Blastic NK-Cell Lymphomas (Agranular CD4+CD56+ Hematodermic Neoplasms)

A Review

Tony Petrella, MD,[1] Martine Bagot, MD,[2] Rein Willemze, MD,[3] Marie Beylot-Barry, MD, PhD,[4] Béatrice Vergier, MD, PhD,[5] Michèle Delaunay, MD,[6] Chris J.L.M. Meijer, MD,[7] Philippe Courville, MD,[8] Pascal Joly, MD,[9] Florent Grange, MD, PhD,[10] Anne De Muret, MD,[11] Laurent Machet, MD,[12] Anne Dompmartin, MD,[13] Jacques Bosq, MD,[14] Anne Durlach, MD,[15] Philippe Bernard, MD,[16] Sophie Dalac, MD,[17] Pierre Dechelotte, MD,[18] Michel D'Incan, MD,[19] Janine Wechsler, MD,[20] and Michael A. Teitell, MD, PhD[21]

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Abstract

Blastic natural killer (NK) cell lymphoma (also termed CD4+CD56+ hematodermic neoplasm*) is a recently described entity, with the first case reported in 1994. It was suggested initially that the disease originates from NK cells. Since 1994, single cases and a few small series have been published. In this review, data from the literature and a series of 30 cases from the French and Dutch study groups on cutaneous lymphomas are discussed. The major clinical, histopathologic, and phenotypic aspects of the disease and diagnostic criteria and data suggesting a plasmacytoid dendritic cell origin for the tumor cells are provided.*

Blastic natural killer (NK) cell lymphoma, also termed *CD4+CD56+ hematodermic neoplasm* (CD4/CD56 HN) is a rare clinical entity encompassing distinct genetic, morphologic, etiologic, and diagnostic criteria. Since 1994, several individual cases or small series of CD4/CD56 HN cases have been reported as distinct entities using an array of names.[1-19] It has been suggested that CD4/CD56 HN originates from the NK-cell lineage mainly because the tumor cells express the CD56 surface antigen. In the current World Health Organization (WHO) classification of lymphoid malignant neoplasms, the diagnostic entity termed *blastic NK-cell tumors* has been proposed for tumors satisfying the diagnostic criteria for CD4/CD56 HN.[20] However, there is scant evidence for an NK-cell lineage origin, and the precise derivation was not asserted in the WHO classification scheme.

History

CD4/CD56 HN is a recently appreciated disease. Starting in 1994, several individual cases suggesting a new entity that match the recent WHO diagnostic criteria for blastic NK-cell tumors were reported.[1] Between 1994 and 1999, there were a total of 7 reports on CD4/CD56 HN **Table 1**. In 1999, Petrella et al[21] reported the largest series at that time of 7 well-documented cases with morphologic, phenotypic, genotypic, and cytogenetic data consistent with CD4/CD56 HN. The report described the main characteristics of these tumors and showed that they did not neatly fit with other tumors in the various lymphoma classifications. The study further demonstrated that the tumor cell lineage was closer to myelomonocytic cells than to NK cells and suggested a very immature cell for which the exact nature remained to be determined.

Table 1
Cases of CD4+CD56+ Hematodermic Neoplasm Reported Between 1994 and 1999

Date/Authors	No. of Cases (Sex, Age [y])	Neoplasm Sites	Phenotype	Additional Features	Diagnosis
1994/Adachi et al[1]	1 (M, 67)	Skin, bone marrow, central nervous system	CD4+, CD56+, CD45–	Germline	New entity?
1995/Brody et al[2]	1 (M, 63)	Subcutaneous, bone marrow, blood	CD4+, CD56+, CD15+	Germline; del(5q)	Blastic NK-cell leukemia
1996/Dummer et al[4]	1 (F, 47)	Skin	CD4+, CD56+, CD43+	Germline	New entity?
1996/Wasik et al[3]	1 (M, 69)	Skin	CD4+, CD56+, HLA-DR+, CD2+, CD7+, CD68+	Myeloproliferative syndrome 10 y before; germline	CD56+ cutaneous large T-cell lymphoma
1997/DiGiuseppe et al[5]	4 (F, 81; M, 82; M, 79; F, 58)	Skin, blood (2)	CD4+, CD56+, CD2+, CD7+	Germline	Blastic NK-cell leukemia; distinct clinicopathologic entity
1997/Savoia et al[7]	5 (M, 55-78)	Skin	CD4+, CD43+, CD56+, HLA-DR+, CD68–, EBV-LMP1+ (2)	Germline; cytoplasmic granulations (2)	NK cell origin
1998/Bastian et al[6]	1 (F, 21)	Skin	CD4–, CD43+, CD56+, CD68–	T-cell clone; regression with radiotherapy	Primary cutaneous NK-cell lymphoma

EBV, Epstein-Barr virus; LMP, latent membrane protein; NK, natural killer.

The finding of CD123 antigen expression by the tumor cells[22] provided a basis for the discovery of the likely cell of origin for CD4/CD56 HN. Few normal cells express the CD123 antigen, which is present mainly on dendritic cells (DCs) and strongly displayed on precursor DCs. Several distinct names by different groups were attributed to CD123+ DCs; however, the current consensus term for these cells now seems to be *plasmacytoid dendritic cell* (PDC). Chaperot and colleagues[23] in 2001 demonstrated a phenotypic and functional link between CD4/CD56 HN tumor cells and PDCs. Except for a subpopulation of PDCs reported in 2002, however, most PDCs do not express the CD56 antigen.[24] This later study showed a close phenotypic resemblance between this PDC subpopulation and CD4/CD56 HN. Feuillard and colleagues[13] recently provided the single largest clinical and biologic data set from 23 cases of CD4/CD56 HN in a series from the French Leukemia Study Group. Several other individual cases also have been reported since 2002.[8-12,14-19,25-27]

Clinical Aspects

In total, more than 100 cases with CD4/CD56 HN diagnostic criteria have now been reported in the literature. The data we discuss here are based on the findings from the literature and the results of our 30 cases (24 cases from the French group and 6 cases from the Dutch group). The French cases were obtained throughout France (Dijon, Créteil, Tours, Rouen, Bordeaux, Pessac, Montpellier, Corbeil, Villejuif, Reims, Caen, Nevers, Colmar, and Clermont-Ferrand). The Dutch cases were collected from Amsterdam (R.W. and C.J.L.M.M.). CD4/CD56 HN remains rare, representing 0.7% of the data set of primary cutaneous lymphomas recorded by the French Study Group on Cutaneous Lymphomas for the past 10 years.

Clinical data for our series of 30 cases (20 males, 10 females) are summarized in **Table 2**. The median age at diagnosis was 65.3 years (range, 8-96 years). Cutaneous involvement occurred in all cases. The skin lesions usually were solitary or localized at disease onset and became multiple and spread with time. Their appearance was variable and included nodules **Image 1A**, patches **Image 1B**, and bruise-like areas **Image 1C**. About half of the cases were unique or localized cutaneous lesions at diagnosis. Because the French and Dutch groups selectively evaluate cutaneous lymphomas, this skin tropism might be considered a bias of sample selection; however, when all published data were examined, more than 94% of CD4/CD56 HN cases manifested with cutaneous lesions.

