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Nodal involvement by cutaneous CD30-positive T-cell lymphoma mimicking classical Hodgkin lymphoma

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Abstract

An association between classical Hodgkin lymphoma (cHL) and mycosis fungoides (MF) or lymphomatoid papulosis (LyP) has been reported in the literature. However, there can be considerable morphologic and immunophenotypic overlap between cHL and nodal involvement by CD30-positive T-cell lymphoproliferative disorders (T-LPD). To examine this potential association, biopsies from patients with a prior history of MF or primary cutaneous CD30-positive T-LPD and lymph node biopsies reported as either CD30-positive T-cell lymphoma (TCL) with Hodgkin-like cells or cHL were retrieved from the authors' institution. Of 11 cases identified, 10 were considered CD30-positive TCL with Hodgkin-like cells, while one was confirmed as cHL upon review. Five cases originally diagnosed as cHL were revised as CD30-positive TCL. Cases of CD30-positive TCL with Hodgkin-like cells showed a male predominance (M:F, 4:1) with a median age of 53 years (range 44–72 years). Nearly all patients (9/10) initially presented with skin lesions. In 7/10 patients the draining lymph node was involved, whereas in 3 cases this could not be confirmed. Tumor cells morphologically resembled Hodgkin/Reed-Sternberg (HRS) cells; they were uniformly strongly positive for CD30 and CD15 was expressed in 9/10 (90%) of cases. A T-cell derivation was confirmed by T-cell antigen expression (7/10) and clonal rearrangement of T-cell receptor genes (9/10). In three cases a common T-cell clone was identified in skin and lymph node. B-cell markers (CD20/PAX5) were consistently negative. In one case the diagnosis of cHL followed by LyP was confirmed, with HRS-cells expressing PAX5, CD30 and CD15. In situ hybridization studies for EBV were negative. We show that cHL is less often associated with MF and primary cutaneous CD30-positive T-cell LPD than previously thought, and that the co-

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expression of CD30 and CD15 in these T-cell lymphomas may lead to a mistaken diagnosis of cHL.

Keywords

CD30 positive T-cell lymphoma; classical Hodgkin lymphoma; lymphomatoid papulosis; mycosis fungoides; transformation; primary cutaneous CD30-positive T-cell lymphoproliferative disorder

Introduction

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (26) accounting for almost 50% of all primary cutaneous T-cell lymphomas. Primary cutaneous CD30-positive T-cell lymphoproliferative disorders (CD30-TLPD) are the second most common group of cutaneous T-cell lymphomas. This group comprises a spectrum of diseases including lymphomatoid papulosis (LyP), primary cutaneous anaplastic large cell lymphoma (c-ALCL), and cases with borderline features (21). Histologic transformation of MF can occur and involvement of extracutaneous sites such as lymph node are common (24). There are rare reports of classical Hodgkin lymphoma (cHL) arising in patients with either MF or CD30-TLPD (2-4, 21). However, a true association has been debated, and in some instances the cHL has been said to be of T-cell derivation (9). The differential diagnosis between cHL and nodal involvement by cutaneous CD30-positive T-cell lymphoma (TCL) with Hodgkin-like cells can be challenging, and will influence the selection of therapy to be employed. In an attempt to explore the nature of the association between cHL and MF or CD30-TLPD, we undertook a study of cases in which a nodal diagnosis of cHL or a Hodgkin's-like lesion was made in a patient with either MF or CD30-TLPD. We analyzed the clinical, morphological, immunophenotypic, and molecular findings of these 11 cases to explore the lineage of the neoplastic cells, and to clarify their relationship to the cutaneous proliferation. We conclude that while many such cases closely resemble cHL, the nodal disease in nearly all instances is a T-cell lymphoma derived from the cutaneous lesion.

