Cutaneous T-Cell Lymphomas: the importance of a multidisciplinary approach

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**History of Cutaneous Lymphomas (CL)**

1806 Alibert
1862 Bazin (three stages)
1938 Sézary syndrome
1939 Pagetoid reticulosis (localized)
1968 Lymphomatoid papulosis
1975 CTCL concept
1980 CL, non-MF/SS (ca. 40%)
- considered and treated as systemic lymphomas

**Classification of CTCL**

Before 1997 (EORTC) or 2005 (WHO-EORTC):
- Diagnosis based on morphological criteria.
- Histologic diagnosis = final diagnosis
- Treatment (mainly) based on histologic diagnosis.

After 1997 (EORTC) or 2005 (WHO-EORTC):
- Diagnosis based on a combination of histology, immunophenotyping, genetics and clinical criteria.
- Histologic diagnosis is often a differential diagnosis (in particular in cases of CTCL).
- Final diagnosis dependent on adequate clinical information.
WHO-EORTC = WHO 2008

Classical CTCL (MF /SS): 51%
Cutaneous CD30+ LPD: 20%
Aggressive/uncommon CTCL: 7%
Cutaneous B-cell lymphoma: 22%

Percentages based on data from the Dutch registry (>3000 patients)

Mycosis fungoides

- Most common type of CTCL (0.3/100,000/year).
- Epidermotropic CTCL characterized by a proliferation of small to medium-sized T-cells with cerebriform nuclei.
- Mainly adults (median age: 55-60 yrs), but may also occur in children and adolescents.
- Male/female ratio: 1.6-2.0 : 1
- Indolent course (years to decades) with slow progression from patches to plaques to tumors.
- Development of nodal or visceral disease in a minority of patients.

To be discussed in MF / SS

- Pitfalls in diagnosis of early MF.
- Phenotype of MF.
- Folliculotrophic MF.
- Definition and prognosis of transformed MF.
- MF versus Sezary syndrome

Histology plaque stage MF

Pautrier micro-abscesses
Haloed cells

Histology patch stage MF
**Histology patch stage MF**

Atypical lymphocytes: hyperchromatic, partly haloed and too large, aligned along epidermal basal layer; no spongiosis

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**Diagnosis MF**

- Diagnosis of MF should always be based on a combination of clinical and histological criteria (= golden standard).
- **Additional** criteria:
  - Immunohistochemistry
    - Loss of pan-T-cel markers (CD2,3,4,5, but not CD7 !!) is strongly suggestive/diagnostic of CTCL.
  - Gene rearrangement analysis: be critical !!

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**Phenotype of MF (marker loss)**

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**Most cases: CD4+ T-cell phenotype**

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**CD8+ MF: behaves as CD4+ MF**

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**Phenotype of MF (CD8+, CD56+)**

Workshop case 37
Ankara, Turkey
**Phenotype of MF IA - IB**

<table>
<thead>
<tr>
<th>βF1</th>
<th>CD4</th>
<th>CD8</th>
<th>TIA-1</th>
<th>CD56</th>
<th>No (%)</th>
<th>Med. survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10 (15%)</td>
<td>160</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>2 (3%)</td>
<td>130</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>5 (7%)</td>
<td>165</td>
</tr>
</tbody>
</table>

Conclusion: phenotype has no effect on prognosis

Massone C. et al; Br J Dermatol 2008

**MF: immunophenotype**

- Most cases: phenotype of CD4+ memory T-cells.
- CD8+ T-cell phenotype not uncommon: > 15%.
- More uncommon: expression of CD30, CD56 or cytotoxic proteins (TIA-1; granzyme B), TCRγ, etc.
- Presence of an aberrant phenotype or marker loss in early stage MF has no **prognostic** significance and is no reason to reject a diagnosis of MF
- Loss of pan-T cell markers should be considered as an important **diagnostic** criterion.

