



Alexey Bobylev. *Summer Evening*, 2006 (detail). Oil on canvas, 57 × 138 cm. Courtesy of the St. Petersburg Art Salon, Russia.

Incorporating molecular and phenotypic criteria will improve the current classification and identify molecular targets for therapy of CD30+ cutaneous lymphomas.

Need for an Improved Molecular/Genetic Classification for CD30+ Lymphomas Involving the Skin

Claudia Droc, MD, Hernani D. Cualing, MD, and Marshall E. Kadin, MD

Background: *The spectrum of diseases that constitute the CD30+ lymphomas, with lymphomatoid papulosis (LyP) at one end, and anaplastic large-cell lymphoma (ALCL) at the other end, shows variable morphology, immunophenotype, and clinical behavior. The border between these diseases is sometimes difficult to establish and there are many grey zones in their classification.*

Methods: *We reviewed the clinical and research literature and guided by our experiences attempted to discern molecular and phenotypic criteria to improve the classification and identify molecular targets for therapy of CD30-positive cutaneous lymphomas.*

Results: *Functional studies of ALCL cell lines clonally derived from LyP have revealed loss of growth inhibition by transforming growth factor beta (TGF- β), due to TGF- β receptor mutations. Studies of genetic variants of the CD30 promoter showed distinct microsatellite alleles associated with development of LyP and lymphoma progression. Studies of LyP and cutaneous ALCL tissues and cell lines suggest a dual role for CD30/CD30 ligand interactions in regression of LyP and progression to lymphoma. CD30 signaling activates NF- κ B in cell lines derived from cutaneous ALCL but not anaplastic lymphoma kinase (ALK)-positive systemic ALCL in which growth arrest occurs through cell cycle inhibitor p21^{WAF1/Cip1}. Other likely biomarkers of disease progression include differential expression of Bcl-2, fascin, cutaneous lymphocyte antigen, and T-cell receptor clonality. These may lead to improved classification, diagnoses, and therapeutic targets.*

Conclusions: *The current clinicopathologic classification of CD30+ cutaneous lymphoproliferative disorders is insufficient. Incorporating genetic and molecular criteria would better define the borders between benign/malignant and aggressive/nonaggressive disorders.*

Introduction

The CD30+ lymphomas of the skin consist of a heterogeneous group with variable morphology and immunophenotype that present as a spectrum of diseases ranging from clinically indolent lymphomatoid papulosis to the more aggressive anaplastic large-cell lymphoma (ALCL) (Table 1).¹⁻¹⁰ Clinically, there is an overlap in the number and size of skin lesions and the tendency for spontaneous regression. In general, individual lesions of lymphomatoid papulosis (LyP) are usually <2 cm in diameter, while those of cutaneous anaplastic large-cell lymphoma (c-ALCL) exceed this dimension. Spontaneous regression, while characteristic of LyP, also occurs in a subset of CD30+ ALCL as currently defined.

Histology is also often inadequate to distinguish between benign and malignant since LyP type C com-

prises sheets of anaplastic cells indistinguishable from ALCL, while neutrophil-rich ALCL contains relatively few anaplastic cells, similar to LyP type A. As stated by the Dutch Cutaneous Lymphoma Group, "The central problem in the correct diagnosis and classification of this group of diseases is that there are no reliable histologic criteria to differentiate between the different types of primary and secondary cutaneous CD30+ lymphoproliferations."¹

Clinical correlation is essential for proper management of these patients. However, at presentation, the natural history of the disease may not be apparent and may be modified by subsequent molecular/genetic changes in the cellular components and their interactions with the host and microenvironment. We propose that a new classification of CD30 lymphomas of the skin will evolve from new knowledge of altered phenotype and

