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CONTROVERSIES IN DERMATOLOGY

Primary Cutaneous CD30⁺ Lymphoproliferative Disorders

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PALABRAS CLAVE

Linfomas cutáneos;
Síndrome
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Papulosis linfomatoide;
Linfoma anaplástico
de célula grande CD30⁺

Abstract

CD30⁺ lymphoproliferative disorders are the most common group of cutaneous T-cell lymphomas after mycosis fungoides and its subtypes. This group includes lymphomatoid papulosis and CD30⁺ anaplastic large-cell lymphoma; these 2 entities are the extremes of a spectrum with numerous intermediate varieties in which it is not possible to establish a clear diagnosis based on clinical and histopathologic criteria. CD30⁺ lymphoproliferative disorders must be differentiated from other lymphoproliferative diseases with CD30⁺ cells in the tumor infiltrates, such as mycosis fungoides or Hodgkin disease, and also from other inflammatory conditions or nonhematological neoplasms that can include this cell type, such as pityriasis lichenoides et varioliformis acuta or certain mesenchymal tumors (CD30⁺ pseudolymphomas). In contrast to their systemic homologues, which arise in the lymph nodes, CD30⁺ lymphoproliferative disorders generally have a good prognosis. It is very important to exclude the presence of a lymphoma of systemic origin with extralymphatic spread, as the prognosis and treatment are different.

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Síndrome linfoproliferativo CD30⁺ cutáneo primario

Resumen

El segundo grupo más frecuente de linfomas cutáneos de células T son los síndromes linfoproliferativos (SLP) CD30⁺, por detrás del grupo de la micosis fungoide (MF) y sus variantes. Estos engloban la papulosis linfomatoide y los linfomas anaplásticos de células grandes CD30⁺, polos de un espectro que dejan en su zona central casos intermedios, donde no se puede establecer con seguridad un diagnóstico en base a criterios clínicos e histopatológicos.

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Los SLP CD30+ deben diferenciarse de otros procesos linfoproliferativos que pueden presentar células CD30+ en sus infiltrados tumorales, como la propia MF o la enfermedad de Hodgkin, y también de otras entidades inflamatorias o neoplasias no hematológicas que presenten estas células, como es el caso de la pitiriasis liquenoide y varioliforme aguda o determinados tumores mesenquimales («pseudolinfomas CD30+»).

En general, el pronóstico de estos SLP CD30+ es favorable, lo que les diferencia de sus homólogos sistémicos, de origen ganglionar. Resulta muy importante descartar la presencia de linfoma de origen sistémico con afectación extraganglionar, pues el pronóstico y el tratamiento serán diferentes.

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Introduction

The scope of this review article on primary cutaneous CD30+ lymphoproliferative disorders (LPDs) will range from basic concepts to new therapies and diagnostic techniques. In addition, some of the most controversial aspects of this field will be discussed.

CD30 (Ki-1)

The CD30 antigen is a 120 kD transmembrane protein belonging to the tumor necrosis factor (TNF) α receptor superfamily.¹ The antigen has the same extracellular domain as other members of the family but the cytoplasmic region and, as a result, the signal transmission mechanisms are different. The gene encoding CD30 is located on chromosome 1p36, in close proximity to genes encoding other members of this family.

CD30L is the ligand of this receptor. It is also a transmembrane protein with an extracellular domain bearing close structural similarity to other proteins such as TNF- α and β and CD40L. The gene that encodes CD30L is located on chromosome 9q33.

CD30 is expressed on activated T and B cells, Reed-Sternberg cells, and Hodgkin cells (cells associated with,

although not pathognomonic of, Hodgkin disease). CD30L is expressed on activated T cells.

In normal lymph nodes, CD30 is present in a small population of large mononuclear cells with prominent nucleoli (T-cell and B-cell blasts) around the B-cell follicles (parafollicular cells) and in germinal centers (centroblasts). Similar cells can be found in the spleen and thymus. CD30+ cells are not normally found outside these sites.

Binding of CD30L to CD30 initiates lymphocyte activation, proliferation, and differentiation, but can also trigger cell death, depending on the type of cell and co-activation of other receptors.

In 1982, the monoclonal antibody Ki-1 was synthesized, initially directed against the CD30 antigen on Reed-Sternberg cells in Hodgkin disease.² In 1985, Ki-1 enabled identification of the CD30 antigen in other cell lines and revealed a new type of non-Hodgkin lymphoma: Ki-1/CD30+ anaplastic large-cell lymphoma (ALCL). Ki-1 is not the only monoclonal antibody available against CD30. Ber-H2 is another antibody and shows affinity to a different region of CD30. Ber-H2 not only stains the cell membrane but also shows dot-like positivity in the Golgi apparatus, where it is likely that there is an 84-kD precursor molecule of CD30.