**To be discussed in MF / SS**

- Pitfalls in diagnosis of early MF.
- Phenotype of MF.
  - **Folliculotrophic MF.**
  - Definition and prognosis of transformed MF.
  - MF versus Sezary syndrome

**Folliculotropic MF: often not recognized**

- Often not recognized / misdiagnosed **clinically**
  - Characteristic patches and plaques are lacking
  - Preferential involvement head and neck region (follicular papules; plaques; tumors)
  - Involvement hair follicles → hair loss
  - Severe pruritus
  - Frequent secondary bacterial infections
  - Less responsive to skin-targeted therapies.
  - More often transformation; peripheral blood involvement.
  - Less favorable prognosis than classical MF
  - Estimated 5-year-survival: 74% (≈ tumor stage MF)

Folliculotropic MF

**Folliculotropic MF**

- No patches and plaques
- No epidermotropism

**Folliculotropic MF**

- Characteristics: characteristic patches and plaques are lacking, preferential involvement head and neck region (follicular papules; plaques; tumors), involvement hair follicles → hair loss, severe pruritus, frequent secondary bacterial infections, less responsive to skin-targeted therapies, more often transformation; peripheral blood involvement, less favorable prognosis than classical MF, estimated 5-year-survival: 74% (≈ tumor stage MF)

Because of distinctive clinicopathologic features (therefore not recognized as MF) and more aggressive clinical behaviour considered as a distinct variant of MF.
Folliculotropic MF

Often not recognized / misdiagnosed histologically
- Folliculotropism; often not epidermotropic.
- Mucinous degeneration (follicular mucinosis).
- Early blastic transformation (often CD30+ blasts)
- Most atypical cells (blasts) in perifollicular; small pleomorphic cells in follicular epithelium (= tumor stage MF).
- More often granulomatous changes, vascular changes, B-cell clusters, admixed plasma cells + eosinophils.
- Diffuse infiltrate; no follicle in sections \(\rightarrow\) DD: PTCL, NOS difficult \(\rightarrow\) keratin staining.

To be discussed in MF / SS
- Pitfalls in diagnosis of early MF.
- Phenotype of MF.
- Folliculotropic MF.
- Definition and prognosis of transformed MF.
- MF versus Sezary syndrome
Large cell transformation in MF (MF-TR)

- Definition:
  - Large cells >25% of total lymphoid infiltrate or
  - Microscopic nodules of large cells.

- Incidence: 5-15%
- Prognostic factor: associated with a poor survival
  - median survival: 12-36 months (→ 100 months)
  - 5-year survival: 11-32% (→ 63%)
Percentage of blast cells < 25% (clusters)

MF + LTR

MF developing skin lesions with a predominance of large T-cells with or without expression of CD30:

- transformed MF

and not

MF developing C-ALCL or PTCL, NOS, etc.

MF + LTR total group (n=100)

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>No</th>
<th>2-yr DSS</th>
<th>5-yr DSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total group</td>
<td>100</td>
<td>65%</td>
<td>40%</td>
</tr>
<tr>
<td>Only skin</td>
<td>75</td>
<td>70%</td>
<td>45%</td>
</tr>
<tr>
<td>LN +/- skin</td>
<td>25</td>
<td>42%</td>
<td>26%</td>
</tr>
<tr>
<td>CD30 +</td>
<td>47</td>
<td>80%</td>
<td>60%</td>
</tr>
<tr>
<td>CD30 -</td>
<td>53</td>
<td>48%</td>
<td>24%</td>
</tr>
<tr>
<td>Folliculotropic MF +</td>
<td>31</td>
<td>56%</td>
<td>29%</td>
</tr>
<tr>
<td>Folliculotropic MF -</td>
<td>69</td>
<td>62%</td>
<td>44%</td>
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</tbody>
</table>

Multivariate analysis for DSS (n=100)

