Advances in cutaneous T-cell lymphomas

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Kempf and Pfaltz
Histological Diagnostics
Zürich
Advances in cutaneous T-cell lymphomas

- **Mycosis fungoides**
  - New clinical and histological manifestations
  - Early MF – new phenotypic markers

- **Sézary syndrome**
  - Differentiation from erythrodermic inflammatory dermatoses

- **Cutaneous CD30+ lymphoproliferative disorders**
  - Cutaneous anaplastic large-cell lymphoma - genetics
  - Lymphomatoid papulosis – new histological and genetic types

- **Cutaneous CD8+ lymphoproliferations**
  - The indolent forms still looking for classification
  - CD8+ granulomatous CTCL and immunodeficiency
Mycosis fungoides

Patch → Plaque → Tumor
## MF evolution

<table>
<thead>
<tr>
<th>Condition</th>
<th>5 years</th>
<th>10 years</th>
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<tbody>
<tr>
<td>Limited patches (&lt;10% BS)</td>
<td>100%</td>
<td>97%</td>
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<tr>
<td>Generalized Patches / Plaques</td>
<td>96%</td>
<td>83%</td>
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<tr>
<td>Tumor stage</td>
<td>80%</td>
<td>42%</td>
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<tr>
<td>LN involvement</td>
<td>40%</td>
<td>20%</td>
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<tr>
<td>Visceral involvement</td>
<td>0%</td>
<td>0%</td>
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</table>

*van Doorn et al. Arch Dermatol 2000*

309 pat. with MF stage I – IV
Mycosis fungoides - variants

5-year-survival rates in MF

- Classic MF (patch/plaque) 96 – 100%
- Syringotropic MF 98-100 %
- Unilesional MF 100%
- Granulomatous MF 66 - 68%
- Folliculotropic / follicular MF 62 - 74%
Follicular mycosis fungoides

Patches and plaques
with loss of hairs

Dense perifollicular and
folliculotropic infiltrates

Small to medium-sized
lymphocytes
Follicular MF

Absence of follicular mucin (30%)

Lack of epidermotropism into the interfollicular epidermis (60% of pat.)
Spiky MF – a manifestation of follicular MF


Spiky follicular mycosis fungoides: a clinicopathologic study of 8 cases.

Abstract

BACKGROUND: The early stages of follicular mycosis fungoides (FMF) have not previously been described in the literature.

OBJECTIVE: Our goal was to better categorize the clinicopathological features of early stages of FMF.

METHODS: The clinical notes of patients with a diagnosis of FMF seen during the previous 5 years were reviewed in search of any cases that at presentation had only hyperkeratotic follicular lesions.

RESULTS: 8 patients (5 male, 3 female) with a mean age of 55.4 years were collected. Noteworthy, FMF was not a clinical consideration in any of these patients at first. Patients presented with disseminated, slightly erythematous, hyperkeratotic, spiky follicular papules which, histopathologically, showed hyperkeratotic columns protruding from follicular plugging in concert with selective infiltration of the infundibular epithelium by atypical, mostly CD4+, lymphocytes. T-cell clonality was demonstrated in 4/8 cases. The mean duration of the lesions before diagnosis was 17.1 months. The course was indolent in most of cases (median follow-up: 18 months), whilst progression to overt FMF was noted in 2 patients.

LIMITATIONS: The number of cases is small and follow-up relatively short.

CONCLUSIONS: Spiky FMF is a deceptive clinicopathologic presentation of FMF that has been poorly described and that can mimic numerous follicular disorders.
Spiky MF

Keratosis pilaris like features („spikes“)  Follicular plugging
Spiky MF

Follicular mucinosis

Nuclear atypia
Spiky follicular mycosis fungoides: a clinicopathologic study of 8 cases.


Author information

Anatomic Pathology, Azienda Ospedaliera Città della Salute e della Scienza, Turin, Italy.

<table>
<thead>
<tr>
<th>Patient n, Age(y), sex</th>
<th>Medical history</th>
<th>Duration before diagnosis (m)</th>
<th>Site of involvement</th>
<th>Clinical diagnosis</th>
<th>Follow-up (m)</th>
<th>PCR</th>
<th>Immunophenotype of follicular lymphocytes</th>
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<tr>
<td>1 (71) M</td>
<td>Hypertension</td>
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<td>Trunk</td>
<td>Follicular keratosis, Lichen planopilaris,</td>
<td>60 AWD³</td>
<td>monoclonal</td>
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<td>2 (61) F</td>
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<td>36</td>
<td>Trunk</td>
<td>Lichen nitidus</td>
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<td>3 (54) F</td>
<td>None</td>
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<td>Face, trunk, upper and lower extremities</td>
<td>Follicular keratosis</td>
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<td>CD3+, CD4+, CD8-, CD5-/dim, CD7-, CD26+, CD30+</td>
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<td>4 (46) M</td>
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<tr>
<td>5 (49) M</td>
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<td>18</td>
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<td>Follicular keratosis</td>
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<td>monoclonal</td>
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</tr>
<tr>
<td>6 (48) M</td>
<td>None</td>
<td>unknown</td>
<td>Trunk, extremities</td>
<td>PRP, psoriasis, secondary syphilis</td>
<td>12 AD⁰*</td>
<td>monoclonal</td>
<td>CD3+, CD4-, CD8+, CD7+, CD26-, CD30±</td>
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</table>
Juvenile mycosis fungoides: Cutaneous T-cell lymphoma with frequent follicular involvement

Ermilia Hodak, MD, Iris Amitay-Laish, MD, Moshe Feinmesser, MD, Batya Davidovici, MD, MSc, Michael David, MD, Alex Parnes, MD, MHA, Felix Pudlowski, MD, Isaac Yaniv, MD, Gali Arvahami, MD, and Dan Ben-Amitai, MD
Petach Tikva, Ramat Gani, Tel Aviv, and Beer-Sheva, Israel

Background: The literature on mycosis fungoides (MF) in children/adolescents is sparse.

