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
Case #1
Question #1

The best diagnosis is:
1. Mycosis fungoides
2. Sézary syndrome
3. Mycosis fungoides/Sézary syndrome
4. Allergic contact dermatitis
5. Pityriasis rubra pilaris
Question #1

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Four issues issues

• Review of clinical and histopathologic features of Sézary syndrome and mycosis fungoides
• Relationship between Sézary syndrome and mycosis fungoides
• Current methods to evaluate blood involvement
• Role of skin biopsy in Sézary syndrome
Four issues issues

• Review of clinical and histopathologic features of Sézary syndrome and mycosis fungoides
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Sézary syndrome

• Triad:
  – Leukemic lymphocytes in skin → erythroderma
  – Leukemic lymphocytes in lymph node
  – Leukemic lymphocytes in blood
• Skin lesions are not preceded by patches, plaques or tumors
• Sézary patients present with full clinical constellation at outset of disease
Histopathology
Mycosis fungoides (MF)

• Clinical presentation different
  – Patches, plaques, tumors, erythroderma (late stage)

• Histopathology may be identical (patch/early plaque)
Classic MF: patch stage
Classic MF: Plaque stage
Classic MF: Tumor stage
MF: Erythroderma
Histopathology: patch

• Low power, patterns
  – Psoriasiform, patchy lichenoid
  – Psoriasiform, patchy lichenoid, spongiosis
  – Lichenoid, atrophic

• Features
  – Epidermotropism - intraepidermal infiltrate of lymphocytes
  – Lymphocytes in papillary dermis
  – Papillary dermal fibrosis
Epidermotropism

- Single lymphocytes or collections of lymphocytes in the absence of spongiotic vesicles
- Haloed lymphocytes
- Linear arrangement of lymphocytes along DEJ
- Pautrier collections
- Lymphocytes in the epidermis larger than lymphocytes in the dermis
Histopathology - Plaque

- Lichenoid psoriasiform pattern
- Epidermotropism, cytological atypia more evident
- Extension of infiltrate into reticular dermis
Histopathology - Tumor

- Dense array of neoplastic cells in reticular dermis
- Atypia often quite pronounced
- Epidermotropism often diminishes
- Often eosinophils, plasma cells, macrophages
Sézary syndrome

Mycosis fungoides
Four issues issues

• Review of clinical and histopathologic features of Sézary syndrome and mycosis fungoides
• Relationship between Sézary syndrome and mycosis fungoides
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Why are MF and SS often equated?
History of cutaneous lymphoma

1968
EM of SS cells

1971
EM - same cells in MF

“In view of the many common features, it may be that Sézary syndrome is a leukemic phase of mycosis fungoides.”

Identification of Sézary cell as T-cell


New Concept:
1975 Cutaneous T-cell lymphoma (CTCL)

Novel and Highly Recurrent Chromosomal Alterations in Sézary Syndrome


Departments of Dermatology and Molecular Cell Biology, Leiden University Medical Center, Leiden, the Netherlands; Department of Dermatology, St Thomas' Hospital, King's College, London, United Kingdom; Department of Dermatology, University Medical Center Groningen, Groningen, the Netherlands; Department of Dermatology, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; Department of Dermatology, Gent University Hospital, Gent, Belgium; Department of Dermatology, Charite, Berlin, Germany; and Department of Genetics and Pathology, Rudbeck Laboratory, University of Uppsala, Uppsala, Sweden

Oncogenic analysis of mycosis fungoides reveals major differences with Sézary syndrome

Remco van Doorn, Marloes S. van Kester, Remco Dijkman, Maarten H. Vermeer, Aat A. Mulder, Karoly Szuhai, Jeroen Knijnenburg, Judith M. Boer, Rein Willemze, and Cornelis P. Tensen

Departments of Dermatology and Molecular Cell Biology, and Center for Human and Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands
## Data synthesis

### Table 2. Comparison of most highly recurrent CNAs in MF and Sz

<table>
<thead>
<tr>
<th>Cytogenetic band</th>
<th>CNA</th>
<th>Affected MF patients, %</th>
<th>Affected Sz patients, %</th>
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<td>Gain</td>
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**Genes**
- FASTK
- MCL1
- STAT genes
- MYC
- p53
Four issues issues

• Review of clinical and histopathologic features of Sézary syndrome and mycosis fungoides
• Relationship between Sézary syndrome and mycosis fungoides
• Current methods to evaluate blood involvement
• Role of skin biopsy in Sézary syndrome
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)

Elise Olsen,1 Eric Vonderheid,2 Nicola Pimpinelli,3 Rein Willemze,4 Youn Kim,5 Robert Knobler,6 Herschel Zackheim,7 Madeleine Duvic,8 Teresa Estrach,9 Stanford Lamberg,2 Gary Wood,10 Reinhard Dummer,11 Annamari Ranki,12 Gunter Burg,11 Peter Heald,13 Mark Pittelkow,14 Maria-Grazia Bemengo,15 Wolfram Sterry,16 Liliane Laroche,17 Franz Trautinger,6 and Sean Whittaker,18 for the ISCL/EORTC
Diagnostic criteria of blood

