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Cutaneous T-cell lymphomas (including rare subtypes). Current concepts. II.

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A B S T R A C T

Background. Cutaneous T-cell lymphomas (CTCL) represent about the 80% of skin lymphomas and comprise a heterogeneous group of diseases with respect to clinical presentation, outcome, histologic and immunophenotypic features. In the recent years, data have been accumulated indicating that clinical and biological differences exists between primary nodal and primary extranodal lymphomas.

Information Sources. On such bases, the cutaneous lymphoma classification by the EORTC (European Organization for Cancer Research and Treatment) but also the recent general lymphoma classification, by the WHO (World Health Organization), have dedicated special attentions to the cutaneous lymphomas including the T and NK-cell subtypes. This paper reviews the most significative subtypes of T-cell lymphoma that affect the skin primarily or secondarily.

State of the Art. Apart from mycosis fungoides with its variants forms and the Sezary's syndrome, we have focused on the CD30⁺ primary cutaneous lymphoproliferative disorders (PCLD) (25% of all CTCL), a fascinating spectrum of disease, extending from lymphomatoid papulosis (LyP) trough to CD30⁺ large cell lymphoma. These disorders have in common large atypical CD30⁺ cells and a frequent spontaneous regression of the skin lesions associated with a relatively favourable outcome (excellent in LyP). The identification of this group of skin disorders is crucial for the patients since most of CD30⁺ PCLD are indolent diseases that do not warrant aggressive treatment. Others types of CTCL include the heterogeneous category of peripheral T-cell lymphoma not otherwise specified (NOS), subcutaneous panniculitis-like T-cell lymphoma and the still controversial group of the cytotoxic lymphomas.

Perspectives. Notably, the latter two subtypes have special relevance to the clinicians because (i) subcutaneous panniculitis-like T-cell lymphoma may be associated with the hemophagocytic syndrome; (ii) skin lesions in cytotoxic lymphomas may represent the first manifestation of an otherwise systemic disease.

Key words: T-cell lymphomas, subtypes.

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Cutaneous T-cell lymphomas (CTCL) which account for about 80% of skin lymphomas, are a heterogeneous group of diseases with respect to clinical presentation, outcome, histologic and immunophenotypic features. Both the recent WHO lymphoma classification¹ and the EORTC cutaneous lymphoma classification² have paid a special attention to the category of cutaneous T/NK lymphomas which has been divided into several subtypes. A comparison between the terminology adopted by these two schemes reveals a wide consensus on the categorization of almost 90% of CTCL subtypes. Minor controversies exist on the classification of the CD30 large cell T-cell lymphoma with non-anaplastic morphology, the use of the term peripheral T-cell lymphoma not otherwise specified and, to a lesser extent, the poorly defined category of the so-called CD56⁺ blastic NK lym-

phoma/leukemia. Future studies on such rare issues will probably reduce the divergences further. In this paper we describe the clinicopathologic features of the most frequent T/NK-cell lymphoma subtypes.

Mycosis fungoides and Sézary's syndrome (WHO 01) Clinical features and morphology

Mycosis fungoides (MF) is the commonest type of cutaneous lymphoma³ and mostly affects adults and the elderly (M/F ratio 2:1; average age about 50 years); sporadic cases have also been reported in children and young adults.⁴ The classical form of MF is clinically characterized by progressive phases (patch, plaque and tumor stage or erythroderma) and a protracted natural history. The early phase consists of erythematous, flat patches (measuring from 1 to 5 cm in diameter). As the patches become increas-

ingly infiltrated they evolve into palpable reddish-brown infiltrated plaques with well-margined borders. Patients with MF plaques may also have typical patch lesions contiguous with the plaques or at other body sites. Patch and plaque lesions usually have an asymmetrical distribution, mostly involving the buttocks, lower trunk, groin, axillae, and breasts. In the late stage of MF the patients show a combination of patches, plaques and nodular/tumor lesions (the latter may progress from pre-existing plaques or arise *de novo*) or diffuse erythroderma often sparing flexural areas. Although the protracted natural history is one of the peculiar clinical features of MF, the rapidity of progression through the various clinical stages is unpredictable. MF patients may have regional nodal enlargement and a grading system for nodal involvement ranging from I (no involvement) to III (diffuse nodal infiltration by the lymphoma cells) has been proposed. However, in advanced clinical stages of MF the lymphoma population may spread to various organs other than skin and lymph nodes.

Histologically, the MF cellular infiltrate is composed of atypical T lymphocytes with hyperconvoluted (cerebriform) or pleomorphic nuclei, which exhibit a variable degree of epidermotropism. Usually, the cytological features and distribution patterns of the MF cellular infiltrate correlate closely with the clinical stage of the disease. In the patch lesions the lymphoma population consists of small T lymphocytes with few atypical cells; the infiltrate involves the upper dermis with a patchy-perivascular, lichenoid or band-like pattern; epidermotropism with single cell exocytosis may occur, but the intraepidermal clusters of atypical cells (Pautrier's microabscess) are rare at this phase. The epidermis may be acanthotic, hyperkeratotic or psoriasiform (in case of erythroderma); fibrosis of the papillary dermis and vessel hyperplasia in the superficial dermis may be present. Much has been written on cytologic features set forth as characteristic of early patch MF, but evidence has accumulated showing that whereas some of these criteria may be helpful others are not.⁵ Widely accepted morphologic criteria favoring a diagnosis of MF include: presence of *haloed* convoluted lymphocytes of approximately the same width as the basal keratinocytes, Pautrier's microabscesses, disproportionate exocytosis, and lymphocytes aligned within the basal layer. In the plaque phase the lymphoma infiltrate is dense and shows a dermal band-like growth pattern; intraepidermal Pautrier's microabscesses may be found in at most 25% of cases. The lymphoma cells are small to medium-sized, pleomorphic and admixed with eosinophils and plasma cells. In the tumor phase, the lymphoma infiltrates the whole dermis and often subcutis with a nodular and/or diffuse growth pattern. The lymphoma population consists of medium-sized atypical pleomorphic

cells; in this phase epidermotropism can be lost. In about 50% of the cases scattered large atypical pleomorphic to anaplastic cells can be found; if the number of the large cells exceeds 25% of the whole infiltrate, transformation/progression into a secondary large cell lymphoma can be hypothesized.

Immunohistochemistry, molecular biology and cytogenetics

In cases of classical MF the lymphoma cells have a T-helper/memory antigenic profile (CD2⁺; CD3⁺; β F1⁺; CD4⁺; CD8⁻; CD5⁺; CD45RO⁺), with frequent loss of the CD7 antigen; rare cases with a T-suppressor CD8⁺/CD4⁻ phenotype have been reported. Sporadically, reactivity for the CD15 has been observed in advanced tumor stages of MF.⁶ The lymphoma cells may also show reactivity for CD30 in the plaque and tumor stages; however, CD30 expression in a previously negative MF case is often associated with progression into large cell lymphoma and a poor outcome. T-cell receptor (*TCR*) gene rearrangement is frequent in most cases of MF in the plaque and/or tumor stages, but is often absent in early MF. Complex karyotypes have been documented in many MF patients especially in advanced disease phases, but no specific genetic abnormalities have been associated with MF.

Differential diagnoses

The diagnosis of MF relies on the combination of clinical presentation and features in addition to histopathologic findings (epidermotropic lymphoma characterized by a dermal infiltrate of T-lymphocytes with cerebriform nuclei and Pautrier's microabscesses). However, because of the heterogeneity of its clinical and histologic patterns, the early MF may be hardly or not distinguishable (both clinically and histologically) from a number of conditions (e.g. actinic reticuloid, pseudo-T-cell lymphomas, lymphomatoid papulosis type B) which may either precede, occur concurrently or simulate MF. The difficulty in diagnosing MF is mainly due to its natural history that tends to evolve slowly, and patients often carry a long-standing diagnosis of eczematoid, lichenoid or psoriasiform superficial dermatitis before a definitive diagnosis can be reached. The major diagnostic difficulties regard large plaque parapsoriasis in which the patients have slightly scaly, erythematous, atrophic patches with or without poikilodermatous changes that cannot be distinguished from MF patches.⁷ Inconclusive biopsy results may be explained by the predominance of reactive T-lymphocytes and lack of specific histologic criteria for a diagnosis of early MF. The modern ancillary techniques (i.e. immunohistochemistry and molecular biology) have failed to fill this diagnostic void. Modifications of the antigenic profile of the T-cell infiltrate (i.e. loss of CD7)