In the present series, all histologic diagnoses were made from skin biopsy specimens. After diagnosis, all but 2 patients had follow-up evaluations for staging and extent of spread that included a total body scan, chest radiography, blood specimen evaluation, and bone marrow biopsy and aspiration.

The sites of tumor infiltration are summarized in **Figure 1**. Of the 28 patients with complete staging, 16 (57%) had skin lesions only; 6 (21%) had skin lesions associated with draining lymph node involvement; 3 (11%) had skin and bone marrow involvement; 1 (4%) had skin, lymph node, and bone marrow involvement; and 2 (7%) had generalized disease, including a leukemic phase. Data about extension of disease were not available for 2 patients (7%).

Of the 30 patients, 28 were treated. Radiotherapy and/or chemotherapy with a variety of agents and protocols generally provided a good initial response (21/28 [75%]), with regression and even disappearance of the disease. Seven of the treated patients (25%) of the patients did not have a response or died

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Table 2
Clinical Summary of 30 CD4+CD56+ Hematodermic Neoplasm Cases

Case No./ Sex/Age (y)	Skin Lesions at Diagnosis	Extension at Diagnosis	Initial Treatment	First Relapse		Outcome (mo)
				Time to (mo)	Sites	
1/M/56	Several nodules	LN, BM, blood	PC	9	NA	Died, 13
2/M/82	1 nodule, forehead	None	RT + PC	12	Skin, LN, BM, blood	Died, 24
3/M/81	10 bruise-like papules, trunk	None	PC	NR	—	Died, 11
4/F/96	1 nodule, cheek	NA	None	NR	—	Died, 1
5/M/77	Plaques and nodules, trunk	None	PC	2	Skin, BM, brain	Died, 7
6/F/54	1 plaque, leg	None	PC + AG	8	Skin, sinus, blood	Died, 40
7/F/33	1 nodule, leg	LN	PC + AG	21	Skin, LN	Died, 27
8/M/69	Papules and nodules, back	NA	None	NR	—	Died, 2
9/M/8	1 bruise-like tumefaction, knee	LN	PC	14	Skin, BM	Died, 33
10/M/37	1 papule, leg	None	PC	28	Skin	Died, 40
11/F/67	Several nodules and plaques, trunk	None	PC	11	Skin, LN, BM, blood	Died, 17
12/M/84	1 bruise-like tumefaction, forehead	LN, BM	PC	5	Skin, BM, blood	Died, 5
13/M/62	Several nodules and plaques, abdomen	None	RT + PC	NR	—	Died, 13
14/M/75	Plaques and nodules, trunk	LN	PC	NR	—	Died, 26
15/M/64	Several plaques and papules, arms, trunk	BM	PC	4	Skin	Died, 12
16/M/69	Multiple disseminated nodules	None	PC	18	Skin, LN, BM, blood	Died, 21
17/F/70	1 nodule, arm	BM	PC	None	—	Alive, 9
18/M/70	1 nodule, cheek	None	PC	None	—	Alive, 14
19/F/88	Multiple disseminated nodules	None	PC	NR	—	Died, 8
20/M/72	1 nodule, shoulder	LN, BM, blood	PC	NR	—	Died, 3
21/F/65	1 nodule, thigh	LN	PC	15	Skin	Died, 17
22/F/86	2 nodules, thigh, leg	LN	PC	4	Skin, BM, blood	Died, 5
23/F/49	1 nodule, cervical	LN	PC	4	Skin, LN, BM	Died, 9
24/M/60	Plaques, scalp	None	RT	13	Skin, LN, BM, blood	Died, 22
25/M/56	Plaques and nodules, trunk	BM	PC	9	Skin, BM, brain	Died, 27
26/M/74	Generalized plaques and nodules	None	PC	10	Skin, BM	Died, 12
27/M/77	Generalized nodules	None	PUVA	NR	—	Died, 7
28/F/43	Generalized plaques	None	PC + RT	NR	—	Died, 6
29/M/64	1 nodule, arm	None	RT	31	Skin, BM	Died, 32
30/M/73	1 nodule, chest	None	RT	2	Skin, BM	Alive, 4

AG, allograft; BM, bone marrow; LN, lymph node; NA, not available; NR, no remission; PC, polychemotherapy; PUVA, psoralen-UV-A; RT, radiotherapy.

during the first course of chemotherapy. For 2 patients, the initial cutaneous tumor disappeared spontaneously before reappearing several weeks later.

Unfortunately, for the 21 patients who had a response to treatment, relapses occurred in 19 (90%) of the cases in the following months. For 1 patient, data on the sites of relapse were not available. The median time at first relapse was 11 months (range, 2-31 months) from diagnosis. Skin always was involved at the first relapse: skin alone for 3 patients (17%); skin and other sites without leukemia for 8 patients (44%); and skin and other sites with leukemia for 7 patients (39%). However, although some patients died before any involvement of blood or bone marrow, a leukemic phase ultimately occurs.

Overall, the outcome for CD4/CD56 HN is very poor. The average survival was 14 months (range, 1-40 months). For patients younger than 40 years, the median survival was 38 months, whereas patients older than 40 years have a median survival of 10 months.

Histologic Aspects

Skin biopsy specimens show an infiltrate of medium-sized lymphoid-appearing cells that display a slightly irregular-shaped nucleus with smooth chromatin **Image 2A**. Depending on the fixative used, one or several medium or small nucleoli can be observed. Nucleoli are more visible with Bouin liquid fixative than with other fixatives. The cytoplasm is scant and difficult to visualize and never exhibits granulation. At low magnification, the lesion appears monomorphous. Large and small cells can be seen within the infiltrate of medium-sized cells but generally are in the minority. An associated inflammatory infiltrate also may be present, which typically is discrete and consists mainly of small T lymphocytes. Generally, there are no plasma cells or eosinophils within the infiltrate. Mitoses are seen in variable numbers but generally are rare.

In the clinical nodular pattern, the infiltrate colonizes the dermis and hypodermis and is very dense, large, and monomorphous and typically spares the epidermis, often with a grenz zone **Image 2B**. Angiocentrism and angiodestruction are not seen. Cutaneous appendages generally are erased by the tumor cell infiltration. In the clinical patches or bruise-like lesion pattern, the infiltrate is less dense, with perivascular collections or scattered nodules **Image 2C**. The epidermis also is always spared.

Lymph node involvement is characterized by a leukemic pattern of infiltration, which starts in the medulla and advances to the sinuses and cortical interfollicular areas.

