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CD30+ Neoplasms of the Skin

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Abstract Cutaneous T-cell lymphomas (CTCLs) are subdivided by lesion morphology, behavior, and surface receptors. Mycosis fungoides (MF) and Sézary syndrome (SS) are derived from CD4+ effector or central memory T-cells respectively. MF presents clinically as patches, plaques, or tumors, and SS presents with erythroderma. After MF/SS, the next most common CTCLs are CD30+ lymphoproliferative disorders: self-regressing lymphomatoid papulosis (LyP) or tumors of anaplastic large-cell lymphoma (ALCL), which express high levels of tumor necrosis factor death receptor member 8, also called CD30. Although MF is not considered to be a CD30+ lymphoproliferative disorder, MF may co-exist with LyP lesions, and MF may express CD30, especially in the setting of large-cell transformation. The development of targeted therapy for CD30+ CTCLs will help in understanding the importance of the CD30 death receptor in pathogenesis and will improve treatment options.

Keywords Cutaneous T-cell lymphoma · Lymphomatoid papulosis · LyP · Anaplastic large T-cell lymphoma · ALCL · Mycosis fungoides · Ki-1 · Hodgkin's lymphoma · Tumor necrosis factor member 8 · CD30 · Lymphoma · Interferon regulatory factor 4 · Large-cell transformation · Anaplastic lymphoma kinase

Introduction

In the classification of cutaneous T-cell lymphomas (CTCLs) by the World Health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC), CD30 is a marker defining a spectrum of clinical disorders ranging from self-regressing papules and small nodules known as lymphomatoid papulosis (LyP) to the more stable, larger tumors with an anaplastic morphology (anaplastic large-cell lymphoma. ALCL) [1]. These two clinical entities are known as CD30+ lymphoproliferative disorders and are separated empirically on the basis of their clinical behavior and tendency to self-regress spontaneously. Mycosis fungoides (MF), the most common CTCL, is diagnosed by the presence of chronic patches, plaques, and tumors expressing CD4+ epidermotropic helper-effector memory cells. Though MF is not considered a CD30+ lymphoproliferative disorder, MF patients can also have regressing LyP lesions. Furthermore, CD30 expression may occur in lesions of all stages of MF, especially when MF transforms to a large-cell phenotype or when tumors are present. This review will discuss the CD30+ lymphoproliferative disorders, their overlap with MF, and the development of targeted therapy.

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What is CD30?

CD30, or tumor necrosis factor receptor superfamily member 8 (TNFRSF8), is a cell surface receptor first identified on Reed-Sternberg cells in Hodgkin's lesions using an antibody in Kiel, Germany. Thus, it was first known as Ki-1 antigen. CD30 staining was first identified immunohistologically by the Ber-H2 antibody, as reported in *Blood* in 1989 [2]. A monoclonal antibody, CON6D/B5, has more recently been reported to work in paraffin-embedded tissues [3]. Soluble Ki-1 (CD30) can also be released by tumor cells and measured using enzyme-linked immunosorbent assay (ELISA) [4].

CD30 expression is absent on normal cells; it is restricted to activated T cells and B cells, including lymphomas, viral infections (herpes, Epstein-Barr [EBV], hepatitis B, and HIV), germ-cell tumors, and rare forms of lung cancer. CD30 interacts with a membrane-associated glycoprotein ligand, CD30L, also known as CD153 (TNFSF8; tumor necrosis factor [ligand] superfamily member 8). The ligand is widely expressed on normal activated lymphocytes, neutrophils, eosinophils, monocytes, and macrophages.

In a study using the Ber-H2 antibody, CD30 was expressed in 17 of 18 cases of Hodgkin's disease, 3 cases of ALCL, 11 of 52 T-cell lymphomas, 13 of 152 B-cell lymphomas, 2 of 3 cases of histiocytosis, and 1 of 4 plasmacytomas [5]. CD30 was significantly more common in T-cell lymphomas than in B-cell lymphomas, and in stage II or higher of T-cell lymphoma. In high-grade T-cell lymphomas, CD30 expression is associated with more favorable overall survival [5].

