WHO/EORTC
Classification of
Cutaneous Lymphomas
2005
Introduction

- Lymphoma in skin, in the past were considered to be manifestations of systemic processes.
- A variety of T- and B-cell neoplasms can involve the skin, either primarily or secondarily.
- After GI, skin is the 2nd most common site of extranodal non-Hodgkin lymphoma, annual incidence of 1:100,000.
- Primary cutaneous lymphomas, completely different clinical behavior and prognosis from histologically similar systemic lymphomas, which may involve the skin secondarily
- Treatment for primary vs secondary is usually different.
Introduction 2

- EORTC – Classification 1997
- WHO – Classification 2001
- Concensus meetings on 2003 and 2004 lead to the 2005 WHO/EORTC classification.
<table>
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<tr>
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<th>Primary CTCL</th>
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<tbody>
<tr>
<td>Indolent</td>
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<tr>
<td>MF</td>
<td>Follicle center cell lymphoma</td>
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<td>MF + follicular mucinosis</td>
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<td>Immunocytooma (marginal zone B-cell lymphoma)</td>
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<tr>
<td>Pagetoid reticulosis</td>
<td></td>
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<tr>
<td>Large cell CTCL, CD30+</td>
<td>Anaplastic, Immunoblastic, Pleomorphic</td>
<td>Intermediate Large B-cell lymphoma of the leg</td>
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<tr>
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<td>Lymphomatoid papulosis</td>
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<td>SS</td>
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<tr>
<td>Large cell CTCL, CD30−</td>
<td>Immunoblastic, Pleomorphic</td>
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<tr>
<td>Provisional</td>
<td>Provisional</td>
<td></td>
</tr>
<tr>
<td>Granulomatous slack skin</td>
<td></td>
<td>Intravascular large B-cell lymphoma</td>
</tr>
<tr>
<td>CTCL, pleomorphic small/medium-sized</td>
<td></td>
<td>Plasmacytoma</td>
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<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
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Abbreviations: CTCL, cutaneous T-cell lymphoma; CBCL, cutaneous B-cell lymphoma; MF, mycosis fungoides; SS, Sezary syndrome.
<table>
<thead>
<tr>
<th><strong>Table 1.2: WHO Classification of NHL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-cell</strong></td>
</tr>
<tr>
<td><strong>Mature B-cell lymphomas</strong></td>
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<tr>
<td>Small lymphocytic lymphoma</td>
</tr>
<tr>
<td>Lymphoplasmacytic lymphoma</td>
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<tr>
<td>Splenic marginal zone lymphoma</td>
</tr>
<tr>
<td>Hairy cell leukaemia</td>
</tr>
<tr>
<td>Plasma cell neoplasms</td>
</tr>
<tr>
<td>Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)</td>
</tr>
<tr>
<td>Nodal marginal zone B-cell lymphoma</td>
</tr>
<tr>
<td>Follicular lymphoma (grades 1, 2, 3a and 3b)</td>
</tr>
<tr>
<td>Diffuse follicle centre lymphoma</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
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<tr>
<td>Diffuse large B-cell lymphoma</td>
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<tr>
<td>Mediastinal (thymic) large B-cell lymphoma</td>
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<tr>
<td>Intravascular large B-cell lymphoma</td>
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<tr>
<td>Primary effusion lymphoma</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td><strong>B-cell proliferations of uncertain malignant potential</strong></td>
</tr>
<tr>
<td>Lymphomatoid granulomatosis</td>
</tr>
<tr>
<td>Post-transplant lymphoproliferative disorder, polymorphic</td>
</tr>
<tr>
<td><strong>T-cell and NK-cell</strong></td>
</tr>
<tr>
<td><strong>Precursor T- and NK-cell lymphomas</strong></td>
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<tr>
<td>Precursor T lymphoblastic lymphoma</td>
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<td>Blastic NK-cell lymphoma</td>
</tr>
<tr>
<td><strong>Mature T-cell and NK-cell lymphomas</strong></td>
</tr>
<tr>
<td>T-cell prolymphocytic leukaemia</td>
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<tr>
<td>T-cell large granular lymphocytic leukaemia</td>
</tr>
<tr>
<td>Aggressive NK-cell leukaemia</td>
</tr>
<tr>
<td>Adult T-cell lymphoma/leukaemia</td>
</tr>
<tr>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
</tr>
<tr>
<td>Enteropathy-type T-cell lymphoma</td>
</tr>
<tr>
<td>Hepatosplenic T-cell lymphoma</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
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<tr>
<td>Mycosis fungoides</td>
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<tr>
<td>Peripheral T-cell lymphoma unspecified</td>
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<td>Angioimmunoblastic T-cell lymphoma</td>
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<td>Anaplastic large cell lymphoma</td>
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WHO/EORTC 2005 Classification

