDARY TO TATTOO PIGMENT
CLH SECONDARY TO TATTOO PIGMENT

CD3

CD20
- Cutaneous involvement by MF, PTCL 11.2%
  - Solitary Pleomorphic 3.8%
  - PTCL Unspecified 1.2%
  - Transformed MF 1.2%
  - CD8 ptcl, epidermotropic 1.2%
  - MF, Alibert Bazin type 3.8%
- Pseudo T cell lymphoma 9%
- Lymphomatoid papulosis and CD30 Cutaneous Lymphomas 5.1%
- Intravascular cd30 T cell lymphoma 2.5%
CD3 immunostain and vbeta clonal assay by flow cytometry
cCD4+pleomorphic T cell lymphoma
CD4+ lymphoma: CD4+ small/medium pleomorphic T cell lymphoma
CD30+ Lymphoproliferative Disorders

Primary cutaneous ALCL CD30+ large cell lymphoma

Lymphomatoid Papulosis histologic variants
Type A- RS-like with eos and neutrophils
Type B- MF like with cerebriform cells
Type C- borderline, monomorphic, dermal, not in SQ, less inflammatory cells
Lymphomatoid Papulosis (LyP)
Lymphomatoid Papulosis (LyP type A)
Lymphomatoid Papulosis (LyP type B)
Lymphomatoid Papulosis (LyP type C)
Primary Cutaneous Anaplastic lymphoma

cd30+ in ALCL
In 1806, mycosis fungoides (MF) was first described\(^1\)
- Alibert, a French dermatologist, described a severe disorder in which large necrotic tumors resembling mushrooms presented on a patient's skin

In 1979, the term cutaneous T-cell lymphoma (CTCL) was proposed at an international workshop sponsored by the National Cancer Institute and as coined by the Lutzner group in 1975 \(^2,3\)
- CTCL was used to describe a heterogenous group of malignant T-cell lymphomas with primary manifestations in the skin
- MF is the most common type of CTCL
- Sézary syndrome (SS) is a variant of MF, occurring in about 5% of all cases of MF

\(^3\) Lutzner, Edelson et al Cutaneous T cell lymphomas: The Sezary Syndrome, MF and related disorders, Ann Int Med 1975
# WHO/EORTC Classification CTCLs

## CTCL, NK-cell Lymphomas

### MF/MF variants and subtypes
- Folliculotropie MF not FM associated MF
- Pagetoid reticulosis or solitary MF
- Granulomatous MF not Granulomatous SS

### Sézary syndrome

### Adult T-cell leukemia/lymphoma

### Primary cutaneous CD30+ lymphoproliferative disorders
- Primary cutaneous anaplastic large cell lymphoma
- Lymphomatoid papulosis

### Subcutaneous panniculitis-like T-cell lymphoma

### Extranodal NK/T-cell lymphoma, nasal type
- cutaneous peripheral T-cell lymphoma, unspecified
- Primary cutaneous aggressive epidemotropie CD8+ T-cell lymphoma in WHO
- Cutaneous gamma/delta T-cell lymphoma (in WHO)
- Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell in WHO

### Mylelomonocytic blasts or PDC Neoplasm
WHO-EORTC 2005 Classification of Cutaneous T cell Lymphomas

CTCLs

- **Indolent**
  - MF: 88%
  - cALCL: 95%
  - LyP: 100%
  - Subcut Panniculitis-like T cell lymphoma: 82%
  - cCD4+pleomorphic T cell lymphoma: 75%

- **Aggressive**
  - Sezary Syndrome: 24%
  - NK/T cell lymphoma, nasal: NR
  - CD8+ T cell lymphoma: 18%
  - Gamma-Delta T cell lymphoma: NR
  - PTCL, unspecified: 16%

_Blood, 2005: 105, 3768_
Primary Cutaneous Lymphomas

- 75% of PCL are T-cell and 25% are B-cell lymphomas
- It is important to distinguish between systemic lymphomas and PCL.
- Except MF, number of primary Cutaneous PTCLs have worse prognosis than the nodal types.
  - In contrast, Cutaneous B cell lymphomas have a much better prognosis than the nodal lymphoma that looks morphologically identical.
  - Pseudolymphomas may be part of continuum
Diagnostic Approach

The diagnosis in CL is established by the combination of CHIP:

- Clinical features
- Histopathology
- Immunophenotypic
- Probes for molecular