TCL1 and CLA Expression in Agranular CD4/CD56 Hematodermic Neoplasms (Blastic NK-Cell Lymphomas) and Leukemia Cutis

Tony Petrella, MD,[1,2] Chris J.L.M. Meijer, MD,[6] Sophie Dalac, MD,[3] Rein Willemze, MD,[7] Marc Maynadié, MD,[5] Laurent Machet, MD,[8] Olivier Casasnovas, MD,[4] Béatrice Vergier, MD,[9] and Michael A. Teitell, MD, PhD[10]

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Abstract

Agranular CD4/CD56 hematodermic neoplasm (CD4/CD56 HN), also termed blastic natural killer cell lymphoma, is characterized by a peculiar immunophenotype and high skin tropism. The lineage of origin is not known, and a plasmacytoid dendritic cell derivation has been proposed. CD4/CD56 HN generally is diagnosed by using tumor skin biopsy, with the most important differential diagnosis being myelomonocytic leukemia cutis. We evaluated the expression of 2 plasmacytoid dendritic cell antigens, T-cell leukemia 1 (TCL1) and cutaneous lymphocyte-associated antigen (CLA), in 29 cases of CD4/CD56 HN and 18 cases of myelomonocytic leukemia cutis. TCL1 and CLA were expressed in 26 (90%) of 29 CD4/CD56 HN cases vs TCL1 expression in 3 (17%) and CLA expression in 14 (78%) of 18 leukemia cutis cases. Furthermore, CLA antiserum displays a peculiar small-dot staining pattern in CD4/CD56 HN. These results suggest that TCL1 and CLA are good markers for CD4/CD56 HN tumor cells and add support for a plasmacytoid dendritic cell origin. The high skin tropism of CD4/CD56 HN might be related to the skin-homing property of CLA.

Agranular CD4/CD56 hematodermic neoplasm (CD4/CD56 HN) is a rare, recently described clinical entity with genetic, morphologic, and etiologic diagnostic criteria that initially was proposed by the French Study Group on Cutaneous Lymphomas in 1999.[1] Since the first CD4/CD56 HN case published in 1994 by Adachi and colleagues,[2] several individual cases or small series of cases have been reported as distinct diagnostic entities under different names.[3,4] It has been suggested that CD4/CD56 HN originates from the natural killer (NK)-cell lineage mainly because the tumor cells express the CD56 antigen. In the current World Health Organization classification of lymphoid malignant neoplasms, the diagnostic entity termed blastic NK-cell lymphoma has been proposed for tumors satisfying the diagnostic criteria for CD4/CD56 HN.[5] However, there remains little evidence of NK-cell lineage origins, and the precise lineage of blastic NK-cell lymphoma was not asserted in the World Health Organization classification scheme.

As earlier suggested, CD4/CD56 HN might originate from a myelomonocytic precursor, because both CD4/CD56 HN and monocytic lineage cells commonly express CD4, CD56, and CD68 surface antigens, and tumors from both cell types might have a deletion of 5q.[1] In a more recent study, CD4/CD56 HN expressed the CD123 antigen and showed a highly similar immunohistochemical profile to that of plasmacytoid dendritic cells (PDCs).[6] We, therefore, revised our proposal and considered that CD4/CD56 HN might originate from a subpopulation of PDCs. Unfortunately PDCs remain a relatively poorly characterized cell type. Low numbers of PDCs reside in fetal cord and adult blood, bone marrow, lymph node, and tonsil, making analysis of their biochemical and immunophenotypic properties challenging.