Table 1. — Clinical Comparison of CD30+ Lymphomas Involving the Skin

	Primary c-ALCL	LyP	Systemic ALCL
Age and gender	Median age 60 years	Median age 45 years	Males <30 years of age
Symptoms	No evidence of extracutaneous disease One to multiple tumors of >2 cm in diameter with erythema and ulceration Spontaneous regression in 42% of patients ¹	Recurrent papulonecrotic eruption on extremities and trunk (most frequent sites) Spontaneous regression of lesions in 4 to 6 weeks Hypo- or hyper-pigmented scar Occurs in crops	Noncontiguous lymphadenopathy B symptoms 40% extranodal disease with skin being the site involved most often Infrequent spontaneous regression of skin lesions Progressive disease
Prognosis	Better survival rate than systemic ALCL Survival rate at 5 years 90%	Clinically benign ²⁻⁴ Can progress to ALCL Increased risk for MF and Hodgkin's lymphoma	Better survival for ALCL than for other large-cell lymphomas Better survival for ALK-positive ALCL than for ALK-negative ALCL ⁵⁻⁷ Worse prognosis than primary c-ALCL
Treatment	Surgical removal ± irradiation Low-dose methotrexate for multifocal skin-restricted disease; multiagent chemotherapy for extracutaneous disease ¹	No treatment PUVA or low-dose methotrexate ⁸ for aggressive disease	Local radiation and combination chemotherapy SGN 30 (anti-CD 30 monoclonal antibody) is in phase II trial study 5F11, a fully human monoclonal antibody directed against CD30, effectively induces killing of CD30-expressing lymphoma cell lines in vitro and in animal models ⁹ ALK inhibitors ¹⁰

PUVA = psoralen plus ultraviolet A.

From the Department of Pathology at the University of South Florida (CD), the Hematopathology and Laboratory Medicine Program at the H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida (HDC), and the Department of Dermatology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (MEK).

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Address correspondence to Hernani D. Cualing, MD, Hematopathology and Laboratory Medicine Program, H. Lee Moffitt Cancer Center & Research Institute, 12902 Magnolia Drive, Room 2071G, Tampa, FL 33612. E-mail: bernani.cualing@moffitt.org

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Abbreviations used in this paper: LyP = lymphomatoid papulosis, ALCL = anaplastic large-cell lymphoma, c-ALCL = cutaneous anaplastic large-cell lymphoma, MF = mycosis fungoides, TRAF = tumor necrosis factor receptor-associated factor, ALK = anaplastic lymphoma kinase, CLA = cutaneous lymphocyte antigen, TGF-β = transforming growth factor beta, NF-κB = nuclear factor-κB.

molecular/genetic abnormalities involved in the pathogenesis and progression of CD30+ cutaneous lymphomas. Several examples of recognized phenotypic and molecular/genetic abnormalities are included in the discussion.

Anaplastic Ki-1+ large-cell lymphoma was first described in 1985 when an antibody Ki-1 directed against CD30 antigen was found to react with a distinct type of large-cell lymphoma.¹¹ In 1989, a genetic lesion characterized by a balanced translocation t(2;5)(p23;q35) was reported to be highly associated with systemic ALCL.^{12,13} A morphologically similar disease located primarily in the skin as a cutaneous lymphoma was further delineated from the systemic group as primary c-ALCL by virtue of its favorable clinical behavior and lack of the t(2;5).¹⁴ We regard systemic ALCL with secondary cutaneous manifestations as a separate disease with a poorer prognosis when compared with the cutaneous primary type. Here we present some of the distinguishing characteristics and grey zones in the classification of these lymphomas. A literature summary of potential biomarkers to better resolve these differences and therefore warrant further evaluation is provided.

Clinical Manifestations

LyP lesions can vary from papules to nodules and often occur in clusters, but they can also present as single, few, or many disseminated lesions (Fig 1A). The distribution can be random or localized to one area of the body, with recurrences in the same area. The eruption shows spontaneous regression within 4 to 6 weeks and can leave a hypo- or hyper-pigmented scar. The lesions spare mucous membranes and are found most often on the extremities and trunk. Patients with LyP are at increased risk to develop mycosis fungoides (MF), Hodgkin's lymphoma, and ALCL.^{1,15,16} These lymphomas are often clonally related to the prior LyP.^{16,17} In 60% of LyP skin lesions, clonal populations of T cells are identified, and the same clone may be present in multiple separate lesions.¹⁷⁻¹⁹

Borderline lesions cannot be readily classified as LyP or ALCL. We use the term borderline to refer to lesions that are not sharply demarcated in clinical appearance or histopathology from either LyP or ALCL. The Dutch Cutaneous Lymphoma Group uses the term borderline to describe lesions that have the clinical appearance of LyP and histology of ALCL or clinical appearance of ALCL and histopathology of LyP.^{2,3}

In most cases, c-ALCL presents as a single large lesion (Fig 2A), as several large fused or clustered lesions or, less often, as multicentric nodules or tumors. These lesions may coexist with papules of LyP.

