Published in final edited form as:

Am J Dermatopathol. 2017 May ; 39(5): 351–357. doi:10.1097/DAD.0000000000000755.

CD30 expression is rare in myeloid leukemia cutis; a study of 55 cases and implications for routine diagnostic algorithms

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Abstract

Expression of CD30 in blastoid cutaneous infiltrates typically signifies a CD30+ lymphoproliferative disorder, often requiring minimal immunohistochemical work-up, if clinically consonant. However, myeloid and other hematologic malignancies often express CD30. We retrospectively examined the prevalence of CD30 expression in 41 patients (median age 59) and 55 biopsies with the diagnosis of leukemia cutis (LC) to determine whether an extensive immunohistochemical workup is warranted in all large, round cell CD30+ cutaneous infiltrates. Each patient had refractory or recurrent disease, the histologic presence of a large mononuclear cell infiltrate, and varied cytogenetics. CD30+ mononuclear cells within the infiltrate ranged from rare to many in twenty-two biopsies (22/55). In eighteen biopsies, CD30+ cells were interpreted as lymphocytic based on morphology, strong cytoplasmic and Golgi staining for CD30, and negative CD34 and CD117 staining. One case showing 3+ staining of lymphocytes was identified as a post-transplant lymphoproliferative disorder. The second 3+ case was favored to represent a subset CD30-positive AML. Three other cases with 1+ membranous and cytoplasmic staining were interpreted as myeloid leukemia. In conclusion, CD30 positivity in myeloid leukemia in the skin is rare and does not often exhibit the strong membranous (2+ or 3+) and/or Golgi staining seen in reactive lymphocytes. AML or myeloid LC may occasionally show 1+ (and rarely 2-3+) cytoplasmic/membranous or non-specific blush nuclear CD30 labeling. Strong diffuse staining for CD30 should prompt consideration of a reactive lymphoid/lymphoproliferative process, and, when the clinical likelihood of CD30+ leukemia cutis is low, may obviate the need for further immunohistochemistry.

Introduction

CD30 is a 120 kD cell membrane glycoprotein that shares sequence homology with tumor necrosis factor (TNF) receptors, and is also known as TNF receptor superfamily member 8 (TNFRSF8).¹ CD30 is expressed by activated B- and T-cells in physiologic states,² and is upregulated in some autoimmune and inflammatory disorders.³ It is also expressed in subtypes of B- and T-cell lymphoma such as classical Hodgkin lymphoma (CHL)⁴ and anaplastic large cell lymphoma (ALCL), as well as a spectrum of primary cutaneous CD30-

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positive T-cell lymphoproliferative disorders (LPD) such as lymphomatoid papulosis (LyP). In cutaneous pathology, the finding of strong CD30 expression by a mononuclear cell infiltrate raises the differential diagnosis of a CD30-positive LPD.

Leukemia cutis (LC) is defined as cutaneous infiltration by neoplastic leukocytes, either myeloid or lymphoid, that results in visible skin lesions. LC most commonly occurs in patients with acute myeloid leukemia (AML), a genetically heterogeneous hematologic malignancy characterized by clonal proliferation of marrow-derived precursor cells that may involve the bone marrow, peripheral blood, and/or extramedullary tissues. Subsets of AML are associated with high-risk cytogenetic abnormalities,⁵ arise from a preexisting myelodysplastic syndrome (MDS), or occur following prior cytotoxic therapy. The frequency of LC differs widely among various subtypes of AML, but is most commonly seen in AML with monocytic (13%) and myelomonocytic differentiation (10-33%).⁶ LC may also be seen in association with other myeloid malignancies such as myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML), as well as lymphoid neoplasms such as chronic lymphocytic leukemia (CLL) and acute lymphoblastic leukemia (ALL). LC may present concurrently with bone marrow disease be the first sign of relapsed disease, or may even precede bone marrow involvement.⁷ The presence of LC may be associated with higher rates of extramedullary leukemic involvement at other sites.⁸

