Peripheral T-cell lymphomas
(Cutaneous)

Alma Mater
Studiorum
1088 d.C.
## MATURE T-CELL AND NK-CELL NEOPLASMS

<table>
<thead>
<tr>
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<td>Lymphomatoid papulosi</td>
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<td>Peripheral T-cell lymphoma, NOS</td>
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<td>Anaplastic large cell lymphoma, ALK negative</td>
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</tbody>
</table>
Primary cutaneous peripheral T-cell lymphomas, rare subtypes

A

Primary cutaneous gamma-delta T-cell lymphoma

B

C

D
Prognosis and predictive factors
PCGD-TCL are resistant to multi-agent chemotherapy and/or radiation and have a poor prognosis with a median survival of approximately 15 months [2254, 2408]. Patients with subcutaneous fat involvement tend to have a more unfavourable prognosis as compared with patients with epidermal or dermal disease only [2254].

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical features</th>
<th>CD3, CD4, CD8</th>
<th>Cytotoxic molecules*</th>
<th>CD56</th>
<th>EBV</th>
<th>T-cell receptor</th>
<th>Lineage</th>
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</thead>
<tbody>
<tr>
<td>SPTCL</td>
<td>Tumours, extremities and trunk</td>
<td>+, -, +</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>R</td>
<td>T-cell</td>
</tr>
<tr>
<td>Primary cutaneous γδ TCL</td>
<td>Tumours, plaques, ulcerated nodules</td>
<td>+, -, /+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>R</td>
<td>T-cell</td>
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</tbody>
</table>
Primary cutaneous aggressive epidermotropic CD8 positive cytotoxic T-cell lymphoma

These lymphomas often have an aggressive clinical course with a median survival of 32 months (209). There is no difference in survival between cases with a small or large cell morphology (174).

The tumour cell have a βF1+, CD3+, CD8+, granzyme B+, perforin+, TIA1+, CD45RA+/-, CD45RO-, CD2-/+, CD4-, CD5-, CD7+/- phenotype (12, 174, 209, 1410, 1934).
Primary cutaneous small/medium CD4 positive T-cell lymphoma
Primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoma: a clonal T-cell lymphoproliferative disorder with indolent behavior

Karen L Grogg, Sungmi Jung, Lori A Erickson, Rebecca F McClure and Ahmet Dogan

Department of Laboratory Medicine and Pathology, Division of Anatomic Pathology, Mayo Clinic, Rochester, MN, USA

Primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoma, a provisional entity in the 2005 WHO-EORTC classification for cutaneous lymphomas, is not well characterized. Fifteen cases meeting the definition of this entity were identified. Fourteen represented solitary lesions on the head/neck ($n=9$), upper extremity ($n=4$), or trunk ($n=1$). One patient presented with multiple lesions on the trunk and extremities. Histologically, the infiltrate showed a nodular pattern in the dermis and subcutis without epidermotropism, and had a polymorphous composition with a predominance of small to medium-sized CD4-positive T cells. Most cases showed normal T-cell antigen expression; diminished/absent expression of CD7 was seen in three cases and CD2 expression was absent in one case. All cases showed a notable reactive infiltrate including frequent B cells, plasma cells, and histiocytes. Clonal TCR gene rearrangements were detected in each case. No clonal Ig gene rearrangements were detected. Out of the 11 patients with follow-up, none showed systemic disease. The majority resolved without relapse, one without treatment, four with excision, and four with radiation therapy. One patient developed local recurrence. The patient with multiple lesions had disease progression despite chemotherapy and stem cell transplant. These cases highlight the polymorphous histology and prominent reactive B-cell component of this entity. Diagnosis requires molecular genetic analysis, as prominent cytologic atypia and immunophenotypic aberrancy are rare. The differential diagnosis includes reactive lymphoid hyperplasia, mycosis fungoides and cutaneous B-cell lymphomas. In patients with isolated cutaneous lesions, the indolent behavior of this rare T-cell neoplasm should be recognized to avoid unnecessary treatment.