- Combines features of both classifications.
- Takes into account morphologic, molecular, and clinical features of each entity.
- Comprises primary cutaneous B, T, and NK lymphomas.
- Terminology is compatible with that of systemic lymphomas (WHO), but reflects the organ specific peculiarities of cutaneous lymphomas.
Table 1. The WHO/EORTC classification for cutaneous lymphomas¹⁻³

**Mature T-cell and NK-cell neoplasms**

*Mycosis fungoides (MF)*

- Variants of MF
  - Pagetoid reticulosis (localized disease)
  - Folliculotropic, syringotrophic, granulomatous variants

- Subtype of MF
  - Granulomatous slack skin

*Sézary syndrome*

CD30⁺ T-cell lymphoproliferative disorders of the skin

- Lymphomatoid papulosis
- Primary cutaneous anaplastic large cell lymphoma

**Subcutaneous panniculitis-like T-cell lymphoma**

*Primary cutaneous peripheral T-Cell lymphoma (PTL), unspecified*

- Subtypes of PTL
  - Primary cutaneous aggressive epidermotropic CD8⁺ T-cell lymphoma (provisional)
  - Cutaneous gamma/delta-positive T-cell lymphoma (provisional)
  - Primary cutaneous CD4⁺ small/medium-sized pleomorphic T-cell lymphoma (provisional)

**Extranodal NK/T-cell lymphoma, nasal type**

- Hydroa vacciniforme-like lymphoma (variant)

**Adult T-cell leukemia/lymphoma**

**Angioimmunoblastic T-cell lymphoma**
Mature B-cell neoplasms

Cutaneous marginal zone B-cell lymphoma (MALT-type)

Primary cutaneous follicle center lymphoma

Growth patterns
  Follicular
  Follicular and diffuse
  Diffuse

Cutaneous diffuse large B-cell lymphoma, leg type

Cutaneous diffuse large B-cell lymphoma, others

Intravascular large B-cell lymphoma

Lymphomatoid granulomatosis

Chronic lymphocytic leukemia

Mantle cell lymphoma

Burkitt lymphoma

Immature hematopoietic malignancies

Blastic NK-cell lymphoma CD4+/CD56+ hematodermic neoplasm

Precursor lymphoblastic leukemia/lymphoma
  T-lymphoblastic lymphoma
  B-lymphoblastic lymphoma

Myeloid and monocytic leukemias

Hodgkin lymphoma

*Definition is restricted to lymphomas of alpha/beta T-cell origin.
†This table also contains entities of extracutaneous lymphomas frequently involving the skin as a secondary site.
‡Recent evidence suggests an origin from a dendritic cell precursor. In recognition of uncertain histogenesis the term CD4+/CD56+ hematodermic neoplasm is preferred.
Cutaneous T-cell lymphomas
*Mycosis Fungoides*

- *Mycosis fungoides* - 44% CL
- MF initially presents in the skin and shows a characteristic stepwise clinical progression with potential extracutaneous involvement.
- Skin lesions do not resolve.
- Patches → thin plaques → thick plaques, minority progress to systemic disease.
Patch Stage
Plague Stage
Epidermotrophysm