Objective: We sought to evaluate the characteristics of juvenile MF in a large cohort.

Methods: Data were collected on all patients with MF, aged 18 years or younger at the time of clinicopathologic diagnosis, who attended the Rabin Medical Center Dermatology Department, Petach Tikva, Israel, between 1994 and 2012 and were followed up prospectively.

Results: There were 50 patients (35 male; mean age 11.4 years at diagnosis); 18 (36%) had Fitzpatrick skin type IV or higher. All were given a diagnosis of early-stage disease (IA-IIB) except 1 (tumor stage, IIB). Eight had classic MF lesions only and 42 had other variants, alone or in combination; these were mainly hypopigmented MF (n = 29) and cases with subtle but clear clinicopathologic features of folliculotropic MF (FMF) (n = 18). Among the various skin-targeted therapies, psoralen plus ultraviolet A (systemic/bath) proved beneficial for FMF. During a follow-up period of 0.25 to 15 years (mean 4.5), 2 patients progressed from stage IA to IB or IIA.

Limitations: Relatively short follow-up is a limitation.

Conclusions: This case series shows that FMF is not uncommon in children and adolescents. It is characterized by more superficial clinical features and less heavy perifollicular lymphocytic infiltrates than adult FMF, and responds well to psoralen plus ultraviolet A. The prognosis of childhood FMF remains unclear. (J Am Acad Dermatol 2014;70:985-1001.)

Keywords: children; cutaneous lymphoma; folliculotropic mycosis fungoides; juvenile; mycosis fungoides; pediatric.

Mycosis fungoides (MF), the most common cutaneous T-cell lymphoma, is diagnosed after 50 years of age in about 75% of cases. North American and European studies report a 0% to 5% rate of occurrence before age 20 years; juvenile MF is more common in Asian countries with a prevalence of up to 25%. The clinicopathologic manifestations of MF in children and adolescents are similar to adults, but

Abbreviations used:
EORTC: European Organization for Research and Treatment of Cancer
FMF: folliculotropic mycosis fungoides
FST: Fitzpatrick skin type
MF: mycosis fungoides
NBUVB: narrowband ultraviolet B
PUVA: psoralen plus ultraviolet A
UV: ultraviolet
WHO: World Health Organization
Follicular mycosis fungoides

Mycosis fungoides
Follicular mycosis fungoides

2001

2002
7 patients reported in the literature: 5 men, 2 women
Mean age at dx: 38 years (2 pats. <18 years)
Limb > trunk > face

Atypical CD4+ lymphocytes
Monoclonal T-cells in 3/6 cases

Excellent prognosis with no multifocal or extracutaneous spread
Unilesional follicular mycosis fungoides: report of two cases with progression to tumor stage and review of the literature

Mycosis fungoides (MF) is the most common type of cutaneous lymphoma and has protean clinicopathological manifestations. Follicular or folliculotropic MF (FMF) is a rare variant, which histopathologically is characterized by pronounced folliculotropism of neoplastic T cells, with or without follicular mucinosis, and clinically by an impaired prognosis compared to classic MF. In contrast, unilesional MF is a very rare variant with an excellent prognosis, with a single case of large-cell transformation reported to date. The combination of folliculotropic and unilesional MF is very unusual, with only two cases reported to date. Here we report two patients with unilesional folliculotropic MF with progression to tumor stage in both patients. To the best of our knowledge, this is the first report on the disease evolution with large-cell transformation and progression of unilesional FMF. Complete remission was achieved by local radiation therapy in both patients. The differential diagnoses, classification and implications for the treatment of unilesional FMF as well as the pertinent literature are discussed.

Keywords: cutaneous lymphoma, dermatopathology, mycosis fungoides


Histologic and immunohistochemical features, n (%)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Count</th>
<th>Percentage</th>
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<tbody>
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<td>Syringotropism</td>
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<td>100</td>
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<tr>
<td>Moderate</td>
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<td>79</td>
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<tr>
<td>Prominent</td>
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<td>21</td>
</tr>
<tr>
<td>Epidermotropism</td>
<td>16</td>
<td>84</td>
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<tr>
<td>Folliculotropism</td>
<td>13</td>
<td>68</td>
</tr>
<tr>
<td>Follicular mucinosis</td>
<td>6</td>
<td>32</td>
</tr>
<tr>
<td>Hyperplastic eccrine structures</td>
<td>12</td>
<td>63</td>
</tr>
<tr>
<td>Moderate</td>
<td>8</td>
<td>42</td>
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<tr>
<td>Prominent</td>
<td>4</td>
<td>21</td>
</tr>
<tr>
<td>Dense nodular infiltrates around the eccrine glands</td>
<td>11</td>
<td>58</td>
</tr>
<tr>
<td>CD4⁺ tumor infiltrate</td>
<td>19</td>
<td>100</td>
</tr>
</tbody>
</table>

Primary cutaneous lymphomas (PCL) are a heterogeneous group of malignancies of skin-homing lymphocytes. Mycosis fungoides (MF) accounts for approximately 50% of all primary cutaneous lymphomas (PCL). The classic type of T-cell lymphoma in the presence of atypical forms and nuclei, and the evel.
Syringotropic MF

K11-206
Mycosis fungoides - Phenotypes

T helper cells

CD3+ CD4+ CD8-
CD3+ CD4- CD8+
CD3+ CD4+ CD8+
CD3+ CD4- CD8-
CD3+ CD4+ CD56+

In all stages, esp. in tumor stage CD30+

Phenotype in MF patch and plaque stage: no prognostic impact

CD8+ CD56+ mycosis fungoides
Pediatric CD8+CD56+ non-poikilodermatous mycosis fungoides: case report and review of the literature.