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PRIMITIVITA' CUTANEA

CRITERI MAGGIORI

• Stadiazione clinica, compresa biopsia osteo-midollare!

• “Follow-up” di almeno 6 mesi (criterio controverso); in alcuni casi eventuali linfonodi loco regionali non modificano lo stadio pregiudizievole)

CRITERI MINORI

• Immunofenotipo?

• Profilo molecolare?
PROCEDURE DIAGNOSTICHE

- Esame Clinico
- Procedure bioptiche
- Stadiazione

Jusepe de Ribera, 1628
PRELIEVI BIOPTICI

- Agoaspirati
- Apposizioni
- "Shave biopsy"
- "Punch biopsy" (solo in alcuni casi)
- Biopsia escissionale!
MF CLASSICA: Definizione

- Linfoma T cutaneo, epidermotropo, a piccole-medie cellule con nuclei irregolari, cerebriformi.
- Definizione limitata alla forma classica di “Alibert-Bazin”, a decorso clinico indolente con lenta progressione da chiazze a placche ed eventualmente tumori (+/- spread viscerale).
- 1/3 dei linfomi cutanei.
- Adulti-anziani (30-60aa); sporadicamente bambini e adolescenti; M/F 2:1.
STADIAZIONE

- Classico Alibert-Bazin (MF):
  1. stadio eczematoso
  2. stadio in placca
  3. stadio tumorale

- Stadio TNM
  T percentuale di superficie cutanea coinvolta (T1-4)
  N linfonodi (N0-3);
  M disseminazione viscerale (MO-1)

- TBI (Tumor Burden Index):
  stima della massa tumorale su percentuale della superficie cutanea totale coinvolta

Indicazioni non univoche!

FENOTIPO

- 80-90% MF fenotipo “T-CD4+ con espressione di antigeni T-correlati; rare forme CD8+ citotossiche.

- 3/4 dei casi perdita uno o più antigeni T: CD7 (64%); CD3 (59%); CD5 (40%); CD2 (14%)

- Perdita del CD7 anche in alcune condizioni reattive

- Assenza di monoclonalità nel 50% degli stadi precoci
• Diagnosi semplice in stadi avanzati di malattia

• In fase precoce "eczematosa" diagnosi difficile, sia clinicamente che istologicamente

• Morfologia, ICH e biologia molecolare anche combinati possono non fornire risposte definitive

• Conseguenza: rischio di "over-diagnosi di MF"

• In alcuni casi, solo il "follow-up" e ripetute biopsie forniscono la diagnosi di certezza
Algoritmico diagnostico per MF iniziale
(la diagnosi richiede un totale di almeno 4 punti)

**CLINICA**
- Base
  - Chiazze persistenti e/o progressive
- Addizionali
  - Non fotoesposto
  - Variazione misura/aspetto
  - Poichiloderma

**ISTOLOGIA**
- Base
  - Infiltrato linfoide superficiale
- Addizionali
  - Epidermotropismo senza spongiosi
  - Atipia linfoide

**FENOTIPO**
- T CD2+, CD3+ e/o CD5+ <50%
- T CD7+ <10%
- Discordanza fenotipica tra infiltrato T epidermico e dermico

**MOLECOLARE**
- Riarrangiamento clonale TCR


Utile, ma in alcuni casi solo il “follow-up” e ripetute biopsie consentono la diagnosi!
**MF follicolare (+/- mucinosi)**

- Adulti/anziani; testa e collo
- Infiltrato follicolare, piuttosto che epidermico; possibile deposizione di mucina entro/intorno follicoli piliferi

**Granulomatous Slack Skin (GSS)**

- 3°/4° decade; bianchi; pieghe inguinali, ascellari, poi lesioni cutanee estese
- Infiltrato di piccoli linfociti; denso in fase avanzata, con cellule giganti.
- Lievemente meno favorevole rispetto MF classica
Syringotropic Mycosis Fungoides: A Rare Variant of the Disease With Peculiar Clinicopathologic Features

Alessandro Pileri, MD, Fabio Facchetti, MD, Arno Rütten, MD, Giuseppe Zuaniani, MD, Sebastiano Boi, MD, Regina Fink-Puches, MD, and Lorenzo Cerroni, MD

Expression of functional biomarkers in mycosis fungoides. Immunohistochemical study of eighteen cases.