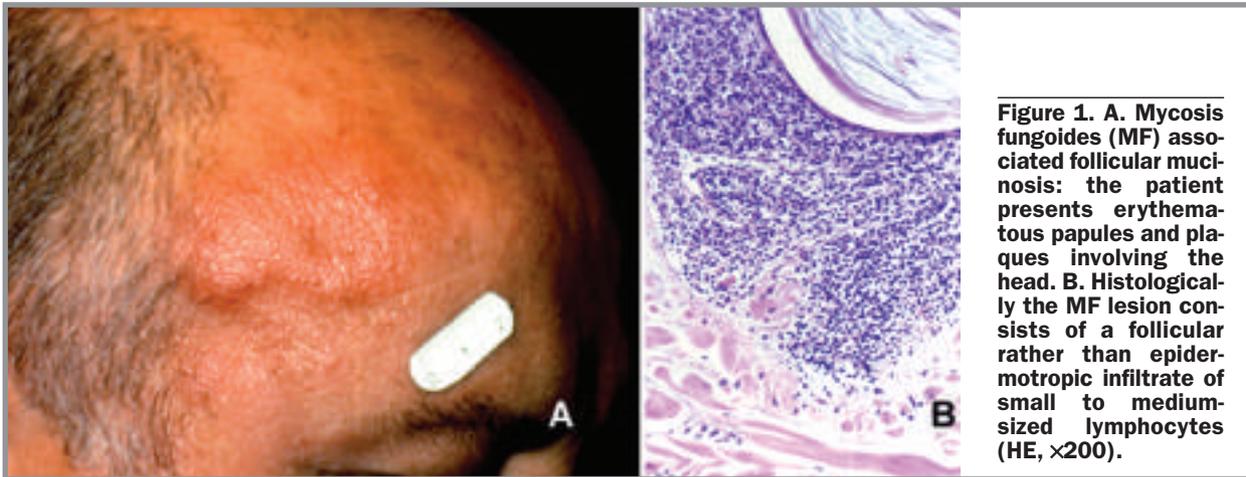


Figure 1. A. Mycosis fungoides (MF) associated follicular mucinosis: the patient presents erythematous papules and plaques involving the head. B. Histologically the MF lesion consists of a follicular rather than epidermotropic infiltrate of small to medium-sized lymphocytes (HE, $\times 200$).

have also been found in inflammatory dermatoses;⁸ thus the presence of an aberrant T-cell phenotype, except for CD7 loss, is often considered as a valuable diagnostic adjunct. Similarly the rate of false-negative results and the increasingly frequent identification of clones in lichen planus, pityriasis lichenoides, spongiotic dermatitis, etc.,⁹ suggests that a demonstration of a clonal proliferation of T-cells does not establish a diagnosis of MF or even, necessarily, of a lymphoma. In conclusion, the diagnosis of MF presently still relies on careful combination of clinical, morphofunctional and molecular information and, often, prolonged follow-up with repeated biopsies.

Juvenile mycosis fungoides

MF may sometimes affect children, adolescents and young adults (less than 35 years) and the onset of MF during the first two decades is probably more common than is generally recognized. Thus MF should be included in the differential diagnosis of chronic dermatoses (atopic dermatitis, pityriasis lichenoides) which can affect children and adolescents. Usually these young patients have limited round or oval erythematous squamous patches and plaques (T1-disease); less frequently papulonodular, follicular, annular or hypopigmented lesions may be observed; erythroderma is rare. Normally the histologic and immunophenotypic features of cellular infiltrate in juvenile MF are similar to those of the adult forms. However special cases have been reported¹⁰ in which the histologic examination of the patch/plaque lesions reveals a prominent epidermotropism of the lymphoma cells which show a peculiar CD8⁺ cytotoxic phenotype. The exact relationship of these unusual cases with respectively the spectrum of cytotoxic CTCL and some special variants of LyP with a natural killer phenotype is to date unexplored. The disease-specific survival of younger and older patients is similar.

MF variants

Numerous clinical and/or histopathological variants of MF have been described in the past but a wide consensus has now been achieved to restrict the term MF to the classical form of the disease. Presently, only three major MF variants are recognized in both the WHO and EORTC classifications. These are (i) MF with follicular mucinosis; (ii) pagetoid reticulosis and (iii) granulomatous slack-skin disease (*this latter included among the provisional entities by the EORTC classification*).

(i) MF associated with follicular mucinosis¹¹ is clinically characterized by the presence of follicular erythematous papules and plaques often involving the head (scalp) and neck areas (Figure 1A). In other skin regions the same patients may show plaques and/or nodules of otherwise classical MF. Patients with MF associated with follicular mucinosis may develop follicular cysts (which harbor MF infiltrate in hair walls) and may mimic MF nodular/tumor lesions. Histologically the lymphoma population consists of a follicular rather than epidermotropic infiltrate of small to medium-sized pleomorphic CD4⁺ T-lymphocytes associated with a variable degree of mucin deposition within and around the hair follicles (Figure 1B). TCR clonal rearrangement can be demonstrated in most cases. (ii) Pagetoid reticulosis¹² is histologically characterized by a strictly epidermal atypical lymphoid infiltrate. Clinically a distinction has been made between patients with localized (Woringer-Kolopp disease) or multiple (Ketrion-Goodman disease) skin lesions. The prognostic outcome seems to be excellent in the localized form of the disease, whereas the cases with multiple lesions pursue an indolent course like the classical MF. The patients have large, erythematous, scaly or hyperkeratotic verrucous patches and plaques (Figure 2A). Lesions usually grow slowly and are localized mostly on the lower part of the limbs. The lymphoma cells show an exquisite epidermotropism and, in

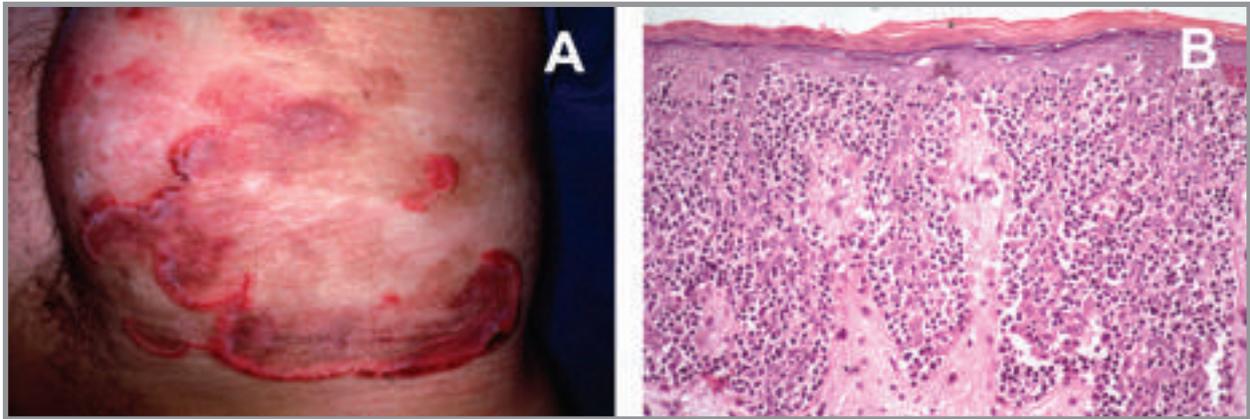


Figure 2. A. MF, pagetoid reticulosis: the patient presents localized (Woringer-Kolopp disease) erythematous, scaly, infiltrated plaques. B. The lymphoma cells show an exquisite epidermotropism (x400).

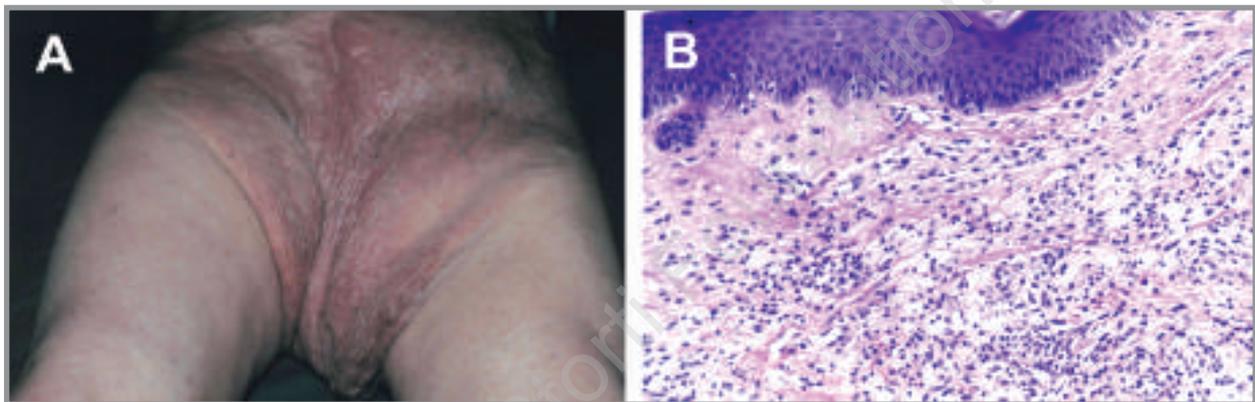


Figure 3. A. MF, granulomatous slack skin variant: the patient has folds of atrophic skin involving the groin. B. The MF lymphoma infiltrate consists of small to medium-sized lymphocytes admixed with histiocytes and scattered giant cells (HE, x200).

most cases, they have a peripheral CD8⁺/CD4⁻ or CD4⁺/CD8⁻ T-cell phenotype, with frequent expression of the Ki-1/CD30 antigen, at least in a proportion of the lymphoma cells (Figure 2B). TCR clonal rearrangement can be demonstrated in most cases. Various authors presently consider that the term pagetoid reticulosis must be restricted to the localized form of the disease only, whereas the disseminated forms of the disease might represent cases of γ - δ or CD8⁺ aggressive-cytotoxic epidermotropic T-cell lymphomas. (iii) granulomatous slack skin disease¹³ is clinically characterized by the presence of slowly developing folds of atrophic skin often involving the neck, axillae and buttocks (Figure 3A). Histologically the lymphoma population diffusely involves the whole dermis and subcutis and consists of a polymorphous appearing infiltrate of small to medium-sized-pleomorphic CD4⁺ T-lymphocytes admixed with CD68⁺ macrophages, a variable number of giant cells (exhibiting elastophagocytosis) and scattered granulomas (Figure 3B). TCR clonal rearrangement can be demonstrated in most cases. Patients with this unusu-

al variant of MF frequently have other associated lymphomas (mostly Hodgkin's lymphoma).