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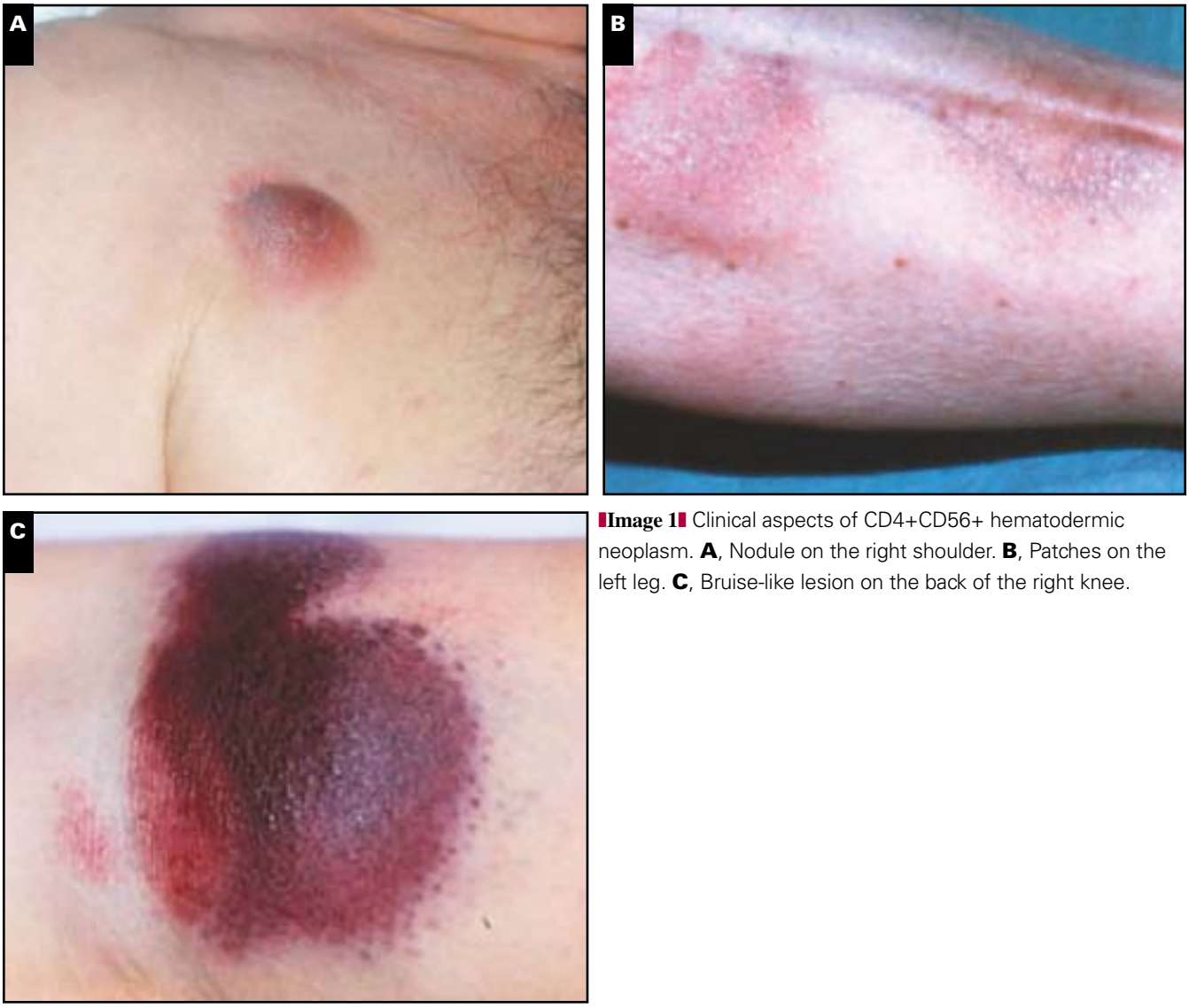

Image 1 Clinical aspects of CD4+CD56+ hematodermic neoplasm. **A**, Nodule on the right shoulder. **B**, Patches on the left leg. **C**, Bruise-like lesion on the back of the right knee.

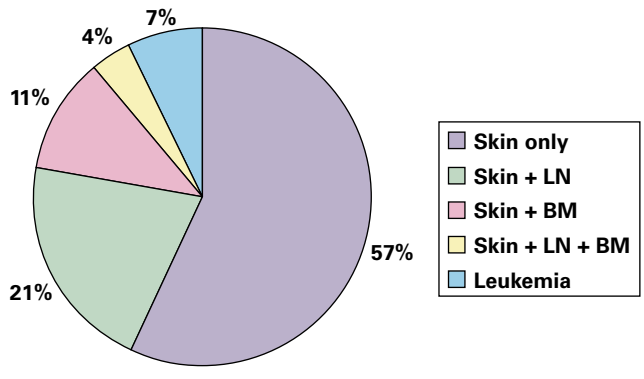

Figure 1 Sites of tumor infiltration at the time of diagnosis in CD4+CD56+ hematodermic neoplasm. BM, bone marrow; LN, lymph node.

Follicular involvement may occur early in the infiltration but eventually disappears. When bone marrow is involved, the infiltrate is of variable intensity. It spans from a discrete interstitial infiltrate, which might require immunostaining for detection, to a massive infiltration erasing the hematopoietic tissue. When myeloid tissue remains, dysplastic features can be seen, particularly in the megakaryocyte lineage. Cytologic examination of blood or bone marrow smears might show undifferentiated, variably sized blast cells **Image 2D**. For some patients, there are mainly small cells, whereas for others, there is a predominance of large cells; some patients have a mixed infiltrate of small, medium, and large cells. The nucleus is mostly round or oval. The chromatin is clear and blastic, typically with one or several visible nucleoli. The cytoplasm generally is visible, weakly basophilic, and without granulation. Two morphologic peculiarities are found in most cases: microvacuoles in the cytoplasm that localize along the