<table>
<thead>
<tr>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD30 expression</td>
<td></td>
</tr>
<tr>
<td>positive</td>
<td>1</td>
</tr>
<tr>
<td>negative</td>
<td>3.1 (1.7-5.8)</td>
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<tr>
<td>Extracutaneous disease at diagnosis MF-TR</td>
<td>0.041</td>
</tr>
<tr>
<td>no</td>
<td>1</td>
</tr>
<tr>
<td>yes</td>
<td>1.8 (1.0-3.2)</td>
</tr>
<tr>
<td>Folliculotropism</td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>1</td>
</tr>
<tr>
<td>positive</td>
<td>1.9 (1.0-3.5)</td>
</tr>
</tbody>
</table>

Multivariate analysis (only skin; n=75)

<table>
<thead>
<tr>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folliculotropism</td>
<td>0.002</td>
</tr>
<tr>
<td>negative</td>
<td>1</td>
</tr>
<tr>
<td>positive</td>
<td>3.5 (1.6-7.7)</td>
</tr>
<tr>
<td>CD30 expression</td>
<td>0.005</td>
</tr>
<tr>
<td>positive</td>
<td>1</td>
</tr>
<tr>
<td>negative</td>
<td>3.4 (1.5-8.1)</td>
</tr>
<tr>
<td>Extent of skin tumors with TR</td>
<td>0.02</td>
</tr>
<tr>
<td>Solitary tumor</td>
<td>1</td>
</tr>
<tr>
<td>Generalized &gt; 5</td>
<td>4.0 (1.2-12.6)</td>
</tr>
</tbody>
</table>

MF + LTR only skin (n=75)

Unfavorable prognostic factors:
1. ≥ 5 skin tumors
2. CD30 negativity
3. Folliculotropic MF

Conclusion: LCT not always associated with a poor prognosis
To be discussed in MF / SS

• Pitfalls in diagnosis of early MF.
• Phenotype of MF.
• Folliculotropic MF.
• Definition and prognosis of transformed MF.
• MF versus Sezary syndrome

Sezary syndrome

• Erythroderma (intensely pruritic).
• Lymphadenopathy
• Clonal T-cell population in peripheral blood (Sezary cells)
• 5-year survival: ca. 20-30%

Histology SS

• May be similar to MF
• Often more monotonous, epidermotropism may be absent (perivascular arrangement).
• In >30% of patients with otherwise classical SS the histologic picture may be non-specific.
• Phenotype: CD3+, CD4+

Programmed Death-1 (PD-1)

• PD-1 (CD279) is a membrane molecule
• Two ligands: PD-L1 (CD274) and PD-L2 (CD273)
• Member of the B7-CD28 family
• Expressed by activated T-cells; in particular by follicular helper T-cells (Tfh cells) in germinal centers.
• PD-1 / PD-L pathway regulates immune responses:
  - Inhibition of T-cell function (proliferation; cytokine production)
• Increased PD-1 expression on CD4+ peripheral blood T-cells in SS versus MF and healthy controls.

Sezary Syndrome

PD-1 expression in skin biopsies MF and SS

<table>
<thead>
<tr>
<th>Type of lymphoma</th>
<th>Number of cases</th>
<th>Neoplastic T-cells PD-1+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Sezary Syndrome</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Mycosis Fungoides</td>
<td>58</td>
<td>6</td>
</tr>
<tr>
<td>MF patch / plaque</td>
<td>28</td>
<td>4</td>
</tr>
<tr>
<td>MF tumor</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Erythrodermic MF</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

One case of SS skin <10% PD-1+ tumor cells, but lymph node >90%
In 5 cases of MF 10-25% of the tumor cells PD-1+.
Conclusions

- PD-1 is highly expressed by neoplastic T cells in SS, but rarely in (erythrodermic) MF (validated by ongoing EORTC study).
- Differential expression of PD-1 between SS and MF adds to an expanding list of differences suggesting that SS is a distinct entity and not merely a leukemic phase or variant of MF.
- Expression of PD-1 in Sezary syndrome
  - may contribute to immune suppression
  - may serve as therapeutic target