Alessandro Pileri§*, Claudio Agostinelli*, Simona Righi, Francesco Bacci, Pier Paolo Piccaluga, Elena Sabattini, Annalisa Patrizi§, and Stefano A. Pileri.

*These authors equally contributed.

From the Units of Dermatology§ and Haematopathology – Bologna University School of Medicine – St. Orsola Hospital – Via Massarenti 3-9 – 40138 Bologna (Italy)
roughly 3 weeks later by rashes and plaques disappearing from the skin. The researchers also showed that Sézary syndrome patients treated with alemtuzumab had surprisingly few infections. “And that’s convincing evidence that resident T cells in skin [which survive alemtuzumab therapy] provide an important barrier against pathogens,” Clark said. What’s more, a lack of lung and gastrointestinal infections after treatment, coupled with unpublished findings from Clark’s laboratory, indicate that alemtuzumab—though generally immunosuppressive—spares some tissue-resident T cells within the body, suggesting that the drugs targeting circulating T cells in blood only.

Clark’s colleague Thomas Kupper, M.D., chair of dermatology at Brigham and Women’s Hospital and a professor at Harvard Medical School, emphasized that although alemtuzumab can be dramatically effective, it isn’t a cure; Sézary syndrome eventually comes back after treatment. But Kupper and Clark are now using the drug to clear leukemic illness before allogeneic stem cell transplantation. “We increasingly think that if we can clear, or mostly clear, patients with aggressive disease, then it makes sense to intervene with a transplant sooner than later,” Kupper said. “The key is to make sure we don’t give transplants to patients who wouldn’t progress without that procedure anyway.” While patients include those with substantial disease burden who achieve only short-term responses to therapy, Kupper explained, whereas those who go into complete remission after photochemotherapy, that is, psoralen plus ultraviolet-A therapy (PUVA), might continue to do well indefinitely, such that transplantation is appropriate.

An expert in allogeneic stem cell transplant, Ducic added that appropriate candidates should be young and able to tolerate the procedure’s challenging side effects, which can require 100 days of hospitalization. “We’ve been doing this since 2001, and most of our Sézary syndrome patients are either cured or in complete remission,” Ducic said. “We’re monitoring them, and we hope this is a durable response.”

**Better Results in Clinical Trials**

Ducic’s view is that better treatment options for CTCL could involve combination therapy. One example, she said, combines platletetrate (Folotyn) and bexarotene (Targretin) in an ongoing, multicenter phase III clinical trial. Folotyn’s manufacturer, Allos Therapeutics in Westminster, Colo., announced interim results for the trial in January. According to the company, among 10 patients with relapsed or refractory CTCL in the treatment group, six achieved positive clinical responses—five partial and one complete. Ducic, a principal investigator in the trial, points out that this result came with minimal toxic effects.

Another new and important treatment, she said, is brentuximab vedotin (Adcetris). The drug is approved now in the U.S. for relapsed cases of Hodgkin’s lymphoma in addition to systemic anaplastic large-cell lymphoma (ALCL), both CD30-associated cancers. MF isn’t typically CD30 positive, though sometimes it progresses to a CD30-positive form of cutaneous ALCL. Brentuximab targets CD30, so this drug is now undergoing investigator-initiated phase II studies for both illnesses—Ducic leads the cutaneous ALCL trial, whereas Youn Kim, M.D., professor of dermatology at Stanford University School of Medicine, heads the trial for MF. Ducic presented interim results at the T-Cell Lymphoma Forum, held Jan. 26–28, 2012, in San Francisco. Eleven of 17 evaluable patients achieved objective responses; she said, including seven complete responses and four partial responses. Brentuximab’s manufacturer, Seattle Genetics in Bothell, Wash., is now planning a phase III trial in CTCL to begin later this year.