Materials and Methods

Tissue specimens and immunohistochemical studies

Biopsies from patients with a suspected or reported diagnosis of nodal cHL and a diagnosis of either MF or CD30-TLPD were retrieved from the archives of the Hematopathology Section of the National Cancer Institute (NCI) Laboratory of Pathology. The corresponding cutaneous lesions were retrieved for review as well. All biopsies were preserved as formalin-fixed paraffin embedded (FFPE) tissue specimens. Immunohistochemical studies were performed on FFPE tissue sections using a panel of monoclonal antibodies (CD30, CD15, PAX5, CD20, CD3, CD4, and CD8) according to previously published techniques (5, 19). Histopathologic diagnosis was rendered by the authors according to the 2008 World Health Organization (WHO) classification (22). Categorization as nodal involvement by CD30-positive TCL required evidence of T-cell lineage using immunophenotypic and molecular criteria, whereas the diagnosis of cHL required evidence of the appropriate immunophenotype including CD30, CD15, and PAX5. The study was approved by the NCI Institutional Review Board.

In situ hybridization for Epstein Barr virus (EBV) encoded RNA (EBER)

In situ hybridization for EBER was performed on FFPE tissue sections using a FITC labeled oligonucleotide probe supplied by Ventana on an automated stainer (Ventana-Benchmark,

Tuscon, AZ, USA). Visualization was achieved using the ISH iView system with Alk-Phosphatase and nitro-blue tetrazolium and 5-bromo-4-chloro-3-indolyl phosphate substrate, with Fast red as contrast. A positive control was run with all cases and stained appropriately.

Molecular studies

T-cell receptor gamma chain gene rearrangements studies (*TRG*) were performed for all cases with available material. In brief, DNA was extracted using the QIAamp DNA FFPE Tissue Kit according to the manufacturer's instructions with minor modifications. PCR for detection of *TRG* was performed as described by Lawnicki *et al.* (15) using primers that interrogate all of the known V γ family members, and the J γ 1/2, JP1/2 and JP joining segments. To allow for fluorescence detection, each joining region primer was covalently linked to a unique fluorescent dye. The products were analyzed by capillary electrophoresis on an ABI 3130xl Genetic Analyzer, and electropherograms were analyzed using GeneMapper software version 3.7 (ABI).

One case (Case 6, Table 1, 2) was assessed in more detail by laser assisted microdissection (LAM) of tumor cells and background T-lymphocytes followed by molecular analysis. Five μ m FFPE tissue sections were mounted on polyethylene naphthalate (PEN) membrane glass slides (MDS Analytical Technologies, Sunnyvale, CA, USA) and stained with Mayer's hematoxylin (Sigma-Aldrich, St. Louis, MO, USA) as previously described (5). Tumor cells and background T-lymphocytes were microdissected separately using Leica LMD 6000 (Leica Microsystems, Wetzlar, Germany). PCR for detection of *TRG* of microdissected cells was performed as described above.

Results

Based on immunophenotypic and molecular studies, nodal biopsies from 10 patients were classified upon review as CD30-positive TCL with Hodgkin-like cells. Five of these cases (Cases 3, 4, 7, 8, 10) had been previously diagnosed as cHL, but the diagnosis was revised upon further studies of the nodal lesion. In one case a diagnosis of cHL was confirmed on the lymph node, whereas the skin biopsy showed features of LyP.

CD30-positive TCL with Hodgkin-like cells

Morphologic and Immunophenotypic Features—Morphologically, the HRS-like cells ranged in size from medium-to-large, had irregular nuclear contours, and vesicular chromatin (Figure 1A, B). The cytoplasm and nucleoli of the HRS-like cells appeared more basophilic as compared to true HRS-cells. Also, the nucleoli in the HRS-like cells tended to be multiple, while in cHL the HRS-cells usually have single prominent eosinophilic nucleoli. The HRS-like cells formed clusters or sheets, often with a finely fibrotic background. Three cases showed more extensive fibrosis (Cases 2, 7, 8) mimicking cHL, nodular sclerosis subtype (Figure 2E). Sinusoidal infiltration by tumor cells was a prominent feature. (Figure 1G, 2G). Some cases (4, 6, 8, 9, 10) contained clusters of eosinophils and neutrophils, further mimicking cHL. The neoplastic cells in all cases were strongly positive for CD30, CD15 (9/10, 90%) (Figure 1E, 1F), and negative for B-cell markers such as PAX5 and CD20, by immunohistochemical stains. T-cell markers (CD2, CD3, CD4, or CD8) were found to be positive in 7/10 cases (Figure 1H and Table 2).