Kempf W¹, Kazakov DV, Broekaert SM, Metze D.
Mycosis fungoides – CD20 expression

148 cases of transformed MF from the French Cutaneous Lymphoma Study Group registry

- CD20 was expressed in 88 / 148 cases (59%).
- 23 cases with > 50% of CD20+ cells
- 6 cases (4%) with coexpression of CD3 and CD20


CD3 IF (D) and CD20 staining (E). F, Superposition of both images (merge) confers a mixed yellow color.
Mycosis fungoides – CD20 expression

6 patients with MF plaque stage and CD3+ CD4+ CD20+ cells
30-40% of the infiltrate showed coexpression, no intraepidermal lymphocytes.
No other B-cell markers and heavy chain immunoglobulin rearrangement

Induction of CD20 by interleukin 2 and mitogen exposure in T-cells
Therapeutic target for anti-CD20-antibody therapy.

Hagen et al. Am J Dermatopathol 2013
MF patch stage

- Superficial perivascular infiltrate
- Subtle or absent epidermotropism
- Small lymphocytes, discrete nuclear atypia.
Basilar epidermotropism (75%): Lining-up of lymphocytes along junctional zone
Pautrier microabscesses (19%)
Absence of exocytosis (5%)

Early MF – phenotypic markers

High-throughput genomic transcription profiling

- 19 genes with specific enrichment in eMF lesions compared to chronic dermatitis.
- TOX and PDCD1: high discrimination power by RNA expression
- TOX expression in intraepidermal and dermal lymphocytes in early MF by IHC

TOX expression levels in 113 MF biopsies

Higher TOX mRNA than the controls in both cohorts (p< 0.0001).

TOX over-expression differentiated MF from the controls (p < 0.0001).

High TOX mRNA levels correlated with increased risks of disease progression (P = 0.003) and disease-specific mortality (P = 0.008).

Huang et al. Oncotarget 2014

TOX expression in CTCL

TOX expression was observed at a high frequency in MF, SS, and PTCL, NOS.

Sézary syndrome

Neoplasm of central memory T-cells

Erythroderma,
Generalized lymphadenopathy
Palmoplantar hyperkeratosis
Intense pruritus

Neoplastic T-cells in skin and peripheral blood
Perivascular or band-like epidermotropic infiltrate

Atypical lymphocytes with cerebriform nuclei

Pautrier microabscesses
Sézary syndrome - Histology

Epidermotropic (38%)
Pautrier microabscesses in only half of the cases

Band-like (30%)

Non-specific (33%)

Non-specific features in up to one third of all SS biopsies

Sézary syndrome - diagnostic criteria

International Society for Cutaneous Lymphomas (ISCL)

Absolute Sézary cell count > 1000 cells/mm$^3$

Demonstration of immunophenotypical abnormalities
   Expanded CD4+ T-cells -> CD4/CD8 ratio > 10
   Loss of T-cell antigens CD2, CD3, CD4, and CD5

Demonstration of a T-cell clone in the peripheral blood

# Sézary syndrome and inflammatory erythroderma

<table>
<thead>
<tr>
<th>Histology</th>
<th>Distinction between SES and EID (14 SES and 29 EID)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blind assessment of HE slides</td>
</tr>
<tr>
<td></td>
<td>-&gt; correct diagnosis only in 31% of cases.</td>
</tr>
<tr>
<td></td>
<td>-&gt; correct differential with certainty in 57% of cases.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Low (10%) CD8:CD3 ratio in the epidermal lymphocytic infiltrate and dermal CD30+ lymphocytes significantly more frequent in CTCL.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>JunB expression by lymphocytes was specific of CTCL, but was inconstant (17%).</td>
</tr>
</tbody>
</table>

Ram-Wolff et al. Am J Dermatopathol 2010
Sézary syndrome and inflammatory erythroderma

**CD 7**
Loss by > 50% of cells in 16/24 (66%) SES and 4/30 (13%) EID cases.
Expression by <20% of cells only in SS (13/24 cases; 54%)

**PD-1**
Expression by > 50% of T-cells in 23 / 25 (92%) of SES and only in 4 / 30 (13%) EID cases


Only few CD7+ cells
High number of PD-1+ cells
Strong expression of TOX

SES rather than EID
Primary cutaneous CD30+ lymphoproliferative disorders

20-25% of all cutaneous T-cell lymphomas

Lymphomatoid papulosis  _____  borderline lesions  _____  Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous ALCL (PCALCL)

**Solitary (53%) or grouped (25%) rapidly growing nodules with ulceration**

Spontaneous regression 6-22%

5-year survival rate: > 90%

Extracutaneous spread 10-14%
Often multifocal tumors

Death (due to lymphoma) 5-8%

Bekkenk et al. 2000
Liu et al. 2003
Assaf et al. 2007
Primary cutaneous ALCL
Primary cutaneous anaplastic large cell lymphoma

The morphologic spectrum of primary cutaneous anaplastic large T-cell lymphoma: a histopathologic study on 66 biopsy specimens from 47 patients with report of rare variants

Background: Primary cutaneous anaplastic large T-cell lymphoma (PCALCL) is a well-defined entity with prognostic differences from the nodal counterpart [nodal anaplastic large cell lymphoma (NALCL)]. Several histological variants of NALCL have been characterized (common, lymphohistiocytic and small cell). However, studies on morphological variants of PCALCL are lacking.

Methods: We analyzed retrospectively the clinicopathologic features of 66 biopsies from 47 patients (M : F = 27 : 20; median age: 53 years; mean age: 51.8 years; range: 14–82) with PCALCL, in order to better characterize the spectrum of this unusual neoplasm.