In addition to being the main marker of ALCL, CD30 is expressed in approximately 30% of all T-cell lymphomas

Table 1 CD30+ Pseudolymphomas

Inflammatory and infectious diseases	Pityriasis lichenoides et varioliformis acuta	
	Atopic dermatitis	
	Toxicoderma (carbamazepine)	
	Immune reconstitution syndrome	
	Viral infections (herpesvirus in immunocompromised patients, molluscum contagiosum, parapoxvirus)	
	Parasite infections (scabies)	
	Mycobacterial infections	
	Neoplastic disease	Cutaneous decidualis (endometriosis)
		Embryonic carcinoma
		Mesenchymal tumors (leiomyomas, rhabdomyosarcomas)
Cutaneous lymphadenoma		
	CD30+ blasts in germinal centers of primary cutaneous B-cell lymphomas	

Adapted from Kempf et al.³

(with positivity in the largest cells) and in centroblasts and immunoblasts of 15% to 20% of B-cell lymphomas.¹

CD30⁺ Pseudolymphomas

Although CD30 is the marker characteristic of the spectrum of CD30⁺ LPDs, there are certain inflammatory and nonhematologic neoplastic processes in which the CD30⁺ cell counts may resemble those of LPDs. Examples are ALCL and lymphomatoid papulosis (LyP) (Table 1).³ These reactive situations are denoted “CD30⁺ pseudolymphomas.” Some differential features are listed below:

1. In pseudolymphomas, the CD30⁺ cells are small- or medium-sized lymphocytes and are present in low numbers. Although some CD30⁺ lymphomas have small- and medium-sized lymphocytes, unlike pseudolymphomas they are usually comprised of large anaplastic cells that massively infiltrate the dermis.
2. There is generally no monoclonal rearrangement of the T-cell receptors (TCRs) in pseudolymphomas.
3. The course of a pseudolymphoma is not one of recurrent flares (as in LyP for example).

T-cell monoclonality may occasionally be present in the CD30⁺ lymphoid infiltrates of pityriasis lichenoides et varioliformis acuta but these are usually CD8⁺ and may be localized in the epidermis, thereby enabling differential diagnosis with LyP.

History of the Classification of CD30⁺ Disorders

After the discovery in 1982 of Ki-1,² and the subsequent observation in the mid-1980s that anaplastic tumor cells were positive for CD30 in LyP and ALCL, CD30⁺ lymphomas became recognized as independent entities. However, there was no distinction between primary cutaneous ALCL and systemic (nodal) ALCL and, moreover, this group did not include LyP. In 1989, the association between translocation t(2;5)(p23;q35) and systemic ALCL was described.^{4,5} Subsequently, primarily cutaneous lymphomas, which contain cells with similar morphology to the systemic forms but which have better prognosis and no translocation, were excluded from this group.

The 1997 classification of primary cutaneous lymphomas by the European Organization for Research and Treatment of Cancer (EORTC) recognized CD30⁺ LPD with skin involvement as an independent entity for the first time.⁶ In the current 2005 World Health Organization/EORTC consensus classification,⁷ LyP and ALCL and borderline cases are all considered as CD30⁺ LPDs.

Once settled the classification of CD30⁺ lymphomas, discussion shifted to whether the terms pleomorphic (cells with different forms and sizes) and anaplastic (large cells generally considered neoplastic) might be used interchangeably to define CD30⁺ cells. In the previous EORTC classification, “large CD30⁺ T-cell lymphomas” encompassed lymphomas composed of pleomorphic,

Table 2 World Health Organization/European Organization for Research and Treatment of Cancer Classification of Primary Cutaneous Lymphomas

Cutaneous T-cell and natural killer (NK)-cell lymphomas

Mycosis fungoides (MF)
 Variants and subtypes of MF
 Folliculotropic MF
 Pagetoid reticulosis
 Granulomatous slack skin
 Sézary syndrome
 Adult T-cell lymphoma/leukemia
 CD30⁺ lymphoproliferative disorders
 Lymphomatoid papulosis
 Anaplastic large-cell lymphoma
 Panniculitic/subcutaneous T-cell lymphoma
 Nasal-type extranodal NK/T-cell lymphoma
 Unspecified primary cutaneous peripheral T-cell lymphoma
 Primary cutaneous aggressive CD8⁺ T-cell lymphoma (provisional entity)
 Cutaneous g/D T-cell lymphoma (provisional entity)
 Primary cutaneous CD4⁺ small-/medium-sized pleomorphic T-cell lymphoma
 Other unspecified peripheral cutaneous T-cell lymphomas

B-cell cutaneous lymphomas

Primary cutaneous marginal zone B-cell lymphoma
 Primary cutaneous follicle-center lymphoma
 Leg-type primary cutaneous large B-cell lymphoma
 Other primary cutaneous large B-cell lymphomas

Precursor hematologic neoplasm

CD4⁺/CD56⁺ hematodermic neoplasm (blastic NK-cell lymphoma)

Adapted from Willemze R et al.⁷

anaplastic, or immunoblastic cells positive for CD30 in at least 75% of neoplastic cells.⁶ Cell morphology was not considered a prognostic factor. In fact, in a series of 219 patients with CD30⁺ LPD, no differences were found in terms of survival between patients with primary cutaneous CD30⁺ ALCL, that is, with anaplastic cells, and those with clearly nonanaplastic CD30⁺ cells.⁸ There was, however, evidence in the same series of a greater tendency towards spontaneous remission in those cases of primary cutaneous CD30⁺ ALCLs histologically similar to LyP, with few CD30⁺ cells, compared to lymphomas with extensive infiltrates of CD30⁺ cells, regardless of morphology.