Sezary's syndrome

Sezary's syndrome (SS) is a rare disease^{14,15} that occurs exclusively in adults and elderly patients who develop erythroderma, generalized lymphadenopathy and a leukemic blood picture with a count of at least 1000 atypical convoluted Sézary's T-cells per mm³. In addition an abnormal CD4/CD8 ratio (at least >10) and the same TCR clonal rearrangement in the skin and peripheral blood must be demonstrated. Cutaneous SS lesions are similar, but usually more intense than those in erythrodermic MF; patients may show alopecia, pruritus and often palmoplantar hyperkeratosis. Histologically, in the skin, the lymphoma infiltrate mimics that of MF, consisting of small to medium sized pleomorphic T lymphocytes, but the epidermotropism may be lost. The demonstration of an increased number of CD4⁺ T-lymphocytes, with an increased percentage of CD4⁺/CD7⁻ or CD4⁺/CD26⁻ lymphocytes and an elevated concentra-

tion of lactate dehydrogenase (LDH) are useful diagnostic parameters. The bone marrow is often infiltrated (sparse and interstitial pattern). SS is an aggressive disease with a poor outcome (the 5-year overall survival is between 10–20%). Progression or transformation into a large cell lymphoma may occur as a terminal event. However cases with an intermediate or indolent progression may be observed, showing leukemic blood involvement, with mild cutaneous erythroderma and absence of lymphadenopathy.

Outcome and therapy

MF is generally characterized by an extremely slow and long natural history. Patients with limited disease usually have an excellent prognosis with a survival similar to that of the background population; in such cases, the disease remains confined to the skin for many years. The risk of extracutaneous spread (initially to regional lymph nodes but later also to the spleen, lungs and liver) may occur as the stage or extent of disease increases. In the more advanced stages, the prognosis is poor with possible transformation into a high grade T-cell lymphoma. Infections (e.g. *Staphylococcus aureus*) still represent one of the major fatal complications in advanced stage MF. Treatment of early stage of MF¹⁶ includes local or systemic steroids, topical nitrogen mustards (NH₂, BCNU), local or systemic psoralens in association with UV-A irradiation (PUVA, Bath-PUVA), interferon- α 2a/b, retinoids, or a combination of the last three modalities. Extracorporeal photophoresis can be used in erythrodermic phase. Local radiotherapy, methotrexate (10–20 mg/weekly) and cyclophosphamide (50–100 mg/day) can also induce partial or complete clinical remissions in stage II–IV of the disease. Experimental trials with vaccines (dendritic cells immunized by using tumor-specific sequences or stimulated by lysate of tumor cells) have also been done. Total body irradiation has now been abandoned or is restricted to MF in later stages, in which systemic mono or polychemotherapy, autologous or allogeneic bone marrow transplantation can also be used. However, in advanced MF cases the response is unsatisfactory in most cases, in spite of aggressive therapy. Stem cell transplantation has recently been attempted in CTCL, including cases of advanced stages MF, with encouraging results.¹⁷

Primary cutaneous CD30⁺ lymphoproliferative disorders (lymphomatoid papulosis, primary cutaneous anaplastic large cell lymphoma and *borderline lesions*)

Definition, epidemiology and clinical features

A spectrum of CD30⁺ primary cutaneous lymphoproliferative disorders (PCLD) with a relatively favorable

prognosis has been described.¹⁸ This spectrum includes lymphomatoid papulosis (LyP), (anaplastic/pleomorphic) large cell CD30⁺ lymphoma (LCL) and *borderline lesions*, the latter showing clinicopathologic features in between LyP and LCL. Cases previously clinically diagnosed as *regressing atypical histiocytosis (RAH)* are now considered to be LCL with prominent regressive features. Apart from MF, the CD30⁺ PCLD account for 25% of all primary CTCL. The features common to all these PCLD are large atypical CD30⁺ cells sometimes resembling Hodgkin and Sternberg-Reed (HSR) cells and, clinically, a frequent partial or complete spontaneous regression of the skin lesions.

Lymphomatoid papulosis

Clinical features and morphology

LyP is a self-healing rhythmic, paradoxical often generalized eruption histologically mimicking a malignant lymphoma, but clinically benign.¹⁹ LyP presents as recurrent crops of reddish papulo-nodular lesions which regress spontaneously (within few weeks) leaving only a small scar or area of altered pigmentation. It usually affects adults but less frequently also elderly patients and children. The trunk and extremities, other than the palms and soles, are the most frequently affected areas (Figure 4A). Some patients may have several skin eruptions within a short period of time, others may have only a few over several years. Classical LyP lesions progress through four clinical stages referring to the natural history and age of the lesions: stage I, early lesions (erythematous dermal papule); stage II, developing lesions (clinical features in between stage I and stage III); stage III, fully developed lesions (hemorrhagic/ulcero-necrotic or crusted papular or nodular lesion); stage IV, resolving lesions (occasionally leaving a varioliform scar or a small area of altered pigmentation). Histologically, the classic LyP lesions show a *wedge-shaped* pattern of dermal involvement with superficial and deep perivascular lymphoid infiltrates (Figure 4B). LyP cellular infiltrates consist of CD30⁺ atypical cells, which may be scattered or in small clusters (2–5 atypical cells), admixed with a reactive cellular background (neutrophils, eosinophils and histiocytes) (Figure 4C–D). The above described composition of LyP cellular infiltrate corresponds to the LyP type A described by Willemze *et al.*,²⁰ who also defined two additional subtypes of LyP (type B and type C). LyP type B consists of a band-like infiltrate of small atypical lymphocytes with cerebriform nuclei and a few inflammatory cells (including eosinophils), but lacking the large atypical CD30⁺ cells. LyP type C has been described as a nodular infiltrate of cohesive sheets of large atypical CD30⁺ cells admixed with a variable number of inflammatory cells.

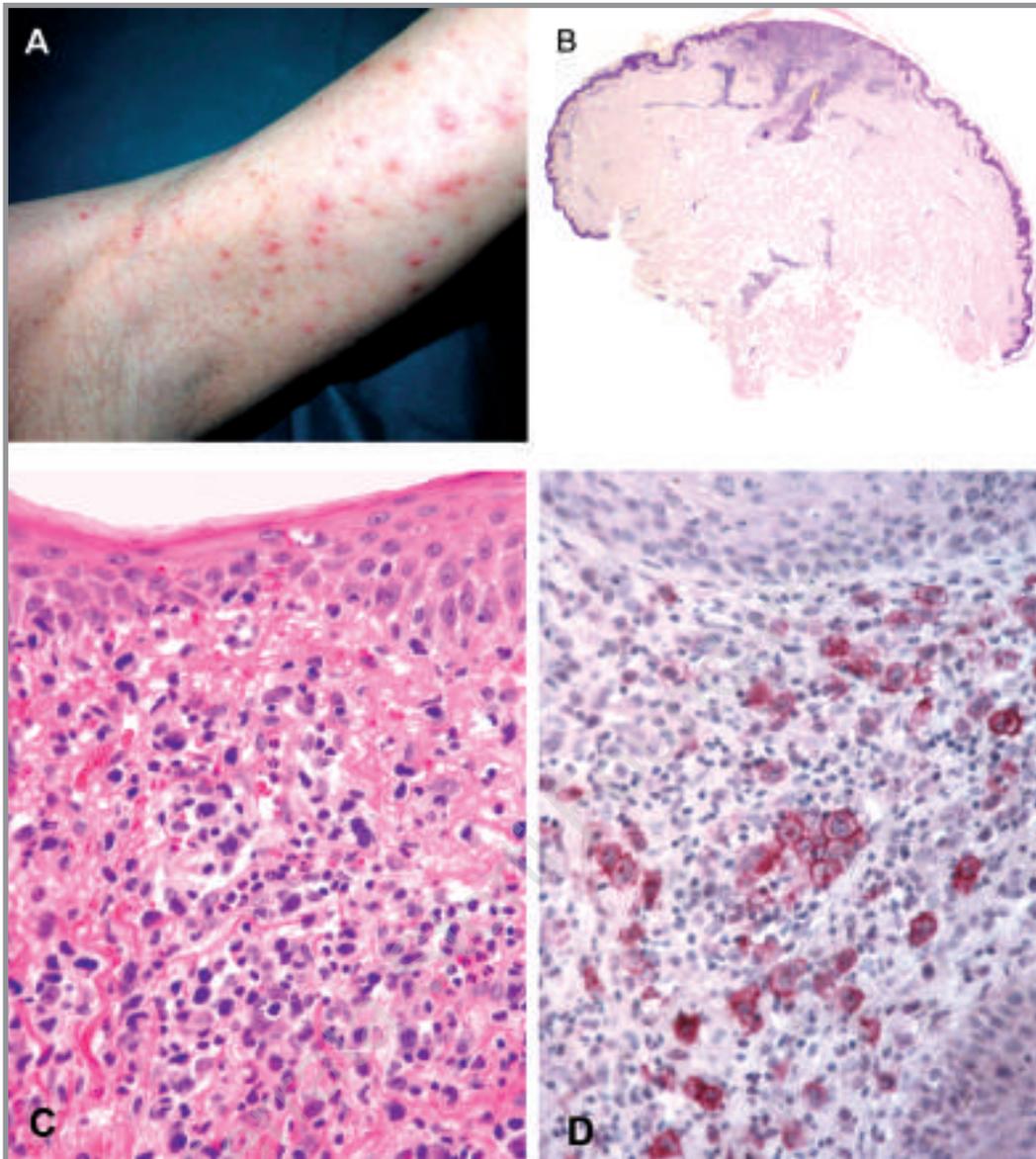


Figure 4. A. Lymphomatoid papulosis (LyP): the patient presents reddish papulo-nodular lesions involving the trunk and extremities. B. Histologically, the classical LyP shows a typical *wedge-shaped* dermal cellular infiltrate. (HE, $\times 20$) consisting of (C) large atypical cells admixed with a reactive cellular background (neutrophils, eosinophils and histiocytes) (HE, $\times 200$). D. The large atypical LyP cells strongly express the CD30/Ki-1 antigen (membrane and paranuclear *dot-like* reactivity). (APAAP, $\times 200$).