Results: The 'common variant' was the most frequent (40.4%). In contrast to NALCL, in PCALCL, marked reactive infiltrates are more commonly present. In fact, 26 cases were classified as 'inflammatory type' (15 cases) and 'lymphohistiocytic' (11 cases). Concerning the predominant cell morphology, large anaplastic cells (33%) were almost as frequent as large pleomorphic (36%) and small to medium-sized cells (26%). We reported for the first time in the skin 2 rare cases with the predominance of large cells with a 'signet-ring'-like appearance. Epidermotropism and presence of cosinophils were found in a proportion of cases in all PCALCL variants.

Conclusions: PCALCL is characterized by variable histopathological presentations and a broad cytomorphologic spectrum.

Cesare Massone, Laila El-Shabrawi-Caelen, Helmut Kerl and Lorenzo Cerroni
Department of Dermatology, Research Unit of Dermatopathology, Medical University of Graz, Graz, Austria


CD30
Primary Cutaneous Anaplastic Large Cell Lymphoma with Angioinvasive Features and Cytotoxic Phenotype: A Rare Lymphoma Variant within the Spectrum of CD30+ Lymphoproliferative Disorders

Werner Kempf, Dmitry V. Kazakov, Bruno E. Paredes, Hubert R. Laeng, Gabriele Palmedo, Heinz Kutzner
81-year-old lady with ulcerated lesion on the right breast. In 1998 primary cutaneous anaplastic large-cell lymphoma, treated successfully with excision and radiotherapy.
CD3+ CD4- CD8+ CD30+ ALK -, EMA –
TIA-1+, Granzyme B + EBER-
Differential diagnosis

Angioinvasive infiltrates

- Extramedullary T/NK-cell lymphoma
- Cutaneous gamma/delta lymphoma
- Peripheral T-cell lymphoma, NOS
  > cytotoxic CD8+ T-cell lymphoma
- Lymphomatoid papulosis type E
Extranodal T/NK cell lymphoma

CD2+ CD3+ (epsilon), CD56+ TIA-1+, Granzyme B+, Perforin+ EBV + (EBER)
Intravascular ALK-negative cutaneous ALCL

Skin-limited ALCL

Intralymphatic growth (D2-40)

Cohesive clusters of large atypical lymphocytes, necrosis

CD3+ CD30+ CD56- EBV-

Indolent course

Intravascular lymphoma

Large atypical cells (blasts) in the lumina of capillaries and venules

**B-cell** phenotype more common (70%). Rare T- and T/NK-cell forms.
Intravascular lymphoma - Phenotype

**T-cell**

Rare form; association with EBV

Aggressive course

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**TABLE 2. Immunohistochemical, Molecular, and In Situ Hybridization Results**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>CD2*</th>
<th>CD3c†</th>
<th>CD4*</th>
<th>CD5*</th>
<th>CD7*</th>
<th>CD8†</th>
<th>CD20†</th>
<th>CD30†</th>
<th>CD45Ro†</th>
<th>CD56*</th>
<th>βF1‡</th>
<th>TIA-1§</th>
<th>B∥</th>
<th>Perforin¶</th>
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<tr>
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Benign Atypical Intravascular CD30⁺ T-cell Proliferation: A Reactive Condition Mimicking Intravascular Lymphoma

Erica Riveiro-Falkenbach, MD,* María Teresa Fernández-Figueras, MD,† and José Luis Rodríguez-Peralto, MD, PhD*

Abstract: CD30 is a transmembrane glycoprotein molecule usually expressed in activated B and T cells. Although it has been considered a reliable marker for CD30 lymphomas, reactive inflammatory disorders may contain a significant number of CD30⁺ cells mimicking lymphoproliferative disorders clinically or histologically. Intravascular lymphoma is a rare variant of non-Hodgkin lymphoma that can involve the skin in 40% of the patients. The majority of cases show a B-cell phenotype, and only a minority of cases are of T-cell or NK-cell origin. Moreover, 2 aggressive cases of intravascular large T-cell lymphoma have been described with a CD30⁺ phenotype. Herein, we report 2 patients with skin lesions showing an atypical intravascular CD30⁺ T-cell proliferation. Both the patients did not present systemic disease and therefore exhibit a favorable outcome. To the best of our knowledge, this is the second report in the literature of a benign intravascular CD30⁺ T-cell proliferation that represents an intriguing differential diagnosis for intravascular lymphoma.

Key Words: atypical intravascular CD30⁺, reactive process, pseudolymphoma CD30⁺, intravascular lymphoma

(Am J Dermatopathol 2011;0:000–000)

CASE REPORT

A 45-year-old man presented to a dermatologist with a few weeks history of a 2.5-cm, ulcerated cutaneous nodule on the trunk. A biopsy was performed with an initial clinical diagnosis of pyogenic granuloma. Sections of the biopsy stained with hematoxylin and eosin show an ulcerated and reactive epidermal hyperplasia. The underlying dermis displays a vascular proliferation, arranged in a lobular pattern, intermingled with a diffuse inflammatory infiltrate mainly composed of lymphocytes, plasma cells and neutrophils (Fig. 1). Many capillaries and venules demonstrate an intravascular atypical lymphoid proliferation (Fig. 2) positive for CD3, CD4, CD5, CD30, and BF-1 (Figs. 2, 3). The intravascular atypical cells do not express CD7, CD8, CD20, or anaplastic lymphoma kinase antigens. The rearrangement of immunoglobulin heavy chain gene (IgH) and T-cell receptor gamma gene (TCR gamma) studied by the polymerase chain reaction were polyclonal. Although, the histopathological findings suggested an intravascular T-cell lymphoma, laboratory tests including a complete blood count were all within normal levels. Computed tomographic scan of the body and bone marrow biopsy did not show any tumor involvement. Moreover, the patient continued to be healthy, without constitutional signs, symptoms, or new lesions 23 months after the initial diagnosis.