The official designation blastic NK-cell lymphoma for CD4/CD56 HN might be an unfortunate one, because an NK-cell origin has not been demonstrated, and, in our experience, the main histopathologic differential diagnosis in skin tumor biopsy specimens is myeloid leukemia cutis rather than NK-cell or T-cell cutaneous lymphoma. True NK-cell or T-cell lymphomas usually are excluded with appropriate immunohistochemical staining. NK-cell lymphomas typically express cytotoxic proteins, including granzyme B, TIA1, or perforin.[7] T-cell lymphomas typically reflect their T-lineage derivation and express CD3 and T-cell receptor (TCR)αβ or TCRγδ protein, with monoclonal *TCR* gene rearrangements that are determined by polymerase chain reaction or Southern blot analysis.[7] In contrast with these 2 entities, myeloid leukemias, particularly those with monocytic differentiation, are phenotypically close to CD4/CD56 HN. The CD4 antigen commonly is expressed by monocytes[8] and monocytic leukemias. Furthermore, a great number of myeloid leukemias express the CD56 antigen.[9-13] To exclude myeloid leukemias from the differential diagnosis, immunohistochemical stains must evaluate the myelomonocytic differentiation antigens, including CD13, CD14, CD33, and CD117, all of which generally are negative in CD4/CD56 HN.[6,14] These antibodies require frozen tissue samples for robust detection of their corresponding surface antigens.

The histologic distinction between CD4/CD56 HN and leukemia cutis could be very difficult on paraffin-embedded sections when the results of myeloperoxidase staining are negative. To provide an improved method for diagnosing CD4/CD56 HN on formalin-fixed, paraffin-embedded tissue sections, we evaluated 2 additional immunohistochemical antigens that are expressed by PDCs: HECA-452[15] and T-cell leukemia 1 (TCL1).[16] HECA-452 antibody recognizes the cutaneous lymphocyte-associated antigen (CLA). CLA is a cell surface glycoprotein that specifically binds to E-selectin.[17] It might have a role in lymphocyte homing to the skin. TCL1 is a small, 14-kd cytoplasmic protein that binds to members of the serine/threonine Akt kinase family.[18-21] TCL1 has an unknown mechanistic role in promoting distinct subtypes of mature T- and B-cell leukemia/lymphoma.[22-26] We evaluated the expression of these 2 PDC differentiation antigens in CD4/CD56 HN to determine whether they could help distinguish between CD4/CD56 HN and leukemia cutis in formalin-fixed, paraffin-embedded tissue sections.

Materials and Methods

We obtained 29 cases of CD4/CD56 HN: 23 from the French Study Group on Cutaneous Lymphomas and 6 from the Dutch Cutaneous Lymphoma Group. Fourteen of these cases have been reported.[1,6] All 29 cases had typical clinical manifestations and conformed to established phenotypic criteria.[6] Clinical data are given in **Table 1**. All cases were CD4+ and CD123+. One case was CD56–.[27] All cases were lineage negative, particularly for the myelomonocytic differentiation markers CD13, CD14, CD15, CD33, and CD117.

Eighteen cases of leukemia cutis (acute myeloid leukemia [AML], 17; chronic myelomonocytic leukemia [CMML], 1) also were evaluated. The 18 cases were assembled from the archives of two of us (T.P., 14 cases; C.J.L.M.M, 4 cases). All 18 cases were diagnosed between 1991 and 2001. In addition to identification in skin biopsy specimens, AML blastic cells also were identified by hematocytologists during leukemic phases that occurred previously, simultaneously, or secondarily (AML-M5) to skin localization. According to the French-American-British subclassification[28] of AML, there was 1 case of AML-M1, 11 of AML-M2, and 5 of AML-M5. Of the 17 AML cases, 3 were secondary to refractory anemia with excess blasts, and 1 was secondary to CMML. Of the 18 cases, 4 were CD4+ only, and 4 expressed CD4 and CD56 **Table 2**. None of the cases expressed only CD56. Myeloperoxidase staining was positive in 12 of the 18 cases (Table 2).