CD30 expression by myeloblasts, first demonstrated in 1993 by Masuya et al.⁹, was recently identified by Zheng et al. in bone marrow specimens from patients with AML and high-grade MDS.¹⁰ Similarly, Fathi et al. reported variable CD30 expression, ranging from 2% to 80%, in bone marrow samples involved by AML.¹¹ The expression of CD30 has garnered significant clinical interest as targeted therapies to the CD30 antigen are now FDA approved and increasingly used in hematologic malignancies, showing durable responses, as in refractory and relapsed CHL and ALCL. Phase II trials with anti-CD30 therapy have been conducted for the treatment of cutaneous T-cell lymphoma (CTCL)/mycosis fungoides and clinical trials are ongoing.¹³⁻¹⁵ While the expression of CD30 by extracutaneous myeloid neoplasms has been evaluated, CD30 expression in LC derived from myeloid neoplasms has not been systematically investigated. To facilitate the distinction of cutaneous CD30-positive LPDs from skin versus cutaneous myeloid neoplasms, we examined the frequency and staining pattern of CD30 expression in myeloid leukemia cutis specimens.

Materials and Methods

The study was conducted in accordance with protocols approved by the institutional review board (IRB) at our cancer center. All patients included in this study were evaluated and treated at our institution. An IRB approved pathology database search for “leukemia cutis” from 2000-2012 identified 41 patients with 55 skin biopsies. Three of these patients were found to have lymphoid leukemia (CLL, B-ALL, T-ALL) and were kept in the study for comparison and demonstrative purposes.

Clinical charts, pathology reports, and histologic material of these 41 patients were reviewed. Immunophenotypic and cytogenetic data were collected for bone marrow biopsy specimens and the immunophenotypic profile of skin biopsies involved by leukemia cutis

was compiled. CD30 immunohistochemical stains were examined if already available, or performed (BER-H2) per routine on 5-micron thick formalin-fixed paraffin embedded (FFPE) tissue sections per the manufacturer's protocol. Histologic sections were examined for architecture and cytomorphology. CD30 expression was assessed for presence/absence, localization (cytoplasmic, membranous, and/or nuclear) and intensity of labeling (on a scale of 1+ to 3+).

Results

The clinicopathologic characteristics of the 38 patients with myeloid leukemia cutis are listed in Table 1. These include 25 male and 13 female patients. The median age was 59 (range 9-81) years. Of these, 37/38 had one or more bone marrow biopsies diagnostic of a myeloid neoplasm, including 30 cases of AML (79 %), 5 cases of CMML (13%), one case of myelodysplastic syndrome (MDS, Refractory anemia with excess blasts-2/RAEB-2; 2.6%), and one case of biphenotypic acute leukemia (AML/T-ALL; 2.6%). In the remaining patient, a bone marrow biopsy performed prior to skin biopsy did not show pathologic findings. Five cases (5/38) were therapy-related MDS/AML, while the rest of the cases were de novo myeloid neoplasms. Three cases of lymphoid leukemia initially identified in our text search were included for proof-of-principle, including CLL, B-ALL, and T-ALL, CLL (one case each). All of the patients were treated with induction chemotherapy, while some also received peripheral blood or double cord blood stem cell transplants.

Bone marrow biopsies, available on all 38 patients, were performed prior to (<30 days; 2/38), around the same time as (within 30 days; 13/38), or subsequent to (>30 days; 23/38) their first skin biopsies. Monocytic differentiation, as supported by morphologic, immunophenotypic, and/or histochemical characteristics, was noted in diagnostic bone marrow biopsies of 27/30 AML, 5/5 CMML, and 1/1 MDS cases, but not in the case of biphenotypic acute leukemia (Table 1). Karyotype and/or FISH studies were normal in 23/38 cases (60.5%), and abnormal in 15/38 cases (39.5%). Chromosomal abnormalities included balanced translocations [t(6;11), t(8;12), t(11;19), t(3;5), t(6;22), t(9;11), t(1;9;11)], trisomies (+8, +18, +21, +14), deletion/gain (-5q, -7q, -6, -12, -16/16q, +1p), and others [der(12), inv(16)]. A complex karyotype (the presence of 3 or more abnormalities) was present in 5/38 cases. A total of 55 skin biopsy specimens were examined from various anatomic locations. Among the 38 myeloid leukemia patients, six had more than one skin biopsy. Histologically, all skin biopsies showed the presence of an intermediate- to large-sized mononuclear cell infiltrate.

