Cutaneous Lymphomas: Diagnostic Challenges

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Case #1

• 50 year old male
• Relatively sudden onset full body erythroderma
• Fevers and weight loss
• Lymphadenopathy on clinical exam
• Flow cytometry from peripheral blood
  - CD4/8 ratio: 48/1
• T-cell gene re-arrangement studies peripheral blood
  - + T-cell clone
The best diagnosis is:
1. Mycosis fungoides
2. Sézary syndrome
3. Mycosis fungoides/Sézary syndrome
4. Pityriasis rubra pilaris
5. Allergic contact dermatitis
Sézary syndrome

- Triad:
  - Leukemic lymphocytes in skin → erythroderma
  - Leukemic lymphocytes in lymph node
  - Leukemic lymphocytes in blood
- Sézary syndrome typically is not preceded by patch/plaque/tumors
- Sézary patients present with full clinical constellation at outset of disease

Mycosis fungoides (MF)

- Histopathology may be identical
- Clinical presentation different
  - Patches, plaques and tumors

Classic MF: patch stage
Classic MF: Plaque stage

Classic MF: Tumor stage
### Results

<table>
<thead>
<tr>
<th>SS</th>
<th>MF Tumor</th>
<th>Chromosomal alteration</th>
<th>Associated gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>75%</td>
<td>23%</td>
<td>Gain 8q24</td>
<td>MYC</td>
</tr>
<tr>
<td>75%</td>
<td>9%</td>
<td>Loss 17p13</td>
<td>p53</td>
</tr>
<tr>
<td>15%</td>
<td>59%</td>
<td>Gain 7q36</td>
<td>FASTK</td>
</tr>
</tbody>
</table>
Question #1

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Pityriasis rubra pilaris
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Spongiotic dermatitis

Utility of skin biopsy in Sézary syndrome

• ~ 60% cases showed diagnostic features

Trotter et al. JCP 1997; 24:280.
Additional information

- Flow cytometry: CD4/8 16:1
- T-cell gene re-arrangement studies: + clone in blood

Peripheral blood evaluation: Former method

- Light microscopy for cell morphology
  - Atypical cells with indented cerebriform/serpentine nuclei

Blood evaluation: limitations based on morphologic methods

- Morphologically similar cells found in erythrodermic dermatoses
- Normal lymphocytes could acquire Sézary cell when stimulated
- Small cell variant of Sézary cell recognized

Evaluation of blood: Current method

Perspective

Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC)

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Diagnostic criteria of blood

Genotypic analysis: clone detected

AND

Flow cytometry:

• CD4/8 > 10

OR

• Loss of T-cell antigens
  • CD7- > 40%
  • CD26- > 30%


Take home points

• Sézary syndrome and mycosis fungoides have overlapping histopathology but are clinically distinct
• If inadequate clinical information, suggest a descriptive diagnosis of epidermotropic T-cell lymphoma
• Current method to detect blood involvement in Sézary syndrome is by a combination of flow cytometry and T-cell gene rearrangement studies
• Histopathology not always specific.
• Consider a comment on spongiotic dermatitis in erythrodermic patients

Case #2

• 35 year-old female presents with multiple erythematous subcutaneous nodules
• Some nodules ulcerated
• +Fevers
Question #2

The best diagnosis is:
1. Subcutaneous panniculitis-like T-cell lymphoma
2. Tumor-stage mycosis fungoides
3. Gamma/delta T-cell lymphoma
4. NK/T-cell lymphoma, nasal type
5. Erythema nodosum
**Question #2**

The best diagnosis is:
1. Subcutaneous panniculitis-like T-cell lymphoma
2. Tumor-stage mycosis fungoides
3. Gamma/delta T-cell lymphoma
4. NK/T-cell lymphoma, nasal type
5. Erythema nodosum

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**Gamma/delta T-cell lymphoma**