The skin biopsies in these patients showed morphologic and immunophenotypic findings consistent with their respective diagnosis. Six cases were classified as LyP, 1 as c-ALCL, and 3 as MF (Figure 2). All 7 CD30-TLPD (LyP, cALCL) were positive for CD30, and negative for CD15 in the 4 cases studied. A T-cell phenotype was confirmed for the

cutaneous lesions. One case expressed CD8, and in that instance the nodal lymphoma was also CD8-positive. All other cases evaluated were positive for CD3 and CD4. In one case of a patient with long standing MF (case 10), the skin biopsies were not available for review.

Clinical Features—The majority of patients with CD30-positive TCL with Hodgkin-like cells were male (M:F, 4:1) with a median age of 53 years (range, 44-72 years) (Table 1). Most cases (9/10) presented with skin lesions initially, followed by nodal involvement. In most patients many years elapsed between the onset of the cutaneous disease and the nodal lymphoma, and the extent of the cutaneous disease was variable. For the 3 patients with MF, skin lesions were present for many years, up to 20 years in one patient. The duration of the cutaneous disease was more variable for the 7 patients with LyP/c-ALCL. In one patient (Case 8) the interval was only one year, with minimal cutaneous lesions that had been largely overlooked at the time of lymph node biopsy. In one patient (Case 7), the nodal disease preceded clinical evidence of cutaneous lesions. In 7/10 patients the draining lymph node proximate to a dominant cutaneous lesion was involved, whereas in 3 cases generalized skin disease was present, precluding establishment of a relationship.

Classical Hodgkin lymphoma and LyP

Clinical, Morphologic and Immunophenotypic Features—Patient (Case 11, Table 1, 2) was a 73-year old male with a history of cHL in long term remission. He also had a history of nummular eczema. He presented with a papular/nodular lesions on the forearm and buttocks, which showed focal ulceration and crusting. The forearm lesion was excised. Two months later he was noted to have bilateral iliac lymphadenopathy, leading to a lymph node biopsy and a diagnosis of recurrent cHL.

The lymph node showed complete architectural effacement with scattered large atypical cells with irregular nuclear contours, vesicular chromatin, and prominent eosinophilic nucleoli, consistent with HRS cells (Figure 3A). The background showed numerous small lymphocytes and epithelioid histiocytes. The HRS cells were positive for CD30, weakly positive for PAX5, and focally positive for CD15 (Figure 3B). Other B-cell associated antigens (OCT-2, BOB.1, CD20) were variably expressed, and were weaker in HRS-cells than in the background small B-cells. T-cell markers (CD3, CD4, and CD8) as well as EBER by in situ hybridization were negative. Following a diagnosis of cHL, mixed cellularity subtype, chemotherapy was instituted.

The skin biopsy demonstrated features characteristic of LyP. It demonstrated a wedge-shaped dermal infiltrate composed of scattered large atypical cells in a mixed inflammatory background composed of small lymphocytes, histiocytes, and eosinophils (Figure 3C, 3D). The epidermis was atrophic and there was minimal exocytosis and superficial dermal fibrosis. CD30 highlighted the scattered large atypical cells that were also positive for CD3.

Molecular Findings and EBER by in situ hybridization—Sufficient material and adequate DNA quality allowed analysis of *TRG* in all cases with CD30-positive TCL with Hodgkin-like cells and 9/10 cases studied revealed a clonal rearrangement by *TRG*. Case 6 had sufficient material for LAM and was further analyzed. Clonal *TRG* with peaks of identical molecular size were detected in tumor cells from the skin biopsy as well as in tumor cells from the lymph node biopsy after enrichment using LAM (Figure 4A, 4B). In contrast, a polyclonal *TRG* was detected from the non-neoplastic background T cells that were microdissected separately from the same lymph node biopsy (Figure 4C).

Two additional cases (Case 3, 8) had sufficient material to compare the skin and lymph node biopsies by *TRG*. Whole mount tissue scrapes were performed and clonal peaks of identical molecular size were detected by *TRG* in the skin and lymph node biopsies. *TRG* performed

on the biopsies of cHL and LyP in a single patient (Case 11) were non-contributory due to poor DNA quality.

EBER was performed on all cases of CD30-positive TCL with Hodgkin-like cells (10/10) and were all negative. Similarly, EBER was negative in the patient's biopsies with cHL and LyP.