Four nonneoplastic lymph nodes with or without follicular hyperplasia were used as positive control tissue samples. All case and control samples were available as formalin-fixed, paraffin-embedded blocks from which serial 5-μm-thick tissue sections were prepared. Immunohistochemical staining was performed using steam retrieval (pH 6.0). TCL1 detection was with a polyclonal rabbit antiserum for which use has been described previously,[24,29] and CLA detection was with HECA-452, a monoclonal antibody, described by Duijvestijn and colleagues[30] and provided by one of us (C.J.L.M.M.). TCL1 antiserum was used at 1:50 dilution, and the HECA-452 antibody was used without dilution. Immunoperoxidase detection was performed with the SuperSensitive immunohistochemical detection system, Stavigen Multilink kit (BioGenex, San Ramon, CA). Cases were scored as positive when more than 10% of the tumor cells expressed the surveyed antigen.

Results

HECA-452 Reactivity in CD4/CD56 HN

Of 29 cases, 26 (90%) expressed CLA as detected by HECA-452 staining (Table 2). Immunostaining was similar in all positive cases, showing a peculiar paranuclear dot pattern within the region of the Golgi apparatus **Image 1A**. Sometimes the dots were very small and seen only at high magnification. Interestingly, a similar paranuclear dot pattern was not observed on lymph node control slides in which

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Table 1
Clinical Summary of CD4/CD56 Hematodermic Neoplasm Cases

Case No./Sex/Age (y)	Skin Lesions at Diagnosis	Extension at Diagnosis	Initial Treatment	Outcome
1/M/56	Several nodules	LN, BM, blood	PC	Dead, 13 mo
2/M/82	1 nodule (forehead)	None	RT and PC	Dead, 24 mo
3/M/81	10 bruise-like papules (trunk)	None	PC	Dead, 11 mo
4/F/96	1 nodule (cheek)	NA	None	Dead, 1 mo
5/M/77	Plaques and nodules (trunk)	None	PC	Dead, 7 mo
6/F/54	1 plaque (leg)	None	PC and AG	Alive, 38 mo
7/F/33	1 nodule (leg)	LN	PC	Dead, 27 mo
8/M/69	Papules and nodules (back)	NA	None	Dead, 2 mo
9/M/8	1 bruise-like tumefaction (knee)	LN	PC	Dead, 33 mo
10/M/37	1 papule (leg)	None	PC	Dead, 40 mo
11/F/67	Several nodules and plaques (trunk)	None	PC	Dead, 17 mo
12/M/84	1 bruise-like tumefaction (forehead)	LN, BM	PC	Dead, 5 mo
13/M/62	Several nodules and plaques (abdomen)	None	RT and PC	Dead, 13 mo
14/M/75	Plaques and nodules (trunk)	LN	PC	Dead, 26 mo
15/M/64	Several plaques and papules (arms and trunk)	BM	PC	Dead, 12 mo
16/M/69	Multiple disseminated nodules	None	PC	Dead, 21 mo
17/F/70	1 nodule (arm)	BM	PC	Alive, 9 mo
18/M/70	1 nodule (cheek)	None	PC	Alive, 14 mo
19/F/88	Multiple disseminated nodules	None	PC	Dead, 8 mo
20/M/72	1 nodule (shoulder)	LN, BM, blood	PC	Dead, 3 mo
21/F/65	1 nodule (thigh)	LN	PC	Dead, 17 mo
22/F/86	2 nodules (thigh and leg)	LN	PC	Dead, 5 mo
23/F/49	1 nodule (cervical)	LN	PC	Dead, 9 mo
24/M/60	Plaques (scalp)	None	RT	Dead, 22 mo
25/M/56	Plaques and nodules (trunk)	BM	PC	Alive, 14 mo
26/M/74	Generalized plaques and nodules	None	PC	Dead, 12 mo
27/M/77	Generalized nodules	None	PUVA	Dead, 7 mo
28/F/43	Generalized plaques	None	PC and RT	Alive, 5 mo
29/M/64	1 nodule (arm)	None	RT	Alive, 22 mo

AG, allograft; BM, bone marrow; LN, lymph node; NA, data not available; PC, polychemotherapy; PUVA, psoralen plus ultraviolet A; RT, radiotherapy.

cells from distinct developmental lineages stained positive with the HECA-452 antibody (monocytes, PDCs, and high endothelial venules). HECA-452 immunostaining on tumor sections was generally diffuse, involving more than 80% of the tumor cells in each positive case. In addition, as previously described,[31] HECA-452 was expressed on epidermal Langerhans cells and dermal dendritic cells.