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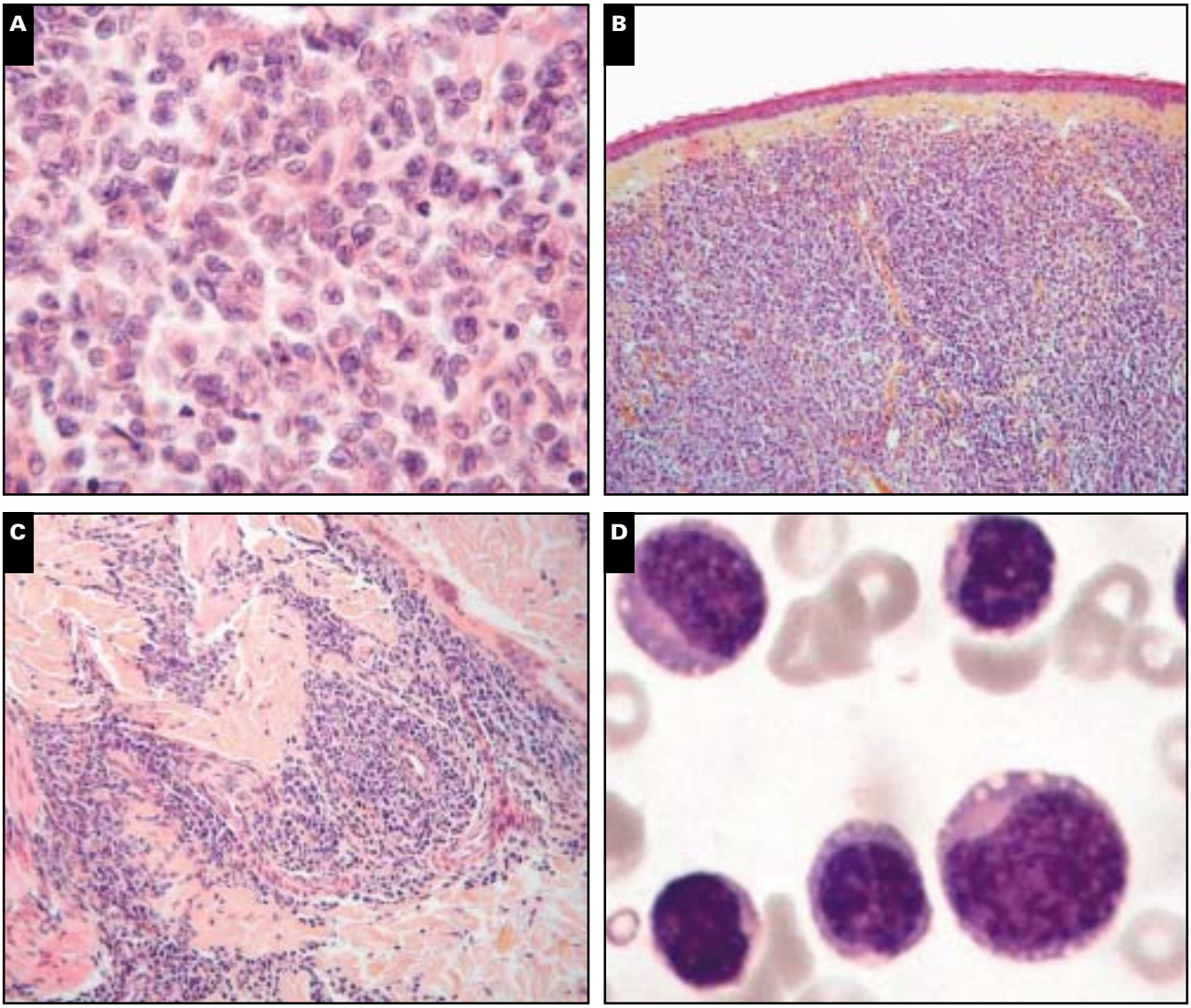

Image 2 Histologic features of CD4+CD56+ hematodermic neoplasm. **A**, Diffuse infiltration of medium-sized blast-like cells (H&E with saffron, ×630). **B**, Massive infiltration of the dermis with a grenz zone (H&E with saffron, ×100). **C**, Nodular and perivascular patterns (H&E with saffron, ×160). **D**, Blast-like cells with small cytoplasmic microvacuoles (Giemsa, ×1,000).

cell membrane, which might resemble a string of pearls, and cytoplasmic pseudopodia. The cytochemical reactions for myeloperoxidase (MPO) and the monocytic butyrate-esterase always are negative.

Immunophenotype

An immunophenotypic evaluation of CD4/CD56 HN requires formalin-fixed and fresh frozen tissue samples because several antibodies do not work with fixed tissues. For our cases, we used the streptavidin-biotin alkaline phosphatase and/or peroxidase methods.[28] The origin of the antibodies and the immunohistochemical results are given in **Table 3**. Antigen retrieving methods were applied as indicated by the antibody providers.

Common B-cell lineage (CD19, CD20, CD23, CD24, CD79A, immunoglobulin), T-cell lineage (CD2, CD3, CD5, CD7, CD8, β-F1, and δ-TCR1), NK-cell lineage (CD16 and CD57), and myelomonocytic cell lineage (CD13, CD14, CD15, CD33, and CD117) markers are negative with rare exceptions.

The positive antigens detected with paraffin-embedded sections include CD4 **Image 3A**, CD43, CD45, CD45RA, CD56 **Image 3B**, and CD68 **Image 3C**. In our experience, all cases are CD4+, CD43+, and CD45+, and CD68 (KP1) is positive in about 50% of cases. When CD68 is positive, the staining pattern characteristically appears as small dots that may be barely visible in the area of the Golgi apparatus.

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Table 3
Immunohistochemical Detection of 30 CD4+CD56+ Hematodermic Neoplasm Cases* (continued on next page)

	Case No.														
Antigen	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
CD123	+	+	+	+	+	+	+	NA	+	+	+	+	+	+	+
CD4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CD43	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CD45	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HLA-DR	NA	+	NA	+	NA	NA	+	NA	+	+	+	+	+	+	+
CD56	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
CLA	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
TCL1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CD101	NA	NA	+	+	NA	–	–	NA	NA	+	NA	–	+	+	+
CD68	NA	+	–	–	+	–	–	+	–	+	–	–	+	–	–
TdT	–	–	–	–	–	+	+	–	–	–	–	–	–	–	–
CD2	NA	+	NA	–	–	–	–	–	–	–	–	–	+	NA	–
CD7	NA	–	NA	–	–	–	–	–	–	–	–	–	+	NA	–
CD10	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CD117	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CD13	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CD138	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CD14	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CD15	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CD16	NA	–	NA	–	NA	–	–	NA	–	–	–	–	–	–	–
CD1a	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CD20	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CD23	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CD3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CD30	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CD33	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CD34	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CD5	NA	–	NA	–	–	–	–	–	–	–	–	–	–	NA	–
CD57	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CD79a	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CD8	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
GrB	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
MPO	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
sIg	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
TIA-1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

CLA, cutaneous lymphocyte-associated antigen; GrB, granzyme B; MPO, myeloperoxidase; NA, no data available; sIg, surface immunoglobulin; TCL1, T-cell lymphoma 1; TdT, terminal deoxynucleotidyl transferase; +, positive; –, negative.

* Percentages were calculated by the number of positive results divided by the number for which data were available. CD123, PharMingen, San Diego, CA; CD3, CD8, CD15, CD20, CD30, CD43, CD45, CD57, CD68, CD79a, CD117, CD138, sIg, and MPO, DAKO SA, Glostrup, Denmark; CD13, CD16, CD33, HLA-DR, and TIA-1, Coulter/Immunotech, Luminy, France; CD1a, CD2, CD4, CD5, CD7, CD10, CD14, CD23, CD34, CD56, GrB, and TdT, Novocastra, Newcastle upon Tyne, England. The TCL1 antibody was provided by M.A.T.; HECA-452 (CLA) antibody by C.J.L.M.M.; CD101 antibody by M.B.