Systemic ALCL has a male predominance and a wide age range, peaking in childhood.²⁰⁻²² In 70% of patients, systemic ALCL at presentation is advanced stage III or IV disease with B symptoms with a rapidly progressive clinical course and noncontiguous lymphadenopathy. Extranodal disease is seen in 40% of cases, with skin being the most common site. There is infrequent regression of the skin lesions compared with primary cutaneous lymphoma. The anaplastic lymphoma kinase (ALK)-negative variant is prevalent in older individuals and has a worse prognosis than the ALK-positive type.

Pathology

LyP consists of three histologic types: A, B, and C. LyP is recognized by large CD30+ cells that vary from scattered infrequent cells in histologic type A to large clusters or sheets of cells resembling ALCL in type C. LyP type B closely resembles MF by virtue of epidermotropism of cerebriform cells and may represent a papular form of MF.²³

Type A consists of large atypical cells that resemble Reed-Sternberg cells and are surrounded by inflammatory cells: neutrophils and eosinophils. The key feature is the presence of neutrophils within vascular spaces, which helps to distinguish the lesion from pityriasis lichenoides (Fig 1B-C). Type B resembles MF.²⁴ The

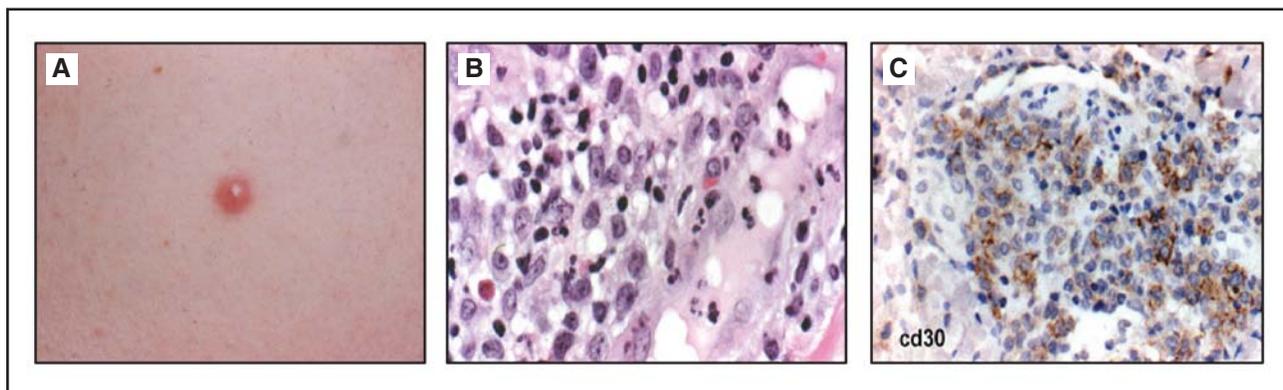


Fig 1A-C. — (A) Papule of lymphomatoid papulosis, type A. (B-C) Large atypical cells that mark with CD30 and are surrounded by inflammatory cells: neutrophils and eosinophils. The key feature is the presence of neutrophils within vascular spaces, which helps to distinguish the lesion from pityriasis lichenoides.

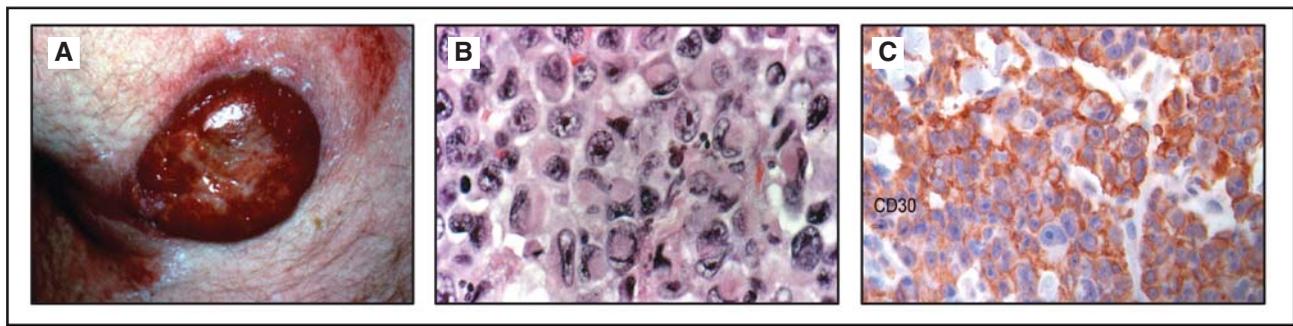


Fig 2A-C. — (A) Cutaneous ALCL presenting as an erythematous tumor nodule. (B-C) Large anaplastic Reed-Sternberg-like cells that are strongly CD30 positive.