TCL1 Reactivity in CD4/CD56 HN

Of 29 cases, 26 (90%) were positive for staining with TCL1-specific antiserum (Table 2). Of the 26 positive cases, 19 showed cytoplasmic **Image 2A** and nuclear staining **Image 2B**. The 7 remaining positive cases showed only cytoplasmic staining. Similar to HECA-452–positive cases, TCL1 immunostaining on tumor sections generally was diffuse and strongly positive in more than 50% of the tumor cells in each positive case.

HECA-452 Reactivity in Leukemia Cutis

Of 18 cases of leukemia cutis, 14 (78%) expressed CLA as detected by HECA-452 staining (Table 2). As for all cases of CD4/CD56 HN, 5 positive cutaneous AML cases showed a paranuclear small-dot immunostaining pattern, while 9 positive cases showed a diffuse cytoplasmic pattern **Image 1B**. Epidermal Langerhans cells and dermal dendritic cells also reacted with the HECA-452 antibody. The case of CMML (case 17, Table 2) was reactive but without a dot-like staining pattern.

TCL1 Reactivity in Leukemia Cutis

Only 3 (17%) of 18 cases of leukemia cutis were positive for TCL1-specific antiserum staining (Table 2). These cases showed only cytoplasmic staining. Two of the 15 TCL1-negative cases showed fewer than 10% of the cells in the cutaneous infiltrate expressing TCL1, probably representing tumor-infiltrating lymphocytes rather than true tumor cells. The CMML case was TCL1-negative.

Discussion

In our series of cases, we showed that 26 (90%) of 29 cases of CD4/CD56 HN were reactive for the CLA antibody HECA-452. Of 18 cases of leukemia cutis, 14 (78%) also reacted with the HECA-452 antibody. Therefore, the HECA-452 antibody alone cannot discriminate between CD4/CD56 HN and cutaneous AML, and the difference in immunostaining for CLA between these entities is not significant.

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Table 2
Immunohistochemical Staining Profile for CD4/CD56 Hematodermic Neoplasms and Leukemia Cutis

Case No.	HECA-452	TCL1	CD4	CD56	MPO
CD4/CD56 hematodermic neoplasms					
1	+	++	+	+	–
2	+	++	+	–	–
3	+	+	+	+	–
4	+	++	+	+	–
5	+	++	+	+	–
6	+	+	+	+	–
7	–	++	+	+	–
8	+	+	+	+	–
9	+	++	+	+	–
10	+	++	+	+	–
11	+	++	+	+	–
12	+	++	+	+	–
13	+	++	+	+	–
14	+	++	+	+	–
15	+	++	+	+	–
16	+	++	+	+	–
17	+	++	+	+	–
18	+	+	+	+	–
19	+	+	+	+	–
20	–	++	+	+	–
21	+	++	+	+	–
22	+	++	+	+	–
23	+	–	+	+	–
24	–	–	+	+	–
25	+	++	+	+	–
26	+	+	+	+	–
27	+	+	+	+	–
28	+	*	+	+	–
29	+	–	+	+	–
Leukemia cutis†					
1 (AML-M2)	–	–	–	–	+w
2 (AML-M2)	–	–	–	–	–
3 (AML-M2; RAEB)	+*	–	–	–	+
4 (AML-M2)	+*	–	–	–	–
5 (AML-M2)	+	–	–	–	+
6 (AML-M2; RAEB)	+*	–	–	–	+
7 (AML-M5)	+*	–	–	–	+w
8 (AML-M2; RAEB)	+	–	–	–	+
9 (AML-M1)	–	–	–	–	–
10 (AML-M5; CMML)	+	–	–	–	+
11 (AML-M2)	+	+	+	–	+
12 (AML-M2)	+	–	+	–	+w
13 (AML-M2)	+	+	+	–	+
14 (AML-M5)	+	–	+	+	–
15 (AML-M2)	–	+	+	+	–
16 (AML-M5)	+	–	+	+w	+
17 (CMML)	+	–	+w	–	+w
18 (AML-M5)	+*	–	+	+	–

AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MPO, myeloperoxidase; RAEB, refractory anemia with excess blasts; TCL1, T-cell leukemia 1; –, negative; +, cytoplasmic positivity; ++, cytoplasmic and nuclear positivity; +w, weak positivity.
* Additional nuclear staining.
† Numbers with AML denote French-American-British classification.