Engagement of CD30 with its receptor CD30L activates TNF receptor-associated factor 2 (TRAF2) and TRAF5, causing NF-κB signal transduction; this may lead to either proliferation or apoptosis. Genes that are upregulated by CD30 signaling include Fas, TRAIL, CCR7, TRAF1 and cIAP2, whereas FasL, perforin, granzyme B, and c-myc seem to be downregulated [6]. CD30 induced apoptosis may lead to the self-regression seen in LyP lesions, whereas proliferation may result in ALCL tumor formation.

There are two isoforms of CD30 from alternatively spliced transcripts, but their biologic significance is not yet known. CD30 signaling limits the proliferation of autoreactive CD8+ effector T cells, protecting the host from autoimmunity. In a recently published mouse model, knockout mice for CD30L were more susceptible to *Listeria* infection and, compared with wild-type mice, had reduced innate memory phenotype CD44+ CD4+ T cells producing gamma interferon in response to interleukin (IL)-12 or IL-15 stimulation in vitro [7]. In another study, ectromelia mousepox viral-encoded vCD30 was found to suppress gamma interferon (Th1) cytokine expression [8]. Viral CD30 binds with high affinity to the CD30 ligand and blocks its interaction with CD30. CD30 is co-expressed on CD4+ T cells that express T helper 2 (Th2) but not Th1 cytokines [9], which may explain why it may be seen in later stages of MF.

Clinical Spectrum of the CD30+ Lymphoproliferative Disorders

Lymphomatoid Papulosis

CD30 staining has been found in a range of cutaneous lesions. LyP was first described by Macaulay in 1968 as a continuing, self-recurring condition that is clinically benign but histologically malignant [10]. Recurrent and self-regressing red papules and nodules (measuring <1.5–2.0 cm) may occur singly or in crops. Lyp lesions may become necrotic in the center and leave scarring. The size of LyP has been loosely defined as less than 1.5 or 2.0 cm (smaller than ALCL lesions), but more commonly they are smaller, measuring about 3 to 8 mm. They also may appear as pink pinpoint macules or may grow rapidly into small (< 1.5–2 cm) papulonodules before involuting spontaneously within 3 or 4 months. It is not uncommon for LyP lesions to appear in clusters or for flares of multiple lesions to occur.

There are four recognized histologic variants of LyP (Table 1). LyP must be distinguished from ALCL through clinical judgment of whether the lesions are tumors or papules, and by histologic evaluation. Differentiation is most difficult when there is a solitary, enlarging, single CD30+ lesion and regression has not yet occurred. Type A LyP, the most common form, is characterized by a wedge-shaped infiltrate with a mixed infiltrate containing eosinophils and histiocytes. Type B is identical to MF lesions and contains T-cell infiltrates with epidermotropism. Some lesions may also show large-cell transformation, defined as 25% of the atypical lymphocytes having nuclei four times larger than normal nuclei. Type C is identical to ALCL in having sheets of large cells with strong CD30 staining in more than 75% of the lymphocytes. Type D is rare; the lymphocytes are CD8+ with cytotoxic TIA-1 staining. Type D can histologically resemble the very aggressive CD8+ lymphoma known as Berti's lymphoma [11], but unlike CD8+ lymphoma, the lesions self-regress. Another aggressive lymphoma with γδ T-cell phenotype may also have a LyP variant [12•].

Kadin et al. [13] suggested that progression from LyP to systemic lymphoma occurs when cells escape from TGF-β and from CD30 ligand. CD30 ligand and CD95 (fas) are both expressed in LyP lesions, which could explain their property of self-regression through induction of apoptosis. Loss of Fas has been associated with transformation to aggressive types of CTCL [14].

Table 1 Histologic variants of lymphomatoid papulosis

Type	Characteristics
A	LyP type: wedge-shape lesion containing CD4+ atypical lymphocytes, mixed infiltrate with eosinophils
B	MF type: epidermotropic lymphocytes; large-cell transformation may be present
C	ALCL type: sheets of CD30+ large T lymphocytes
D	CD8+, TIA-1+ (resembles Berti's lymphoma)

ALCL anaplastic large-cell lymphoma; *LyP* lymphomatoid papulosis; *MF* mycosis fungoides; *TIA-1* T-cell–restricted intracellular antigen-1

Epidemiology

Patients with LyP may present with one of the following malignancies in 20% of cases or with increased susceptibility to one of several future malignancies. Most common are MF, primary cutaneous ALCL, or Hodgkin's disease, in that order. The clinical and histologic overlap among these entities may result in the incorrect overdiagnosis of LyP as a systemic lymphoma, especially large-cell lymphoma. Administration of unnecessary chemotherapy fails to cure LyP. In a study of 219 patients with long-term follow-up, all patients with LyP or primary cutaneous ALCL who were treated with multiagent chemotherapy had one or more relapses in skin [15].