Immunohistochemically, the cutaneous leukemic infiltrates showed expression of CD43, CD68, myeloperoxidase and muraminidase/lysozyme in a varying proportion of cases. Giemsa and Leider histochemical stains were also positive in a subset of cases. The majority of myeloid cases were CD34-negative (9) except one case (case 27), which was also muraminidase positive. B and T-cell markers were uniformly absent in myeloid cases, except in two cases that were CD3 positive.

Twenty two of the 55 (40.0%) skin biopsies showed CD30 positivity by a mononuclear cell infiltrate, the intensity of which ranged from 1+ to 3+. Among these 22 biopsies with CD30

positivity, 18 showed strong cytoplasmic and Golgi staining, a pattern consistent with lymphocytes. Of note, one CD30 positive patient with 3+ staining of four different biopsies was re-evaluated as having a reactive lymphoid process given the robust cytoplasmic staining pattern, in the context of morphology (patient 30, figure 1A-C). One case was equivocal and showed a subset of 3+ positive large CD3-, MPO-, lysozyme- cells in a myeloid leukemia background (case 4, figure 1D-F and figure 3A). The CLL case showed 2+ CD30 positivity in rare scattered large cells (patient 16, figure 2A-C). Three total cases (3/51) showed diffuse pale, membranous staining by leukemic cells, one of which also showed cytoplasmic staining (patients 13, 18, 38, figure 2D; Table 2 and figure 3B). The diagnostic bone marrows of these three cases showed CMML-1, AML, and mixed phenotype acute leukemia, T/myeloid (1 case each). In addition, two (2/55) of the AML skin biopsies showed blush nuclear staining (figure 2E). None of the myeloid leukemia cutis cases showed diffusely strong membranous, cytoplasmic, or nuclear CD30 expression.

In addition to expression by leukemic and reactive lymphoid infiltrates, CD30 immunoreactivity was also noted in rare mast cells (figure 2F). Melanin, hemosiderin and edge effects of the stained slides were confounding factors in the analysis of staining patterns.

No associations could be made between cytogenetic findings and CD30 expression in the four myeloid LC cases showing membranous CD30 expression. Two of the four cases had a normal karyotype, while the other two had different abnormal cytogenetic findings (Table 1). No significant associations could be made between CD30 expression, biopsy site, concurrent bone marrow, blast percentage in the marrow (when available), and other immunophenotypic findings. Three cases with CD30-positive cutaneous leukemic infiltrates showed monocytic differentiation by blasts in bone marrow (1 CMML-1, AML, and 1 AML/T-ALL) (Table 3).

Discussion

Expression of CD30 in cutaneous mononuclear cell infiltrates often suggests the presence of a cutaneous CD30-positive T-cell LPD such as LyP or ALCL. For either diagnosis (particularly LyP), both clinical information and histologic characteristics of the CD30-positive infiltrate are often sufficient to confirm the diagnosis. The diagnosis of LyP, for example, relies on 3 parameters: typical papulonecrotic or papulonodular lesions, supportive histopathologic features, and a clinical course marked by spontaneous disappearance and recurrence. In contrast, patients with ALCL often present with more systemic symptoms and clinically persistent, sometimes ulcerated nodules. CD30 is also expressed in systemic lymphomas such as peripheral T-cell lymphoma,¹⁶ aggressive systemic mastocytosis,¹⁷ and primary cutaneous T-cell lymphoma such as mycosis fungoides. It has been shown that 30-70% of extracutaneous myeloid neoplasms express CD30.¹¹ To our knowledge, expression of CD30 in myeloid leukemia cutis (LC) has not been reported.

In this study, we showed that CD30 positivity may be seen in skin biopsies involved by myeloid LC with cytoplasmic/Golgi, membranous, cytoplasmic, and blush, nuclear staining-patterns. Cytoplasmic/Golgi-staining was mostly associated with an intervening lymphoid infiltrate consisting of reactive lymphocytes. In fact, one case of CLL showed strong