The HECA-452 epitope is part of an inducible carbohydrate on the P-selectin glycoprotein ligand-1.[32] It specifically binds to E-selectin expressed by endothelial cells and particularly on lymph node high endothelial venules.[33] Furthermore, it is expressed on most T cells at cutaneous sites, on cutaneous T-cell lymphomas,[34] and on lymphoid cells derived from human skin.[35] Therefore, CLA might have an important role in lymphocyte homing to the skin. Facchetti and colleagues[15] demonstrated that plasmacytoid T cells (former name of PDCs) in reactive lymph nodes strongly expressed CLA. Furthermore, PDCs have been detected within the dermis, first by Facchetti and colleagues[36] in Jessner-Kanoff syndrome and more recently by Wollenberg and colleagues[37] in a variety of inflammatory skin diseases. These findings suggest that any potential homing role for CLA to skin is not restricted to lymphocytes but also might include other cell types, such as PDCs. These observations also suggest that the dermis is a target organ for PDCs. This may not be surprising because mature dendritic

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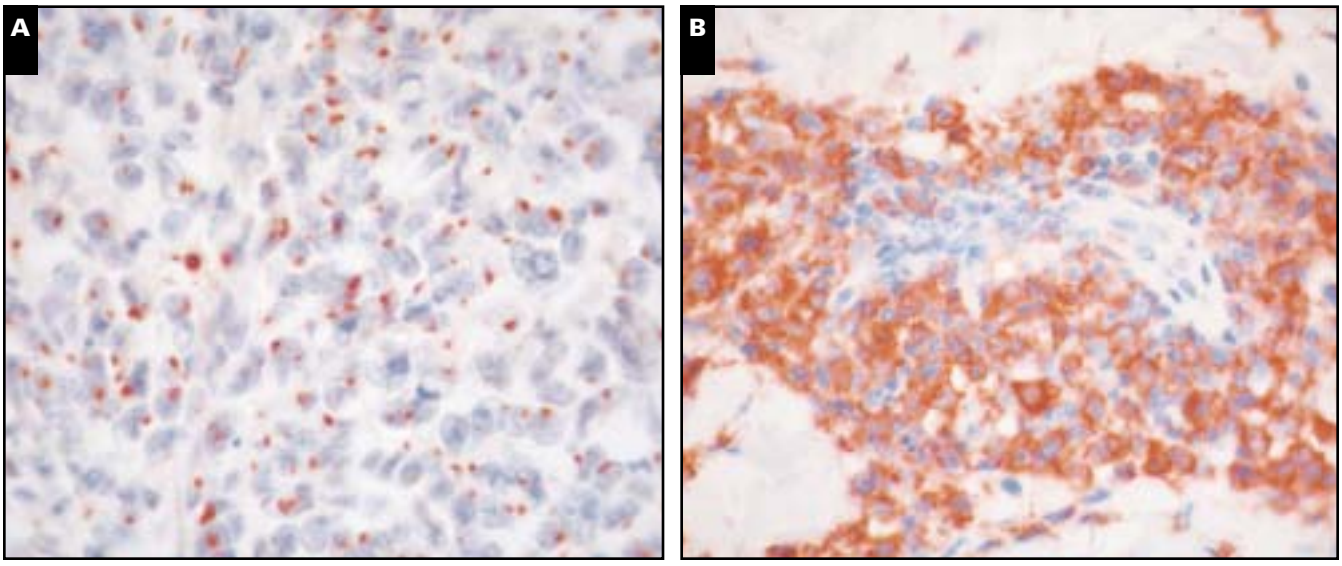

Image 1 **A**, CD4/CD56 hematodermic neoplasm. A small-dot paranuclear pattern of positive immunostaining (HECA-452, ×1,000). **B**, Leukemia cutis. Cytoplasmic and membranous immunostaining activity (HECA-452, ×630).