Ducic points out that every approval (or pending approval) for CTCL involves a biologic rather than a chemotherapeutic agent. That’s important, she said, given the need to avoid immunosuppression and the potentially lethal threat of infectious complications in CTCL patients. Unlike chemotherapy, which tends to be broadly immunosuppressive, biologic agents induce immunologic effects selectively, as indicated by alemtuzumab’s selective targeting of circulating T cells in blood. Doctors sometimes mistake MF for psoriasis and give immunosuppressive tumor necrosis factor inhibitors that can dramatically worsen the illness. That’s particularly unfortunate, Ducic said, given that often, the body’s CD8 T-cell response will keep MF in check for long durations. “We’ve also heard of CTCL patients progressing rapidly after cyclosporin treatment, presumably because that also compromises T-cell activity,” Kupper said.

Foss points out that CTCL has won a remarkable number of new-drug approvals given its orphan disease status. And as more such new molecular pathways also look promising, she said, notably the JAK–STAT signaling pathway, which appears to have broad regulatory actions on T-cell biology. Now a new U.S. Cutaneous Lymphoma Consortium, headed by Eloise Olsen, M.D., professor of dermatology and oncology at Duke University Medical Center in Durham, N.C., is developing a national patient registry that will record disease stage, treatment, and response data for all newly diagnosed patients. “We’re also looking into conducting clinical trials and studies that will relate molecular biomarkers to clinical data,” Olsen said. The consortium’s emphasis on uniform staging, evaluation, and classification is particularly important, Olsen added, given that clinical guidelines for characterizing CTCL have become available.
SINDROME DI SÉZARY

• Linfoma T a fenotipo maturo (“peripheral”) con eritrodermia generalizzata, linfodenopatie e linfociti T neoplastici nel periferico.

• Diagnosi richiede la presenza nel periferico di almeno 1000 Sézary cells/mm³

• Cellule T con nuclei cerebriformi (cellule di Lutzner) o grandi cellule (Sézary) con frequente perdita di CD7 e CD26

• Variante aggressiva della MF
Diagnosi Linfomi Cutanei T

Step 1
CTCL primitivi
→ MF e varianti

Disordini Linfoproliferativi Cutanei Primitivi CD30+
- Papulosi Linfomatoide
- Casi borderline
- Linfoma a grandi cellule anaplastiche

Step 2
CD30+

Step 3
CTCL primitivi non MF/SS CD30-
→ T-Pleomorfo
→ T-immunoblastico

Forme rare

Dutch Cutaneous Lymphoma Study Group propose un algoritmo diagnostico per i CTCL che fondato sull’impiego dell’immunocolorazione con l’anti-CD30

Primary Cutaneous CD30-Positive Large Cell Lymphoma: Definition of a New Type of Cutaneous Lymphoma with a Favorable Prognosis
A European Multicenter Study of 47 Patients
Rob C. Beljaards, M.D.,* Peter Kaudewitz, M.D.,† Emilio Berti, M.D.‡
Raffaele Gianotti, M.D.¶ Christine Neumann, M.D.¶ Renato Rosso, M.D.,∥
Marco Paulli, M.D.,∥ Chris J. L. M. Meijer, M.D.,§ and Rein Willemsen, M.D.*
Disordini Linfoproliferativi Cutanei Primitivi CD30+ (PCLDs)

BACKGROUND (1989)


![Graph showing survival rates for different conditions](image)
PAPULOSI LINFOMATOIDE

“A self-healing, rhythmic, paradoxical eruption histologically malignant but clinically benign” (MacCaulay, 1968)

• 30-40 aa, rara nei bambini; non sintomi sistemici
• Numerose lesioni papulo-nodulari (0,2-1 cm) non pruriginose; regressione spontanea
• Tronco, arti; risparmiati palmo mani e pianta piedi
• “Survival” 100% a 5aa
**LyP Classica: morfologia**

Infiltrato dermico “V-shaped” con sparse grandi cellule atipiche CD30+, più spesso a fenotipo T CD4+ e con espressione di molecole citotossiche (TIA-1, Perforina, Granzyme-B)
Biologia Molecolare