cytoplasmic/Golgi-staining and the typical membranous pattern seen in the spectrum of CD30-positive lymphoproliferative disorders (figure 2A-C). In contrast, reactive lymphocytes in AML cases showed a similar staining pattern but with much less intensity. A Golgi (perinuclear dot-like) staining pattern has been reported in reactive lymphocytes in CHL,¹⁸ while a diffuse-staining pattern is seen in some nonhematologic neoplasms.¹⁹ We noted membranous CD30 expression in only four of the examined myeloid LC cases. The staining was generally weak, similar to reported findings in extracutaneous AML cases with monocytic differentiation. The neoplastic infiltrates in skin biopsies examined in this study were CD34- and CD117-negative in all but one case that was CD34-positive but CD117-negative. This is consistent with the presence of monocytic differentiation that was confirmed in bone marrow biopsies. CD34 and CD117 were not examined in the cases that showed membranous CD30-staining. In addition, all myeloid leukemia cases and the concomitant skin biopsies were confirmed to be of myeloid derivation based on bone marrow morphologic examination and immunophenotypic studies of myeloid markers essentially excluding the possibility of a CD30-positive LPD.

In contrast to extra-cutaneous AML, in which it has been suggested that cases with high-risk cytogenic abnormalities and treatment refractoriness highly express CD30,¹⁰ no correlation was seen between CD30 expression and cytogenetic findings. All cases in our study were either relapsed and/or refractory to treatment. Our study showed no correlation between CD30 expression and the development of LC after receiving chemotherapy for primary bone marrow AML. Conversely, Zheng et al.¹⁰ reported an increased incidence of CD30 expression in patients with active disease who had been actively treated with chemotherapy. They also noted that, contrary to peripheral blood, CD30 expression was consistently higher in bone marrow specimens, suggesting that CD30 expression in AML may be site-specific. Future studies comparing concurrent bone marrow and skin specimens might clarify this issue.

Interestingly, Zheng et al.¹⁰ also reported a correlation between blast percentage and CD30 expression and noted that in cases with low blast percentage by flow cytometry, CD30 expression was attenuated and technically difficult to assess. In this study, blast percentage of bone marrow biopsy performed at or around the time of leukemia cutis presentation did not correlate with CD30 expression. The aforementioned study showed that CD30 is expressed by myeloblasts in many cases of AML with either de-novo presentation or arising from MDS, while monoblasts or background monocytes did not express this marker. Of the three cases with diffuse membranous CD30 expression in our study, two exhibited monocytic differentiation (cases 13 and 18; Table 3), an observation differing from the Zheng et al.¹⁰ study. However, this represents only a small subset of myeloid LC cases with monocytic differentiation, suggesting that CD30 expression in the bone marrow is differentially expressed compared with the skin.

We encountered several issues that made the qualitative assessment of CD30 expression in skin specimens challenging. One issue of note was the low incidence and intensity of CD30 expression in LC. In addition, reactive lymphocytes²⁰ as well as mast cells²¹ express CD30, confounding the assessment of weak CD30 expression by blasts. CD30 expression by reactive T-cells is of particular interest since some of the patients in this study received

allogeneic stem cell transplants and a report by Chan et al.²⁰ showed CD30 expression in subsets of T-cells involved in alloimmune responses. However, it should be noted that CD30-positive reactive lymphocytes were also present in patients who did not receive allogeneic stem cell transplants.

In summary, our study supports the use of a judiciously limited work-up in the diagnosis of a cutaneous CD30-positive LPD hematolymphoid infiltrate in the characteristic clinical setting. Specifically, the vast majority of myeloid LC cases lacked CD30 expression. This is an important finding since cutaneous myeloblastic infiltrates may appear morphologically similar to a CD30+ LPD on routine histology, and may show aberrant T-cell antigen expression. CD30+ LPDs may arise in patients who previously received hematopoietic stem cell transplants,^{22, 23} a frequently used treatment of AML. The incidence of post-transplant lymphoproliferative disorder in transplant recipients is further increased by additional risk factors such as T-cell depletion and utilization of drugs for both prophylaxis and treatment of graft-versus-host disease, including donor derived lymphomas (e.g. LyP).²²⁻²⁶

In summary, CD30 expression in myeloid leukemia cutis is variable, and typically weak, and may be used to help to differentiate leukemia cutis from reactive lymphocytes. Further studies with a larger number of cases would be helpful to validate this finding.

Acknowledgments

Sources of support: This research was funded in part through the **NIH/NCI Cancer Center Support Grant P30 CA008748**.

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Figure 1.