CD30⁺ Lymphoproliferative Disorders

Table 2 presents the current consensus classification of the WHO-EORTC for primary cutaneous lymphomas.⁷ CD30⁺ LPDs are the second most common type of cutaneous T-cell lymphoma (CTCL), accounting for approximately 25% of all such lymphomas. The most common group—the so-called classic CTCLs—includes mycosis fungoides (MF)

Table 3 CD30⁺ Lymphoproliferative Disorders: Clinicopathologic Features and Differential Diagnosis With Systemic Anaplastic Large-Cell Lymphomas^a

	LyP	Primary Cutaneous ALCL	Systemic ALCL
Clinical	Age 45 y Papules/necrotic nodules Self-limiting Recurrent	Age 60 y Single or multiple (20%) grouped nodules Self-limiting (40%) Rare extracutaneous involvement (10%)	Age < 30 y Lymph node swelling B symptoms Progression Extranodal involvement: 40% (skin is the most frequent site) Worse than cutaneous ALCL Better than other large-cell lymphomas
Prognosis	Excellent Association with/ Progression to ALCL, MF, or HD (5%-20%)	Favorable	
Treatment	Observation MTX Phototherapy	Surgery Radiotherapy MTX CT	Radiotherapy + CT SGN30 5F11
Histology	Type A and C: large anaplastic cells Type B: small cerebriform cells	Large anaplastic cells in dermis and subcutaneous cellular tissue No epidermal involvement	Multinucleated cells and Reed-Sternberg cells in lymph nodes (paracortical)
IHC	CD30 ⁺ CD2 ⁺ ·CD3 ⁺ ·CD4 ⁺ CD8 ⁻ ·CD25 ⁺ ·CD71 ⁺ CD7 ⁻ ·CD15 ⁻ HLA-DR ⁺ CLA ⁺ (100%) EMA ⁻ TIA-1, granzyme B ⁺ (70%) Bcl-2 absent Fascin (24%) CD56 ⁺ (infrequent)	CD30 ⁺ (>75%) CD2 [±] ·CD3 [±] ·CD5 [±] CD4 ⁺ ·CD8 [±] CD25 ⁺ ·CD71 ⁺ CD15 ⁻ HLA-DR ⁺ CLA ⁺ (44%) EMA ⁻ TIA-1, granzyme B ⁺ (frequent) Bcl-2 ⁺ (30%) Fascin (64%) CD56 ⁺ (infrequent, prognosis not worse)	CD30 ⁺ (>75%) CD2 ⁺ ·CD3 [±] CD4 ⁺ ·CD8 [±] CD25 ⁺ ·CD71 ⁺ CD15 ⁻ HLA-DR ⁺ CLA [±] (18%) EMA ⁺ TIA-1, granzyme B ⁺ (frequent) Bcl-2 ⁺ Fascin (91%) CD56 ⁺ (frequent, worse prognosis)
Genetics	ALK absent TGF-β receptor mutations absent <i>JunB</i> (overexpression)	ALK rare TGF-β receptor mutations absent <i>JunB</i> (overexpression, 70%)	ALK frequent TGF-β receptor mutations present <i>JunB</i> (overexpression)

Abbreviations: ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; CT, chemotherapy; EMA, epithelial membrane antigen; HD, Hodgkin disease; IHC, immunohistochemistry; MTX, methotrexate; LyP, lymphomatoid papulosis; SGN30 chimeric anti-CD30 antibody; TIA, T-cell intracellular antigen; 5F11 humanized anti-CD30 antibody.²⁴⁻²⁷

^aAdapted from Droc C et al.²⁹

and its variants and Sézary syndrome; together, these types account for 65% of CTCLs.

CD30⁺ LPDs should be considered as a clinical-pathologic spectrum. LyP and CD30⁺ ALCL lie at either end of the clinical-pathologic spectrum and between them would fall unclassifiable cases in which the clinical and histologic features do not allow clear differentiation between LyP and CD30⁺ ALCL.

Table 3 presents the characteristics of CD30⁺ LPD and includes systemic forms.