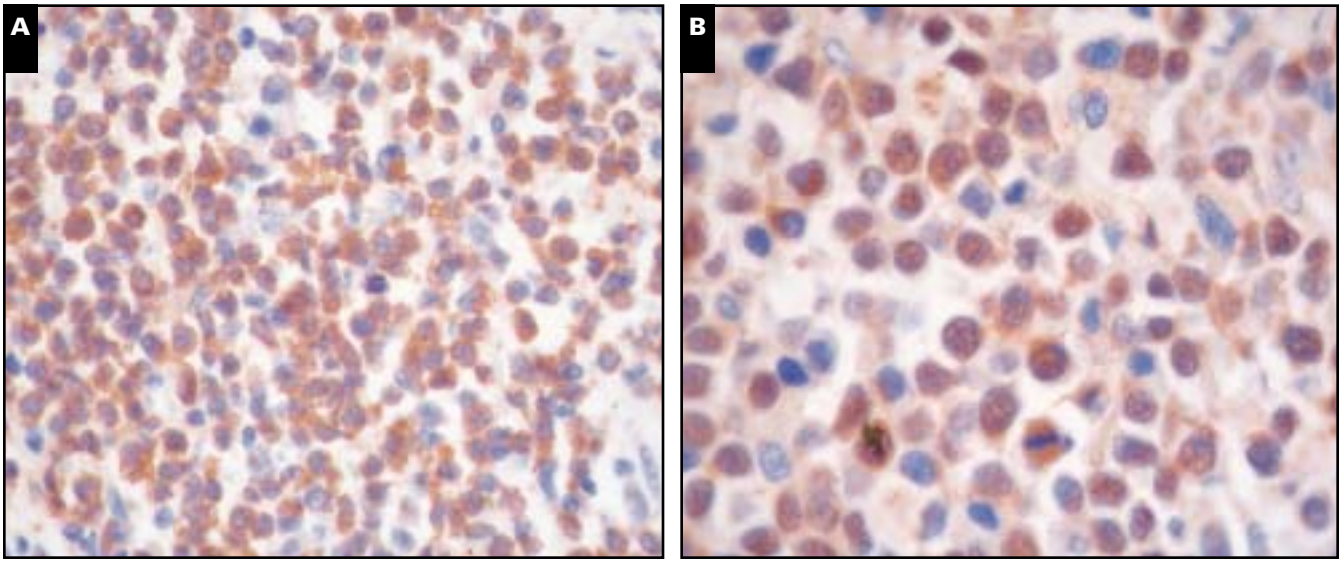

Image 2 CD4/CD56 hematodermic neoplasm. **A**, Cytoplasmic immunostaining (T-cell leukemia 1 [TCL1], ×630). **B**, Nuclear immunostaining (TCL1, ×1,000).

cells reside in the skin, where PDCs might have a major role in antigen presentation. Interestingly, mature dendritic cells also express a HECA-452 epitope, which is likely from CLA, that is weak in the dermis and strong in the epidermis.[38]

It is tempting to speculate that intense HECA-452 staining supports an important role for CLA in the skin tropism of CD4/CD56 HN and most cases of leukemia cutis. It remains unclear whether CD4/CD56 HN cases are primary or secondary neoplasms of the skin. If skin is a target organ for PDC localization, as suggested by CLA expression and dermal tropism, it is logical to consider CD4/CD56 HN as a primary skin tumor, in agreement with clinical data.