However it is relevant to note that (i) LyP type B is often histologically indistinguishable from early MF and the absence of CD30⁺ cells enhances the diagnostic difficulties (ii) LyP type C is histologically indistinguishable from CD3⁺ LCL and/or borderline lesions. However, both LyP type B and C seem to differ both histologically and, in part, clinically from the LyP features originally described by Macaulay. Thus, the diagnosis of any LyP other than the classical type A requires caution and should be made only after other differential diagnostic possibilities have been evaluated and excluded.

Immunohistochemistry, molecular biology and cytogenetics

In the classical (type A) LyP the atypical CD30⁺ cells have a CD4⁺ T-helper phenotype (CD3⁺, CD4⁺, CD8⁻);²¹ aberrant phenotypes with loss of one or other of the T-cell antigens may occur. Atypical LyP cells are also positive for various cytotoxic granule-associated proteins (TIA-1, perforin and granzyme B).²² Rare cases of LyP with a natural killer phenotype (CD30⁺; CD56⁺; CD3⁻; CD4⁻; CD8⁻) have been reported²³ and CD15 may be expressed in cases of LyP associated with MF or classi-

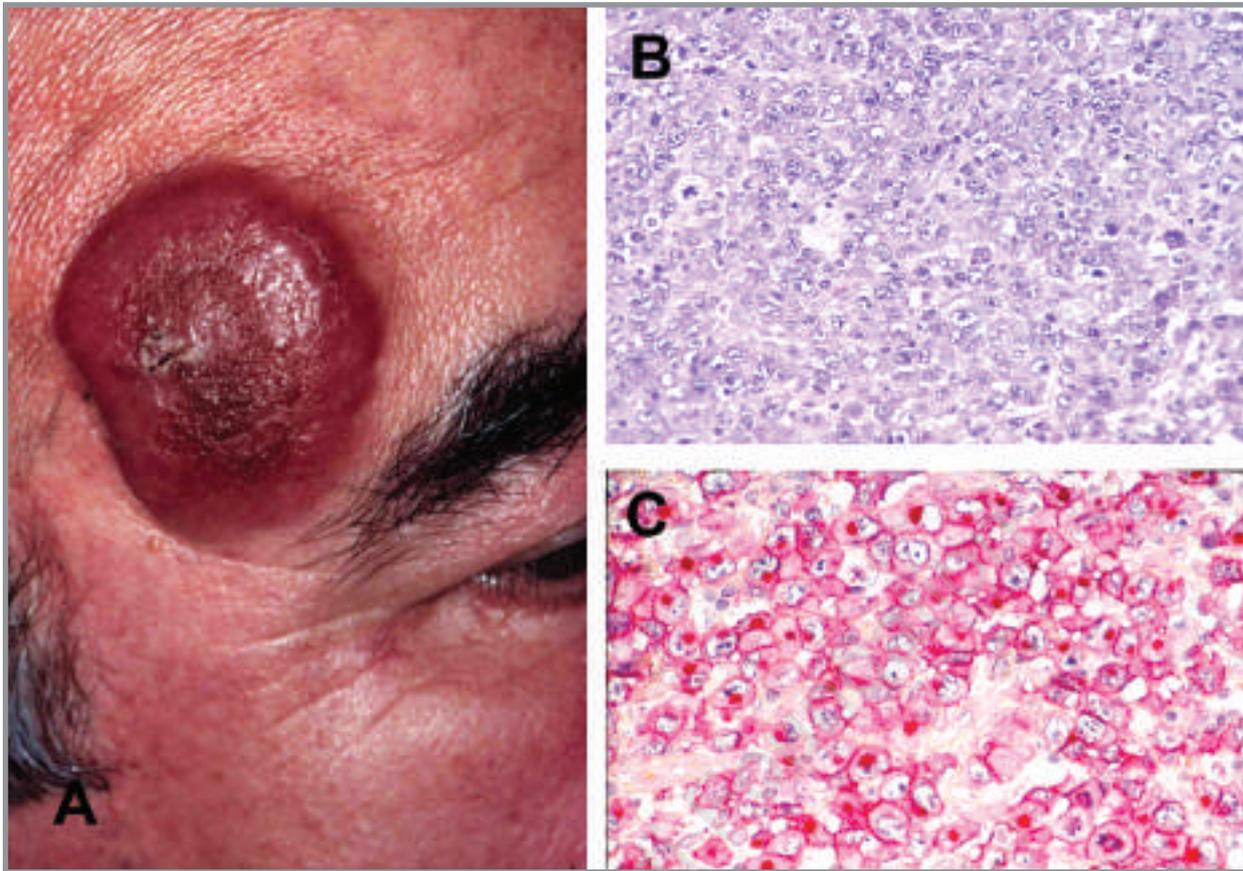


Figure 5. A: CD30⁺ primary cutaneous anaplastic large cell lymphoma: the patient presents a large reddish tumor lesion. **B:** histologically, the lymphoma population is composed of a predominant population of large, anaplastic cells (HE, ×200) which (C) uniformly and strongly express the CD30/Ki-1 antigen (APAAP, ×400).

cal Hodgkin's lymphoma. Clonal rearrangement of TCR genes can be demonstrated in about 40% of cases and, indeed, a higher percentage of clonal rearrangement has recently been reported²⁴ in a study using TCR- γ analyses on DNA extracted from CD30⁺ laser-microdissected cells instead of on DNA obtained from the whole cellular infiltrate. It is currently widely accepted that neither t(2;5), nor ALK protein expression is found in CD30⁺ PCLD.²⁵ Searches for Epstein Barr virus (EBV) RNA or EBV gene products are similarly negative.

Differential diagnoses

LyP must be differentiated from other CD30⁺ PCLD, rare cases of primary or secondary cutaneous Hodgkin's lymphoma and also from reactive CD30⁺ skin lymphoid infiltrates including follicular lymphoid hyperplasia with a high content of activated CD30⁺ blast cells,²⁶ cutaneous infection by parapoxvirus (i.e. milker's nodule)²⁷ and drug reactions.²⁸

CD30⁺ large cell lymphoma

Clinical features and morphology

LCL usually presents as a single or multiple medium-sized to large reddish nodules or tumors (Figure 5A) that may initially show temporary regression, but often persist; loco-regional lymph node involvement occurs in about 10% of cases, but visceral spread is rare.²⁹ Cases previously clinically diagnosed as regressing atypical histiocytosis (RAH) characterized by a single nodular lesion (Figure 6A), often superficially ulcerated or crusted, are now considered to be CD30⁺ ALCL with prominent regressing features.³⁰ CD30⁺ cutaneous LCL usually affects adults and elderly patients and less frequently children and adolescents. Morphologically the LCL lesions show a grossly nodular and/or diffuse pattern of dermal involvement with frequent extension to the subcutis (Figure 5B). In some cases the overlying epidermis may show a variable degree of pseudo-epitheliomatous hyperplasia, which may be pronounced in the cases pre-