Lymphomatoid Papulosis

LyP is as a chronic disease characterized by flares of disseminated, self-limiting lesions with histologic features highly suggestive of lymphoma.^{7,9-12}

The pathogenesis of this entity is not known, although it seems that CD30⁺ regulatory T cells are activated by CD30L, which is produced by circulating neutrophils and eosinophils. These T cells secrete tumor growth factor (TGF) β, which suppresses local immune response, thereby leading to the development of LyP lesions. After a while, the same TGF-β induces apoptosis of CD30⁺ cells. The resulting recovery of immune response leads to regression of the lesion.¹³ Exploration of a possible relationship with retrovirus has yielded no conclusive results.^{14,15}

LyP is a rare disease (with an incidence of 0.1-0.2 cases/100000 population) that affects mainly adults.¹² The mean age of onset is 45 years, although cases have been reported in children. It is somewhat more common in males (male:female ratio of 1.5:1). Asymptomatic papules that are often ulcerated appear on the trunk and limbs. The



Figure 1 Multiple, papulosquamous lesions of lymphomatoid papulosis.

lesions are self-limiting in 3 to 12 weeks and often, though not always, heal to leave superficial, varioliform scars. They are recurrent and can be present in different stages of the clinical course in the same patient (Figures 1 and 2).

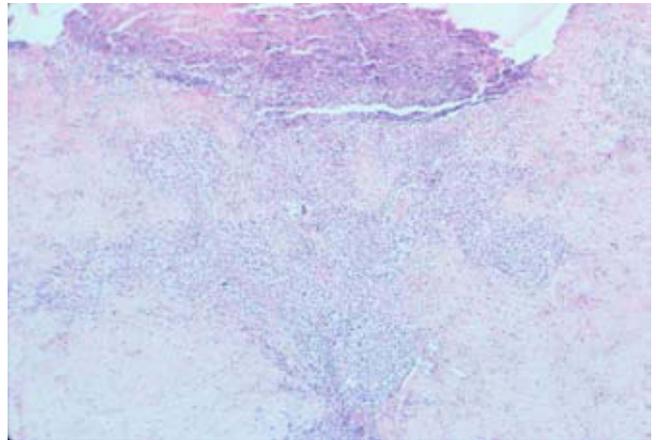


Figure 3 Type A lymphomatoid papulosis. Wedge-shaped infiltrate abutting the epidermis (hematoxylin-eosin×100)



Figure 2 Papulous, crusted lesion with varioliform scars.

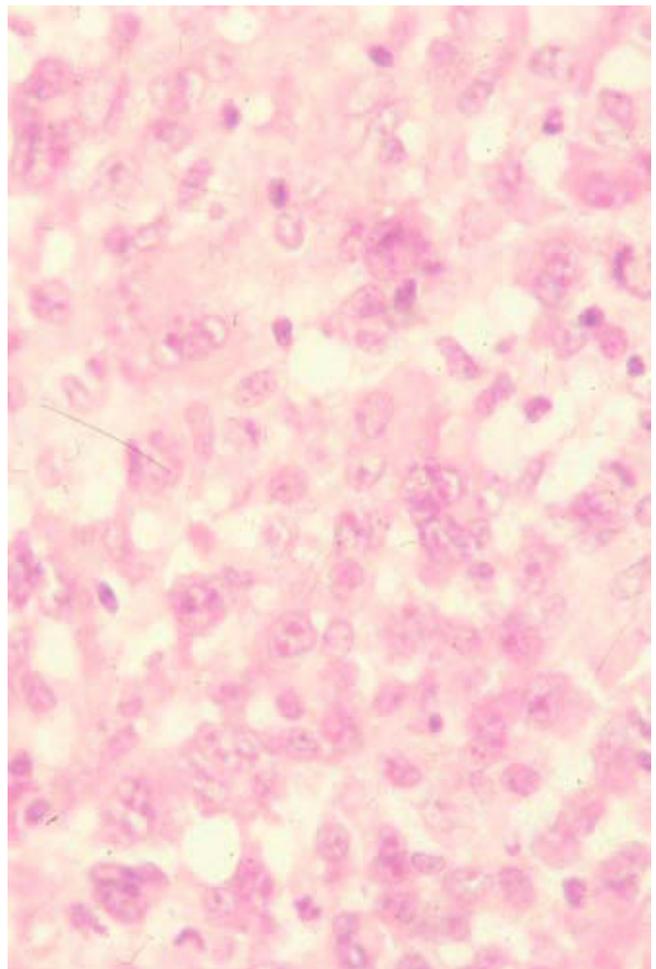


Figure 4 Detail of infiltrate of type C lymphomatoid papulosis, indistinguishable from that which appears in an CD30+ anaplastic large-cell lymphoma (hematoxylin-eosin×400)

Traditionally, 3 types of LyP can be distinguished in histological studies^{7,9}:

1. Types A and C: These forms are similar to ALCL, with large atypical, anaplastic cells with irregular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm. Type A has few tumor cells, interspersed individually or in small clusters, among mainly inflammatory cells (neutrophils, eosinophils, histiocytes, small lymphocytes), forming a wedge-shaped infiltrate abutting the epidermis (Figure 3). Type C LyP is characterized by more extensive infiltrates of atypical cells and, to a lesser extent, accompanying inflammatory cells (Figure 4). In LyP, the infiltrate is confined to the dermis (unlike in ALCL, where it can extend to the hypodermis).
- 2 Type B: This form is uncommon (less than 10% of cases) and is characterized by small, atypical cells with cerebriform nuclei embedded in an infiltrate with marked epidermotropism, similar to MF. The same patient may have lesions of different histological types at the same time.¹⁶

The immunophenotypic characteristics are as follows¹²:

1. Large atypical cells (sometimes multinucleated Reed-Sternberg type cells): CD30⁺, CD3⁺, CD4⁺, CD8⁻ (equivalent to those of ALCL), CD2⁺, CD5⁺, and CD7⁻.



Figure 5 Papulous, crusted lesions of lymphomatoid papulosis with mycosis fungoides plaque.

Expression of HLA-DR and CD25 (interleukin-2 receptor) is also observed along with positivity for cytotoxic molecules such as T-cell intracellular antigen (TIA) 1 and granzyme B in 70% of cases. CD56 is expressed in only 10% of cases and CD15 is negative.

2. Small, atypical cells: CD30⁻, CD3⁺, CD4⁺, CD8⁻.

In LyP, clonal rearrangement of the *TCR* gene can be observed in 60% to 70% of cases. Translocation t(2;5) (p23;q35), characteristic of systemic ALCL, and other specific genetic mutations are also characteristic of LyP.

Prognosis in LyP is good. Bekkenk et al⁸ undertook follow-up of 118 patients with LyP for 77 months, and only 4% developed systemic lymphoma and 2% died. In that series, disease-free survival was 100% at 5 years. On the other hand, between 5% and 20% of cases of LyP are preceded by or associated with other forms of cutaneous lymphomas, generally MF (Figure 5), ALCL, or Hodgkin disease.⁹⁻¹² It is not known what risk factors are implicated in progression, though greater expression of fascin has been suggested.³

In view of the good prognosis, and given that there is no curative treatment, a conservative approach to management of LyP is generally accepted. No therapy at all may be appropriate in the mildest cases. The most effective treatment is low doses of methotrexate (5-20 mg/wk), although phototherapy (UV-B or psoralen-UV-A) is a good therapeutic alternative.^{7,11}

CD30⁺ Anaplastic Large-Cell Lymphoma

CD30⁺ anaplastic large-cell lymphoma comprises large cells of anaplastic, pleomorphic, or immunoblastic morphology that are positive for CD30 in more than 75% of the tumor cellularity.^{7,12} CTCLs such as LyP or MF should be ruled out, as should systemic ALCL with secondary cutaneous involvement.⁷

ALCL usually occurs in adults, with onset between 50 and 60 years, and shows a male preponderance (male:female ratio, 2-3:1).^{7,12} It presents as solitary or grouped nodules or tumors, generally on the limbs or head. These are multifocal in only 20% of cases (Figures 6a and b). Nodules may become ulcerated and are self-limiting in 10% to 40% of cases, although tending to recur. Extracutaneous involvement occurs in 10% and almost always takes the form of spread to regional lymph nodes.^{7,11}

Histologically, the tumor cells are as described for type A and C LyP. Only 20% to 25% of cases adopt a morphology that is more pleomorphic or immunoblastic, that is, not purely anaplastic, and some small cells might even be present. Cell morphology does not have any prognostic value.¹¹ These cells, which are mainly CD30⁺ (Figure 7), form a diffuse infiltrate in the dermis with no epidermotropism and are accompanied by reactive lymphocytes. The ulcerated lesions may simulate LyP with abundant accompanying inflammatory cellularity.⁷

Immunophenotyping of the tumor cells reveals activated CD4⁺ T-cells (only 5% are CD8⁺ T cells), with variable loss of CD2, CD5, and CD3. Cytotoxic proteins are often expressed (granzyme B, TIA-1, perforin). Expression of CD56 is rare



Figure 6 Two infiltrated tumor lesions several centimeters across, on the dorsum of the foot (a) and the deltoid region (b). Histological and immunohistochemical study consistent with CD30⁺ anaplastic large-cell lymphoma.

and of no prognostic value.⁷ Unlike Hodgkin lymphoma, CD15 staining is negative in this setting, and unlike systemic CD30⁺ lymphomas (that is, those that affect lymph nodes), primarily cutaneous ALCLs express cutaneous lymphocyte antigen and do not express epithelial membrane antigen (EMA) or anaplastic lymphoma kinase (ALK), product of t(2;5)(p23;q35) translocation.^{11,12}

Most of these lymphomas (more than 90%) show *TCR*-positive monoclonal rearrangement.¹²