We further observed that 26 (90%) of 29 CD4/CD56 HN cases expressed the TCL1 cytoplasmic differentiation antigen. These results are consistent with the previous results of Herling and colleagues,[16] which showed that 86% of the CD4/CD56 HN cases tested expressed TCL1 protein. Of 3 TCL1-negative cases, 2 were distinct from the 3 HECA-452–negative CD4/CD56 HN cases, indicating that these antigens are not invariantly coordinately regulated in this disease. We conclude from these 2 studies that TCL1 indeed is a frequently positive antigenic marker for CD4/CD56 HN. In contrast with the frequent expression of TCL1 in CD4/CD56 HN, only 3 (17%) of 18 leukemia cutis

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cases expressed TCL1. This difference seems highly significant ($P < .001$; χ^2 test). However, the use of TCL1 alone to distinguish between CD4/CD56 HN and cutaneous AML should be avoided because the small percentage of TCL1-positive AML cases could result in misdiagnosis.

TCL1 is a small, β-barrel–shaped cytoplasmic protein that augments the activation of the cell survival kinase Akt by physical association and multimer formation.[19,39,40] Its pattern of expression during B- and T-cell development suggests critical stage-specific developmental functions, rather than a broad role throughout the life span of a lymphocyte.[19] Reflecting its B-lineage pattern of expression, TCL1 is expressed in a large number of B-cell malignant neoplasms, from pre–B-cell lymphoblastic leukemia/lymphoma through germinal-center derived follicular, Burkitt, and diffuse large B-cell lymphomas.[24,29,41,42] TCL1 also marks mature T cell leukemias, such as T-cell chronic lymphocytic leukemia and T-cell prolymphocytic leukemia, owing to overexpression by 14q32.1 chromosomal translocations.[43,44] As such, TCL1 has diagnostic usefulness in mature B- and T-lineage tumors. Its role in normal PDC biology or in malignant initiation and progression of CD4/CD56 HN is less clear, although its robust, high-frequency expression suggests an origin of CD4/CD56 HN from PDC rather than from the NK-cell lineage, which is negative for TCL1 expression.[16,25]

CLA and TCL1 frequently are coexpressed markers for CD4/CD56 HN that are demonstrated easily in formalin-fixed, paraffin-embedded tissue sections. Used in combination with additional immunohistochemical stains, HECA-452 antibody and TCL1 antiserum are useful for diagnosing this clinical entity. In addition, we observed for cutaneous AML and particularly for CD4/CD56 HN a distinct paranuclear HECA-452 immunostaining pattern in small dots within the area of the Golgi apparatus. The significance of this unique staining pattern, which was not observed in normal lymphoid tissues, deserves further study. The clear-cut difference of TCL1 expression between CD4/CD56HN and AML strongly suggests that the 2 diseases are distinct. However, common patterns of HECA-452 staining also might underlie a possible relationship between CD4/CD56 HN and AML or perhaps an overlap between CD4/CD56 HN and some undifferentiated cases of AML. This area clearly requires further study. Finally, the high skin tropism of CD4/CD56 HN might be related to the skin-homing property of CLA.

From the [1]Centre de Pathologie, the Departments of [2]Pathology, [3]Dermatology, [4]Clinical Hematology, and the [5]Laboratory of Hematology, Centre Hospitalo-Universitaire du Bocage, Dijon, France; [6]Department of Pathology, Vrije Universiteit Medical Center, Amsterdam, the Netherlands; [7]Department of Dermatology, Leiden University Medical Center, Leiden, the Netherlands; [8]Department of Dermatology, Centre Hospitalo-Universitaire Trousseau, Tours, France; [9]Department of Pathology, Hôpital du Haut Lévêque, Pessac, France; and [10]Departments of Pathology and Pediatrics, Center for Cell Mimetic Studies, Jonsson Comprehensive Cancer Center, David Geffen School of Medicine at UCLA, Los Angeles, CA.

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Address reprint requests to Dr Petrella: Centre de Pathologie, 33 rue Nicolas Bornier, 21000, Dijon, France.

Dr Teitell is a scholar of the Leukemia and Lymphoma Society, White Plains, NY.

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