lesions are distinguished from those of the MF by their clinical appearance: papules with spontaneous regression. Neutrophils and eosinophils are infrequent or absent. Type C resembles diffuse large-cell lymphoma. The cells are confined to the upper dermis and there is no infiltration of the fatty tissue. There is some overlap among these three types of LyP, and some patients might have more than one histologic type.¹⁷

Primary c-ALCL consists of sheets of tumor cells that invade the skin appendages and extend into the subcutaneous fatty tissue. Histologically, ALCL contains large tumor cells (Fig 2B-C), which extensively infiltrate the dermis and subcutis. The epidermis is often spared. Mitoses and apoptotic bodies are frequently present. Vascular invasion is also noted. Variable inflammatory infiltrate is seen, and sometimes a neutrophil-rich variant can be mistaken for pyoderma.^{25,26} The large tumor cells have irregular nuclei. Multinucleated Reed-Sternberg-like forms are seen, and cells with horseshoe or wreath-like configurations are also identified.²⁷ The cells can also resemble immunoblasts. The cells express CD30, and prognosis is favorable.

Systemic ALCL has large cells with prominent nucleoli that infiltrate the sinuses and the paracortical regions of lymph nodes.²² There are multinucleated cells, Reed-Sternberg-like cells,²⁷ “doughnut” cells, and hallmark cells.²⁰ Multiple histologic variants are recognized. The common variant has hallmark cells, multinucleated cells, and Reed-Sternberg-like cells. Others include small-cell variant,²⁸ lymphohistiocytic variant,²⁹

Hodgkin’s-like variant,^{30,31} sarcomatoid variant,³² and neutrophil-rich variant.^{25,26,33}

Distinction Between LyP and ALCL

Since distinguishing between LyP and ALCL is often difficult, we endeavor to identify cell biomarkers that can help to classify ambiguous or borderline lesions, predict prognosis, and guide clinical management. Among the markers identified thus far are Bcl-2, Fascin, cutaneous lymphocyte antigen (CLA), CD56, and clonality. Bcl-2 is rarely expressed by large atypical cells in LyP but is often expressed in pleomorphic cells of CD30+ large-cell lymphoma and 30% of c-ALCL.³⁴⁻³⁶ Fascin is expressed more frequently in ALCL and LyP associated with ALCL than in uncomplicated LyP.³⁷ CLA is invariably expressed by large cells in LyP but variably in c-ALCL and is decreased in extracutaneous spread of ALCL (Fig 3A-B).^{38,39} CLA is more common in c-ALCL than in systemic ALCL (44% vs 18%, respectively).⁴⁰

Lymphomatoid papulosis is often CD56-negative, with less than 10% positive in contrast with the primary c-ALCL, which is positive in 12% to 75%,⁴¹⁻⁴³ and systemic ALCL, which is often positive. Clonality demonstrated by T-cell receptor (TCR) gene rearrangement analysis is evident in virtually all ALCL but varies from 40% to 100% of LyP lesions analyzed.^{44,45}

Detection of a clonal T-cell population to discriminate LyP from ALCL requires further study. Gellrich et al⁴⁶ analyzed CD30+ cells in 4 patients with primary cutaneous CD30+ ALCL by single-cell polymerase chain reaction (PCR) amplification of TCR- β genes followed by sequencing. Although most of the large CD30+ cells had identical TCR- β gene rearrangements, polyclonally rearranged T cells were present in all CD30+ samples. In addition, 1 patient showed a second clone in a separate biopsy. The investigators con-

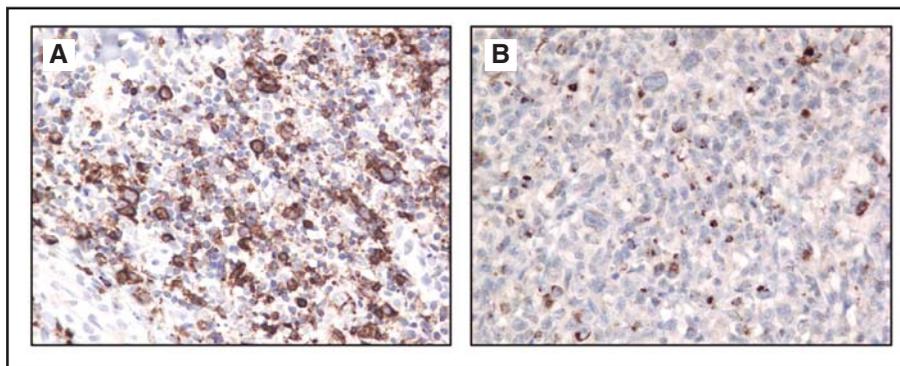


Fig 3A-B. — (A) CLA expression by large atypical cells in LyP. (B) Reduced CLA expression in extracutaneous ALCL clonally derived from LyP.