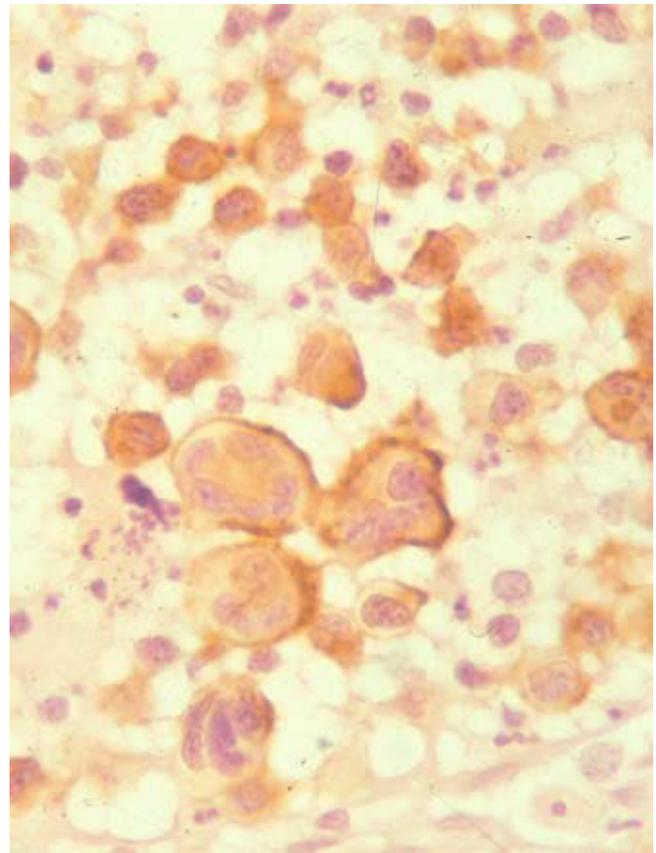


Figure 7 Immunohistochemistry. Positivity for CD30 in most atypical large cells of a primary cutaneous anaplastic large-cell lymphoma (CD30×400).

Survival at 10 years is greater than 90%, and so prognosis is good and generally not affected by multiple tumor lesions or secondary involvement of regional lymph nodes.¹² In contrast, the systemic variant, which affects children and adolescents, has a worse prognosis, follows a more aggressive course, and requires chemotherapy.¹⁷

In localized forms and solitary lesions, radiotherapy or simple resection are the mainstay therapeutic options. In the case of multiple lesions, treatment consists of low-dose methotrexate or radiotherapy if the lesions are very localized.¹⁷ If there is already lymph node or extracutaneous involvement, combination chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) should be considered.

Other CD30⁺ Lymphomas (Not Included in the CD30⁺ LPD Group)

Table 4 shows the types of cutaneous and systemic lymphomas that may present certain CD30⁺ elements among their tumor cells.³

In approximately half the cases of MF and Sézary syndrome that transform into large high-grade large-cell lymphoma, CD30⁺ cells are present, but this does not influence prognosis. In cases of MF in patch and plaque stages, CD30⁺ cells are not often found in the epidermis.³

Table 4 Lymphoproliferative Processes with CD30⁺ Cells

CD30⁺ lymphoproliferative disorders (WHO/EORTC 2005 classification)	Lymphomatoid papulosis CD30 ⁺ anaplastic large-cell lymphoma
Others	Transformation of mycosis fungoides and Sézary syndrome Pagetoid reticulosis Adult T-cell leukemia/lymphoma Hodgkin lymphoma Childhood angiocentric cutaneous T-cell lymphoma (hydroa-like lymphoma) Cutaneous reactions of atypical CD30 ⁺ cells associated with leukemias and lymphomas

Modified from Kempf W et al.³

The differential diagnosis between transformation of MF or Sézary syndrome and primary cutaneous ALCL can only be made according to the presence of patches, plaques, or erythroderma in the clinical history in the case of transformations, as it is almost impossible to distinguish these entities by histology or phenotype of the tumor cells. The large-cell transformation of MF can appear during the plaque phase,¹⁸ but it tends to be more frequent in the most advanced stages (up to 50% of cases in the tumor phase). To consider transformation to have taken place, some authors require that large or blast cells comprise 25% of the infiltrate, while others put the figure at 50%.¹⁸ It seems that stage and lactate dehydrogenase (LDH) and β_2 -microglobulin elevation are predictors of transformation of MF into large-cell lymphoma.¹⁸

There may be cutaneous involvement in up to 50% of cases of T-cell leukemia/lymphoma in adults. Differential diagnosis in these cases requires measurement of human T-lymphotrophic virus (HLTV), the causative agent. Lesions can appear as papules, plaques, nodules, tumors, or erythroderma, while histological features include a diffuse infiltrate of medium or large pleomorphic cells with T-cell phenotype, with or without epidermotropism, that may express CD30⁺.