TCL1 **Image 3D** and CLA (cutaneous lymphocyte-associated antigen) **Image 3E** also generally are positive.[17,29] 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.[30-32] CLA is recognized by the HECA-452 antibody. The HECA-452 epitope is part of an inducible carbohydrate on the P-selectin glycoprotein ligand-1.[33] However, this staining pattern does not exclude other entities in the differential diagnoses.

The following stains are negative in paraffin-embedded sections: CD10, CD14, CD15, CD21, CD23, CD30, CD34, CD57, and CD138. Terminal deoxynucleotidyl transferase (TdT) staining has been reported in several cases.[11,12,18,19,26] In our series, 8 cases of 30 were positive for TdT, with expression ranging between 10% and 80% of tumor cells. Occasionally, CD2 and CD7 antigens might be positive.

Frozen sections might be required to confirm CD4 and/or CD56 expression, which sometimes are negative or faintly positive in paraffin-embedded sections. This is especially true for CD4 antigen, for which the available antibodies are inconsistently efficient in paraffin-embedded sections. Furthermore, frozen sections are necessary to demonstrate CD123, HLA-DR, and CD101 antigen expression. CD123 antigen is the α-chain of the interleukin (IL) 3 receptor. It is expressed highly by PDCs and by CD4/CD56 HN tumor cells[24] **Image 3F**. CD101 is a human leukocyte cell surface molecule expressed by a minor subset of circulating T lymphocytes, intestinal mucosal T lymphocytes, and a major DC subset, including DC2.[34] This antigen also is frequently positive on CD4/CD56 HN tumor cells[35] **Image 3G**. Occasionally, antigens such as CD33, CD36, and CD38 are positive. Frozen sections are necessary to exclude expression of myelomonocytic antigens such as CD13 and CD33.

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Table 3
Immunohistochemical Detection of 30 CD4+CD56+ Hematodermic Neoplasm Cases* (cont)

	Case No.															
Antigen	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**%**
CD123	NA	NA	+	+	+	+	+	+	+	+	+	NA	NA	NA	+	100
CD4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
CD43	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
CD45	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
HLA-DR	NA	NA	NA	+	+	+	+	+	NA	NA	NA	NA	NA	NA	NA	100
CD56	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	97
CLA	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	90
TCL1	+	+	+	+	+	+	+	–	–	+	+	+	+	–	+	90
CD101	+	NA	+	+	+	+	–	+	NA	NA	NA	NA	NA	NA	NA	75
CD68	NA	–	NA	+	+	+	+	+	–	–	–	–	–	NA	+	42
TdT	–	–	–	–	+	–	–	–	+	+	+	+	+	–	–	27
CD2	–	NA	NA	NA	–	–	–	–	+	–	+	–	+	–	NA	22
CD7	–	NA	NA	NA	–	–	–	–	+	–	–	–	–	–	–	8
CD10	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
CD117	–	–	–	NA	–	–	–	–	NA	NA	NA	NA	NA	NA	–	0
CD13	–	–	–	–	–	–	–	–	NA	NA	NA	NA	NA	NA	–	0
CD138	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	0
CD14	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
CD15	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
CD16	NA	NA	NA	NA	–	–	–	–	NA	NA	NA	NA	NA	NA	NA	0
CD1a	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
CD20	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
CD23	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
CD3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
CD30	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
CD33	–	–	–	–	–	–	–	–	NA	NA	NA	NA	NA	NA	–	0
CD34	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
CD5	–	NA	NA	–	–	–	–	–	NA	NA	NA	NA	NA	NA	–	0
CD57	–	–	–	NA	–	–	–	–	–	–	–	NA	–	–	–	0
CD79a	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
CD8	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	0
GrB	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	0
MPO	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
sIg	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
TIA-1	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	0

Epstein-Barr Virus Status

Epstein-Barr virus (EBV) is not detected in CD4/CD56 HN tumor cells as well with the latent membrane protein-1 protein as it is with the EBV-encoded small nuclear RNA (EBER) probe.

Polymerase Chain Reaction and Clonality

Evaluation of B-cell receptor gene rearrangements has not been reported. Generally, monoclonal T-cell receptor (*TCR*) gene rearrangements do not occur; however, 3 reports indicate TCR clonality found by polymerase chain reaction.[6,14,36] These samples deserve additional study to be certain that the *TCR* gene rearrangements occur in the tumor cells.

Cytogenetics

Two thirds of patients with CD4/CD56 HN have an abnormal tumor cell karyotype. Petrella et al[21] reported frequent deletion of 5q as an isolated occurrence or in association with other karyotypic abnormalities. In general, the karyotype is complex with an average of 6 to 8 abnormalities, and the cells are mainly hypodiploid or tetraploid. Six recurring abnormalities were recognized,[37] including abnormalities of 5q with 2 target areas, 5q21 and 5q34 (72% of cases); deletions of 12p minimally involving 12p13 (64% of cases); abnormalities of chromosome 13, including chromosomal loss and/or deletions minimally involving the region between 13q13 and 13q21 (64% of cases); deletions on 6q, the region 6q23-qter being a minimal common region of deletion (50% of cases); loss of chromosome 15 (43% of cases); and loss of chromosome 9 (28% of cases).