Pathogenesis

To study the pathogenesis of LyP, we retrospectively examined 84 patients with diagnosis and follow-up at MD Anderson Cancer Center between 1999 and 2005 [16•]. The demographics are shown in Table 2. Of these 84 LyP patients, 61 (71%) had no sign of lymphoma at presentation; a lymphoma was diagnosed at the diagnosis of LyP in 12 patients (14%) and later in 11 others (13%) (median time to onset, 3.04 years). Overall, 34 (40%) of the 84 LyP patients were found to have either a pre-existing or a delayed onset of lymphoma. MF was diagnosed in 16 patients, ALCL in 15, and both MF and ALCL in 2. One of these two had also been diagnosed with Hodgkin's disease. One had peripheral T-cell lymphoma. Of six patients who later developed MF, only one had histologic evidence of large-cell transformation. The median time from diagnosis of LyP to any lymphoma was 17.6 years (range, 0–49.8 years), and the CI was not reached. We performed logistic regression for risk factors. Men were 2.5 times more likely than women to get lymphoma (P=0.04). ALCL occurred in more than 50% of the men and only 27% of the women, but 64% of the women with LyP also had MF.

Table 2 Demographics of 84 patients with lymphomatoid papulosis (LyP) in a retrospective analysis

Factor	Result
Sex	F, 46; M, 38
Race	White, 67; African American, 12; Hispanic, 5
Time to diagnosis	4.27 months (range 0–492 months)
Time to follow-up	6.05 years (range 0–44 years)
Lymphoma at diagnosis	12/84 (14%)
Lymphoma after LyP	11/84 (13%); median time to onset 3.04 years

Data from Kunishige et al. [16]

Patients with a history of EBV infection or a positive serology for EBV had a 4.77 higher risk of getting lymphoma.

Primary Cutaneous ALCL

Cutaneous ALCL tumors are defined as being larger than 1.5 to 2.0 cm, and 80% are solitary at presentation. After treatment, primary cutaneous ALCL frequently relapses in skin, and 10% of tumors spread to regional lymph nodes. The tumors frequently occur on an extremity and can initially be mistaken for insect bites or abscesses. Cutaneous ALCL tumors can also regress over time in about 20% to 25% of cases [17]. The histopathology of LyP and ALCL are identical, so the clinical and histologic overlap makes it difficult to distinguish LyP from cutaneous ALCL at first presentation. Hence the term "CD30+ lymphoproliferative disorders" was adopted to take this difficulty into consideration.

A biomarker that may help to differentiate LyP from ALCL or to differentiate primary cutaneous ALCL from other T-cell neoplasms is interferon regulatory factor 4 (IRF4). Translocations of IRF4 were studied using fluorescence in situ hybridization (FISH) in 204 biopsies taken from patients with T-cell proliferative disorders [18]. A translocation was found in 9 (20%) of 45 cases of ALCL cases and only 1 (3%) of 32 cases of LyP; other T-cell lymphoma types were negative. Among all cutaneous T-cell tumors, FISH positivity had a specificity of 99% and a positive predictive value of 90% for primary cutaneous ALCL (P=0.00002, Fisher's exact test) [18].