A. Hematoxylin and eosin, 400 $\times$, showing atypical lymphocytes in a biopsy of a post-transplant lymphoproliferative disorder (patient 30). B. CD3, 400 $\times$ in same patient. C. CD30, 400 $\times$ in same patient. D. Hematoxylin and eosin, 400 $\times$, showing atypical mononuclear cells in a perivascular and interstitial distribution in the dermis (patient 4). E. CD3 highlights some enlarged cell within the field, but is not seen in all lymphocytes. F. CD30 labels some of the atypical mononuclear cells with 3+ intensity, consistent with a CD30+ subset of myeloid leukemia cutis.

Figure 2.

A. Hematoxylin and eosin, 400× showing a diffuse sheet of small mostly monomorphic lymphocytes in the dermis. B. CD20 (400×) highlights the majority of these cells, as expected for the diagnosis of chronic lymphocytic leukemia. C. (400×) CD30 labels scattered enlarged mononuclear cells in a membranous and golgi predominant pattern with a 2+ intensity. D. CD30 (400×) shows bluish nuclear positivity in myeloid leukemia cells in the dermis. E. CD30 (400×) showing 1+ cytoplasmic positivity in myeloid leukemia cells in the perivascular dermis. F. CD30 (400×) shows 2+ labeling of mast cells within a reactive infiltrate.

Figure 3.

A. Ulcerated lesion of leukemia cutis that showed subset 3+ CD30 positivity (Patient 4; see also figure 1 above). Photo courtesy Liang Deng. B. Macules, patches and plaque lesions showed 1+ CD30 positivity in this patient's biopsy (Patient 38). Photo courtesy of Mario Lacouture.

Table 1
Clinical, histologic and cytogenetic characteristics of leukemia cases with bone marrow and skin biopsy

Case No	Age/gender	Cutaneous Dx	BM Dx	Blasts BM bx	Cytogenetics
1	9/M	AML	AML	52%	Normal
2	81/M	AML	AML	84%	Normal
3	67/F	CMML	CMML	2%	Normal
4	68/M	Reactive	AML (s/p CMML)	91%	Normal
5	49/F	AML	AML	20%	t(6;11)(q27;23)
6	72/M	AML	AML	75%	Normal
7	6/F	B-ALL	B-ALL	67%	Normal
8	42/F	AML	AML	32%	Normal
9	35/M	AML	AML with inv(16)	NA	Trisomy 8,16,21
10	69/M	AML	AML (s/p MDS)	24%	del(16q)
11	18/M	AML	AML	62%	Normal
12	76/M	AML	AML	59%	Normal
13	46/M	CMML	CMML-1	6%	del(9q)
14	62/F	AML	AML (s/p CMML)	38%	t(11;19)(q23;p13)
15	53/F	AML	AML	58%	Normal
16	44/F	CLL	CLL	0	Normal
17	70/F	AML	AML	80%	del(7q), trisomy 8
18	61/M	AML	AML	42%	t(3;5)(q21;q13), del(3)
19	13/F	T-ALL	T-ALL	86%	del(1p)
20	58/F	AML	AML	85%	Normal
21	76/F	AML	AML	57%	del(5)(q15q31), del(6)(t(6;11)(q13;q13), -7, -10, del(12)(t(3;12)(p11;q15), -16, +mar
22	38/M	MDS (RAEB-2)	MDS (RAEB-2)	18%	Normal
23	71/M	AML	AML	20%	Trisomy 8
24	58/M	NEL	NEL	3%	Trisomy 8, del 1p, t(1;9;11)(q32;p22)
25	59/M	AML	AML	100%	Normal
26	28/F	AML	AML	78%	Normal
27	62/M	AML	AML	87%	Normal
28	23/M	AML	AML	87%	Normal

Case No	Age/gender	Cutaneous Dx	BM Dx	Blasts BM bx	Cytogenetics
29	19/M	AML	AML	42%	Normal
30	60/F	Secondary LPD	AML	54%	Normal
31	78/M	CMML	CMML-1	2%	Normal
32	36/M	AML	AML	80%	Trisomy 8, trisomy 14
33	55/M	CMML	CMML-2	14%	Normal
34	20/M	AML	t-AML	60%	t(6;22); t(9;11)
35	68/M	AML	AML	38%	Normal
36	62/M	CMML	CMML-1	3%	Normal
37	64/M	AML	AML	53%	Normal
38	64/M	AML/T-ALL	Biphenotypic AML/T-ALL	43%	Normal
39	48/F	AML	AML	65%	Normal
40	44/F	AML	AML	68%	Normal
41	58/F	AML	AML	43%	Normal