The second patient is a 17-year-old woman who was admitted in

FIGURE 2. Patient 1: Higher power of skin biopsy with a vascular proliferation, diffuse infiltrate of inflammatory cells (A) and an intravascular atypical lymphoid proliferation (B and C). The majority of intravascular atypical cells express CD30 (D).
Intralymphatic CD30+ atypical T-cell proliferation
Intralymphatic CD30+ atypical lymphocytosis
Intralymphatic CD30+ atypical lymphocytosis
Intralymphatic CD30+ atypical lymphocytosis

Table 2: Diagnostic criteria for atypical intravascular CD30+ T-cell proliferation:

(1) Association with trauma, ulceration and/or inflammatory processes
(2) Intralymphatic accumulation of medium-sized to large activated lymphocytes
(3) Expression of T-cell markers and CD30 and lack of B.cell marker expression by the medium-sized and large intravascular lymphocytes.
(4) No loss of T-cell markers (e.g., CD3; except for CD7) and absence of EBV RNA (EBER) or EBV-associated proteins in the atypically appearing CD30+ lymphocytes.
(5) Absence of monoclonal rearrangement of T-cell receptor beta or gamma genes.
(6) No indication for cutaneous or systemic lymphoma by staging examinations.
(7) Indolent course with complete resolution after regression of ulceration or inflammatory process. No development of lymphoma during follow-up.
**pcALCL**

- **CD2+ CD3-/+ CD4+**
- **CD30+ > 75% of tumor cells positive**
- **CD8-/+ CD56-/+**
- **EMA-, ALK-, lack of t(2;5)**

DeCoteau et al. 1996; Wood et al. 1998
PCALCL – phenotype

Phenotypic Variability in Primary Cutaneous Anaplastic Large T-cell Lymphoma: A Study on 35 Patients
Caterine Massone, MD and Lorenzo Cerroni, MD

35 pcALCL cases

T-helper phenotype in 12 cases (34%)
CD4+/CD82, TIA-1+ (5/8)

T-cytotoxic phenotype in 6 cases (18%)
CD42/CD8+ and TIA-1+

CD4+ CD8+ TIA-1 (4/4) in 7 cases (20%)

CD4- CD8- TIA-1- 9 cases (26%)

11 cases (31%) lacking several T-cell markers.

Massone & Cerroni Am J Dermatopathol 2014
Primary cutaneous vs. systemic ALCL

ALK  \[ t (2; 5) \rightarrow npm \text{ alk} : p80 \text{ transforming activity} \]

Absence or rarely (10-20%) found in pc ALCL

DeCoteau et al. 1996; Wood et al. 1998

\begin{tabular}{|l|c|c|c|}
\hline
1\textdegree & cutaneous ALCL: & CLA+ & EMA- & ALK- & HOX C5+ \\
2\textdegree & cutaneous ALCL: & CLA- & EMA +/- & ALK+ & HOX C5 +/- \\
\hline
\end{tabular}
ALK-positive primary cutaneous ALCL
ALK-positive primary cutaneous ALCL
ALK-positive primary cutaneous ALCL
ALK+ cutaneous ALCL

Pediatric and adult primary cutaneous ALCL ALK+ with mostly excellent prognosis
Some cases following after insect bites

Phenotype
ALK+ (6/6), EMA+ (5/5); CD3 negative (4/6)
Cytotoxic marker+ (6/6)

ALK as a therapeutic target for ALK inhibitor crizotinib.
pcALCL and 6p25.3

IRF4-DUSP22 locus on 6p25.3

Rearrangements in 28% PCALCL cases
Pham-Ledard et al. J Invest Dermatol 2010

FISH for 6p25.3 rearrangements:
a specific marker for PCALCL with a specificity of 99%
Wada et al. Mod Pathol 2011

6p25.3 rearrangement in a subset of LyP cases
PCALCL with 6p25.3 rearrangement

Three cases with 6p25.3 rearrangement (FISH)

Biphasic pattern with

- Diffuse dermal infiltrate of atypical medium-to-large cells
- Marked epidermotropism with small, atypical intraepidermal lymphocytes
Lymphomatoid papulosis

Localized or multifocal (70%) papules and nodules up to 1-2 cm, usually asymptomatic

Spontaneous regression of skin lesions after weeks (to months)
LyP – histological types

Type A

Type B

Type C

Type D

Type E
LyP type A

Most common histologic type (80%)

Scattered and in clusters arranged CD30+ pleomorphic or anaplastic cells

Numerous neutrophils and/or eosinophils
LyP type B

Rare histologic type (<5%)

Epidermotropic small to medium-sized lymphocytes

**Phenotype:** CD4+ CD30 - / + (0-77%)
Cohesive sheets of large pleomorphic and anaplastic tumor cells, only few reactive cells at the periphery of the lesion.
CD3+, CD4, CD8+ CD30+ (90%); TIA-1 or granzyme B (100%)
Simulating aggressive epidermotropic lymphoma
Papules with spontaneous regression -> LyP

Angioinvasive LyP (type E)

Ulceration, necrosis
Angiocentric and angiodestructive infiltrates
Medium-sized to large pleomorphic cells
CD3+ CD4- CD8+ (70%) CD30+