It is more essential to distinguish primary cutaneous ALCL from systemic ALCL than from clinically benign LyP [19]. ALK is a tyrosine kinase that through translocation has become fused to an activating promoter that increases proliferation through the Ras/erk signal transduction pathway. Staining for anaplastic lymphoma kinase (ALK) protein and epithelial membrane antigen (EMA) are negative in primary cutaneous ALCL and may be used to distinguish it from systemic nodal ALK+ALCL. The most common translocations are t(2;5), t(2;3), or t(2;22). The t(2;5)(p23;q35) translocation is detected in ALCL but is not present in Hodgkin's disease or in LyP [20]. Although systemic ALCL can be either positive or negative for ALK, primary cutaneous ALCL and LyP lesions are always ALK$^-$. This finding is something of an enigma, as patients with systemic ALCL patients who are ALK$^-$ have a poorer prognosis than those who are ALK+. Children who present with nodal and cutaneous disease are ALK+, which may explain the favorable prognosis of ALK+systemic ALCL [21]. A highly glycosylated transmembrane glycoprotein, MUC-1, results from t(1;14)(q21;32) and confers inferior overall survival if present in systemic ALCL.

The association between expression of ALK and CD30 was not explained in cutaneous ALCL. ALK drives lymphoma cell proliferation, and Jun B, which is increased in ALK+systemic lymphoma, drives the CD30 promoter. Biopsies from cutaneous lesions should be stained for ALK expression, and if the lesion is positive, then a systemic workup is required to evaluate the patient for systemic disease.

Recently, there have been reports of CD30+ ALCL cells associated with textured silicone breast implants, resulting in a black box label [22]. Large, atypical T cells with CD30+ staining have been detected in seromas (48%) or capsules (69%) with or without symptoms. The presentation was predominantly unilateral and symptomatic, although similar effusions were also seen with removal of asymptomatic implants. Among 24 women who presented with a palpable mass, 31% were found at surgery, 21% had pain, 14% had redness, and 7% had capsular contraction. Only two patients had implant ruptures. Seventy-nine percent had a positive cytology and all cases were ALK$^-$. Refuting this study was one showing that the incidence of non-Hodgkin's lymphoma in a study of 43,000 women with implants was less than expected [23].

CD30 Expression in Primary Cutaneous Hodgkin's Disease

Hodgkin's disease usually manifests as a nodal lymphoma, but it rarely can present with skin lesions. Cerroni et al. [24] reported seven patients who presented with nodular sclerosing Hodgkin's disease, with nodes and skin lesions studied using immunohistochemistry. Clinically, the lesions reported were reddish-brown papules, plaques, nodules, and ulcerated tumors (which are also clinical manifestations of LyP and ALCL). The accompanying cellular infiltrate was a mixture of T lymphocytes with variable numbers of monocytes/macrophages and eosinophils (which is similar to type 1 LyP). Thus, there is clinical and histologic overlap between cutaneous Hodgkin's disease and the CD30+ lymphoproliferative disorders LyP and cutaneous ALCL.

CD30+ Expression in Mycosis Fungoides

MF, the most common CTCL, is not considered one of the CD30+ lymphoproliferative disorders. However, there can be considerable overlap between MF and the CD30+ lymphoproliferative disorders, and they often co-exist in the same patient. LyP lesions, as well as tumors expressing CD30, can occur in patients with well-established patches and plaques of MF. To explore the percentage and degree of CD30 expression in MF, we studied expression of CD30 in MF patients' lesions across all stages. We also asked whether CD30 expression in MF was always associated with histology of large-cell transformation [25]. CD30 positivity (defined as >10% expression in lymphocytic tumor infiltrates) was detected by immunohistochemistry across all stages of MF, but expression was less than 20% in 90% of cases. CD30 staining was positive in less than 5% of MF patients with skin stages T1 or T2. There was most variation in lesions from patients with advanced stages of MF, including tumors (stage T3 or IIB), and only one patient had greater than 75% expression. There were significantly more CD30+ patients with late-stage MF (10 of 42) than with early-stage MF (2 of 64; $P=0.003$). Positive CD30 expression of greater than 10% was significantly associated with large-cell transformation of MF ($P<0.01$). Only 4 (8%) of 49 of patients with advanced disease (Stage 3–4) co-expressed CD25 and CD30.