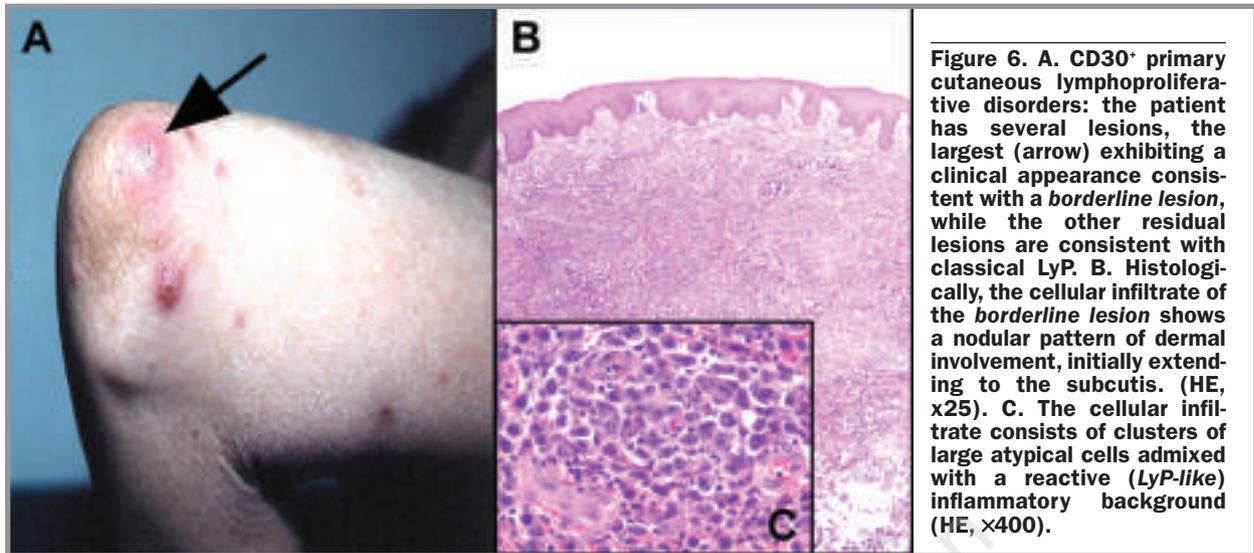


Figure 6. A. CD30⁺ primary cutaneous lymphoproliferative disorders: the patient has several lesions, the largest (arrow) exhibiting a clinical appearance consistent with a *borderline lesion*, while the other residual lesions are consistent with classical LyP. B. Histologically, the cellular infiltrate of the *borderline lesion* shows a nodular pattern of dermal involvement, initially extending to the subcutis. (HE, x25). C. The cellular infiltrate consists of clusters of large atypical cells admixed with a reactive (LyP-like) inflammatory background (HE, x400).

viously classified as RAH. The lymphoma population consists of large anaplastic cells grouped in large, confluent cohesive sheets; transepidermal elimination mostly occurs in the *RAH* forms, which are also characterized by an intense reactive/inflammatory cellular background. In the WHO lymphoma classification,¹ the category of cutaneous CD30⁺ LCL only includes cases displaying the classic anaplastic cytology; in contrast the EORTC scheme² identifies three different subtypes of CD30⁺ LCL: anaplastic, immunoblastic and pleomorphic. However, this cytomorphologic differentiation has limited/no clinical relevance because the outcome of CD30⁺ cutaneous lymphomas is favorable, irrespectively of the anaplastic *versus* non-anaplastic (immunoblastic, pleomorphic) cytology.²⁹ Furthermore, at least in some cases, the fixation and embedding procedures might be responsible for technical artefacts resulting in cytomorphological features of the lymphoma cells.

Immunohistochemistry, molecular biology and cytogenetics

A *conditio sine qua non* for a diagnosis of CD30⁺ LCL is the detection of the CD30 (Figure 5C) in almost 75% of the lymphoma cells;²⁹ if only scattered positive cells are found the lymphoma must be classified into another subtype. Other antigens expressed include CD25, HLA-DR, CD71 and EMA, although this last was reported as negative in some previous studies. Most CD30⁺ LCL have a peripheral T-helper phenotype (CD3⁺;CD4⁺;CD8⁻)²¹ with variable loss of some T-cell markers (i.e. CD2; CD5; CD7) and expression of cytotoxic granule-associated proteins (i.e. TIA-1; perforin and granzyme B). Less than 10% of cases have a CD8⁺ phenotype and sporadic cases show a *null* (non-B, non-T) phenotype. CD56 expression is rare and, in contrast with previously published data, its biological and prognostic rele-

vance is unknown. Cutaneous CD30⁺ LCL are uniformly negative for CD15. Clonal rearrangement of the TCR genes can be demonstrated in most primary CD30⁺ cutaneous LCL, including the majority of cases with a *null* (non-B, non-T) phenotype. t(2;5) is not associated with CD30⁺ PCLD,²⁵ which also lack the ALK protein. Recently, an allelic deletion at 9p21-22 was reported³¹ in a small number of cases of cutaneous CD30⁺ LCL, but confirmation on large series of cases is awaited.

Differential diagnoses

CD30⁺ LCL must be differentiated respectively from other CD30⁺ PCLD and large cell pleomorphic/anaplastic, but CD30 negative, primary cutaneous T-cell lymphomas. It is also clinically relevant to distinguish between primary cutaneous CD30⁺ LCL and secondary/transformed CD30⁺ LCL that have progressed from other primary cutaneous lymphomas (mostly MF), the latter being characterized by an aggressive clinical course and poor outcome. The absence of ALK protein in the CD30⁺ PCLD, including LCL, may be useful, particularly in children and young adults, for distinguishing these lesions from a secondary skin dissemination of systemic (nodal) CD30⁺ ALCL which are often ALK positive. However, caution is required when interpreting such a finding because cases do exist of systemic (nodal) but ALK negative CD30⁺ ALCL, mostly affecting middle-aged and elderly patients. Loco-regional lymph node involvement may occur in primary cutaneous CD30⁺ LCL, but clinical evidence seems to indicate that it does not affect prognosis, which remains favorable in most cases. A partial or less frequently complete spontaneous regression of the lymphoma has been reported (in up to 25% of cases in certain series). Risk factors predictive for extracutaneous lymphoma spread (10% of cases) are presently unknown.



Figure 7. A. Subcutaneous panniculitis-like T-cell lymphoma: the patient presents multiple lipoma-like subcutaneous nodules involving the trunk and extremities. B. The lymphoma infiltrates the subcutaneous adipose tissue and consists of small to medium-sized pleomorphic lymphocytes (HE, $\times 200$). C. Lymphoma cells intensely express cytotoxic molecules (perforin) (SABC, $\times 400$).

Borderline lesions

Within the spectrum of primary cutaneous lymphoproliferative disorders, the term *borderline lesions* refers to a group of cases with divergent clinical features and histological appearance, preventing them from being readily distinguished from LyP or CD30⁺ ALCL.^{1,32} Instead of the term *borderline lesions* the EORTC classification² has introduced the term LyP type C, to identify cases with similar clinical and morphological features. We prefer the term *borderline lesions* because it fits the ambiguous features of such rare cases well. Borderline lesions usually present with solitary, nodular lesions rather than papular ones, but cases with *LyP-like* papular appearance have been described (Figure 6A). The lesions may ulcerate and undergo partial or complete spontaneous regression. Histologically, they exhibit features in between LyP and ALCL with a nodular pattern of dermal involvement, sometimes extending to the subcutis (Figure 6B). The cellular infiltrate consists of atypical CD30⁺ anaplastic cells grouped in clusters but often admixed with a mild to prominent reactive *LyP-like* cellular background (Figure 6C). In some areas, mostly in the deepest part of the lesions, the CD30⁺ cells may form large confluent sheets. Apoptotic features can be numerous. Associated dermal and/or epidermal modifications include spongiosis, parakeratosis, epidermal pseudoepitheliomatous hyperplasia and, often, ulceration. Borderline lesions are rare and limited data are available on their biological features, but it seems that their antigenic and molecular features largely overlap with those just described for the LyP and CD30⁺ LCL cellular infiltrate.¹ Borderline lesions must be differentiated from other CD30⁺ PCLD, but no reliable clinicopathologic criteria exist which allow a clear-cut distinction between borderline lesions and LyP or CD30⁺ LCL.

CD30⁺ PCLD: outcome and therapy

CD30⁺ PCLD have a very favorable clinical outcome in most cases. In spite of its postulated association with malignant lymphoma (up to 20% in certain series and mostly MF and Hodgkin's lymphoma),³³ LyP has an excellent prognosis preventing the patients from receiving unnecessary aggressive treatment.^{32,34} Possible therapies should therefore be directed mainly at controlling symptoms or slowing down the rate of relapses. Systemic steroids and PUVA have been used with partial success; some favorable results have also been achieved with low-dose methotrexate over a long period of time. Limited information is available on the prognostic outcome of the borderline lesions; although it has been suggested that patients with borderline lesions have a higher risk of developing a CD30⁺ LCL than do LyP patients, most of these cases have a favorable outcome similar to LyP.^{30,32} The prognosis of primary cutaneous CD30⁺ LCL is good, but less favorable than that of LyP and borderline lesions because some of the patients with multifocal skin disease may develop extracutaneous disease.^{32,34} However, the involvement of a single loco-regional lymph node does not seem to affect prognosis adversely. In cases with disease confined to the skin, local therapy (i.e. surgical excision and radiotherapy) is recommended; chemotherapy is reserved to cases with multifocal or generalized skin disease at high risk of visceral spread.