Discussion

Hodgkin-like cells may be encountered in the skin lesions of patients with primary cutaneous CD30-T-LPD, and more rarely MF, and therefore, it is not surprising that when lymph node involvement occurs, the process may closely mimic cHL. Additionally, better understanding of the nature of these disorders has led to expanded immunophenotypic panels for this distinction, with cHL manifesting evidence of a B-cell lineage with expression of PAX5 in most cases. Thus, older reports of cHL following MF or LyP might not be validated using current criteria, (9, 11, 20, 21, 27), perhaps leading to misconceptions regarding a relationship between these conditions. In this report we describe 10 patients with MF or CD30-TLPD who developed nodal disease that resembled cHL; further studies led to final diagnosis of nodal involvement by CD30 positive TCL with Hodgkin-like cells. In five cases a diagnosis of cHL had been made, leading to treatment for cHL in 3 instances.

In the cases of CD30 positive TCL with Hodgkin-like cells evidence for a T-cell origin was based on expression of T-cell associated antigens in 7/10 cases, and the demonstration of a clonal T-cell gene rearrangement by PCR in 9/10 cases studied. In Case 6 we microdissected the HRS-like cells from the lymph node and showed clonal relationship with the skin lesion diagnosed as LyP, whereas in Cases 3 and 8, clonal peaks of the same size were demonstrated in DNA obtained whole mount tissue sections of both skin and lymph node lesions by *TRG*. While it is difficult to totally exclude occult involvement by the T-cell lymphoproliferative process in a lymph node also involved by cHL as the basis for the T-cell clones, the negativity for PAX5 on the neoplastic cells in these cases both in the skin and lymph nodes argues against the diagnosis of cHL. This conclusion was further substantiated by an absence of a T-cell clone in the background lymphocytes of Case 6, not enriched for the large pleomorphic cells.

A CD30-positive, CD15-positive immunophenotype used to be regarded as highly specific for cHL, perhaps leading to misclassification in older reports. More recent studies have shown that some T-cell lymphomas can show co-expression of both CD30 and CD15 (1, 25). Molecular studies helped to confirm the T-cell lineage in these aggressive T-cell lymphomas, and absence of staining for PAX5 is an additional useful finding, since most cHL express this marker, albeit weakly (7, 13). While PAX5 is usually strong evidence for a B-cell lineage, and would favor a diagnosis of cHL, rare cases of ALCL have been reported to express PAX-5 secondary to amplification of the *PAX5* gene (6). The case reported by Willenbrock et al. may have fallen into this category, as it was reported to show T-cell receptor beta gene rearrangement, and was positive for PAX5 as well (27). The status of the *PAX5* gene was not evaluated in that report. Peripheral T-cell lymphomas can also mimic cHL secondary to EBV-positive Hodgkin-like B-cells, but our cases were all EBV-negative (17).

One might question whether these cases of CD30-positive TCL with Hodgkin-like cells may represent a "T-cell type" of cHL because of the clonal *TRG* and T-cell antigen expression on the tumor cells. However, lineage is still considered a major factor in the definition of lymphomas, and the current view defines cHL as a tumor of B-cell genotype, albeit with a disordered differentiation profile (14). Evidence of this disordered differentiation was

reported by Tzankov *et al.* in which HRS cells aberrantly expressed T-cell associated antigens and in rare instances had clonal rearrangement of TCR genes (23). However, those authors found evidence of B-cell origin as well, with expression of PAX5 or CD20. Disordered differentiation was also observed in some cHL cell lines, which despite exhibiting some T-cell features, had a gene expression profile similar to that of cHL cell lines with a B-cell phenotype (28). None of our cases of CD30-positive TCL with Hodgkin-like cells expressed any B-cell associated markers (i.e. CD20, PAX5). Whether a true T-cell form of cHL exists remains controversial, with no confirmed cases since the initial reports in 2000 (16, 18).