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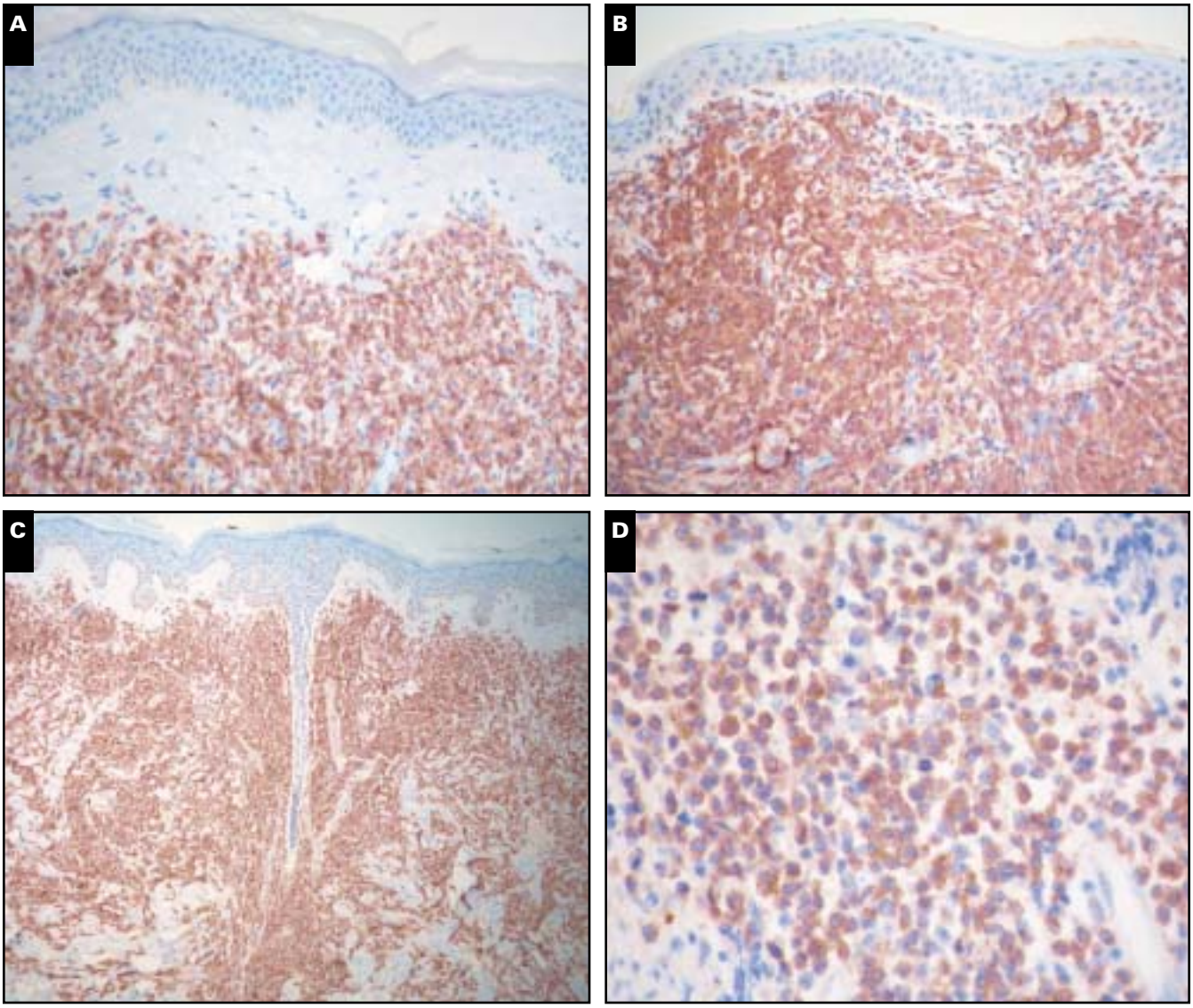

Image 3 Immunohistochemical features of CD4+CD56+ hematodermic neoplasm. **A**, CD4 positivity in paraffin-embedded sections (×200). **B**, CD56 positivity in paraffin-embedded sections (×200). **C**, CD68 positivity in paraffin-embedded sections (×400). **D**, TCL1 positivity in paraffin-embedded sections (×400). (continued on next page)

Diagnostic Criteria and Differential Diagnoses

CD4/CD56 HN is a disease with specific clinical manifestations and phenotype. The diagnosis, especially in its early phase, relies almost exclusively on an accurate laboratory evaluation, which means that dermatopathologists in particular must be cognizant of this entity and have criteria for establishing the diagnosis. Biopsy of a patch or a nodule generally is referred to the pathologist with a clinical suspicion of lymphoma. Routine histologic examination shows a rather monomorphous dermal infiltrate with medium-sized cells containing slightly irregular nuclei, at first suggesting a possible pleomorphic T-cell lymphoma. However, routine B- and T-cell markers, CD20 and CD3, are negative despite a positive CD45 marker, indicating a probable hematologic tumor and prompting additional marker evaluations, such as CD4 and CD56. From the most current data available, CD4/CD56 HN is diagnosed based on the expression of CD4, CD43, CD56, CD68 in a "small-dots" distribution, and CD123. For lesions with this clinical presentation, the main differential diagnoses in our experience include cutaneous T-cell lymphomas, cutaneous NK-cell lymphomas, and skin involvement of myeloproliferative disorders.

For T-lineage tumors, it is necessary to exclude primary and secondary cutaneous medium-sized pleomorphic T-cell lymphomas.[38,39] The morphologic features of these lymphomas can be close to CD4/CD56 HN. This exclusion is relatively straightforward because these tumors almost always express the

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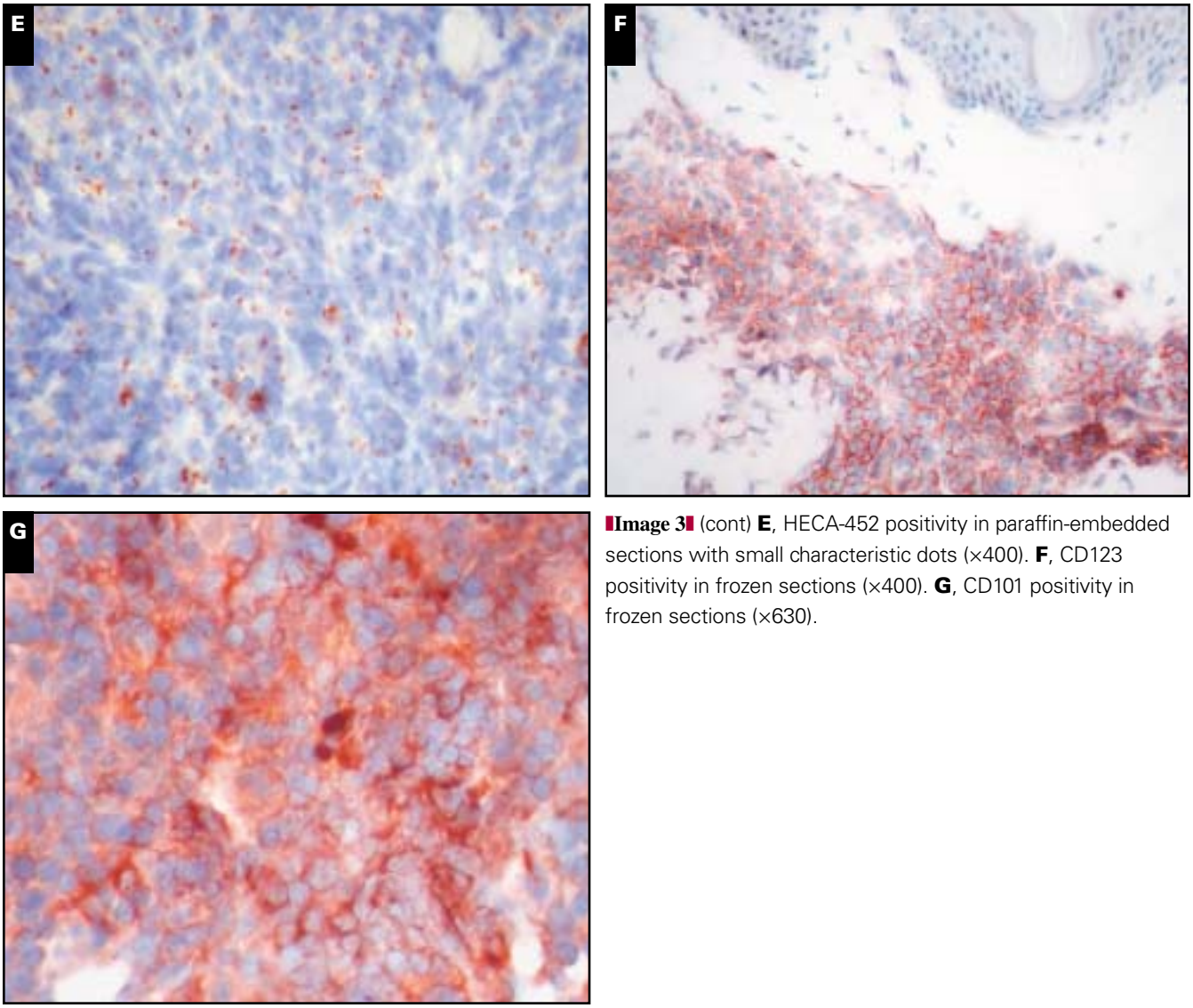