WHO-EORTC classification

- Classical CTCL (MF /SS): 51%
- Cutaneous CD30+ LPD: 20%
- Aggressive/uncommon CTCL: 7%
- Cutaneous B-cell lymphoma: 22%

Percentages based on data from the Dutch registry (>3000 patients)

Primary cutaneous CD30+ LPD

Spectrum of primary cutaneous CD30+ LPD:
- Lymphomatoid papulosis (LyP)
- cutaneous anaplastic large cell lymphoma (C-ALCL)
- Borderline cases

Lymphomatoid papulosis

LyP: chronic, recurrent, selfhealing
Primary cutaneous CD30+ LPD

- C-ALCL and LyP overlap (spectrum).
- Definitive diagnosis cannot be made on the basis of histology alone, but is based on clinical presentation and clinical behavior (chronic, recurrent, self-healing).
- **Pathologist:** can only make a diagnosis of primary cutaneous CD30+ LPD.
- **Dermatologist:** crucial role in making correct diagnosis.

Borderline in 1993

Clinical features: LyP; Histology: C-ALCL → LyP

Clinical features: C-ALCL; Histology: LyP → C-ALCL

Borderline in 2000

Somewhere in spectrum cutaneous CD30+ LPD, but we cannot yet make a definite diagnosis at the time of presentation, but probably can within few months. (Bakker MW et al.; Blood 2000)

C-ALCL: diagnostic pitfall

Differential diagnosis of skin infiltrate with histological features of C-ALCL (diffuse infiltrate of CD30+ blast cells):
- C-ALCL
- Lymphomatoid papulosis
- Transformed mycosis fungoides
- Skin localization systemic ALCL (ALK- or ALK+)
- Benign mimickers (viral infections, etc.)

C-ALCL ?

Clinical presentation

Diagnosis: lymphomatoid papulosis
C-ALCL?

MUMC

CD3
CD30

MUMC

CD3

MUMC

MUMC

DD. Diffuse CD30+ infiltrate

+ solitary tumor → C-ALCL
+ waxing and waning of skin lesions → LyP
+ history or concurrent patches/plaques of MF → transformed MF.

Etc.

MUMC

WHO-EORTC classification

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Percentages based on data from the Dutch registry (>3000 patients)
Aggressive / uncommon types of CTCL

- Subcutaneous panniculitis-like T-cell lymphoma
- Extramodal NK/T-cell lymphoma, nasal type
  - Hydroa vacciniforme (like T-cell lymphoma)
- Primary cutaneous PTCL, NOS, rare subtypes:
  - Primary cutaneous gamma/delta T-cell lymphoma
  - Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (provisional)
  - Primary cutaneous CD4-positive small/medium pleomorphic T-cell lymphoma
- PTCL, not otherwise specified (NOS).

RESULTS EORTC WORKSHOP

<table>
<thead>
<tr>
<th></th>
<th>SPTCL-AB (N=64)</th>
<th>SPTCL –GD (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype</td>
<td>TCRbeta1+, CD4-, CD8+, CD56-</td>
<td>TCRdelta1+, CD4-, CD8+, CD56+</td>
</tr>
<tr>
<td>Architecture</td>
<td>Subcutaneous</td>
<td>Subcutaneous a/o epidermal/dermal</td>
</tr>
<tr>
<td>HPS</td>
<td>Rare (17%)</td>
<td>Common (45%)</td>
</tr>
<tr>
<td>5-year survival</td>
<td>HPS+: 91% vs 46%, 11%</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Systemic steroids</td>
<td>Systemic chemotherapy</td>
</tr>
</tbody>
</table>

WHO 2008

SPTCL, CGD-TCL

SPTCL (alpha/beta T-cell phenotype)

SPTCL

CGD-TCL (previously: SPTCL, γ/δ T-cell phenotype)

CGD-TCL (previously: SPTCL, γ/δ T-cell phenotype)
**CGD-TCL** (previously: SPTCL, γ/δ T-cell phenotype)