Treatment

Lymphomatoid Papulosis

No currently available therapy for LyP cures the disease, although some patients have long-lasting remissions spontaneously. When there is a trigger factor such as herpes simplex infection, suppression with an antiviral agent may be successful. Treatment can be divided into conservative, topical therapies or systemic therapies for patients who have many active and scarring lesions. When LyP lesions are few or infrequent, they can often be ignored or can be suppressed by application of strong steroid cream, topical bexarotene, or imiquimod. Topical mupirocin is recommended to prevent infection of ulcerated lesions. For patients with multiple and frequent lesions, a weekly low dose (10–25 mg) of oral methotrexate is often selected because of ease of administration. Methotrexate should be tapered to the lowest possible dose that suppresses the outbreaks of LyP lesions. Other therapies used successfully include phototherapy with either PUVA (psoralen and UVA) or UVB, interferon α, or oral bexarotene. For extensive LyP or concurrent MF or ALCL, we have successfully used denileukin diftitox [26].

Since LyP lesions express high levels of CD30, we studied the safety and efficacy of SGN-30, a humanized antibody to CD30, in 23 patients with CD30+ LyP, primary cutaneous ALCL, CD30+ MF, or a combination of any of these [16•]. The initial dose of 4 mg/kg was increased to 12 mg/kg and administered every 3 weeks for six doses. Three patients with LyP were taken off their methotrexate to participate in the trial, and all had significant flares during their washout period and the first two infusions. Two of three patients with LyP had long-lasting clinical remissions lasting 1 to 2 years after they received antibody infusions. A modified antibody, SGN-35 (brentuximab vedotin;

Seattle Genetics, Bothell, WA, USA), is currently being evaluated in a clinical trial of patients with LyP, MF, and cutaneous ALCL (see below).

ALCL

The overall survival for patients with ALCL is favorable, with a 4-year survival rate of 90% [27]. When solitary or regionally limited tumors are present, primary cutaneous ALCL can be managed effectively using excision or localized radiotherapy. Small tumors can be treated like LyP, as discussed above. Only 10% of cases of cutaneous ALCL present with multifocal tumors in more than two anatomic regions, which would require systemic therapy [27]. The most commonly used first-line systemic therapies used for multifocal cutaneous ALCL are multiagent CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) or single agents such as oral methotrexate, bexarotene or isotretinoin, interferon α, or denileukin diftitox [28].

The restricted CD30+ antigen is an ideal tumor marker for targeted therapy. In a phase II study of the naked antibody, SGN-30, in patients with cutaneous CD30+ lymphoproliferative disorders, there was a 70% response rate (16 of 23 patients), and 87% had either complete or partial responses or stable disease [29]. Of the 23 patients treated, 10 had complete responses that were durable, including 4 years in one patient with transformed MF. The safety reports in patients receiving the antibody were limited to pruritus and rash in one patient each, which was unlikely to be related to the treatment.

A modified antibody called SGN-35 (Brentuximab vedotin) is the SGN-30 antibody conjugated with a tubulin inhibitor, mono-methyl auristatin E. In clinical trials, SGN-35 has shown safety with an 86% response rate, including 63% complete responses, in relapsed, systemic ALCL [30•] and a 41% response rate in relapsed Hodgkin's disease [31]. SGN-35 antibody is currently in clinical trials for cutaneous CD30+ proliferative disorders and should have efficacy equal to or better than that seen for SGN-30 [29]. SGN-35 was recommended for accelerated FDA approval by the Oncology Drug Advisory Committee on July 15, 2011.

Conclusions

CD30, a member of the TNF receptor family, is expressed in LyP, ALCL, MF, and viral infection, especially herpes simplex and zoster infections. It is considered an activation antigen for T cells as well as a tumor marker. Recommendations for therapy and diagnosis of the cutaneous CD30+ lymphoproliferative disorders are evolving. Targeted therapy with a CD30 antibody is soon to become widely available and may give an alternative to methotrexate suppression. CD30+ lymphoproliferative disorders have been recently reviewed in depth by Dr. Werner Kempf, and a consensus statement by the cutaneous lymphoma working groups from the EORTC, International Society for Cutaneous Lymphomas (ISCL), and United States Cutaneous Lymphoma Consortium has been submitted for publication. This document may aid in better diagnosis and appropriate therapy choices.

Disclosure Conflicts of Interest: M. Duvic: Consulting fees from Millennium Pharmaceuticals for design of CD30+ Phase III Trial and research support from Seattle Genetics for conduct of two clinical trials.

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