- Primary cutaneous lymphoma, often centered on subcutis
- Histopathology: Atypical lymphocytes in the subcutis, often with involvement of the epidermis and dermis
- Immunophenotype:
  - Positive for: CD3/TIA-1/CD56/GM3
  - Negative for: CD4/CD8/BetaF1/EBV/CD30
- Clinical: ulcerating lesions, fevers, hemophagocytic syndrome
- Prognosis: 5-year overall survival 11%

Evolution of subcutaneous lymphomas

• Initial description of lymphomas that mostly involved the subcutis
• Aggressive clinical course, often associated with hemophagocytic syndrome
• “Subcutaneous panniculitis-like T-cell lymphoma”


Sub-classification of subcutaneous panniculitis-like T-cell lymphoma

• Gamma/delta T-cells
• Alpha/beta T-cells
  • Clinical: non-ulcerating, +/- fevers, rarely associated with hemophagocytic syndrome
  • Prognosis: 5-year overall survival 82%
  • Histopathology – subcutis only, BetaF1+/GM3-/CD56-


Two classes of T-cell receptors

Two classes of T-cell receptors

http://course1.winona.edu/kbates/Immunology/Chapter5-09.htm

SPTCL
WHO-EORTC 2005 classification of primary cutaneous lymphomas

Cutaneous T-cell and NK-cell lymphomas
- Mycosis fungoides
- MF variants and subtypes
- Folliculotropic MF
- Pagetoid reticulosis
- Granulomatous slack skin
- Sézary syndrome
- Primary cutaneous AITL
- Primary cutaneous CD30+ lymphoproliferative disorders
- Primary cutaneous anaplastic large cell lymphoma
- Lymphomatoid papulosis

Subcutaneous panniculitis-like T-cell lymphoma

Endemic type T-cell lymphoma, nodal type

Primary cutaneous peripheral T-cell lymphoma, unspecified

Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma

Cutaneous vH T-cell lymphoma (provisional)

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

Cutaneous B-cell lymphomas
- Primary cutaneous marginal zone B-cell lymphoma
- Primary cutaneous follicle center lymphoma
- Primary cutaneous diffuse large B-cell lymphoma, leg type
- Primary cutaneous diffuse large B-cell lymphoma, other
- Intravascular large B-cell lymphoma
- Primary hematologic malignancy

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Tumor stage mycosis fungoides

- Clinical- concomitant patches and plaques
- Histopathology – centered upon dermis
- Immunophenotype – CD3+/CD4+/GM3-/CD56-
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NK/T-cell lymphoma, nasal type

- Can show similar clinical presentation
- Typically: CD3+/CD56+/EBV+
- Distinguished by EBV-positivity, ethnicity and T-cell clone

Question #2

The best diagnosis is:
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Erythema nodosum

- Prototypical septal panniculitis
- Clinical: Erythematous nodules that do not ulcerate
- Histopathology:
  - Cytologically bland lymphocytes along with histiocytes, including multinucleated giant cells, in the septa of the fat
  - Septal fibrosis
Take home points

• SPTCL has been sub-classified into gamma/delta T-cell lymphoma and alpha/beta SPTCL
• Gamma/delta T-cell lymphoma
  — Clinical: ulcerative lesions
  — Histopathology: associated with epidermal and dermal involvement
  — Immunophenotype: CD3+/GM3+/CD56+/TIA-1+/Beta-F1-
  — Prognosis: 5-year overall survival 11%
• Alpha/beta SPTCL
  — Clinical: non-ulcerating subcutaneous nodules
  — Histopathology: usually confined to the subcutis
  — Immunophenotype: CD3+/GM3-/CD56-/TIA-1+/Beta-F1+
  — Prognosis: 5-year overall survival 82%

Case #3

• 51-year old female
• Forehead
• Accompanying requisition, "Erythematous nodule x 1 month"
Question #3

The best diagnosis is:
1. Mycosis fungoides – tumor stage
2. Primary cutaneous CD4-positive small/medium pleomorphic T-cell lymphoma (SMPTCL)
3. Marginal zone lymphoma
4. Anaplastic large cell lymphoma
5. Both 1 and 2 are possible
Classic MF: Tumor stage