Unlike ALCL, cutaneous involvement in Hodgkin disease is rare (1%) and a marker of poor prognosis. Primarily cutaneous cases are unusual. Clinically, they present as papules, plaques, or ulcerated nodules, formed by infiltrates of Hodgkin cells and, in up to half the cases, of Reed-Sternberg cells. All are positive for CD30 and a large percentage of them also express CD15, thereby enabling differential diagnosis with CD30⁺ LPDs.

Controversies

Clonality

The clonality of CD30⁺ cells is vigorously debated,³ even when extremely sensitive methods are used for detecting rearrangement. Some authors, on studying cases of LyP, contend that CD30⁺ cells are monoclonal whereas CD30⁻ cells are polyclonal.¹⁹ Others, however, have found monoclonality in accompanying small CD30⁻ cells, whereas large CD30⁺ cells were polyclonal.²⁰ The question remains whether morphology correlates with clonality (large polyclonal CD30⁺ cells vs small monoclonal CD30⁻ cells).

While not all cases of LyP show monoclonality among infiltrated cells, most CD30⁺ ALCL are clearly clonal, with this clonality originating from large anaplastic CD30⁺ cells.¹³ It seems that 1, or possibly more than 1 clone, probably with a predominance of CD30⁺ cells, arises from a set of polyclonal CD30⁺ T cells.¹³

A clonal relationship has been reported in 22 cases of LyP associated with other lymphomas (MF, Hodgkin disease, or primary cutaneous or systemic ALCL).¹³ As a possible explanation for this phenomenon, in 1992 Kadin et al²¹ proposed the presence, in all such cases, of an anomalous occult T-cell clone from which the subclones with acquired genetic mutations were derived to give rise to LyP, MF, and Hodgkin disease in the same patient.

Diagnostic Difficulties: Spectrum of CD30⁺ Lymphoproliferative Disorders

Diagnostic difficulties arise for 2 reasons³:

1. Differential diagnosis between LyP and primary cutaneous ALCL. The major difficulty arises with type C LyP. Isolated or multiple lesions limited to an anatomical region suggest CD30⁺ ALCL, whereas disseminated lesions are more characteristic of LyP. In addition, tumor infiltration in ALCL usually goes deeper, affecting subcutaneous cellular tissue. However, often a certain diagnosis emerges only with time, as the disease develops. Differential diagnosis between type B LyP and MF is also difficult; in this case, the clinical presentation (patches, plaques) provides key information. This is further complicated in recently reported cases of papulous MF,²² particularly if this type of lesion is not accompanied by typical patches or plaques.
2. Differential diagnosis between primary and secondary cutaneous CD30⁺ ALCL: there are no clinical or histological differences between these 2 entities, but immunohistochemical staining (for ALK and EMA) and genetic features (translocation t[2,5]) are positive when the cutaneous lymphoid infiltration is secondary to systemic CD30⁺ ALCL. Likewise, greater expression of *bcl-2* and fascin in systemic ALCL may also be useful. Staging also plays an important role. It should also be remembered that primary cutaneous lymphomas, unlike secondary ones, are rare in children, not associated

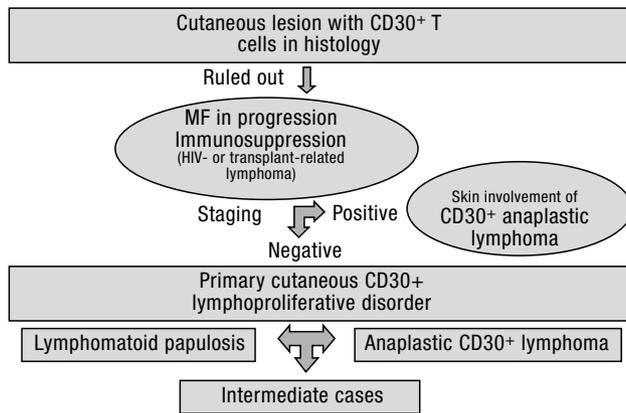


Figure 8 Differential diagnosis with CD30+ lymphoproliferative disorders. Modified from Bekkenk et al.¹³ HIV indicates human immunodeficiency virus; mycosis fungoides; MF.

with Epstein-Barr virus infection, and generally have a good prognosis.

In both groups, rearrangement studies are not useful for establishing a definitive diagnosis.

It may be useful to be aware of the diagnostic algorithm proposed by Bekkenk et al⁸ for these CD30+ LPDs (Figure 8).

What's New?

New Diagnostic Variants

Lymphomatoid Papulosis

Of note are clinical forms such as regional or localized LyP, follicular LyP (Figure 9), which has already been reported,²³ and pustular LyP. Less clear are cases of LyP with exclusively (oral) mucosal involvement.³ The authors have seen a case of LyP with a flare of lesions on the vulvar mucosa (unpublished observation). Histologically, there are follicular and syringotropic forms, which may or may not be associated with follicular mucinosis (as occurs with follicular MF). Cellular infiltrates may be angiocentric.³

CD30+ Anaplastic Large-Cell Lymphomas

From the histological point of view, of note are cases of so-called neutrophil-rich CD30+ with massive neutrophil infiltration.³ Clinically, these lesions predominate on the face, grow quickly, are pustular, and may resemble pyoderma gangrenosum. The accompanying neutrophils may sometimes even mask the true tumor cells.

