Cutaneous lymphoproliferative disorders (CLD) include reactive lymphoid hyperplasias, so called cutaneous "pseudolymphomas", prelymphomatous conditions and definite malignant lymphomas of low and high grade malignancy. Reactive benign lymphoid proliferations in the skin, either localized or disseminated, mimicking primary lymphoma have been termed pseudolymphomas (PSL). These either resolve spontaneously or after elimination of the causative factor (e.g. drugs). Cutaneous prelymphomatous ("abortive") disorders (PLD) include a variety of idiopathic chronic dermatoses often unresponsive to topical therapy with persistent T-cell clones that should be recognized by dermatologists. Careful characterization and follow-up of these cases is essential to ensure accurate diagnosis and to evaluate the potential progression to frank lymphoma. The WHO-EORTC is the most current and widely used classification of primary cutaneous lymphomas based on clinical, histological, immunohistochemical, molecular and cytogenetic features. Although these tumours have some morphological features in common with nodal lymphomas, some differ in their behaviour, prognosis and treatment requirements. This article summarizes the features of cutaneous lymphoproliferative disorders and provides a few case studies as examples of the major categories of disease.

Keywords: Cutaneous lymphoma, cutaneous pseudolymphoma, mycosis fungoides, WHO/EORTC classification of cutaneous lymphomas

皮膚淋巴細胞增生性疾病（CLD）可包括反應性淋巴組織增生（即所謂皮膚 "假性淋巴瘤"），淋巴瘤前病變及明确的低度和高度惡性淋巴瘤。皮膚的良性反應性淋巴組織增生，無論是局限性或播散性的，型態皆與原發性淋巴瘤極為相似，故有假性淋巴瘤之稱。它們多會自行或在去除病因（例如藥物）後痊癒。皮膚淋巴瘤前（"頓挫性"）病變（PLD）包括各式的特發性慢性皮膚病，皆對外敷治療無效，並持續顯示出T細胞克隆，皮膚科專科醫生當可辨識。而這些病例務必一一仔細鑑別和跟進，以確保精確無誤的診斷，及評估潛在演變為真正淋巴瘤的可能性。WHO-EORTC 皮膚淋巴瘤分類為最新及最廣泛使用的原始性皮膚淋巴瘤分類方法，其建基於組織學，臨床，免疫組織化學及細胞遺傳學等各種特徵。雖然這些腫瘤與淋巴結淋巴瘤有著一些共同的形態特徵，但部分在表現，預後和治療要求方面有所差別。本文總結了皮膚淋巴細胞增生性疾病的特徵，並提供了幾個主要類別的案例研究以作參考。

關鍵詞：皮膚淋巴瘤，皮膚假性淋巴瘤，蕈樣肉芽腫，WHO-EORTC 皮膚淋巴瘤分類
Cutaneous lymphoproliferative disorders

dermatologist and pathologist. Depending on
the predominant cell type PSL are broadly
characterized as T-cell, B-cell and CD30 positive
PSL. PSL may resolve spontaneously, after
cessation of the causative factor (e.g. drugs) or
after non-aggressive treatment.

Although strictly speaking PSL are idiopathic,
T-PSL includes conditions such as actinic reticuloid
(chronic actinic dermatitis), lymphomatoid drug
eruption and lichenoid pigmented purpuric
dermatosis. B-PSL includes conditions such as
lymphocytoma cutis sometimes associated with
Borrelia species, post vaccination or tattoo lesions
and pseudolymphomatous folliculitis etc. CD30-
PSL often includes viral infections and infestations
such as orf-milker’s nodule, molluscum
tangiosum, herpes simplex, EBV, HIV, arthropod
bites and nodular scabies etc. Some patterns of
lobular panniculitis, particularly lupus profundus
may mimic subcutaneous panniculitis-like T-cell
lymphoma.1

The diagnosis of primary cutaneous T-cell
lymphomas, especially mycosis fungoides, may
take many years to become clearly established.
Rarely patients experience a variety of distinct pre-
lymphomatous conditions (cutaneous T-cell
lymphoid dyscrasias). This is an evolving concept
with the more widespread use of T-cell receptor
gene rearrangement technology. Such cases may
include persistent atypical forms of pigmented
purpuric dermatoses, follicular mucinosis,
pityriasis lichenoides, parapsoriasis, clonal
erythroderma, hypopigmented T-cell dyscrasia,
atypical lobular panniculitis and syringolymphoid
hyperplasia with alopecia in which a more
restricted oligoclonal to monoclonal T-cell
repertoire is demonstrable. These conditions
should be followed carefully for the possible
progression to frank, albeit usually low grade,
lymphoma.2

Cutaneous B-cell lymphoid dyscrasias are less
clearly described although there may be a link
between the presence of certain inciting antigens
like Borrelia species in the progression of B-cell
lymphomagenesis from the benign counterpart of
lymphocytoma cutis to primary cutaneous
(extranodal) marginal zone B-cell lymphoma.3