cluded that the CD30+ population in primary cutaneous CD30+ ALCL contains the tumor clone; however, CD30 expression does not define the tumor clone as bystander T cells, and additional clones are present as well. The same group of investigators found that the clonal population in LyP did not reside within the CD30+ population but rather within the CD30-negative smaller T cells.⁴⁶ This is in contradiction with results of the study of Steinhoff et al,¹⁹ who found the CD30+ cells in LyP were clonal, even when lesions at different time points were analyzed. Thus, it will be important to determine if the CD30+ population evolves from a polyclonal benign population in LyP to a clonal malignant population in CD30+ cutaneous lymphoma.

Gene expression arrays have shown increased expression of genes promoting cell proliferation, cell survival, and drug resistance, as well as decreased expression of genes favoring apoptosis, cell adhesion, suppressors of cell cycle, and genomic integrity in cell lines derived from advanced stages malignant lymphoma clonally derived from LyP.⁴⁷ Among the genes found to be downregulated in advanced lymphoma was a negative regulator of cell cycle progression p16. This result is consistent with the decreased expression of p16 in primary cutaneous CD30+ large-cell lymphoma reported by Boni et al.⁴⁸ In addition, an association of CD30+ cutaneous lymphoproliferative disorder with genetic variants of the CD30 promoter has been described. The CD30 promoter has a polymorphic microsatellite (MS) that represses CD30 transcription.⁴⁹ Because CD30 cross-linking activates nuclear factor-kappa B (NF-κB) and enhances proliferation of cutaneous lymphoma

cells, we hypothesized that genetic variants of the MS might be associated with CD30+ cutaneous lymphoproliferative diseases. To test this hypothesis, we determined the distribution of germline CD30 MS alleles of 40 patients with CD30+ cutaneous lymphoproliferative diseases and compared the distribution with a control population of 57 individuals without lymphoproliferative disease. We found that two MS alleles were associated with CD30+ cutaneous lymphoproliferative disease, and one of these alleles was markedly increased in LyP patients who had progressed to lymphoma.⁵⁰ We plan to further test this hypothesis in a larger multicenter study involving more diverse ethnic populations. Additional gene expression studies are needed to better understand the biology, classification, prognosis, and optimal management of patients with CD30+ cutaneous lymphomas (Table 2).^{34,35,37-43,46,47,51-58}

Distinction Between Cutaneous and Systemic ALCL

Skin is the most common site of extranodal disease in systemic ALCL. The skin lesions of systemic ALCL are highly variable in clinical appearance and histopathology. Systemic ALCL is associated with the ALK kinase oncogene in most childhood and young adult cases. Systemic ALCL in patients over 30 years of age is often ALK-negative. CD30 signaling results in activation of NF-κB in Hodgkin's lymphoma and in cell lines derived from cutaneous T-cell ALCL but not in systemic ALK+ ALCL (Fig 4). CD30 signaling activates NF-κB in cell