Pautrier Microabscess

Lymphocytes aligned on basal layer
Histologic features of MF

- Pautrier microabscesses – 10%
- Psoriasiform – lichenoid pattern
- Lymphocytes aligned in the basal layer (at tips of rete ridges)
- Epidermotropism 95%
- Cerebriform cells seen in 50% of cases
- Eosinophils, plasma cells, and macrophages may be admixed.
Mycosis Fungoides

- Immunohistochemistry is helpful but not necessary for dx.
- CD2+, CD3+, CD4+, CD5+ TCRbeta+
- CD8-, Cd30–
- Rare cases may be CD8+ or CD30+
- 5yr survival 90%
- Tx Skin-targeted therapies as photo (chemo)–therapy PUVA, topical nitrogen mustard or chlormustine (BCNU), or radiotherapy, including total skin electron beam irradiation.
MF variants

- Folliculotrophic MF

Worse px
5yr 80%
MF variants
Pagetoid Reticulosis

- Solitary or multiple
- T(H) phenotype
  - CD4, CD5, CD3 +
  - CD8-
- Strong expression of CLA, and alpha E beta 7
- May mimic superficial melanoma or paget’s disease
- 100% 5 yr survival
MF variants
Granulomatous slack skin (GSS)

- Bulky skin lesions on major skin folds
- Band like infiltrate with giant cells
- Elastophagocytosis and emperipolesis
- T(H) phenotype
- Giant cells are CD68 +
- 100 % 5 yr survival
Sezary Syndrome
Sezary Syndrome

- ISCL (International society of cutaneous lymphoma
  - Absolute sezary cell count of 1000 cells/mm
  - Expanded CD4 population resulting in CD4/CD8 ratio of > 10
  - Loss of any of the T cell antigens (CD2, CD3, CD4, and CD5) or demonstration of T cell clonality by molecular studies.
- 20% 5 yr survival
- Tx Extracorporeal photopheresis (ECP), either alone or in combination with other treatment modalities (interferon alpha, methotrexate, campath)
CD 30 + T cell lymphoproliferative disorders of the skin

- Lymphomatoid papulosis
- Primary cutaneous anaplastic large cell lymphoma
- Hallmark is CD 30+, however both entities differ in clinical and histologic presentations.
- Represent 30% of cutaneous lymphomas
Lymphomatoid Papulosis

- Three histologic subtypes of LyP (types A, B, and C) have been described, which represent a spectrum with overlapping features.
- LyP type A lesions, scattered or small clusters of large, sometimes multinucleated or Reed-Sternberg–like, CD30+ cells are intermingled with numerous inflammatory cells, such as histiocytes, small lymphocytes, neutrophils, and/or eosinophils.
- LyP type C lesions demonstrate a monotonous population or large clusters of large CD30+ T cells with relatively few admixed inflammatory cells.
- LyP type B is uncommon (less than 10%) and is characterized by an epidermotropic infiltrate of small atypical cells with cerebriform nuclei similar to that observed in MF.
- The large atypical cells in the LyP type A and type C lesions have the same phenotype as the tumor cells in C-ALCL.
- The atypical cells with cerebriform nuclei in the LyP type B lesions have a CD3+, CD4+, CD8- phenotype and do not express CD30 antigen.
- Clonally rearranged T-cell receptor genes have been detected in approximately 60%–70% of LyP lesions.
Lymphomatoid Papulosis

- Chronic recurrent, self-healing papulonecrotic or papulonodular skin eruption with histologic features of a malignant lymphoma.
- Histologically malignant but clinically benign
- Considered a low-grade cutaneous T-cell lymphoma
- Adults, median age 45, M:F 1.5, trunks and limbs
- Individual lesion disappear within 3 to 12 weeks
- 10-15% of the cases may be followed by a cutaneous lymphoma, usually MF
- 4% develop systemic lymphomas
- Px - 98% 5yr survival
- Tx – Long term follow up without active tx
Primary Cutaneous Anaplastic Large Cell Lymphoma

- Shares histologic and immunohistochemical features with nodal type.
- Differs in age of onset, genetic features, etiology, and prognosis.
- Presents as single or multiple grouped nodules or tumors confined to one extremity of body area.
Primary Cutaneous Anaplastic Large Cell Lymphoma