There were a number of histological features that proved useful in the distinction of CD30-positive TCL with Hodgkin-like cells from cHL (Table 3). In cases of cutaneous CD30-positive TCL, as compared with cHL, the cytoplasm was more basophilic with multiple, usually basophilic nucleoli. Variation in cell size of the HRS-like cells from medium-to-large was commonly seen as compared to the consistently large size of HRS-cells in cHL. The tumor cells often formed cohesive clusters or small sheets, and neoplastic cells showed prominent sinusoidal infiltration. (Figure 1G, 2G). Even in aggressive variants of cHL, sinusoidal infiltration is rare. Fibrosis was usually evident and variable in extent. While in half of the cases, the inflammatory background consisted mainly of lymphocytes and histiocytes, in five of the cases focal clusters of eosinophils and neutrophils were present. Therefore, this particular finding is not reliable in the distinction between cHL and CD30-positive TCL with Hodgkin-like cells. In fact, five cases (Case 3, 4, 7, 8, 10, Table 1, 2) were initially misdiagnosed as cHL. These cases also had a thickened capsule and prominent bands of fibrosis, mimicking cHL, nodular sclerosis subtype.

Patients with both cutaneous T-cell lymphoma and cHL have been described rarely (2-4, 9, 11, 12). A few of these case reports (Table 4) described the lymph node tumor as containing sheets of tumor cells, sometimes with a sinusoidal pattern, and positive for *TRG* (4, 9). We feel that these cases are reminiscent of our 10 cases and likely represent a CD30-positive TCL with Hodgkin-like cells rather than cHL. Sinusoidal involvement is not a common feature observed in cHL and likely represents lymph node involvement by the cutaneous TCL.

In the majority of cases of CD30-positive TCL with Hodgkin-like cells (7/10) the nodal lesions were in the lymphatic drainage of the dominant cutaneous lesion, and prominent sinusoidal infiltration also supports lymphatic invasion as a mode of spread. The single case of cHL and LyP (Case 11) had lesions that were distant from each other (skin-left forearm, lymph node-right iliac). We attempted *TRG* in both specimens of Case 11; however no amplified products were detected in either specimen due to poor DNA quality. Our case of cHL with LyP of the skin was in line with previous case reports in that both lesions were also negative for EBV by EBER in situ hybridization (2, 10). The case reported by Gellrich *et al.* also found clonal immunoglobulin gene rearrangement in the cHL lymph node but not in the LyP lesions, supporting the diagnosis (8).

True instances of cHL following a cutaneous T-cell lymphoma are likely rarer than previously described. The distinction between nodal involvement by cutaneous CD30-positive TCL with Hodgkin-like cells and cHL can be extremely difficult. However, with proper immunohistochemical stains, molecular studies, careful examination of the tumor morphology, pattern of infiltration, and thorough clinical history, the distinction between these two entities can be made. These cases further emphasize the lack of reliability of the CD30+/CD15+ immunophenotype as pathognomonic for cHL.

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Figure 1.

A. CD30-positive T-cell lymphoma with Hodgkin-like cells involving the lymph node. (Case 2) **B.** At higher power tumor cells infiltrate in sheets and show variability in size, irregular nuclear contours, vesicular chromatin, and prominent nucleoli (**inset**) reminiscent of HRS cells. **C.** Lacunar-like cells were seen in some cases (Case 1). **D.** Some cases had a thickened capsule and broad bands of fibrosis mimicking cHL, nodular sclerosis subtype (Case 2). **E.** CD30 highlights the tumor cells forming nodular aggregates divided by dense fibrosis, and (**inset**) the variability in cell size of the tumor cells (Case 2). **F.** The HRS-like cells are positive for CD15 (Case 9) but negative for PAX5 (not shown) **G.** Sinusoidal infiltration was prominent in most cases (Case 5). **H.** Tumor cells are positive for T-cell-associated markers such as CD2 (Case 1).

Figure 2.

A. Skin biopsy (Case 8) shows features of LyP with a dense dermal infiltrate composed of **(B)** atypical medium to large cells that are positive for CD8 **(C)** and CD3 **(inset)**, as well as CD30 **(D)**. **E.** The same patient had an inguinal node containing a pleomorphic infiltrate with sinusoidal infiltration by **(F)** large HRS-like cells that were positive for CD30 **(G)**, CD15 **(inset)**, and CD8 **(H)**.

Figure 3.

A. Lymph node (Case 11) with features of cHL, mixed cellularity subtype. HRS cells are present in an inflammatory background. **B.** The HRS cells are positive for CD30 as well as PAX5 (**inset**), showing dim staining for the latter. **C.** The skin biopsy shows a wedge-shaped infiltrate sparing the epidermis composed of **(D)** large atypical cells in a background of histiocytes, small lymphocytes, and eosinophils.