Table 2. — Pathology of CD30+ Lymphomas

	Primary c-ALCL	LyP	Systemic ALCL
Histology	Sheets of large cells that invade the dermis and subcutis Epidermis is usually spared	Type A: large cells similar to Reed-Sternberg cells Type B: cerebriform cells that resemble MF Type C: large cells that resemble systemic ALCL	Hallmark cells, multinucleated cells, and Reed-Sternberg-like cells that invade the sinuses and paracortical regions of the lymph nodes
Immunohistochemistry	CD30+ (75% cells) Fascin (64%), ³⁷ CD2+, CD3+, CD4+, CD25+, HLA-DR+, CD71+ EMA absent CLA variable ³⁹ Bcl-2+ (30%) ^{34,35} CD56+ (12% to 75%) ^{42,43}	CD30+ Fascin (24%), ³⁷ CD2+, CD3+, CD4+, CD8+, few CD25+, HLA-DR+, CD71+ EMA absent CLA high ^{38,39} Bcl-2 absent ^{34,35} CD56 often negative ^{42,43}	CD30+ Fascin (91%)+, ⁵¹ CD2+, CD3-often CD4+, CD8±, CD25+, HLA-DR+, CD71+ EMA+ ⁴³ CLA low ⁴⁰ Bcl-2+ ⁵² CD56+ worse prognosis ⁴¹⁻⁴³
Molecular/Genetic Features	ALK rare; TGF-β receptor mutations unknown; downregulation of tumor suppressor p16 ⁴⁶ High expression (70%) of JunB ⁵⁷	ALK absent; TGF-β receptor mutations unknown ⁴⁶ High expression of JunB ⁵⁷	ALK common ^{53,54} TGF-β receptor mutations occur ⁵⁵ High expression of JunB ^{57,58}
HLA-DR = human leukocyte antigen-DR, EMA = epithelial membrane antigen.			

lines derived from cutaneous ALCL but not anaplastic lymphoma kinase (ALK)-positive systemic ALCL in which growth arrest occurs through cell cycle inhibitor p21^{WAF1/Cip1}. Further studies are needed to determine the utility of NF- κ B and tumor necrosis factor receptor-associated factor (TRAF) adapter proteins in the distinction of primary c-ALCL and systemic ALCL with cutaneous manifestations.⁵⁹⁻⁶³

Systemic ALCL shows surface and Golgi staining for CD30 and surface staining for CD25, CD71, and HLA-DR. Tumor cells are positive for epithelial membrane antigen (EMA) and CD45 and negative for CD15 and frequently positive for CD4 and CD2, but they usually lack CD3.²⁷ Few cases are positive for CD8. T-cell markers are lacking in some cases, such as null cell ALCL. Cases of CD56+ ALCL are associated with a worse prognosis.⁴³ Tumor cells contain TIA-1, granzyme B, and/or perforin.^{64,65} Clusterin is a marker of ALCL⁶⁶ and has been found in primary c-ALCL but not in Hodgkin's lymphoma. Most systemic ALCL cases are positive for ALK nuclear and cytoplasmic staining, but there are variants with only cytoplasmic staining.^{67,53,54}

Primary c-ALCL has an activated T-cell phenotype expressing CD25, CD30, CD71, HLA-DR, and one or more T-cell antigens, most commonly CD4 and CD2. At

least 75% of large anaplastic or pleomorphic cells express CD30. EMA and ALK staining are usually negative, but there are rare exceptions. CD56 is positive in 12% to 75% of primary c-ALCL, but CD56 expression has no prognostic significance in primary c-ALCL in contrast to the adverse prognostic significance of CD56 in systemic ALCL.⁴¹⁻⁴³ A study showed CD56 expression found in approximately 10% of CD30+ cutaneous lymphoproliferative disorders (both LyP and primary CD30+ cutaneous T-cell lymphoma). However, these CD56+ cases were not found to have a different prognosis from CD56 negative cases.⁴¹⁻⁴³

The frequent ulceration in primary c-ALCL appears to be due to the release of the cytotoxic proteins (granzyme B and/or perforin) from CD30+ cells and neutrophils infiltrating the skin lesions.⁶⁸ Some variants show a different phenotype. Frequent ulceration is also seen in CD8+ lymphomas.^{69,70} In children, primary c-ALCL can show ALK positivity.⁷¹ About 40% of cases of primary c-ALCL are positive for clusterin.^{66,72} Recent studies show that CD95 is preferentially expressed in cutaneous CD30+ lymphomas and suggest that CD95 might play a role in spontaneous regression of CD30+ skin lesions.⁷³⁻⁷⁵