Cutaneous lymphomas expressing a T-cytotoxic or natural killer cell phenotype

As confirmed by a recent study of the EORTC Cutaneous Lymphoma Task Force, "...cutaneous lymphomas expressing a cytotoxic or natural killer (NK) cell phenotype represent a group of lymphoproliferative disorders for

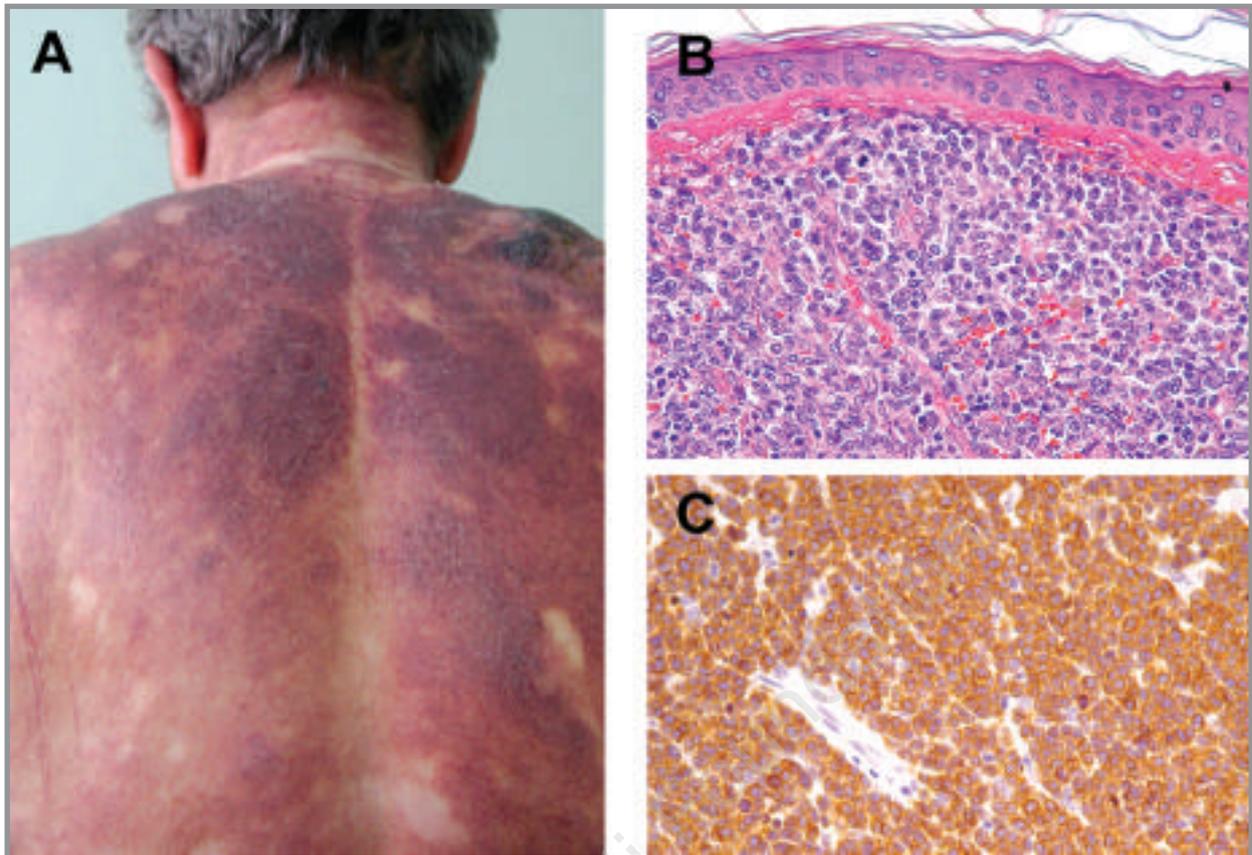


Figure 8. A. Blastic NK lymphoma/leukemia: the patient presents diffuse reddish to bluish infiltrated plaques. **B. Histologically,** the skin lesion consists of a densely packed dermal and subcutaneous infiltrate composed of medium to large cells, sometimes resembling myeloid blasts (HE, x200) which express **(C) the CD56/ NCAM antigen (SABC, x200).**

which there is currently much confusion and little consensus regarding the best nomenclature and classification...³⁵ In particular, it is debated whether at least some of these malignancies can indeed be retained as primary cutaneous lymphomas or whether they actually represent the first manifestation of a systemic lymphoma/leukemia which involves the skin secondarily. The major subtypes of T/NK lymphomas listed in the WHO lymphoma classification¹ include the subcutaneous panniculitis-like T-cell lymphoma, the extranodal NK/T-cell lymphoma, nasal type, and the blastic NK-cell lymphoma.

Subcutaneous panniculitis-like T-cell lymphoma

Clinical features and morphology: Subcutaneous panniculitis-like T-cell lymphoma (SPLTCL) is a rare, aggressive lymphoma subtype which preferentially infiltrates the subcutaneous tissue,³⁶ expressing a cytotoxic CD8⁺ or CD56⁺ phenotype.^{37,38} SPLTCL affects both sexes and people of a broad age range, including children and young adults. Lymphoma lesions consist of multiple subcutaneous nodules and/or erythematous, infiltrated plaques (CD8⁺ cases) or ulcerated skin tumors (CD56⁺), mostly located on the trunk, extremities, and face (Fig-

ure 7A). Clinical symptoms include malaise, fatigue, myalgia and weight loss; manifestations of systemic involvement are fever, hepatosplenomegaly, mucosal ulcers and sometimes serosal effusions. Some patients may develop hemophagocytic syndrome, a complication often precipitating the clinical course.³⁹ Such cases may have been diagnosed in the past as *malignant* cytophagic histiocytic panniculitis (CHP).³⁶ Morphologically, the lymphoma infiltrate involves the lobules of the subcutaneous tissue, resulting in a typical lobular-panniculitis-like pattern (CD8⁺ cases)(Figure 7B), although in some cases (usually CD56⁺) dermal and epidermal involvement may be seen.³⁷⁻³⁸ The lymphoma cells are small to medium in size with moderate pale cytoplasm; the nuclei are round to irregular to indented/pleomorphic and often hyperchromatic. The lymphoma cells tend to surround individual fat cells giving these latter a typical rimmed appearance. A variable number of reactive non-neoplastic histiocytes can be found, scattered and close to the areas of necrosis. Apoptotic bodies (karyorrhectic nuclear fragments) are a frequent finding but an angiocentric and/or angiodestructive pattern are not among the typical histological features of SPLTCL.

Table 1. T-cell and NK- lymphomas (according to the WHO 97 lymphoma classification) with frequent or constant skin involvement.**Primary cutaneous T-cell lymphomas**

Mycosis fungoides
Sézary's syndrome
Primary cutaneous CD30⁺ lymphoproliferative disorders
Subcutaneous panniculitis-like T-cell lymphoma

Other T-or NK-cell Lymphomas with primary or secondary skin involvement.

Extranodal NK/T-cell lymphoma, nasal type
Blastic NK-cell lymphoma/leukemia
Precursor T-lymphoblastic lymphoma/leukemia

Table 2. Primary cutaneous T-cell lymphomas, other than MF, listed in the EORTC classification.**Indolent**

Large cell CD30⁺ CTCL
Lymphomatoid papulosis

Aggressive

Large cell CD30 negative CTCL
CTCL, pleomorphic small/medium-sized*
Subcutaneous panniculitis-like T-cell lymphoma*

*: provisional entities.

Immunohistochemistry, molecular biology and cytogenetics

The lymphoma cells express the CD2⁺; CD3⁺; CD45RO⁺ T-cell phenotype; but may express CD8⁺; CD4⁻; CD45RO⁺, CD56⁻, BF1^{-/+} or the CD56⁺; CD4⁻, CD8^{-/+}, BF1^{-/+}, TCR- δ -1^{-/+} T-cell associated molecules,⁴⁰⁻⁴¹ with expression of cytotoxic molecules (i.e. TIA-1, granzyme B and perforin) (Figure 7C). Most cases derive from α/β T-cells but about 10% to 25% of CD56⁺ PLTCL have a γ/δ origin.^{37-38,41} In some cases a minority of the neoplastic cells may express the CD30 antigen. Clonal rearrangement of the TCR can be found in most cases;⁴¹ search for EBV is negative in most cases.^{40,41} To date, no specific genetic features have been associated with this lymphoma. However, in a child affected by SPLTCL, we have recently documented defective expression of the perforin gene (*unpublished data*), an abnormality that is known to be associated with familial hemophagocytic syndrome.⁴²

Differential diagnoses

The subcutis is a primary site of numerous pathological changes, most of which are inflammatory. Differentiation from non-neoplastic mainly lobular panniculitis (erythema induratum-nodular vasculitis, lupus panniculitis and connective tissue-related panniculitis, etc.) and from other subtypes of CTCL mainly relies on the peculiar clinical features (subcutaneous lesions coupled

with systemic symptoms) of SPLTCL rather than on morphologic and immunophenotypic features which are less distinctive. However, the presence of a discrete infiltrate formed by pleomorphic hyperchromatic lymphoid cells forming a rim around the individual fat cells may be indicative of a lymphoma involving the subcutaneous tissues, whereas the presence of reactive B-follicles is indicative of an autoimmune disorder (*lupus panniculitis*). A definitive diagnosis of SPLTCL may require multiple sequential biopsies of the lesions and confirmation by molecular analyses.