- βF1 stains α/β+ T-cells
- TCRγ stains γ/δ+ T-cells

**Survival SPTCL with or without HPS**

- Overall survival SPTCL-AB
- Overall survival SPTCL-GD

**Take home message**

**SPTCL(-AB) without HPS:**
- No multiagent chemotherapy
- Immunosuppressive agents
- Solitary lesion: radiotherapy

**Questions:**
- otherwise classical SPTCL, but βF1-, or even TCRγ+?
- SPTCL in young children?

**Extranodal NK/T-Cell lymphoma, nasal type (lethal midline granuloma)**

- Nasopharynx/nasal cavity; less commonly at other sites
- Rare; more common in Asia and central and south America
- EBV-associated (nearly 100%)
- Usually NK-cell phenotype; more rarely a cytotoxic T-cell phenotype
- Very poor prognosis; No major difference between “primary” and “secondary” cutaneous involvement (median survival 24 vs 5 months).
Extranodal NK/T-Cell lymphoma

- CD56
- EBER

Aggressive epidermotropic CD8+ CTCL

- CD8
- TIA-1
- Berti E. et al; Am J Pathol 1999;155: 483-492

Cutaneous PTCL, NOS

Primary cutaneous PTCL, NOS

- Presentation with ulcerating lesions; staging negative; D= 13 months
- Non-epidermotropic; Phenotype: CD3+, CD4-, CD8+, TIA-1++

Summary aggressive CTCL

- Extranodal NK/T, (rare subtypes) of PTCL, NOS:
- Overlapping clinicopathologic features (differential diagnosis requires many antibodies; difficult)
- Poor prognosis in common; no fundamental differences between “primary” and “secondary” cases.
- Should be treated with aggressive chemotherapy by hematologists, but effective therapy not yet available.
- Should always be differentiated from MF !!!
Clinical information at referral

- Male, 68 years.
- In 2000 enlarged inguinal lymph node: Hodgkin lymphoma → chemotherapy + RT → CR
- Rapidly growing tumor on the left buttock for 4 months.
- PA: peripheral T-cell lymphoma (PTCL), NOS
- Staging negative.
- Please advice which type of chemotherapy.

No PTL, NOS, but tumor stage MF?

Additional information

- "eczematous" skin lesions initially on buttocks, later on more generalized.
- Histology patch: classical MF
- Revision lymph node histology (2000): diffuse infiltration by large CD2+, CD30+, PAX-5- T-cells consistent with MF with blastic transformation (CD30+).
- Hodgkin's lymphoma nearly always express PAX-5 (pan-B cell marker).

Diagnosis

Clinical exam: suggestive of MF
Histology: Patch: MF
Diagnosis: MF with blastic transformation
Staging: negative
Treatment: PUVA + RT tumor buttock
Follow-up: minimal skin lesions 62 mo after therapy.

Patient 36 (PA: R04-81303)

- Female, 31 year
- Rapidly growing tumor on the scalp for six weeks.
- Biopsy: aggressive CTCL, probably PTCL, NOS
- History: atopic dermatitis for many years.
- Question: suggestion for treatment of tumor scalp?
**Patient 36 (PA: R04-81303)**

**Patient 36: atopic dermatitis?**

**MF, stage IIB (T3N0M0B0)**

TREATMENT OPTIONS

* Tumor stage MF
  - **First choice of treatment:**
    - total skin electron beam
    - PUVA + RT
  - **Alternatives:**
    - PUVA + IFNa or + retinoids
    - (multi-agent chemotherapy)

* PTCL, unspecified
  - **First choice of treatment:**
    - systemic chemotherapy
    - (results disappointing)
  - **Alternatives:**
    - allogeneic bone marrow transplantation

* If a pathologist makes a diagnosis PTCL, unspecified: always look for and biopsy eczematous or psoriasiform skin lesions to exclude MF!!