- Large cells with an anaplastic, pleomorphic, or immunoblastic cytomorphology
- There is no clinical evidence or history of LyP, MF, or another type of CTCL
- CD30 antigen by more than 75% of tumor cells.
- Activated T cell phenotype, CD4+, CD25, CD71, HLADR.
- Variable loss of CD2, CD3, and CD5
- CLA +, EMA -, ALK-
- Lack translocation 2:5, 90% have clonal rearrangement of TCR.
- Px is excellent, 10 yr survival of over 90%
- Tx radiotherapy or surgery
Subcutaneous panniculitis like T-cell lymphoma

- Adults and children, no sex predilection
- Most often on legs
- Systemic symptoms such as fever, fatigue, and weight loss may be present.
- Can be associated with hemophagocytic syndrome, rapidly progressive course.
Subcutaneous panniculitis like T-cell lymphoma

- Panniculitis like growth of T cells with hyperchromatic nuclei and often many macrophages.
- Overlying epidermis and dermis are typically uninvolved.
- Rimming of individual fat cells by neoplastic T cells
- Necrosis, karyorrhexis, and cytophagocytosis are common findings
- Plasma cells and reactive lymphoid follicles are generally absent, in contrast to lupus profundus, and other forms of lobular panniculitis.
- Cytotoxic T-cell lymphoma, subcutaneous infiltrates of pleomorphic T cells.
Subcutaneous panniculitis like T-cell lymphoma

- α/β T cells, CD 2+, CD3+, CD5+, CD4-, CD8+, CD43+, TIA-1+ granzyme B+, perforin +
- Neoplastic T cells show clonal T-cell receptor (TCR) gene rearrangements
- 5-year survival of 80%
- Tx Doxorubicin-based chemotherapy and radiotherapy
Primary cutaneous peripheral T-cell lymphoma, unspecified

- T-cell neoplasms that do not fit into any of the better defined subtypes of T-cell lymphoma/leukemia.
- 10% of CTLs
- Cutaneous gamma/delta T-cell lymphoma
- Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma
- Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma
Cutaneous gamma/delta T-cell lymphoma

- Clonal proliferation of mature, activated γ/δ T cells expressing a cytotoxic phenotype.
- Epidermotropic, dermal, and subcutaneous.
- Dermal and epidermal involvement often coexists with subcutaneous disease, in contrast to SPTCL of α/β origin.
- Apoptosis and necrosis are common, often with vascular invasion.
- CD3+, CD2+, CD43+, CD45RO+,
- CD15-, CD30-, CD20-, CD25-
- CD4-, CD8 –
- Positive for TIA-1 and the cytotoxic proteins granzyme B, granzyme M, and perforin.
Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma

- Clinically, this form of CD8+ cutaneous lymphoma differs from the slowly progressive CD8+ form similar to classic MF. It presents with erosive plaques rather than patches. It exhibits an unfavorable prognosis with rapid course.
- The tumor cells have a CD3+, CD8+, granzyme B+, perforin+, TIA-1+, CD45RA+, CD45RO-, CD2-, CD4-, CD5-
- The neoplastic T cells show clonal TCR gene rearrangements. Specific genetic abnormalities have not been described.
- Median survival of 32 months
- Patients are generally treated with doxorubicin-based multiagent chemotherapy.
Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma

- This is a non-cytotoxic CTCL characterized by a predominance of small to medium-sized CD4+ pleomorphic T cells with clinical features not compatible with MF.
- Diffuse or nodular lymphoid infiltrate, predominantly perivascular and periadnexal and shows a tendency to extend to the subcutaneous tissue.
- It consists of small-to-medium-sized pleomorphic lymphoid cells with irregular hyperchromatic nuclei and a pale scanty cytoplasm
- Patients are commonly adults, who present with solitary, localized, or more frequently generalized nodules or tumors. No sites of predilection have been recorded
Cutaneous B-cell lymphomas