<table>
<thead>
<tr>
<th>Type</th>
<th>Histology</th>
<th>Histologic mimicker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A</td>
<td>Scattered CD30+, large</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>Type B</td>
<td>Epidermotropic CD30-/+ small</td>
<td>Mycosis fungoides</td>
</tr>
<tr>
<td>Type C</td>
<td>Cohesive sheets CD30+, large</td>
<td>ALCL</td>
</tr>
<tr>
<td>Type D</td>
<td>Epidermotropic CD30+ CD8+ small</td>
<td>AECTCL (Berti lymphoma)</td>
</tr>
<tr>
<td>Type E</td>
<td>Angioinvasive CD30+ CD8+&gt;CD4+</td>
<td>Extranodal NK/T, GD-TCL</td>
</tr>
<tr>
<td>Type</td>
<td>Histology</td>
<td></td>
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<tr>
<td>--------</td>
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</tr>
<tr>
<td>Type A</td>
<td>Scattered CD30+ large cells</td>
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<tr>
<td>Type E</td>
<td>Angioinvasive CD30+ CD8+/&gt;CD4+ medium to large cells</td>
<td></td>
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</tbody>
</table>

- Overlapping features in individual lesions
- Various types in the same individual patient
- No differences in clinical presentation
- All LyP types share the same biologic behaviour
- No prognostic impact
Chromosomal Rearrangements of 6p25.3 Define a New Subtype of Lymphomatoid Papulosis

Laszlo J. Karai, MD,*† Marshall E. Kadin, MD,‡ Eric D. Hsi, MD,§ Jason C. Sluzevich, MD,‖ Rhett P. Ketterling, MD,¶ Ryan A. Knudson, BS,‖ and Andrew L. Feldman, MD¶

Abstract: Lymphomatoid papulosis (LyP) is an indolent cutaneous lymphoproliferative disorder with clinical and pathologic features overlapping those of both reactive conditions and aggressive lymphomas. Recurrent genetic abnormalities in LyP have not been previously identified. Here, we describe the clinical, immunophenotypic, and genetic characteristics of cutaneous lymphoproliferative lesions showing distinctive and previously undescribed histologic features in 11 patients. All patients were older adults (67 to 88 y) with predominantly localized lesions and clinical presentations suggesting benign inflammatory dermatoses or low-grade epithelial tumors. Histologically, lesions showed a biphasic growth pattern, with small cerebriform lymphocytes in the epidermis and larger transformed lymphocytes in the dermis. All had a T-cell immunophenotype. The pathologic features raised the possibility of an aggressive T-cell lymphoma such as transformed mycosis fungoides. However, no patient developed disseminated skin disease or extracutaneous spread. Untreated lesions regressed spontaneously. All cases harbored chromosomal rearrangements of the DUSP22-IRF4 locus on 6p25.3. The overall findings suggest that these cases represent a newly recognized LyP subtype characterized by 6p25.3 rearrangements. The benign clinical course in all 11 patients despite pathologic features mimicking an aggressive lymphoma emphasizes the importance of clinicopathologic correlation, incorporating molecular genetic analysis when possible, during the evaluation of cutaneous lymphoproliferative disorders.

Key Words: lymphomatoid papulosis, cutaneous CD30-positive T-cell lymphoproliferative disorder, T-cell lymphoma, chromosomal translocation, fluorescence in situ hybridization, DUSP22, genetics

(Lymphomatoid papulosis (LyP) is a chronic, recurring CD30-positive T-cell lymphoproliferative disorder (TLPD) that presents as multifocal papular lesions on the trunk, buttocks, and extremities of patients ranging in age from 4 to 88 years.1,2 Five subtypes currently are recognized and/or have been proposed on the basis of their histologic and immunophenotypic features.3-8 The most frequent, type A, is characterized by a dermal infiltrate of large transformed lymphocytes in a mixed inflammatory background.9 Type B lesions have a predominantly intraepidermal lymphocytic infiltrate mimicking mycosis fungoides (MF). Type C lesions have sheets of large transformed lymphocytes in the dermis, with or without significant epidermotropism.5 Type D LyP is a CD8-positive cytotoxic T-cell variant with epidermotropism.6 Kempf et al8 recently proposed another oligoantigenic, ulcerative, angioinvasive variant (type E).

We report 11 elderly patients with localized skin lesions clinically suggestive of inflammatory dermatoses, infections, or low-grade epithelial skin tumors. Pathologic findings raised the possibility of an aggressive lymphoid malignancy and consisted of a combination of pagetoid reticulosis-like intraepidermal lymphocytosis and a cohesive, nodular dermal infiltrate of highly proliferative CD30-positive tumor cells. However, all lesions showed
Epidermotropic and dense nodular and cohesive infiltrate of CD30+ small to medium-sized to large cells. Eosinophils often absent.

LyP with 6p25.3 rearrangement
**LyP with 6p25.3 rearrangement**

**Phenotype**
- CD3+ CD4- CD8- CD30+ betaF1+
- Ki-67 ++ (80%)

**Genotype**
- Break-apart probe for IRF4-DUSPP22 locus on 6p25.3

Abnormal split signal (green: centromeric; red: telomeric) vs. normal intact fusion signal (f)
LyP with 6p25.3 rearrangement

Often localized manifestation, spontaneous regression of lesions

No spread to extracutaneous sites

Complete remission after several months

Fig. 4 from Karai et al. AJSP 2013
NPM1-TYK2 gene fusion in CD30+ LPD

Whole transcriptome sequencing
- chimeric fusion involving NPM1 (5q35) and TYK2 (19p13)
- encoding NPM1-TYK2 protein

Fluorescence in situ hybridization
- NPM1-TYK2 fusions in 2 of 47 (4%; 1 LYP, 1 ALCL) CD30+ LPD
- absent in other mature T-cell neoplasms (n = 151; including sALCL)

NPM1-TYK2 induce constitutive TYK2, STAT1, STAT3 and STAT5 activation.