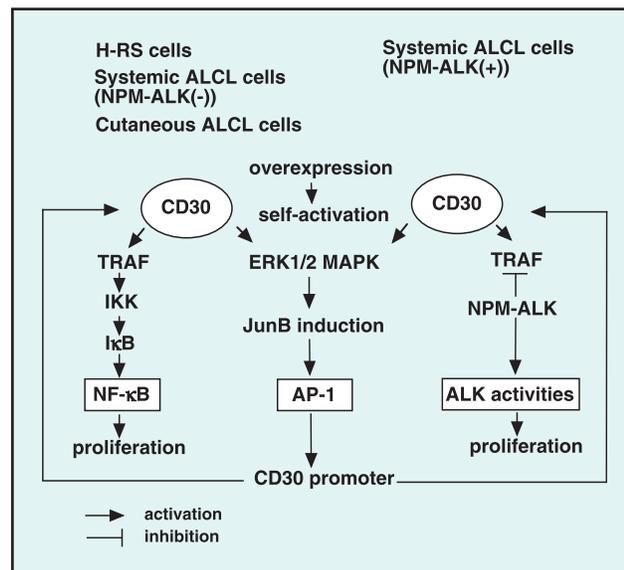


Fig 4. — NPM-ALK appears to block recruitment and aggregation of TRAF adapter molecules required to mediate CD30-induced activation of NF- κ B and its putative mechanism is shown above. In Hodgkin's-Reed-Sternberg cells, NPM-ALK(-) systemic ALCL and cutaneous ALCL cells (left), overexpressed CD30 activates the TRAF-IKK-I κ B-NF- κ B pathway. In systemic ALCL NPM-ALK(+) cells (right), the TRAF-IKK-I κ B-NF- κ B pathway is interrupted by association of NPM-ALK with TRAF. Activation of ALK tyrosine kinase supports the growth of systemic ALCL cells. CD30-ERK1/2MAPK-JunB-AP1 is a TRAF independent common pathway that stabilizes overexpression of CD30 in H-RS cells, NPM-ALK (+) and (-) systemic ALCL cells, and cutaneous ALCL cells. From Watanabe M, Sasaki M, Itoh K, et al. JunB induced by constitutive CD30-extracellular signal-regulated kinase 1/2 mitogen-activated protein kinase signaling activates the CD30 promoter in anaplastic large cell lymphoma and Reed-Sternberg cells of Hodgkin's lymphoma. *Cancer Res.* 2005;65:7628-7634. Reprinted with permission of American Association for Cancer Research.

Treatment and Prognosis

In LyP, patients usually do not require treatment, but if the lesions are severe, psoralen with ultraviolet A or weekly low-dose methotrexate⁸ is recommended. Successful treatment may prevent progression to ALCL but is unlikely to prevent development of MF or Hodgkin's disease.

Primary c-ALCL is managed by surgical removal or local irradiation. Multicentric disease is an indication for low-dose methotrexate as for aggressive LyP. Extracutaneous disease requires multiagent chemotherapy such as cyclophosphamide, hydroxydoxorubicin (Adriamycin), vincristine, and prednisolone (CHOP).¹ The 5-year survival rate is greater than 90%.^{1,76} Regional lymph node involvement does not represent a poor prognostic factor.¹

In systemic ALCL, treatment is combination chemotherapy. Survival is better for ALK-positive ALCL than for ALK-negative ALCL.^{5,6,77} Several advanced protocols of targeted antigen approaches are available. In animal models and in vitro, 5F11, which is a fully human monoclonal antibody directed against CD30, effectively induces killing of CD30-expressing lymphoma cell lines.⁹ SGN 30 (anti-CD30 monoclonal antibody) is being studied in a phase II trial. Several fused pyrrolocarbazole (FP)-derived kinases effectively inhibit ALK-dependent biologic activities in ALK-positive cells with minimal cellular toxicity toward ALK-negative cells.¹⁰ Studies have shown that the ablation of

ALK should be pursued as an efficient strategy for the clinical treatment of ALCL, such as silencing a specific gene using RNAi (RNA interference), small peptides, and antisense molecules.⁷⁸

Altered Gene Expression as a Basis for Classification and Targeted Therapy

Bcl-2 overexpression is a common characteristic of follicular lymphomas and CD30+ cutaneous lymphomas.³⁴ Bcl-2 was not found to be expressed by CD30+ large atypical cells in LyP, thus providing a molecular distinction between LyP and a pleomorphic subset of c-ALCL. Antisense Bcl-2 has been used for treatment of follicular lymphoma⁷⁹ and therefore can be considered for therapy of selected pleomorphic CD30+ cutaneous lymphomas^{34,35} protected from apoptosis by Bcl-2.