- Clinical
  - Solitary erythematous papule or nodule
  - Face, neck, upper trunk
  - Rarely multiple lesions
**Additional clinical history**

- Solitary lesion only
- No lesions concerning for patches and plaques of mycosis fungoides

Primary cutaneous CD4-positive small/medium pleomorphic T-cell lymphoma

**Classification: 1990**

- MF/SS
- CD30-negative T-cell lymphomas
- CD30-positive T-cell lymphomas

**Dermal-based. Cell size mattered**

1994

- N=9
  - Most lymphocytes were small and medium-sized
  - Admixed large cells, <30%

- N=26
  - Most lymphocytes were large

**Clinical presentation and immunophenotype mattered too**

2003

- n=19
  - Small/medium dermal-based CD30- T-cell lymphoma
  - Some with multifocal skin lesions
  - Others with solitary/localized lesions
  - 7/19 Alive. 6/7 had solitary/localized lesions, CD4+
  - 11/19 Died. Most with multifocal lesions, CD8+

Evolution of cutaneous lymphomas classification system

- For CD30-negative dermal-based T-cell lymphomas, cell size, clinical presentation and immunophenotype defined disease
- Additional studies showed most lesions were a few centimeters or smaller
- Proposed name, “Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma” (SMPTCL)

SMPTCL

- Clinical
  - Solitary erythematous papule or nodule
  - Face, neck, upper trunk
  - Rarely multiple lesions
Clinical presentation crucial
SMPTCL vs. T-cell pseudolymphoma: What is the difference?

- On anti-epileptic medication
- Histopathology suggestive of MF
- Rash resolved with discontinuation of medication
- No T-cell clone (Southern blot)
- Nodular-to-diffuse dermal infiltrate without epidermotropism with variable number of small, medium and large cells, usually CD4+

T-cell pseudolymphoma

SMPTCL: Prognosis

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Prognosis</th>
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<tr>
<td>Grogg K et al.</td>
<td>15</td>
<td>All alive (Follow-up 9 months)</td>
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<tr>
<td>Beltraminelli H et al.</td>
<td>136</td>
<td>All alive (Follow-up 63 months)</td>
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<tr>
<td>Baum C et al.</td>
<td>10</td>
<td>All alive (Follow-up 24.5 months)</td>
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<tr>
<td>Garcia-Herrera A et al.</td>
<td>24</td>
<td>19 alive -(Follow-up 23 months)</td>
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<td></td>
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<td>5 died of disease</td>
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<tr>
<td></td>
<td></td>
<td>-Clinical lesions &gt; 5 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 - multifocal lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 - problems with CD4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 - co-expression CD20</td>
</tr>
</tbody>
</table>

**T-cell pseudolymphoma, cont.**

- PCR replaced Southern blot as assay
- Detection limit ~ 1% vs. 5% for Southern blot
- Using PCR, many cases formerly classified as pseudo-T-cell lymphoma had clones

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**SMPTCL: identity crisis**

“Cutaneous nodular proliferation of pleomorphic T lymphocytes of undetermined significance”

“Spectrum of pseudo-T-cell lymphoma/primary cutaneous CD4+ SMPTCL”


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**PD-1 use in the differential diagnosis**

- Rosettes in SMPTCL
- Scattered positivity in T-cell pseudolymphoma
- Conclusion: SMPTCL probably different from pseudolymphoma


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**Management – UCSF style**

- Typically, no staging is performed
- Preferentially treated with either intralesional steroids or surgical excision
- Sometimes radiation
- Followed for many years
Take-home points

• SMPTCL is an indolent condition
• Rendering a firm diagnosis requires CPC
• Pathologic requisition: size, number, other morphologies
• Significant overlap between SMPTCL and T-cell pseudolymphoma
• The distinction between them may be non-meaningful
• Management should be conservative
• PD-1 may help in differentiating from other diagnoses

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