Velusami et al. Blood 2014

NPM1-TYK2 gene fusion is the first translocations targeting tyrosine kinases in CD30+ LPD, but only in a small subset of cutaneous CD30+ LPD.
<table>
<thead>
<tr>
<th>Tumour Type</th>
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<tbody>
<tr>
<td>Extranodal marginal zone lymphoma</td>
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<tr>
<td>Nodal marginal zone lymphoma</td>
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<tr>
<td>Paediatric nodal marginal zone lymphoma</td>
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<tr>
<td>Follicular lymphoma</td>
<td>9690/3</td>
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<tr>
<td>Paediatric follicular lymphoma</td>
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<tr>
<td>Primary cutaneous follicle centre lymphoma</td>
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<tr>
<td>Mantle cell lymphoma</td>
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<tr>
<td>Diffuse large B-cell lymphoma (DLBCL), NOS</td>
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<td>T-cell/histiocyte rich large B-cell lymphoma</td>
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<tr>
<td>Primary DLBCL of the CNS</td>
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<td>Primary cutaneous DLBCL, leg type</td>
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<td>EBV positive DLBCL of the elderly</td>
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<td>Lymphomatoid granulomatosis</td>
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<td>Primary mediastinal (thymic) large B-cell lymphoma</td>
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<tr>
<td>Intravascular large B-cell lymphoma</td>
<td>9712/3</td>
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<td>ALK positive large B-cell lymphoma</td>
<td>9737/3</td>
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<tr>
<td>Plasmablastic lymphoma</td>
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<td>Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease</td>
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<td>Primary effusion lymphoma</td>
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<tr>
<td>Burkitt lymphoma</td>
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<tr>
<td>B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma</td>
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<td>B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma</td>
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<td>Systemic EBV positive T-cell lymphoproliferative disease of childhood</td>
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<td>Hydroa vacciniforme-like lymphoma</td>
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<td>Sézary syndrome</td>
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<td>Anaplastic large cell lymphoma</td>
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<td>Primary cutaneous T-cell lymphoma</td>
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<td>Primary cutaneous CD8 positive aggressive T-cell lymphoma</td>
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<td>Lymphomatoid papulosis</td>
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<tr>
<td>Primary cutaneous T-cell lymphoma</td>
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<tr>
<td>Primary cutaneous CD4 positive small/medium T-cell lymphoma</td>
<td>9709/3</td>
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<tr>
<td>General T-cell lymphoma, NOS</td>
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<tr>
<td>Lymphomatoid papulosis</td>
<td>9705/3</td>
</tr>
<tr>
<td>Lymphomatoid papulosis</td>
<td>9714/3</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma, ALK negative</td>
<td>9702/3</td>
</tr>
</tbody>
</table>

**HODGKIN LYMPHOMA**

- Nodular lymphocyte predominant Hodgkin lymphoma | 9659/3 |
- Classical Hodgkin lymphoma                      | 9650/3 |
- Nodular sclerosis classical Hodgkin lymphoma   | 9663/3 |
- Lymphocyte-rich classical Hodgkin lymphoma      | 9651/3 |
- Mixed cellularity classical Hodgkin lymphoma    | 9652/3 |
- Lymphocyte-depleted classical Hodgkin lymphoma  | 9653/3 |

**MATURE T-CELL AND NK-CELL NEOPLASMS**

- T-cell prolymphocytic leukaemia                  | 9834/3 |
- T-cell large granular lymphocytic leukaemia      | 9831/3 |
- Chronic lymphoproliferative disorder of NK-cells | 9831/3 |
- Aggressive NK cell leukaemia                     | 9948/3 |
Nodular CD8+ infiltrates
Indolent CD8-positive Lymphoid Proliferation of the Ear
A Distinct Primary Cutaneous T-cell Lymphoma?

Tony Petrella, MD,* Eve Maubec, MD,† Pascale Cornillet-Lefebvre, MD,‡ Rein Willemze, MD,§
Michel Pluot, MD,‖ Anne Durlach, MD, PhD,¶ Eduardo Marinho, MD,#
Jean-Luc Benhamou, MD,** Patty Jansen, MD, PhD,† † Alistair Robson, MRCPATH, DipRCPath,‡‡‡
and Florent Grange, MD, PhD§§

Indolent CD8-positive lymphoid proliferation on the face: part of the spectrum of primary cutaneous small-/medium-sized pleomorphic T-cell lymphoma or a distinct entity?

We report two cases of a CD8-positive lymphoid proliferation presenting as solitary lesions on the ear and nose, respectively. Histopathologically, both cases were characterized by a diffuse non-epidermotropic dermal proliferation of dural medium-sized CD8-positive T-lymphocytes with a lymphblast-like appearance, having cells with large folded nuclei, prominent nucleoli and ameboid or pale eosinophilic cytoplasm. Staging procedures excluded systemic involvement, and both lesions were successfully treated with localised radiotherapy without evidence of recurrence after 12 and 24 months' follow up, respectively. Previously reported cases on the ear had similar clinicopathological and immunophenotypical features, and together raise the possibility of a distinct entity; an indolent CD8-positive lymphoid proliferation.


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Accepted for publication: September 8, 2009
Indolent CD8⁺ lymphoid proliferation of acral sites: a clinicopathologic study of six patients with some atypical features

The authors report six further cases of a cutaneous lymphoid proliferation that share many of the features of a case series previously described as indolent CD8-positive lymphoid proliferation of the ear. Previous reports of this entity have described the slow growth of cutaneous papules and nodules, with a predilection for the ear, associated with specific histopathologic and immunophenotypic features and a benign clinical course. These include the presence of a clear Grenz zone without epidermotropism, and a CD8⁺ granzyme B-immunophenotype with a low proliferative index. The current case series presents some atypical clinical features, including site of disease beyond the ear and recurrent disease. Despite this, indolent clinical evolution is apparent. Histopathologically, three of the six cases showed a moderate-high proliferative index, while two cases had very focal epidermotropism and Paucity collections. A single example had significant granzyme B expression. These previously unreported features add to our understanding of this rare entity, which is not currently recognized in the World Health Organization (WHO)/European Organization for Research and Treatment of Cancer (EORTC) classification.