Outcome and therapy

The clinical behavior and outcome of PLTCL is variable but the median survival is usually less than 3 years. In most cases this lymphoma has an aggressive clinical course; nodal and/or visceral spread may occur but in the end-stage of the disease. Hemophagocytic syndrome and sepsis are frequent and often fatal complications. However, two different studies have recently reported that patients with SPTCL with a α/β phenotype have a more favorable prognosis than those with a γ/δ phenotype.^{37-38,43} Future studies might clarify whether these two molecular subtypes should be clinically separated. To date the choice treatment for SPTCL consists of aggressive systemic chemotherapy which, in sporadic cases, has been followed by autologous bone marrow transplantation.⁴⁴

Extranodal NK/T-cell lymphoma, nasal type**Clinical features and morphology**

NK/T-cell lymphoma nasal and nasal type^{45,46} are relatively frequent in Asia, Mexico, Central and South America but they only sporadically occur in European countries. This lymphoma has a predilection for extranodal sites, in particular the nasal cavity and nasopharynx⁴⁵ but the skin, soft tissues and intestine can also be involved;⁴⁷ nodal spread is uncommon. Similar lesions located on the nose have previously been called *lethal midline granuloma*. The patients usually have advanced stage disease at presentation with multiple extranodal sites of disease and often peripheral blood involvement; hemophagocytic syndrome is a possible complication. Clinically, the skin lesions consist of nodules, frequently ulcerated, but plaques, purpuric and/or bullous lesions, erythematous macular-papular rashes and subcutaneous panniculitis-like lesions have also been observed. The most frequent sites of skin involvement include the face, trunk and the extremities; nasal disease may follow presentation in the skin. The histological features of this lymphoma are similar irrespectively of the primary disease site (nasal vs extranasal).⁴⁸ The

lymphoma infiltrates the dermis and subcutis showing a diffuse growth pattern. Angiocentric and angiodestructive features are frequent and associated with fibrinoid changes, coagulative necrosis and the presence of numerous apoptotic bodies. The lymphoma cells have a broad spectrum of cytological appearances from small to medium-sized to large-anaplastic; however, in most cases, the predominant lymphoma population consists of medium to large cells. Nuclei may be irregular, elongated or vesicular; cytoplasm is usually pale to clear and moderate in amount. The lymphoma population may be accompanied by a heavy inflammatory background of histiocytes, plasma-cells and granulocytes (mostly eosinophils).

Immunohistochemistry, molecular biology and cytogenetics

The lymphoma cells have a CD2⁺, CD56⁺, CD3c⁺, CD43⁺, CD45RO⁺ phenotype and lack surface CD3,^{45,46,49} other T- and NK cell markers (i.e. CD4, CD5, CD8, CD16 and CD57) are usually negative, whereas the new specific NK-cell markers CD94, PEN-5 (CD161) and Nkp46 are usually positive, but only if tested on frozen sections.⁵⁰ CD7 and CD30 may be sporadically expressed. Cytotoxic granule-associated proteins (TIA-1, perforin and granzyme B) are positive in most cases. Usually, the TCR and immunoglobulin genes are in germline configuration.⁵¹ In the vast majority of cases, EBV can be detected by means of various techniques (ICH, ISH and molecular investigations) thus suggesting a possible pathogenetic role for this virus.⁵² Various cytogenetic abnormalities, particularly del(6)(q21q25) and i(6)(p10) have been reported, but so far no specific chromosomal translocation has been identified.⁵³

Differential diagnoses

Differential diagnoses are other T/NK malignancies (i.e. blastic NK lymphoma/leukemia and SPLTCL), a few cases of CD30 negative peripheral T-cell lymphoma and, rarely, inflammatory processes. The presence of the EBV (which is always negative in blastic NK lymphoma/leukemia) is a useful and distinctive diagnostic parameter coupled with the usual absence of the CD4. The presence of EBV, the antigenic profile, the germline configuration of the TCR and the clinical features also facilitate the distinction between the rare cases of this lymphoma characterized by pronounced subcutaneous infiltrates and otherwise typical cases of SPLTCL.

Outcome and therapy

The prognosis of these lymphomas is variable but they generally have an aggressive clinical behavior associated with a high mortality rate despite aggressive chemotherapy.^{45,47} To date, no real predictive prognostic marker has been identified.

Blastic NK-cell lymphoma/leukemia

Clinical features and morphology

This unfrequent subtype of lymphoma/leukemia⁵⁴ usually affects middle-aged or elderly patients. The lymphoma tends to involve multiple sites⁵⁵ with a predilection for the skin and soft tissues; however, lymph nodes, peripheral blood and bone marrow can also be involved. Clinically the skin localizations appear as reddish to bluish, often purpuric, nodules, tumors and/or infiltrated plaques (Figure 8A), sometimes ulcerated.^{56,57} Histologically the skin lesions consist of a densely packed dermal and often subcutaneous cellular infiltrate that often shows a periadnexal and perivascular distribution. Cytologically, the neoplastic cells vary in size and shape, from medium to pleomorphic to large elements resembling myeloid blasts; chromatin is finely particulate and nucleoli are inconspicuous (Figure 8B). Apoptotic phenomena and an angiocentric/angiodestructive pattern are not prominent in blastic NK lymphoma. Mitoses are frequent.

Immunohistochemistry, molecular biology and cytogenetics

The neoplastic cells have a CD4⁺, CD56⁺ (Figure 8C); CD43⁺; CD45RA^{+/-}; CD123⁺; TDT^{+/-}; TCL-1^{+/-} phenotype; CD68 is frequently expressed, whereas CD2, CD7, cytoplasmic CD3 and cytotoxic molecules (TIA-1, granzyme-B) are variably expressed,^{56,57} some cases may be positive for CD34.⁵⁸ There is no rearrangement of the TCR and the search for EBV is always negative.⁵⁸

Differential diagnoses

Because of the morphologic and, in part, antigenic overlap between lymphoblastic and myeloblastic neoplasms the diagnosis of blastic NK lymphoma requires caution and should only be made in the absence of commitment to the T-cell or myeloid lineages (negativity for CD3s, MPO and CD33). These malignancies have been variably classified and the cell of origin has been proposed to be an NK-cell precursor, an immature myelo-monocyte precursor, or a mixed NK/myelomonocyte precursor. In the WHO lymphoma classification these cases are considered as blastic NK-cell lymphoma.¹ However, there are accumulating findings that reveal very close similarities between the phenotypic features of this lymphoma/leukemia and plasmacytoid dendritic cells (P-DC), thus suggesting their possible relationship and origin from this subpopulation. Such a hypothesis has been supported by *in vitro* experiments showing that the leukemia cells may be modulated to function as P-DC and to secrete interferon- α . On such bases it has been proposed to rename this entity as early pDC leukemia/lymphoma.⁵⁶ However, additional experimental investigations are required to clarify unequivocally



the exact lineage from which the cells of the *blastic-NK lymphoma/leukemia* originate.

Outcome and therapy

This lymphoma/leukemia usually pursues a very aggressive clinical course and the disease often terminates with massive bone marrow infiltration, overt leukemia and sometimes neurological involvement.⁵⁵ In certain series the median survival after diagnosis was 30 months (ranging between 14 and 46 months).⁵⁶ The response to conventional regimens used for non-Hodgkin's lymphomas is poor but a partial one may be achieved, at least in some cases, using an *acute leukemia-like* regimen; however relapses rapidly occur.⁵⁶ In a study only 2 allotransplanted patients were reported as long survivors.⁵⁷ It has been suggested that patients with lesions confined to the skin may have a better prognosis, but these observations need to be confirmed on larger series.⁵⁹

Peripheral T-cell lymphoma, not otherwise specified (PTL NOS) (WHO 2001)

Clinical features and morphology

This is a controversial category of T-cell malignancies. The EORTC cutaneous lymphoma classification² distinguished various subtypes of peripheral primary cutaneous T-cell lymphomas other than MF, namely, pri-

mary cutaneous CD30 negative large T-cell lymphomas and the pleomorphic small/medium sized CTCL (included among the provisional entities). In contrast, since a number of distinct entities corresponding to recognizable subtypes of nodal and/or extranodal T-cell malignancies have already been separately described, the WHO lymphoma classification¹ found no clinical justification to subtype the remaining group of nodal and (sporadically) extranodal T-cell malignancies further. Thus, this group of T-cell lymphomas has been referred to by using the term unspecified, highlighting that they do not belong to any of the better defined entities. However, irrespectively of the terminology adopted in the different classifications, this heterogeneous category of T-cell malignancies accounts for about 50% of all peripheral T-cell lymphomas in western countries. They usually affect adults and the elderly although there are sporadic cases in children. The skin is often the site of presentation of an otherwise systemic disease⁶⁰ but exceedingly rare examples of true primary cutaneous forms exist and in two recent reports^{1-2,61} the frequency of these forms was 2.9% and 5% of all primary cutaneous lymphomas. Furthermore it seems that a small minority of primary cutaneous T-cell lymphomas previously classified in this category can be separated as a provisional entity: these include cutaneous γ/δ T-cell lymphomas, aggressive epidermotropic CD8⁺ cytotoxic lymphomas and small-medium pleomorphic CD4⁺ T-cell lymphomas. Cases previously clinically diagnosed as MF