The diagnosis and classification of
cutaneous lymphoproliferative disorders
has undergone major change since the early
days of pure morphology. The application
of immunohistochemistry and polymerase chain
reaction (PCR) detection of immunoglobulin (IgH)
and T-cell receptor (TCR) gene rearrangements in
conjunction with detailed clinicopathological
correlation and long term multi-centre follow-up
continues to finely tune diagnostic criteria.4,5

The skin is the second most common site of
extranodal lymphomas, following the
gastrointestinal tract. Some skin lymphomas differ
from their nodal counterparts in a number of ways
as illustrated in the WHO/EORTC classification
of cutaneous lymphoma (2005)(Table 1).6

T-cell lymphomas e.g. mycosis fungoides are more
common than B-cell lymphomas in the skin. The
classical Alibert type of mycosis fungoides (MF) is
not uncommon, the histological variants of
mycosis fungoides are however rare, difficult to
diagnose and include folliculotrophic (pilotropic)
and syringotrophic MF, pagetoid reticulosis and
granulomatous slack skin.7

Cutaneous CD30 positive lymphoproliferative
disorders are a spectrum of disease from waxing
and waning lymphomatoid papulosis to persistent
ALK negative primary cutaneous anaplastic large
cell lymphoma.8

Recent studies show clinical, histological and
immunophenotypic differences between
subcutaneous panniculitis-like T-cell lymphoma
(SPTL) with an alpha-beta to those with a gamma-
delta T-cell phenotype suggesting they represent
different entities. Whereas SPTL with an alpha-
beta T-cell phenotype are homogenous with a
rather indolent clinical behaviour, SPTL with a
gamma-delta T-cell phenotype overlap with the
gamma-delta T/NK cell lymphomas and
invariably run a very aggressive clinical course. SPTL is now restricted to those lymphomas with an alpha-beta T-cell phenotype.\(^9\)

Some disorders can be separated out as provisional entities from the broader group of peripheral T-cell lymphoma, unspecified (PTL, unspecified) in the WHO classification. These include the aggressive epidermotropic CD8 positive T-cell lymphoma, cutaneous gamma-delta T-cell lymphoma (including cases formerly diagnosed as SPTL with a gamma-delta phenotype) and primary cutaneous small/medium sized pleomorphic T-cell lymphoma (all provisional entities).\(^6\)

In contrast to nodal follicular lymphoma primary cutaneous follicle centre lymphomas (PCFCL) do not generally express bcl-2 and are not typically associated with the t(14;18) translocation. Most patients present with localized skin lesions on the head and neck or trunk and, regardless of the histological growth pattern or number of blasts, are highly responsive to radiotherapy and have an excellent prognosis.\(^10\)

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL, leg type) affects mostly elderly people and has a higher relapse rate and a more unfavourable prognosis than PCFCL with a diffuse large B-cell morphology. PCLBCL, leg type has a predominance of centroblasts and immunoblasts rather than large centrocytes, and consistently strongly expresses bcl-2 protein and Mum-1/IRF4.\(^11\)

### Clinical cases

**Case 1** – Drug associated T-cell pseudolymphoma (T-PSL) (Atypical pigmented purpuric dermatosis associated with use of both beta-blocker and calcium channel inhibitor). Male 61, cayenne pepper discoloration of lower legs associated with plaque on dorsum of left foot (Figure 1). Photomicrographs showing capillaritis and a pattern simulating mycosis fungoides (H&E x 200) (Figure 2). Graph of PCR T-cell receptor gamma gene (Figure 3) showing a "reactive" polyclonal pattern.

**Case 2** – Cutaneous T-cell lymphoid dyscrasia (Primary idiopathic follicular mucinosis). Female 32, solitary tumid erythematous plaque over left eyebrow with some hair loss (Figure 4) and photomicrographs showing follicular mucinosis with mucin highlighted by alcian blue at pH2.5 (H&E x 200). Graph of PCR T-cell receptor gamma gene (Figure 5) showing a monoclonal pattern indicative of persistent T-cell clonality.

### Table 1. WHO-EORTC consensus classification of primary cutaneous lymphomas (2005)

<table>
<thead>
<tr>
<th>Cutaneous T &amp; NK-cell lymphomas</th>
<th>Cutaneous B-cell lymphomas</th>
</tr>
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<tbody>
<tr>
<td>• Mycosis fungoides – Alibert-Bazin, folliculocentric, pagetoid reticulosis, granulomatous slack skin.</td>
<td>• Marginal zone B-cell lymphoma</td>
</tr>
<tr>
<td>• Sezary syndrome</td>
<td>• Follicle centre cell lymphoma</td>
</tr>
<tr>
<td>• Primary Cutaneous CD30+ lymphoproliferative disorders – primary cutaneous anaplastic large cell lymphoma – lymphomatoid papulosis spectrum.</td>
<td>• Diffuse large B-cell lymphoma, leg type</td>
</tr>
<tr>
<td>• Subcutaneous panniculitis-like T-cell lymphoma</td>
<td>• Diffuse large B-cell lymphoma, other – e.g. intravascular B-cell lymphoma.</td>
</tr>
<tr>
<td>• Extramedullary NK/T-cell lymphoma, nasal type</td>
<td></td>
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</tbody>
</table>
Figure 1. Case 1. Cayenne pepper discoloration of lower legs associated with plaque on dorsum of left foot.