- Riarrangiamento monoclonale TCR < 50% con PCR tradizionale, > 90% con PCR su LMC
- Negatività per t(2;5) e ALK/CD246

Terapia/Prognosi

- PUVA, no CHT!
- Aumentato rischio di linfoma (?)
- Sopravvivenza 100% a 5aa!
A Variant of Lymphomatoid Papulosis Simulating Primary Cutaneous Aggressive Epidermotropic CD8+ Cytotoxic T-cell Lymphoma. Description of 9 Cases

Andrea Saggini, MD,*‡ Andrea Gulia, MD,*‡ Zsolt Argenyi, MD,§ Regina Fink-Puches,* Amelia Lissia, MD,∥ Mario Magaña, MD,¶ Luis Requena, MD,# Ingrid Simonitsch, MD,** and Lorenzo Cerroni, MD*

Abstract: Lymphomatoid papulosis (LyP) is a recurrent, self-healing eruption belonging to the spectrum of cutaneous CD30+ lymphoproliferative disorders. Three main histologic subtypes of LyP are recognized: type A (histiocytic), type B (mycosis fungoides—(MF)-like), and type C (anaplastic large cell lymphoma—like). We reviewed 26 biopsies from 9 patients (M:F = 6:3; median age: 29; mean age: 27.2; age range: 10 to 38) who presented with clinical features typical of LyP but with histopathologic aspects that resembled primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. In all but 1 case atypical lymphoid cells showed expression of CD30, and in 8 of 9 cases a T-cell cytotoxic phenotype could be observed (βF1+, CD3+, CD4−, CD8+). Expression of at least 1 cytotoxic marker (TIA-1, granzyme B) was observed in all cases. Polymerase chain reaction analysis of the T-cell receptor genes revealed a monoclonal rearrangement in 2 of 5 cases tested. Follow-up data available for 8 patients (mean follow-up time: 84 mo; median: 32.5 mo; range: 1 to 303 mo) revealed that none of them developed systemic involvement or signs of other cutaneous lymphomas. This cytotoxic variant of LyP may be histopathologically indistinguishable from primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, and may be the source of pitfalls in the diagnosis and classification. We propose the term LyP type D for this unusual variant of the disease. Accurate clinicopathologic correlation is required in this setting, with crucial implications regarding prognosis and management of patients.

Key Words: lymphomatoid papulosis, primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, mycosis fungoides, cytotoxic lymphoma, cutaneous T-cell lymphoma

(Am J Surg Pathol 2010;34:1168–1175)
La natura della LyP rimane oggetto di dibattito: non sono disponibili risposte definitive

- Decorso benigno praticamente in tutti i pazienti
- A rigore quindi non si tratta di linfoma, ma piuttosto di un disordine linfoproliferativo atipico eventualmente clonale ma ad incerto potenziale di malignità.
ALCL Primitivi Cutanei CD30+

• Noduli singoli/multipli con occasionale regressione ma più spesso persistenti

• Adulti e anziani (età media 60aa); M:F=1,5:1

• Tronco, volto, estremità

• Raro interessamento nodale o viscerale; sintomi B (nelle forme generalizzate)
• Infiltrato dermo-ipodermico nodulare/diffuso

• Grandi cellule con nuclei a ferro di cavallo, sparse cellule simil-RS e “Hodgkin-like”

• Fenotipo T CD4+ e riarrangiamento per TCR nella maggior parte dei casi; positività per le molecole citotossiche; no t(2;5); ALK/CD246-
Brief report

Discovery of recurrent t(6;7)(p25.3;q32.3) translocations in ALK-negative anaplastic large cell lymphomas by massively parallel genome sequencing

Andrew L. Feldman,1 Ahmet Dogan,1 David I. Smith,1 Mark E. Law,1 Stephen M. Ansell,2 Sarah H. Johnson,3 Julie C. Porcher,2 Nazan Özsan,4 Eric D. Wieben,5 Bruce W. Eckloff,5 and George Vasmatzis9

1Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; 2Division of Hematology, Mayo Clinic, Rochester, MN; 3Department of Molecular Medicine and Center for Individualized Medicine, Mayo Clinic, Rochester, MN; 4Department of Pathology, Ege University, Izmir, Turkey; and 5Advanced Genomics Technology Center, Mayo Clinic, Rochester, MN

The genetics of peripheral T-cell lymphomas are poorly understood. The most well-characterized abnormalities are translocations involving ALK, occurring in approximately half of anaplastic large cell lymphomas (ALCLs). To gain insight into the genetics of ALCLs lacking ALK translocations, we combined mate-pair DNA library construction, massively parallel (“Next Generation”) sequencing, and a novel bioinformatic algorithm. We identified a balanced translocation disrupting the DUSP22 phosphatase gene on 6p25.3 and adjoining the FRA7H fragile site on 7q32.3 in a systemic ALK-negative ALCL. Using fluorescence in situ hybridization, we demonstrated that the t(6;7)(p25.3;q32.3) was recurrent in ALK-negative ALCLs. Furthermore, t(6;7)(p25.3; q32.3) was associated with down-regulation of DUSP22 and up-regulation of MIR29 microRNAs on 7q32.3. These findings represent the first recurrent translocation reported in ALK-negative ALCL and highlight the utility of massively parallel genomic sequencing to discover novel translocations in lymphoma and other cancers. (Blood. 2011;117(3):915-919)

Table 1. Genetic characteristics of 29 ALK-negative ALCLs with 6p25.3 rearrangements

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age, years</th>
<th>Sex</th>
<th>Disease distribution</th>
<th>Breakpoint on 6p25.3*</th>
<th>7q32.3 BAP FISH</th>
<th>t(6;7) D-FISH</th>
<th>No. of fusion signals</th>
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<td>46</td>
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<td>Systemic</td>
<td>DUSP22</td>
<td>Break</td>
<td>Fusion</td>
<td>1 or 2</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>Male</td>
<td>Cutaneous</td>
<td>DUSP22</td>
<td>Break</td>
<td>Fusion</td>
<td>1</td>
</tr>
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<td>6</td>
<td>68</td>
<td>Male</td>
<td>Cutaneous</td>
<td>DUSP22</td>
<td>Break</td>
<td>Fusion</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>Female</td>
<td>Systemic</td>
<td>DUSP22</td>
<td>Break</td>
<td>Fusion</td>
<td>1</td>
</tr>
<tr>
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<td>Systemic</td>
<td>DUSP22</td>
<td>Break</td>
<td>Fusion</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>50</td>
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<td>DUSP22</td>
<td>Break</td>
<td>Fusion</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>51</td>
<td>Male</td>
<td>Systemic</td>
<td>IRF4</td>
<td>Break</td>
<td>Fusion</td>
<td>1</td>
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<tr>
<td>11</td>
<td>85</td>
<td>Male</td>
<td>Cutaneous</td>
<td>Incomerminate</td>
<td>Break</td>
<td>Fusion</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>77</td>
<td>Male</td>
<td>Cutaneous</td>
<td>IRF4</td>
<td>Break</td>
<td>Tissue depleted</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>65</td>
<td>Male</td>
<td>Systemic</td>
<td>Incomerminate</td>
<td>Break</td>
<td>Tissue depleted</td>
<td>—</td>
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</table>
Lesioni “Borderline”

- Caratteristiche clinico-istologiche al confine tra LyP ed ALCL CD30+

- Lesioni papulo-nodulari, solitarie; possibile regressione spontanea

- Decorso favorevole, simile a quello della LyP
• **CTCL**: ampio spettro di entità
• **Necessaria stretta collaborazione tra DERMATOLOGO & PATOLOGO poiché...**

“At any rate...the fate of the patient is what counts after all”

PP Piccaluga, E Sabattini, F Bacci, C Agostinelli, M Rossi, C Sagramoso, S Righi, A Gazzola, T Sista, M Piccioli, MR Sapienza, C Mannu, F Fuligni, F Sandri, P Artioli, G De Biase, G Da Pozzo, C Tigrini, M Monari and D Bignami