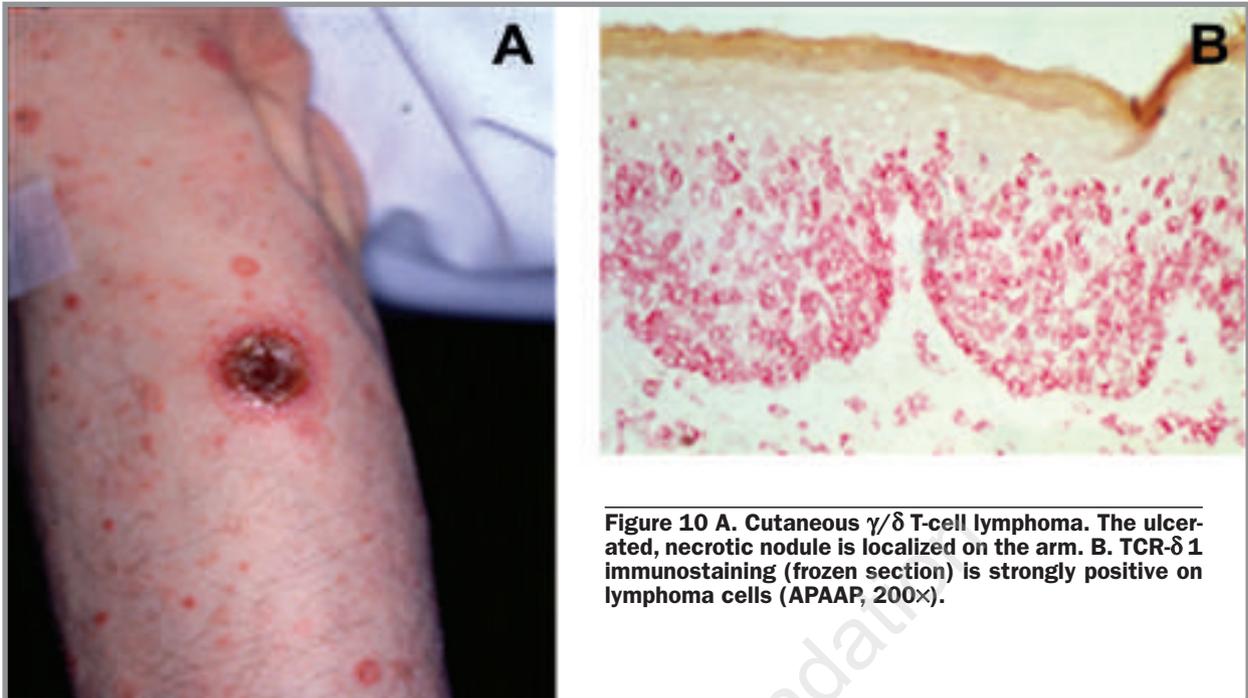


Figure 10 A. Cutaneous γ/δ T-cell lymphoma. The ulcerated, necrotic nodule is localized on the arm. B. TCR- δ 1 immunostaining (frozen section) is strongly positive on lymphoma cells (APAAP, 200 \times).

tumeur d'emblée and some primary CTCL with angio-centric features are probably included within this category and are described below in more detail.

PTL NOS, rare variant: aggressive epidermotropic CD8⁺ cytotoxic lymphoma (AeCD8⁺cx)

Clinical features and morphology

AeCD8⁺cx lymphoma is a very rare form of cutaneous T-cell lymphoma, first reported by Jensen *et al.* in 1980.⁶² In 1999 Berti *et al.*⁶³ reported 8 cases of AeCD8⁺cx lymphoma and compared them with 9 cases expressing CD8⁺, but classifiable as indolent lymphomas (MF or CD30⁺-like disorders), suggesting a possible new entity with an aggressive clinical behavior. The clinical presentation is characterized by a sudden eruption of localized or disseminated nodules with central necrosis, (Figure 9A) or by superficial, hyperkeratotic patches and plaques as in pagetoid reticulosis (Ketrion-Goodman type). AeCD8⁺cx lymphomas histologically show an acanthotic or atrophic epidermis, necrotic keratinocytes and moderate to marked spongiosis, with blister formation. Tumor cells are small to medium or medium to large with pleomorphic or blastic nuclei (Figure 9B).

Prominent epidermotropism was observed in late tumor lesions, with a linear configuration in the basal cell layer or involvement of the entire epidermis with a pagetoid pattern; adnexal involvement, angiocentricity and angioinvasion were frequently observed.^{36,64}

Immunohistochemistry, molecular biology and cytogenetics

AeCD8⁺cx lymphomas express a β -F-1⁺, CD3⁺, CD8⁺, TIA-1⁺, CD45RA⁺, CD45RO⁻, CD2⁻, CD5⁻, phenotype.^{36, 64} No consistent genetic alterations have been identified, and there is no involvement of EBV or other oncogenic viruses.

Differential diagnoses

SPTCL, nasal and extranasal NK/T T-cell lymphoma, γ/δ T-cell lymphoma, rare cases of mycosis fungoides, and CD30⁺ primary cutaneous anaplastic lymphomas may express CD8⁺ in the context of different clinicopathologic and immunohistochemical features.^{63,65}

Outcome and therapy

Patients frequently show simultaneous visceral involvement or progression to visceral sites in less than 6 months. Polychemotherapy with or without doxorubicin and radiotherapy are the most frequently used forms of therapy. The median survival of the 8 analyzed patients with AeCD8⁺cx lymphoma was 32 months.⁶³

PTL/U, rare variant: primary cutaneous γ/δ T-cell lymphoma (PCGD-TCL)

Clinical features and morphology

PCGD-TCL is characterized by disseminated plaques and/or necrotic nodules and tumors.⁶⁶⁻⁶⁹ (Figure 10A), which occur more frequently on the extremities.⁶⁹⁻⁷⁰ The

lymph nodes, spleen and bone marrow are not usually involved but the disease may disseminate to extranodal/ mucosal sites. Histologically the infiltrate is formed by medium to large pleomorphic cells, with coarsely clumped chromatin and a few large blastic cells with vesicular nuclei and prominent nucleoli. Angiogenesis, apoptosis and necrosis are common. Three major histologic patterns of involvement can be observed: epidermotropic, dermal, and subcutaneous. Epidermal infiltration is variable, from mild epidermotropism to marked pagetoid pattern.^{63,71-73} Subcutaneous involvement may be panniculitis-like or more dense, without lymphocytes rimming the fat cells or foamy histiocytes. There is frequently co-existing dermal, epidermal and subcutaneous involvement.

Immunophenotype, molecular biology and cytogenetics

Neoplastic cells are TCR- δ -1⁺ (Figure 10B), CD3⁺, CD2⁺, CD7^{+/-}, CD5⁻.⁶⁷ Most cases lack CD4 and CD8 markers although some are CD8⁺.⁶⁶ The cells are positive for TIA-1 and the cytotoxic proteins granzyme B, and perforin.⁷⁴ CD56 is frequently expressed. The cells usually show clonal rearrangement of the TCR γ and TCR δ genes. TCR β may be rearranged or deleted, but is not expressed. EBV is generally negative in PCGD-TCL.⁷⁵

Differential diagnosis

The features of PCGD-TCL overlap with those of some cases of subcutaneous panniculitis-like T-cell lymphoma (SPTCL) and PCGD-TCL shares many features with other extranodal (usually CD8⁺) cytotoxic T-cell lymphomas.⁶⁹ A similar and closely related disease may present in mucosal sites; the exact relationship between γ/δ TCL in cutaneous and other extranodal sites is unclear.⁷⁵

Outcome and therapy

PCGD-TCL is an aggressive disease resistant to multiagent chemotherapy regimens and/or radiation.^{63,73} In fact, 66% (22 of 33) of analyzed patients were dead within 5 years of diagnosis; TCR- δ -1 expression was a negative prognostic index ($p < 0.0001$).⁷³

PTL/U: pleomorphic small/medium CD4⁺ lymphoma

Clinical features and morphology

This lymphoma is considered as a provisional entity in the EORTC classification² and does not fall into a specific category in the WHO classification, thus being termed as PTL/UN.¹ The patients must present with pri-

mary cutaneous papules and nodules without any sign of precursor lesions of MF, even during the follow-up. Two types of presentation and clinical course can be seen: some patients show solitary nodules, commonly located on the face, neck and upper part of the trunk, while others develop groups of papules, nodules and plaques in different sites of the body.^{76,77} Patients are usually adults with a median age of 65 years,⁷⁸ but isolated lesions can also be observed in children. The prognosis is favorable in the case of localized lesions⁶¹ and the lesions can be treated surgically or irradiated, while in cases with disseminated lesions the disease shows an intermediate grade of aggressivity,⁷⁸ characterized by frequent relapses and progression to lymph nodes and visceral organs, in spite of radio-polychemotherapy. The localized lesions show a nodular infiltrate in the entire dermis formed by pleomorphic small to medium-sized lymphocytes, with focal epidermotropism and a perivascular and periadnexal distribution, with possible granulomatous reactions.

Immunohistochemistry, molecular biology and cytogenetics

In the case of localized lesions the infiltrate expresses the CD3⁺, CD4⁺, CD7^{+/-}, CD45RO⁺ phenotype. In case of multiple tumoral lesions some pan T-cell markers (CD2, CD5) can be lost and the cells may express CD30 or CD56. A variable number of reactive B-lymphocytes and many macrophages can be present.

The infiltrate is usually clonal; no specific cytogenetic alterations have been reported.

Differential diagnosis

The existence of this entity is debated, mainly because of its clinicopathologic similarities with mycosis fungoides (unilesional MF, *tumeur d'emblée* MF) and in some cases also with pseudolymphomas of the T-cell type.

Outcome and therapy

Localized cutaneous pleomorphic small/medium T-cell lymphoma is usually confined to the skin and can be treated surgically or by local radiotherapy. In the case of multiple lesions and progression, locoregional lymph nodes are involved and the patients should be treated by *conventional* polychemotherapy.

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