Figure 4.

T-cell receptor γ chain gene rearrangement studies of CD30-positive T-cell lymphoma with Hodgkin-like cells (Case 6) identified clonal peaks of identical size in the microdissected tumor cells of the skin biopsy (**A**) and the lymph node biopsy (**B**), whereas DNA from microdissected background T-lymphocytes were polyclonal TCR gene rearrangements (**C**).

Table 1

Characteristics of 10 patients with CD30-positive T-cell lymphoma with Hodgkin-like cells and 1 patient with LyP and cHL

Case No	Gender	Age	Clinical presentation, treatment and outcome (months)	Draining lymph node involvement
1	M	56	History of longstanding MF; nodular lesion of scapula followed by left sided axillary lymphadenopathy.	Yes
2	M	68	History of multiple skin lesions (scalp, right upper arm, and waist) histologically diagnosed as c-ALCL. Patient developed an enlarged right neck lymph node, which was biopsied	Yes
3	F	50	History of LyP; lymph node biopsy initially suspected as cHL; patient treated with CHOP chemotherapy followed by MTX; recurrent skin lesions. Alive with cutaneous disease only (21).	NE
4	F	72	History of LyP, presented with a skin nodule on the right cheek, and right submandibular lymphadenopathy; treated for cHL with Stanford V chemotherapy. Achieved CR for 31 months, but relapsed with recurrent lymphoma. Died (40).	Yes
5	M	56	History of MF on right thigh, treated with topical creams and PUVA with no further therapy required; 11 years later developed right groin mass, diagnosed as ALCL, consistent with progression of MF. Treatment with 4cycles of CHOP, then romidepsin. Patient declined further therapy. Alive with disease (170).	Yes
6	M	65	History of multiple skin lesions diagnosed as LyP; developed iliac lymphadenopathy and B-symptoms.	NE
7	M	44	Diagnosed with cHL (right inguinal lymph node) in remission; 1 year later presented with skin lesions on the right leg.	Yes
8	M	48	History of erupting and resolving skin lesions on the right lower leg, left arm, and trunk; 1 year later developed right inguinal adenopathy. Lymph node biopsy initially diagnosed as cHL. Skin lesions subsequently biopsied and diagnosed as LyP.	Yes
9	M	47	History of MF for more than 20 years with involvement of scrotum, inguinal, and axillary region. Recent onset of lymphadenopathy in the left neck and both axillae, leading to cervical lymph node biopsy	NE
10	M	42	History of LyP with skin lesions for the past 20 years on the knees, ankles, elbows, left buttock, and hip. No B-symptoms but now with inguinal lymphadenopathy.	Yes
11	M	73	History of cHL in long term remission; presented with papulo/nodular lesions of forearm and buttocks, diagnosed as LyP. Subsequent recurrent iliac lymphadenopathy, and diagnosis of recurrent cHL. Treated with Gemcitabine, Cisplatin, and Decadron. Alive in CR (6).	No

M = male, F = female, MF = mycosis fungoides, C-ALCL = cutaneous anaplastic large cell lymphoma, LyP = lymphomatoid papulosis, cHL = classical Hodgkin lymphoma, MTX = methotrexate, CR = complete remission, NE = not evaluable, CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone.

Table 2

Immunophenotypic and Molecular Features

Case No.	Biopsy site	LN Diagnosis	CD30	CD15	PAX5	EBER	CD3	CD4	CD8	Other	TCR
1	LN, left axilla	CD30+TCL	++	++	-	-	-	++	-	+CD2	Clonal
2	LN, right neck	CD30+TCL	++	+	-	-	+	-	-		Clonal
3	LN, right axilla	CD30+TCL	++	++	-	-	-	-	-		Clonal*
4	LN, right submandibular	CD30+TCL	++	-	-	-	-	++	-		Clonal
5	LN, right groin	CD30+TCL	++	++	-	-	-	++	-		Clonal
6	LN, right iliac	CD30+TCL	++	+	-	-	-	+	-		Clonal*
7	LN, right inguinal	CD30+TCL	++	++	-	-	-	-	-		Clonal
8	LN, right inguinal	CD30+TCL	++	+	-	-	-	-	+	+CD43, +CD2	Clonal*
9	LN, left cervical	CD30+TCL	++	++	-	-	-	-	-	+CD2	Clonal
10	LN, left femoral	CD30+TCL	++	++	-	-	-	-	-		PC
11	LN, right iliac	cHL	++	+	+	-	-	-	-		NC