Keywords: CD8+, indolent, lymphoid proliferation, lymphoma


Primary cutaneous CD8+ small/medium-sized T-cell LPD

Histology
Nodular infiltrate
Grenzzone

Small to medium-sized cells
No or subtle epidermotropism

Eosinophils, plasma cells

Kempf et al. Am J Dermatopathol 2013
CD3+ CD4- CD8+ CD30-, TIA-1+, Granzyme B-, EBER-
Monoclonal rearrangement of TCR gamma genes
CD8+ granulomatous CTCL

CD8+ granulomatous cutaneous T-cell lymphoma: A potential association with immunodeficiency

Bryan Gammon, MD,1,2 Aliatar Robson, FRCPath,3 Janyara Deonizio, MD,3 Lisa Arkin, MD,4 and Joan Gutierrez, MD1

Chicago, Illinois; Santa Barbara, California; and London, United Kingdom

Background: Granulomatous cutaneous T-cell lymphoma (G-CTCL) is a rarely encountered entity. Most G-CTCL is CD4+, with granulomatous mycosis fungoides representing the vast majority of cases. Because of the rarity of CD8+ G-CTCL, there is a paucity of data regarding the clinicopathologic features and expected course.

Objective: To describe the clinical and histopathologic features of G-CTCL.

Methods: This is a retrospective review of collected cases.

Results: We present 4 cases of CD8+ G-CTCL. Patients presented with papules and nodules on the trunk and extremities without antecedent patch or plaque disease. In all cases, biopsy specimens were obtained, and these revealed a dense granulomatous infiltrate accompanied by a systemic lymphoid infiltrate of CD8+ T cells. T-cell clonality studies were positive in 3 of 4 cases. Staging was negative for nodal involvement, but lung granulomas were seen in all cases. In all 4 cases, the patient’s medical history was significant for immunodeficiency, either primary or iatrogenic. All patients had slowly progressive disease.

Limitations: This is a small retrospective case series.

Conclusions: CD8+ G-CTCL appears to be associated with immunodeficiency. The finding of a CD8+ G-CTCL should prompt an evaluation for underlying immunodeficiency. Additional studies are required to validate these conclusions. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2014.05.028.)

Key words: common variable immunodeficiency; cutaneous T-cell lymphoma; cytotoxic; granulomatous; immunodeficiency; mycosis fungoides; X-linked agammaglobulinemia.

Granulomatous cutaneous T-cell lymphomas (G-CTCLs) comprise a poorly described heterogeneous collection of T-cell lymphomas. The most common entities in this category are granulomatous slack skin (GSS) and granulomatous mycosis fungoides (GMF). GMF is exceedingly rare; in a recent case control study, GMF accounted for only 6.9% of cases of MF reported at a tertiary care center. The extreme clinical and histopathologic heterogeneity observed in reported cases of G-CTCL makes it difficult to ascertain if the observed histologic pattern is representative of a specific disease or is a nonspecific inflammatory tissue reaction, such as has been seen in patients with pityriasis lichenoides,12,13 mycosis fungoides,14,15 folliculotropic mycosis fungoides,16 CD8+ lymphoproliferative disorders,17 and secondary cutaneous involvement by systemic T-cell lymphomas.18 For all of its heterogeneity, G-CTCL is typically CD4+. Only 5 cases of CD8+ GMF have been reported in the literature to date,19,20 and there are only rare case reports of cytotoxic G-CTCL.11

Granzymes, perforin, and surface markers are investigated in G-CTCL, but their expression is not diagnostic. CD8+ G-CTCL presents with a generalized papulonodular eruption and may have an underlying immunodeficiency.

The histopathologic findings of a CD8+ clonal granulomatous process should prompt an evaluation for immunodeficiency.

CAPSULE SUMMARY

• Granulomatous cutaneous T-cell lymphoma (G-CTCL) is a rarely encountered entity. Most G-CTCLs are CD4+.

• Patients with CD8+ G-CTCL present with a generalized papulonodular eruption and may have an underlying immunodeficiency.

• The histopathologic findings of a CD8+ clonal granulomatous process should prompt an evaluation for immunodeficiency.

43-year-old man
X-linked / Bruton agammaglobulinemia
Multiple brownish plaques and nodules

Conclusions

- Unusual clonal CD8-positive and histiocyte-rich infiltrates

→ consider underlying congenital immunodeficiency disease

- Biology of CD8+ LPD in CVID is yet unclear.
Disseminated Primary Cutaneous CD8+ Small/medium-sized Pleomorphic T-cell Lymphoma Responding to Hydroxychloroquine.


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Summary

Cutaneous B-cell lymphomas
- Clinicopathological variants of MZL and FCL
- EBV- and MTX-associated B-cell LPD
- Post-transplant CBCL

Cutaneous T-cell lymphomas
- MF variants and new markers in early MF
- CD30+ LPD: new clinicopathological and genetic variants
- CD8+ LPD with indolent course
- Granulomatous CD8+ CTCL as indicator of CVID
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J. Galambos

Dermatopathology Friedrichshafen
H. Kutzner
Achal Mycosis Fungoides With Epidermal Microvesiculation Mucinosis.

Riveiro-Falkenbach E¹, Ruano Y, Garrido M, Ortiz-Romero PL, Rodríguez-Peralto JL.
ALK+ PC-ALCL

Tumor cells expressing a cytoplasmic-only variant of ALK protein

Absence of the t (2;5)(p23;q35) was confirmed by FISH and reverse transcription PCR.

FISH using the ALK break-apart probe set, and dual-target hybridizations with NPM and ALK locus-specific probes:

No rearrangements involving the ALK gene.

Cytoplasmic ALK protein in tumor cells was phosphorylated/activated.