- Cutaneous marginal zone B cell lymphoma
- Primary cutaneous follicle center lymphoma
- Cutaneous large B cell lymphoma, leg type
- Cutaneous large B cell lymphoma, other
- Cutaneous intravascular large B cell lymphoma
Cutaneous marginal zone B-cell lymphoma (MZL)

- Adults trunk or extremities, especially the arms
- The nodular or diffuse infiltrate
- Small to medium-sized lymphocytes
- Irregular nuclei, dispersed chromatin, inconspicuous nucleoli and an abundant pale cytoplasm
- Monocytoid appearance (reniform nuclei) or plasma cell differentiation.
- Typified by darker centers surrounded by brighter zones of pale-staining cells.
- Dutcher bodies and intracytoplasmic PAS+ globular inclusions may be seen
Grenz zone

Darker center

Lighter Periphery

Monocytoid lymphocytes
CD20 + Neoplastic cells

CD 3 + Reactive T cells
Cutaneous marginal zone B-cell lymphoma (CMZL)

- Immunophenotype: CD19+, CD20+, CD22+, CD79a+, bcl-2+, CD5-, CD10-, CD23-, bcl-6-
- IgH genes are clonally rearranged in >70% of cases
- MZL, the t(11;18) not seen in primary cutaneous MZL
- t(14;18)(q32;q21) translocation involving IGH and MALT1 seen in 1/3 of cases.
- The prognosis of CMZL is excellent with a 5-year survival close to 100%.
- Tx radiotherapy or surgical excision
Primary Cutaneous Follicle Center Lymphoma

- Solitary or grouped plaques and tumors
- Scalp, forehead, and trunk
- Synonyms, reticulohistiocytoma of back, or Crosti lymphoma
- The skin lesions gradually increase in size over years, but dissemination to extracutaneous sites is uncommon.
Mixed population of centrocyte like and centroblast like cells

Nodular infiltrate
CD 20 positive

Bcl-2 negative

Bcl-6 positive
Primary Cutaneous Follicle Center Lymphoma

- Neoplasm of follicle center cells (centrocytes and centroblasts)
- Follicular, follicular and diffuse or a diffuse growth pattern
- Grading of primary cutaneous FCL as in its nodal counterpart based is not prognostically relevant.
- Few mitosis, and no tingible body macrophages seen (present in pseudolymphoma)
- CD19+, CD20+, CD22+, CD79a+, CD5-, CD43-, bcl-2-, bcl-6 +
- Bcl-2 gene rearrangement and t(14;18) chromosomal translocation are absent in most cases.
- 5-year survival of more than 95%
- Tx radiotherapy or surgical excision
Cutaneous diffuse large B-cell lymphoma (DLBCL)

- composed of large B cells (centroblasts and immunoblasts)
- DLBCL, leg-type and DLBCL, other
- DLBCL, leg type, is the most common variant, occurs on the leg and less frequently at other sites.
- DLCL other include; Tcell/histiocyte-rich DLBCL, plasmablastic lymphoma and others that do not fulfill the criteria for a DLBCL, leg-type
Diffuse large B-cell lymphoma (DLBCL), leg-type

**Histology**

- Diffuse growth pattern, monomorphous infiltrate, entire dermis involvement, adnexal structures are usually destroyed.
- The epidermis is often spared, Grenz zone.
- Centrocytes are absent.
- Mitotic figures can frequently be detected.
- Nuclei are round with coarsely clumped chromatin.
- Minimal inflammatory component and little stromal reaction.
Destroyed adnexa

Mum 1 +

Strongly + Bcl-2
Diffuse large B-cell lymphoma (DLBCL), leg-type

- CD19+, CD20+, CD22+, and CD79a+ CD10-, Bcl-6 + in most cases.
- Combination + Bcl-2, and + MUM-1/IRF4 is characteristic regardless of site and distinguish from FCL diffuse type.
- The t(14;18) can be detected in secondary cutaneous large B-cell lymphomas but not in primary cutaneous diffuse large B-cell lymphomas.
- The 5-year survival 55%
- PCLBCLs on the leg have an inferior prognosis compared to PCLBCLs presenting at other
- Tx Radiotherapy and Rituximab
Diffuse large B-cell lymphoma, other