Figure 2. Case 1. Photomicrographs showing capillaritis and a pattern simulating mycosis fungoides (H&E x 200).

Figure 3. Case 1. Graph of PCR T-cell receptor gamma gene showing a "reactive" polyclonal pattern.
**Figure 4.** Case 2. Solitary tumid erythematous plaque over left eyebrow with some hair loss and photomicrographs showing follicular mucinosis with mucin highlighted by alcian blue at pH2.5 (H&E x 200).

**Figure 5.** Case 2. Graph of PCR T-cell receptor gamma gene showing a monoclonal pattern indicative of persistent T-cell clonality.
Case 3 – Mycosis fungoides, folliculotropic variant. Female 44, leonine facies (Figure 6) with infiltrative ‘boggy’ plaques, eyebrow hair loss and weeping. Photomicrographs (Figure 7) showing follicular mucinosis and features of mycosis fungoides with Pautrier microabscesses (H&E x 200). Graph of PCR T-cell receptor gamma gene (Figure 8) showing a monoclonal pattern confirming lymphoma.

Case 4 – Cutaneous CD30 positive lymphoproliferative disorder (primary cutaneous anaplastic large cell lymphoma). Female, age 32 with persistent violaceous plaque gradually increasing in size over left elbow (Figure 9). Photomicrograph showing diffuse infiltrate of highly atypical large mononuclear cells (H&E x 200) (Figure 10). Immunohistochemistry (Figure 11) showing the tumour cells to be CD30+ and ALK -. CD30 positive lymphoproliferative disorders – a spectrum from lymphomatoid papulosis to anaplastic large cell lymphoma (Figure 12).
Figure 8. Case 3. Graph of PCR T-cell receptor gamma gene showing a monoclonal pattern confirming lymphoma.

Figure 9. Case 4. Persistent violaceous plaque gradually increasing in size over left elbow.

Figure 10. Case 4. Photomicrograph showing diffuse infiltrate of highly atypical large mononuclear cells (H&E x 200).
Figure 11. Case 4. Immunohistochemistry showing the tumour cells are CD30+ and ALK-.

- **Lymphomatoid papulosis (LyP)**
- **Anaplastic large cell lymphoma (C-ALCL)**

Figure 12. Case 4. CD30 positive lymphoproliferative disorders – a spectrum from lymphomatoid papulosis to anaplastic large cell lymphoma.
Case 5 – Subcutaneous panniculitis-like T-cell lymphoma. Female 26 with low grade fever, night sweats and 10 lbs weight loss, painful deep seated red nodules over arms, lower legs, thighs and neck & photomicrographs (Figure 13) showing a lymphocytic lobular panniculitis (H&E x 100), prominent rimming of fat cells by lymphocytes (H&E x 200) & immunohistochemistry showing CD8>CD4, TIA-1+, bF1+ (alpha-beta T-cell phenotype), Ki67 5% (Figure 14). Graph of PCR of T-cell receptor gamma gene (Figure 15) showing a monoclonal pattern confirming lymphoma.

**Figure 13.** Case 5. Painful deep seated red nodules over arms, lower legs, thighs and neck & photomicrographs showing a lymphocytic lobular panniculitis (H&E x 100).

**Figure 14.** Case 5. Prominent rimming of fat cells by lymphocytes (H&E x 200) & immunohistochemistry showing CD8>CD4, TIA-1+, bF1+ (alpha-beta T-cell phenotype), Ki67 5%.
Case 6 – Primary cutaneous marginal-zone B-cell lymphoma. Female 57, red to violaceous nodules over left arm (Figure 16) with night sweats. Photomicrographs showing diffuse sheets of monocytoïd and centrocyte-like cells in the dermis (H&E x 100 & x 200) (Figure 17). Immunohistochemistry (Figure 18) showing tumour cells to be CD20+, CD43+, CD10- & bcl-6-.

Figure 15. Case 5. Graph of PCR of T-cell receptor gamma gene showing a monoclonal pattern confirming lymphoma.

Figure 16. Case 6. Red to violaceous nodules over left arm.

Figure 17. Case 6. Photomicrographs showing diffuse sheets of monocytoïd and centrocyte-like cells in the dermis (H&E x 100 & x 200).
Case 7 – Primary cutaneous diffuse large B-cell lymphoma, leg type. Male 59
Large persistent nodule on right knee, photomicrograph with a diffuse dermal infiltrate of centroblasts and immunoblasts (H&E x 200). Immunohistochemistry showing tumour cells to be CD20+ (B-cell) & bcl-2+ (Figure 19).

**Figure 18.** Case 6. Immunohistochemistry showing tumour cells to be CD20+, CD43+, CD10- & bcl-6-.

**Figure 19.** Case 7. Large persistent nodule on right knee, photomicrograph with a diffuse dermal infiltrate of centroblasts and immunoblasts (H&E x 200). Immunohistochemistry showing tumour cells to be CD20+ (B-cell) & bcl-2+. 
Acknowledgements

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