Image 3 (cont) **E**, HECA-452 positivity in paraffin-embedded sections with small characteristic dots (×400). **F**, CD123 positivity in frozen sections (×400). **G**, CD101 positivity in frozen sections (×630).

CD3 antigen. They also might express CD4 but generally do not express CD56. If a molecular analysis is carried out, they will show monoclonal T-cell gene rearrangements.

For NK-lineage tumors, the main differential diagnoses with CD4/CD56 HN include cutaneous localization of nasal-type T/NK-cell lymphoma or aggressive NK-cell lymphoma/leukemia.[38,40] Morphologically, the infiltration pattern can be similar to CD4/CD56 HN, and the cells generally are medium-sized and monomorphous with a somewhat irregular nucleus. The cytoplasm is distinct because these NK lesions generally show basophilic granulations with Giemsa stain. The main morphologic distinction is the presence of angiotropism, with angiodestruction and necrotic areas that are not observed in CD4/CD56 HN. Immunophenotypically, NK tumor cells express CD56 but not CD4 antigen. CD3 sometimes is expressed, but the main distinguishing feature between NK tumors and CD4/CD56 HN are cytotoxic proteins such as TIA-1, granzyme B, and/or perforin in the NK-cell lesions.[41] Also, nasal-type NK-cell lymphomas are almost always associated with EBV. In situ hybridization is EBER+, whereas EBER always is negative in CD4/CD56 HN. Aggressive NK-cell lymphoma/leukemia generally manifests with a different clinical picture characterized by a leukemic phase with concurrent hepatosplenomegaly, although cutaneous involvement is possible.[40]

The most difficult lesions to exclude from the differential diagnosis are skin localizations of myelomonocytic disorders. CD4 antigen is expressed by monocyte lineage cells,[42] and its expression is retained by leukemias with monocytic differentiation. In addition, these leukemias frequently coexpress the CD4 and CD56 antigens.[43-47]

Cutaneous involvement of myelomonocytic leukemia is not rare and might precede the leukemic phase of the disease.[48,49] Skin infiltrates vary from faint perivascular to massive

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dermal invasion. The leukemic cells generally are medium-sized, showing a round or oval blastic nucleus. The presence of cytoplasmic granulations must be evaluated carefully on Giemsa stain.

When cytoplasmic granulations are present, immunostaining for MPO generally is positive, whereas CD4/CD56 HNs always are MPO–. In addition to CD4 and CD56, myelomonocytic leukemia cells generally express CD43 and also can express CD68, again features in common with CD4/CD56 HN. CD68 immunostaining shows a distinct pattern and is rarely in small dots as observed in CD4/CD56 HN. Furthermore, myeloid leukemia also might express HLA-DR, CD2, CD7, CD36, or CD38. Myeloid leukemias are negative for B-cell antigens such as CD20 and T-cell antigens such as CD3.

In the immature forms without cytoplasmic granulation, it is necessary to evaluate myelomonocytic differentiation markers such as CD13, CD14, CD15, CD33, CD34, and CD117. CD13 and CD33 cannot be examined on paraffin-embedded sections, so frozen sections are required to have confidence in diagnosing CD4/CD56 HN vs a myelomonocytic lineage tumor. The CD123 antigen is not a discriminator because it can be positive in some cases of myeloid leukemia.[24]

Petrella et al[29] recently evaluated the expression of the TCL1 (T-cell lymphoma 1) antigen in CD4/CD56 HN and acute myeloid leukemia (AML) cells and found that TCL1 was expressed in 90% of CD4/CD56 HN, whereas only 17% of AMLs expressed TCL1. From this study, we concluded that TCL1 could be helpful in distinguishing between CD4/CD56 HN and AMLs.[29] Furthermore, CD4/CD56 HNs are negative for naphthol-butyrate esterase and peroxidase reactions. In contrast, these cytochemical reactions generally are positive for myeloid or myelomonocytic leukemias.

Origin of CD4/CD56 HN

A myelomonocytic precursor as the cell of origin for CD4/CD56 HN has been suggested by several investigators.[19,21,50] This proposal was based on several observations. First, the CD4 antigen, although it is a T-cell marker, also is an antigen commonly expressed by monocytes. Second, the CD56 antigen can be expressed by monocytic leukemia blast cells (20%-40%). Third, CD68 is expressed on monocytes and on about 75% of CD4/CD56 HN tumor cells. Last, several cases of CD4/CD56 HN contain a del(5q), which is a relatively common cytogenetic finding in myelodysplastic syndromes.

In searching for an alternative to an unlikely NK-cell origin, an important discovery of strong expression of the CD123 antigen by CD4/CD56 HN tumor cells was made.[13,23,24] Few normal cells express CD123, and these mainly include DCs and PDCs. 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. PDCs were observed initially in 1958 by Lennert and Remmele,[51] who called them *plasmacytoid T cells* because they localize in T cell–rich areas of lymph nodes and display plasma cell morphologic features. In 1988, Facchetti and colleagues[52] demonstrated immunophenotypic similarities with monocytes and renamed these cells *plasmacytoid monocytes.* Facchetti and colleagues[53] subsequently showed that the quantity of PDCs in a lymph node could increase in certain pathologic circumstances, such as granulomatous lymphadenitis,[53] Kikuchi disease,[54] Castleman disease,[55] and Hodgkin disease.[56] PDCs also were demonstrated in allergic rhinitis.[57] In 1997, Grouard and colleagues[58] showed that PDCs were able to differentiate into DCs and were given the additional name *pre–DC2 cells.*

Morphologically, PDCs assume a plasma cell–like shape with an eccentric nucleus. Immunophenotypically, they strongly express CD4, CD123, and HLA-DR. They express lower levels of CD43 and CD68. They are lineage-negative and do not express CD11c, in contrast with most DCs. Other antigens such as CLA,[59] granzyme B,[60] and TCL1[17] also are expressed by PDCs. Three main properties are characteristic of PDCs[58]: (1) expression of high-level CD123 (IL-3 α-chain receptor); (2) the main interferon-α–producing cell; and (3) able to differentiate into DCs in culture with IL-3 and CD40-ligand treatments.