- Neoplastic large B-cells that lack the typical features of DLBCL, leg-type and do not conform to the definition of primary cutaneous FCL with diffuse growth pattern.
- T cell rich, histiocyte rich, plasmablastic (HIV) variants
- CD19+, CD22 +, and CD79a+, with light-chain restriction, negative for CD15 and CD30, which excludes Hodgkin lymphoma.
- 5 yr survival 65%
- Tx Radiotherapy and Rituximab
Intravascular large B-cell lymphoma (IVL)

- Rare highly malignant large-cell lymphoma with systemic spread
- Tumor cells in the lumina of small vessels, particularly capillaries and venules.
- Skin and the nervous system are preferential sites of primary manifestation.
- The tumor cells express B-cell markers in the vast majority of cases; rarely a T-cell phenotype is found
- Patients with disease limited to the skin (cutaneous variant) have a significantly better outcome than the other patients with IVL. 3-year overall survival: 56% versus 22%
- Tx Multiagent chemotherapy
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<th>Bcl-2</th>
<th>Bcl-6</th>
<th>CD10</th>
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<th>MUM1/IRF4</th>
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<td>MZL/ICY</td>
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<td>Secondary FCL</td>
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MZL/ICY, marginal zone lymphoma/immunocytoma; FCL, follicle center lymphoma; Secondary FCL, secondary cutaneous FCL; DLBCL, diffuse large B-cell lymphoma; PSL, pseudolymphoma or reactive lymphoid hyperplasia. The term pseudolymphoma is used by dermatologists as a synonym for any type of reactive infiltrate in the skin that is extensive enough to cause a tumor or nodule.
Blastic NK-cell lymphoma or CD4+/CD56+ hematodermic neoplasm

- Cell of origin is not yet completely elucidated
- Cytogenetically, they are related to dendritic cells.
- Skin involvement occurs in 87% of the patients and manifests with contusiform, brownish infiltrated plaques or nodules.
- The oral mucosa is commonly involved.
- The cells express CD4, CD56, CD123 and TCL-1 but are negative for other T-, B-, NK-cell, or myeloid markers.
- median survival, 14 months)
- Systemic chemotherapy
Bruiselike skin lesion
Grenz zone

Diffuse dermal infiltrate

Erythrocyte extravasation is a characteristic feature, explaining the bruise-like appearance.

CD 56 + tumor cells
Extranodal NK/T-cell lymphoma, nasal type

- Adults, males, Asia, Central America, and South America.
- Multiple plaques or tumors preferentially on the trunk and extremities, ulceration is common.
- Dense infiltrates in dermis and often the subcutis.
- Epidermotropism, prominent angiocentricity and angiodestruction and extensive necrosis.
- Small to large cells with irregular or oval nuclei, moderately dense chromatin, and pale cytoplasm, histiocytes, plasma cells, and eosinophils can be seen.
- Express CD2, CD56, cytoplasmic CD3, and cytotoxic proteins (TIA-1, granzyme B, perforin), but lack surface CD3.
- In rare CD56- cases detection of EBV by in situ hybridization and expression of cytotoxic proteins are required for diagnosis.
- EBV is expressed almost in all cases, suggesting a pathogenetic role of this virus.
Ulceration
Necrosis
Angiocentric infiltration
Extranodal NK/T-cell lymphoma, nasal type

- Nearly always EBV+ lymphoma of small, medium, or large cells usually with an NK-cell, or more rarely a cytotoxic T-cell, phenotype.
- The skin is the second most common site of involvement after the nasal cavity/nasopharynx.
- Skin involvement may be a primary or secondary manifestation.
- Since both groups show an aggressive clinical behavior and require the same type of treatment, distinction is not useful.
- Median survival of 27 months was reported, compared with 5 months for patients presenting with cutaneous and extracutaneous disease.
- Tx systemic hemotherapy
Conclusion

- The new WHO/EORTC classification of cutaneous lymphomas, employs a terminology compatible with systemic lymphomas but also reflects the organ-specific peculiarities of cutaneous lymphomas.
References