There is a keratoacanthoma-type ALCL, with pseudoepitheliomatous hyperplasia over the CD30+ cell infiltrate.³ Pseudoepitheliomatous hyperplasia may be present in LyP lesions, possibly due to synthesis of epidermal growth factor by CD30+ cells. A sarcomatoid variant, with abundant spindle tumor cells, should also be mentioned.

Therapeutic Approaches

Since the mid 1990s, the CD30 antigen has been considered not only as a guide to diagnosis but also as a

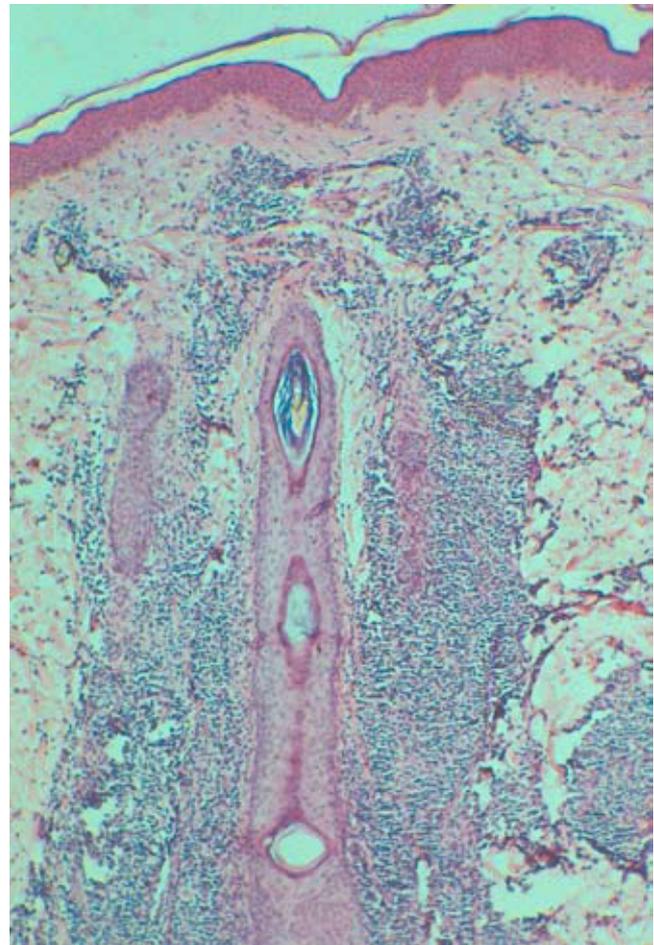


Figure 9 Follicular lymphomatoid papulosis.

possible therapeutic target for monoclonal antibodies, that is, anti-CD30 antibodies.¹ A point in favor of targeting this antigen is its minimal expression in normal cells localized exclusively in lymphoid tissue. From the hematological point of view, there are studies with chimeric antibodies (SGN30) and humanized antibodies (MDX-060, 5F11) directed against CD30 for the treatment of systemic ALCL, and preliminary results point to efficacy in combination with chemotherapy.²⁴ In the case of SGN30, Forero et al^{25,26} presented the results of a phase II study in which 6 patients with systemic CD30+ ALCL refractory to other therapies were given weekly cycles of chemotherapy for 6 weeks. Response was achieved in half the patients, with complete remission in one of them. In a more recent study, the most frequently reported adverse effects were mild and included fever, asthenia, and nausea.²⁷

In a recent update on CTCL treatment, Whittaker et al²⁶ referred to a new study that evaluated the efficacy of this drug in patients with cutaneous CD30+ ALCL and transformation of CD30+ MF. Response in 5 of 6 patients with minimal toxicity was reported. Previously, Sheehan et al²⁸ had reported a case of multifocal cutaneous CD30+ ALCL that was refractory to other treatments and that was treated with CD30+ monoclonal antibody in a clinical trial setting. After 1 month of treatment (weekly cycles), the patient remained in complete remission for at least

3 months. The authors added the caveat that longer follow-up would be needed to establish clear conclusions.

Conclusion

CD30⁺ LPDs are the second most frequent type of CTCL. Diagnosis is not always easy and requires knowledge of clinical course as well as consideration of histological and immunohistochemical features, particularly for differential diagnosis with other CTCLs and systemic lymphomas. Many aspects of the diagnosis and pathogenesis of these LPDs remain unclear, but new therapeutic approaches are nevertheless becoming available.

Conflicts of Interest

The authors declare no conflicts of interest.

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