Overexpression of AP1/JunB has been recognized as a characteristic of cutaneous T-cell lymphoma, including CD30+ ALCL.⁵⁶ This may result from amplification of JunB at chromosome 19p13 as indicated by comparative genomic hybridization studies.⁵⁶ We have found JunB expression maintains the high activity of the CD30 promoter in ALCL and Hodgkin's lymphoma.⁵⁸ JunB induction was found to be largely independent of NF- κ B in ALCL and Hodgkin's lymphoma. JunB expression was also found to be a feature of LyP.⁵⁷ Thus, JunB may be a molecular target for therapy of CD30+ cutaneous lymphomas but does not appear to be a reliable marker for distinction between benign LyP and CD30+ ALCL.

NF- κ B has been shown to be activated in MF⁸⁰ and in CD30+ cutaneous T-cell lymphoma clonally derived from LyP.⁷³ Proteasome inhibitors such as bortezomib have been used to suppress NF- κ B activation in Hodgkin's lymphoma⁸¹ and multiple myeloma, among other hematologic malignancies. Thus, proteasome inhibitors may have a role in the therapy of advanced CD30+ cutaneous lymphoproliferative disorders.

We found that nucleophosmin-anaplastic lymphoma kinase (NPM-ALK) oncoprotein abrogates CD30 signaling and constitutive NF- κ B activation in ALCL.⁸² NPM-ALK appears to block recruitment and aggregation of TRAF adapter molecules required to mediate CD30-induced activation of NF- κ B (Fig 3A-B). Unexpectedly, transduced NPM-ALK was found to induce an ALCL-like morphology and expression of the ALCL-associated proteins clusterin and EMA/MUC1 in cell lines of Hodgkin's lymphoma. Our results not only confirmed that NPM-ALK-positive ALCL represents a unique entity but also suggested the possibility that there might be no clear distinction of cellular origin between Hodgkin's lymphoma of T-cell origin, ALK-negative systemic ALCL, and ALK-negative c-ALCL. However, the cutaneous site and microenvironment appear to confer

a better prognosis on ALK-negative c-ALCL for unexplained reasons that hopefully will be defined by further molecular/genetic analyses.

Transforming growth factor beta (TGF- β) is a multifunctional cytokine that can exert either a positive or negative effect on proliferation, differentiation, and cell death depending on the developmental stage of the target cell and its microenvironment, as well as in the context of *in vitro* studies.⁸³ We have found loss of TGF- β receptor growth inhibition of clonal T lymphocytes in the progression of LyP to aggressive CD30+ anaplastic T-cell lymphomas.⁸⁴ Loss of TGF- β receptor growth inhibition was found to be due to a dominant negative mutation of the type II receptor⁸⁵ or deletion of the initiating sequence for translation of the type I receptor for TGF- β .⁵⁵ Thus, we proposed that altered TGF- β receptor/SMAD signaling is a major step in the progression of LyP to CD30+ ALCL.⁵⁵ Novel small molecules that can overcome TGF- β receptor defects and "short-circuit" the TGF- β /SMAD signaling pathway potentially could restore growth regulation to the abnormal T-cell clone.

CLA is an E-selectin ligand that facilitates adhesion of T lymphocytes to cutaneous vascular endothelium, initiating egress of T lymphocytes at cutaneous sites of inflammation. We found that CLA is highly expressed by CD30+ large atypical cells in LyP but may be expressed at low levels in c-ALCL or progression of LyP to extracutaneous lymphoma.³⁹ The mechanism of decreased CLA expression in extracutaneous spread of lymphoma is presently unknown. CLA is a glycosylated molecule that requires activity of fucosyl VII transferase. Once the mechanism of downregulated CLA in advanced cutaneous lymphoma is discovered, therapies directed at upregulation of CLA could help to prevent extracutaneous dissemination of CD30+ lymphoproliferative disorders, thus preventing the most adverse prognostic factor in the spectrum of CD30+ cutaneous lymphoproliferative disorders.⁷⁶

Negative cell cycle regulator p16 is downregulated in primary c-ALCL and in advanced CD30+ ALCL clonally derived from LyP.⁴⁸ It will be valuable to determine if p16 expression is preserved in LyP uncomplicated by lymphoma. This could provide a differential diagnostic tool as well as insight into the biological differences between LyP and clonally related lymphoma.

We propose that the current clinicopathologic classification of CD30+ cutaneous lymphoproliferative disorders is insufficient and can be improved by incorporating genetic and molecular criteria to better define the borders between benign and malignant disorders and aggressive and nonaggressive disorders. In turn, the molecular/genetic abnormalities (eg, CD30/TRAF/NF- κ B and TGF- β /SMAD signaling pathways) will serve as therapeutic targets, in harmony with advances in other more common lymphomas.

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