**Aggressive / uncommon types of CTCL**

- Subcutaneous panniculitis-like T-cell lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
  - Hydroa vacciniforme (like T-cell lymphoma)
- Primary cutaneous PTCL, NOS, rare subtypes:
  - Primary cutaneous gamma/delta T-cell lymphoma
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  - Primary cutaneous CD4-positive small/medium pleomorphic T-cell lymphoma
- PTCL, not otherwise specified (NOS).

**Definition PCSM-TCL**

CTCL characterized by a predominance of small to medium-sized CD4+ pleomorphic T-cells with clinical features different from MF (WHO-EORTC; WHO 2008).
Clinical features:
- Solitary plaque or tumor (face; neck; upper trunk); generalized lesions less common.
- Favorable prognosis in most cases (5y-surv: 60-80%)

Histologic features:
- Nodular to diffuse dermal infiltrates; no or minimal epidermotropism.
- Small pleomorphic T-cells (<30% large cells).
- Considerable admixture with CD8+ T-cells, B-cells, histiocytes

Phenotype: CD3+, CD4+, CD8-, CD30-, TIA-1-, PD-1+

Genetics: clonal T-cells (DD: pseudo-T-cell lymphoma)

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

OR

Pseudo-T-cell lymphoma (Atypical lymphoid hyperplasia)?
Pseudo-T cell lymphoma

Lymphomatoid reactions (pseudo-T cell lymphoma)
- Histologic features suggestive of CTCL.
- Clinical features not consistent with CTCL.
- Actinic reticuloid (CD8+ !!)
- Lymphomatoid drug reactions
- Lymphomatoid contact dermatitis
- Idiopathic pseudo-T cell lymphoma (>95%)
  - Band-like pattern: resembles plaque MF
  - Nodular pattern: resembles tumor MF or PTCL, NOS

Differentiation from CTCL (Bakels V.; Am J Pathol, 1997):
- No marker loss
- No clonality (Southern blot).

New findings:
- atypical T-cells in these pseudo-T-cell lymphomas consistently express PD-1, often in combination with bcl-6 and CXCL13 (markers of follicular helper T-cells (TFH cells)).
- Most pseudo-T-cell lymphomas including drug-associated cases show clonal TCR gene rearrangements using the Biomed 2 protocol.
Pseudo T-cell Lymphoma -- MF-like pattern

Pseudo T-cell Lymphoma -- nodular pattern

PD-1 staining in PCSM-TCL/pseudo-T

PCSM-TCL or pseudo-T cell lymphoma?

- Most PCSM-TCL show clinicopathologic features of the nodular pseudo-T-cell lymphomas from the past:
  - Presentation with solitary tumor mostly in head and neck region.
  - Minor proportion of large CD4+ T-cells (TFH phenotype)
  - Many admixed CD8+ T-cells, B-cells and histiocytes.
- Demonstration of clonality in such cases has been instrumental to consider these cases now as PCSM-TCL.
- Recognition of such cases is important → no staging; no aggressive therapy
- CD4+ S/M pleomorphic CTCL that do not meet above criteria are rare.

<table>
<thead>
<tr>
<th>Type of lymphoma</th>
<th>Number of cases</th>
<th>Neoplastic T cells</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycosis fungoides</td>
<td>58</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>PTCL, NOS</td>
<td>15</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>PCSM-TCL / pseudo-T-cell lymphoma</td>
<td>24</td>
<td>24</td>
<td>100</td>
</tr>
</tbody>
</table>

PCSM-TCL:
- Band-like pattern: 8/10 clonal (including one lymphomatoid drug eruption)
- Nodular pattern: 9/12 clonal TCR gene rearrangement

PCSM-TCL or pseudo-T cell lymphoma?

- Preferred term for both cases with:
  - Cause known and unknown (e.g., drug-associated)
  - Band-like and nodular pattern
  - Clonal or nonclonal T-cells

**Primary cutaneous CD4+ small/medium pleomorphic T-cell proliferation**