LN = lymph node, NC = non-contributory by TRG, PC = polyclonal by TRG, * indicates both lymph node and skin biopsy have identical peaks by TRG, - = negative, + = focally positive, ++ = positive, CD30+TCL = CD30-positive T-cell lymphoma, cHL = classical Hodgkin lymphoma

Table 3

Morphologic, immunophenotypic, and clinical differences between classical Hodgkin lymphoma (cHL) and CD30-positive T-cell lymphomas (TCL) with Hodgkin-like cells

Features	cHL	CD30-positive TCL with Hodgkin like-cells
Clinical	B-symptoms. Mediastinal or nodal involvement at presentation. Cutaneous involvement rare. Young adult; F > M for cHL, nodular sclerosis	No B-symptoms. Skin lesions at initial presentation. Involved lymph nodes in drainage path of dominant skin lesion. Older, M > F
Morphology	Slightly basophilic cytoplasm, single prominent eosinophilic nucleoli. HRS cells are scattered and are <5% of total cells. Cell size uniformly large. Rare mitotic figures.	Basophilic cytoplasm and multiple nucleoli (usually smaller than typical HRS cell nucleoli). HRS-like cells cluster or form small sheets with frequent sinusoidal invasion. Variation in cell size from medium to large, often polylobated. Mitoses frequently seen.
Inflammatory background	Small lymphocytes, plasma cells, eosinophils, histiocytes, neutrophils	Small lymphocytes, histiocytes; eosinophils and neutrophils may be present focally
Immunohistochemistry	Weak/variable expression of B-cell associated markers (CD20 and PAX5); CD30 positive; CD15 variably positive	Negative for B-cell associated markers (CD20, PAX5); CD30 positive; CD15 variably positive
EBV	Positive (75% mixed cellularity, 10-25% nodular sclerosis).	Negative in tumor cells
Molecular Studies	Positive for <i>IGH</i> (usually only with microdissection), negative for TRG	Positive for TRG, negative for <i>IGH</i>

EBV = Epstein-Barr-Virus, F = female, M = male, cHL = classical Hodgkin lymphoma, PTCL = peripheral T-cell lymphoma, LyP = lymphomatoid papulosis, TRG = T-cell receptor gene rearrangement, IGH = immunoglobulin gene rearrangement, HRS =Hodgkin/Reed-Sternberg

Table 4

Prior reports of cutaneous T-cell lymphoma or CD30+ T-LPD with classical Hodgkin lymphoma

Author	Year	# Cases	Skin Diagnosis	Extracutaneous Diagnosis	Sinusoidal infiltration	Contiguous nodal involvement	TRG performed on cHL component
Chan et. al	1979	3	MF	cHL, NS	NR	No (1), Yes (2)	ND
Simrell et al.	1986	1	MF	cHL, NS	No	NR	ND
Kaudewitz et. al	1990	2	LyP	cHL, MC	NR	No (2)	ND
Davis et. al	1992	1	MF, LyP	cHL, MC, ALCL	Yes	No	Clonal*
Broussett et. al	1996	2	MF	cHL, NS	NR	NR	Polyclonal
Kadin et. al	2001	1	CD30+ T-LPD	cHL, NS	Yes	Yes	Clonal*
Kremer et. al	2001	1	MF	cHL**	NR	NR	Polyclonal
Willenbrock et al.	2002	1	CD30+ T-LPD	cHL, MC	No	NR	Clonal*
Gellrich et al.	2004	1	LyP	cHL	NR	NR	ND***

MF = Mycosis fungoides, LyP = lymphomatoid papulosis, CD30+ T-LPD = Primary cutaneous CD30-positive T-cell lymphoproliferative disorder, cHL = classical Hodgkin lymphoma, NS = nodular sclerosis subtype, MC = mixed cellularity subtype, ALCL = anaplastic large cell lymphoma, * = identical clone in lymph node and skin, ** = bone marrow involvement, *** = clonal by immunoglobulin gene rearrangement. NR = not reported, ND = not done, TRG = T-cell receptor gene rearrangement