Genotypic analysis: clone detected

AND

Flow cytometry:

- CD4/8 > 10

OR

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

Four issues issues

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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
How to report spongiotic dermatitis in erythrodermic patient

• Consider a comment that Sézary syndrome cannot be excluded

• Consider recommending blood studies
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How to report in absence of clinical information

- Descriptive diagnosis: Epidermotropic T-cell lymphoma
- Obtain additional clinical information
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SS/MF

Spongiotic dermatitis
Nummular dermatitis

Mycosis fungoides
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Pityriasis rubra pilaris
Take home points

- Sézary syndrome and mycosis fungoides have overlapping histopathology but are clinically and molecularly 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
- +Fever
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
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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:
  – Negative for: CD4/CD8/BetaF1/EBV/CD30
• Clinical: ulcerating lesions, fevers, hemophagocytic syndrome
• Prognosis: 5-year overall survival 11%

Question #2

The best diagnosis is:

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Evolution of subcutaneous lymphomas

1991

• 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-cell lymphoma

• Alpha/beta T-cell lymphoma
  • 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

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

• CD3+/BetaF1+/GM3-/CD56-
WHO-EORTC 2005 classification of primary cutaneous lymphomas

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Precursor hematologic neoplasm
Question #2

The best diagnosis is:

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5. Erythema nodosum
Tumor stage mycosis fungoides

- Clinical- concomitant patches and plaques
- Histopathology – centered upon dermis
- Immunophenotype – CD3+/CD4+/GM3-/CD56-
The best diagnosis is:

1. Subcutaneous panniculitis-like T-cell lymphoma
2. Tumor-stage mycosis fungoides
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5. Erythema nodosum
CD3ε (Clone F7.2.38)
CD56
In situ hybridization for EBV
The best diagnosis is:
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3. Gamma/delta T-cell lymphoma
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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
• GM3 new antibody for gamma/delta T-cells that can be used in paraffin-embedded tissue
• 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
The best diagnosis is:
1. Mycosis fungoides – tumor stage
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3. Marginal zone lymphoma
4. Anaplastic large cell lymphoma
5. Both 1 and 2 are possible
MF – tumor stage
MF – tumor stage
SMPTCL

MF: Tumor stage
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
### WHO-EORTC 2005 classification of primary cutaneous lymphomas

#### Cutaneous T-cell and NK-cell lymphomas

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### Precursor hematologic neoplasm
Classification: 1990

- MF/SS
- CD30-negative T-cell lymphomas, dermal based
- CD30-positive T-cell lymphomas
Classification: 1990

- MF/SS
- CD30-positive T-cell lymphomas
- CD30-negative T-cell lymphomas, dermal based
Dermal-based. Cell size mattered

1994

PRIMARY CUTANEOUS T-CELL LYMPHOMA: CLINICOPATHOLOGICAL FEATURES AND PROGNOSTIC PARAMETERS OF 35 CASES OTHER THAN MYCOSIS FUNGOIDES AND CD30-POSITIVE LARGE CELL LYMPHOMA

ROB C. MEIJERS*, CHRIS J. L. M. MEIJER+, SIBASTIEN C. J. VAN DER PUTTEL, HARRY HOLLEMA+S, MARIE-LAURE GEERTS, P. DICK BEZEMER+ AND RUN WILLEMZEG

Departments of Dermatology*, Pathology+, and Epidemiology and Biostatistics§, Free University Hospital of Amsterdam, The Netherlands; †Department of Pathology, University Hospital of Utrecht, The Netherlands; ‡Department of Pathology, University Hospital of Groningen, The Netherlands; §Department of Dermatology, University Hospital of Gent, Belgium

Received 24 June 1993
Accepted 24 September 1993

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

- N=26
  - Most lymphocytes were large

Favorable prognosis

Poor prognosis

N=35
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 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
MF – tumor stage
MF – tumor stage
## SMPTCL: Prognosis

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<tr>
<th>Study</th>
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<th>Outcome and Follow-up</th>
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<tr>
<td>Grogg K et al.</td>
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<td>Beltraminelli H et al.</td>
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<td>All alive (Follow-up 63 months)</td>
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<td>Baum C et al.</td>
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<td>All alive (Follow-up 24.5 months)</td>
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<td>Garcia-Herrera A et al.</td>
<td>24</td>
<td>19 alive (Follow-up 23 months) 5 died of disease  -Clinical lesions &gt; 5 cm 1 - multifocal lesions 1 - problems with CD4 1 - co-expression CD20</td>
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SMPTCL vs. T-cell pseudolymphoma: What is the difference?
T-cell pseudolymphoma

- 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, 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
SMPTCL: identity crisis

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

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


PD-1 use in the differential diagnosis

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

Management – UCSF style

- Typically, no staging is performed
- Preferentially treated with either intralesional steroids or surgical excision
- Sometimes radiation
- Followed for many years
The best diagnosis is:

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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
Marginal zone lymphoma

SMPTCL
Question #3

The best diagnosis is:

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Anaplastic large cell lymphoma

SMPTCL
Anaplastic large cell lymphoma
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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