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; BM, bone marrow; Dx, diagnosis; Hx, history; Bx, biopsy; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; RAEB, refractory anemia with excess blasts; CLL chronic lymphocytic leukemia; LPD, lymphoproliferative disorder

Table 2
Immunoreactivity for CD30 in 41 cases of leukemia cutis

Case No.	Location of skin biopsy	Cutaneous Dx	CD30 Intensity	CD30 Localization
1	Chest	AML	–	
2	Abdomen	AML	–	
3	L arm	CMML	–	
4	Lower back	AML	3+	Subset AML, membranous
5	R upper arm	AML	–	
6	R superior scalp L upper cheek	AML	– –	
7	R forearm	B-ALL	1+	Reactive lymphocytes
8	L upper arm	AML	–	
9	L upper back	AML	1+	Reactive lymphocytes
10	Flank	AML	–	
11	Scalp	AML	–	
12	R back L back L forearm	AML	1+ 1+ 1+	Reactive lymphocytes Reactive lymphocytes Reactive lymphocytes
13	R flank Chest	CMML	1+ –	Membranous
14	Abdomen	AML	–	
15	L upper back	AML	–	
16	L axilla	CLL	2+	Reactive lymphocytes
17	R knee	AML	–	
18	L thigh	AML	1+	Membranous
19	R upper arm	T-ALL	–	
20	R upper back	AML	–	
21	L groin	AML	1+	Blush nuclear, reactive lymphocytes
22	Chest	MDS (RAEB-2)	1+	Reactive lymphocytes
23	R thigh	AML	1+	Reactive lymphocytes
24	L back	NEL	–	
25	R thigh R thigh L lower back R medial thigh	AML	– – – 1+	Blush nuclear, leukemic cells
26	L abdomen	AML	1+	Blush nuclear, leukemic cells
27	R abdomen	AML	–	
28	R chest	AML	–	
29	L forearm L wrist L posterior arm	AML	– – 1+	Blush nuclear, histiocytes
30	R thigh Tongue Chest L arm	Reactive	3+ 3+ 3+ 3+	Cytoplasmic/ membranous
31	Abdomen	CMML	–	
32	R upper arm	AML	–	

Case No.	Location of skin biopsy	Cutaneous Dx	CD30 Intensity	CD30 Localization
33	R lower leg	CMML	–	
34	L thigh	AML	–	
35	Abdomen Back	AML	– –	
36	R lower leg	CMML	–	
37	R thigh	AML	1+	Scattered lymphocytes
38	R back	AML/T-ALL	1+	Cytoplasmic/ membranous
39	R lateral hip Abdomen	AML	– –	
40	L back	AML	1+	Reactive lymphocytes
41	R nipple	AML	–	

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; LPD, lymphoproliferative disorder; MPO, myeloperoxidase; Dx, diagnosis; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; RAEB, refractory anemia with excess blasts; CLL, chronic lymphocytic leukemia; NEL, no evidence of leukemia

Table 3
Leukemia cutis cases that show monocytic differentiation in bone marrow biopsies

Case No.	CD30 in LC cells	Monocytic Differentiation
1	-	Yes
2	-	Yes
3	-	Yes
4	+	Yes
5	-	Yes
6	-	Yes
7	-	N/A
8	-	No
9	-	Yes
10	-	Yes
11	-	No
12	-	Yes
13	+	Yes
14	-	Yes
15	-	Yes
16	-	N/A
17	-	Yes
18	+	Yes
19	-	N/A
20	-	Yes
21	-	Yes
22	-	Yes
23	-	Yes
24	-	N/A
25	-	Yes
26	-	Yes
27	-	Yes
28	-	Yes
29	-	Yes
30	-	No
31	-	Yes
32	-	Yes
33	-	Yes
34	-	Yes
35	-	Yes
36	-	Yes
37	-	Yes
38	+	No
39	-	Yes

Case No.	CD30 in LC cells	Monocytic Differentiation
40	–	Yes
41	–	Yes

LC, Leukemia cutis, BM, Bone marrow; +, immunoreactivity.–, no immunoreactivity.