Similarities between PDCs and CD4/CD56 HN tumor cells occur at the phenotypic and functional levels. Phenotypically, they share CD4, CD43, CD68, CD123, and HLA-DR antigen expression and are negative for the major T-, B-, NK-, and myeloid-cell differentiation antigens. They also coexpress TCL1 and CLA.[17,29] Furthermore, Chaperot and colleagues[23] have shown functional similarities between these entities. These authors demonstrated that CD4/CD56 HN cells secreted interferon-α, underwent a differentiation to DCs with IL-3 stimulation, and were able to stimulate naive T lymphocytes. From these findings, the PDC is a strong candidate for the normal counterpart cell of CD4/CD56 HN tumor cells. However, an important obstacle remained, because the CD56 antigen had never been demonstrated in PDCs.

The rarity of PDCs in the human body makes their in vitro evaluation very difficult. Grouard and colleagues[58] required a large number of fresh tonsils to extract PDCs. PDC sorting requires complex enrichment techniques and multiple rounds of antigen depletion with antibody cocktails of high specificity and avidity. One group solved this issue by FLT3-ligand injections to stimulate PDC growth and increase the number of blood PDCs for harvest.[61] With this approach, large amounts of PDCs are obtained without preliminary enrichment procedures. A study of voluntary donors who received injections of FLT3-ligand resulted in the isolation of a PDC

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subpopulation expressing CD56.[24] Blood cells were sorted based on their expression of CD123. Analysis of the CD123-expressing population showed the existence of a fraction of PDCs that express CD56. This subpopulation represented about 17% of the PDCs and showed marker expression patterns that suggest this subpopulation represents activated PDCs. Our current hypothesis is that this activated PDC subpopulation represents the physiologic normal counterpart of CD4/CD56 HN tumor cells, although this postulate must be confirmed with additional studies.

Recently, BDCA2 and BDCA4 (blood dendritic cell antigen 2 and 4, respectively) have been demonstrated as highly specific markers for PDCs.[62-64] These antigens have been detected in CD4/CD56 HN cells by flow cytometry.[19,65,66] To date, we have been unable to detect these 2 antigens by immunohistochemical methods on frozen sections of CD4/CD56 HN samples (data not shown).

Facchetti and colleagues[60] underlined the likely heterogeneity of tumors originating from PDCs based on variable immunophenotypic findings. PDCs likely represent a heterogeneous cell population because they are precursor cells capable of distinct differentiation pathways toward B-, T-, NK-, or myeloid-lineage cells.[67,68] The collection of PDCs may express B- or T-lymphoid transcripts such as pre-β, λ-like, V-pre-B, and Spi-B,[69] and they also might express myelomonocytic markers such as CD31, CD36, and CD38.[70] Comeau and colleagues[70] identified 2 subtypes of PDCs that exhibit lymphoid or myeloid features. This normal-cell heterogeneity logically portends tumor-cell heterogeneity, which could explain occasional unexpected marker alterations, such as cytoplasmic CD3ε expression,[16,24] a lack of CD56 expression,[71] or CD33 expression.[25,72]

When leukemic relapses occur, blast cells exhibit the same phenotype as the initial tumor. However, sometimes the leukemic phase blast cells undergo myeloid maturation and express myeloid-lineage markers, including CD13 and CD33 (data not shown). Cases with transformation to myelomonocytic leukemias also have been reported.[11,17]

To date, 2 other kinds of tumors thought to stem from PDCs have been described: the so-called plasmacytoid T-cell lymphomas and the tumor-forming accumulation of plasmacytoid monocytes associated with myeloid disorders. Plasmacytoid T-cell lymphomas seem very rare, and only a few cases were reported from 1983 to 1992.[73-80] They exhibit a nodal proliferation of plasmacytoid T cells and generally are associated with or result in myelomonocytic leukemia. Vermi and colleagues[81] reported 9 cases of nodal and extranodal expansions of PDCs in patients with myeloid disorders. These patients had lymph node and occasionally bone marrow and skin accumulations of cells with morphologic and phenotypic characteristics of PDCs. The patients otherwise were treated for myeloid disorders (5 of 9 were monocytic disorders). This study demonstrated a clonal relationship between expanding cells and myeloid blasts by fluorescence in situ hybridization analysis of chromosomes 7 and 17.

There are similarities between these 2 pathologies, and we wonder whether they represent the same diagnostic entity. However, they differ from CD4/CD56 HN because they are located predominantly in lymph nodes and do not express CD56. Furthermore, chromosomes 7 and 17 are not involved in the recurring chromosomal abnormalities of CD4/CD56 HN. However, they share the same final leukemic phase and the frequent association with chronic myelomonocytic leukemia. Nevertheless, they represent a heterogeneous group of neoplasms related to PDCs.

A Primary or Secondary Cutaneous Tumor?

For hematologists, CD4/CD56 HN would be considered a leukemia that originates from a bone marrow tumor cell that secondarily involves the skin. This position is based on the homology with the myelomonocytic leukemias, which occasionally manifest with cutaneous tropism. Furthermore, rare cases in the series of Feuillard and colleagues[13] do not show cutaneous involvement.

We postulate that a primary cutaneous origin is not excluded by the available data. Clinically, all cases we have classified as CD4/CD56 HN have an initial cutaneous involvement, and 77% had no bone marrow involvement at diagnosis. Furthermore, 30% had lymph node involvement in the lymphatic draining area of an associated skin tumor. These tumor kinetics are more suggestive of a skin primary disease than a primary leukemia. The presence of PDCs has not been demonstrated in normal skin; however, recent studies have shown skin recruitment of PDCs in inflammatory or tumor conditions. Facchetti and colleagues[82] have shown the presence of skin PDCs in Jessner and Kanoff syndrome. More recently, Wollenberg and colleagues[83] demonstrated the presence of PDCs in various inflammatory skin diseases. PDCs also have been demonstrated in the stroma of skin melanoma.[84,85] Furthermore, Facchetti and colleagues[59] showed that PDCs, like CD4/CD56 HN tumor cells, express CLA, which likely has a role in PDCs homing to the skin.[33]

The debate of a primary or secondary skin tumor remains unresolved. However, we must still name this distinct clinicopathologic entity. Blastic NK-cell lymphoma is an inappropriate name given all the features suggesting an NK lineage–independent origin. We propose this lesion be named *CD4/CD56 hematodermic neoplasm* when the diagnosis is made on a cutaneous biopsy specimen without a leukemic phase and *CD4/CD56 leukemia* when the disease is diagnosed from blood workup of a leukemic phase.

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Treatment

Whatever type or regimen of chemotherapy and radiotherapy is tried, the outcome remains dismal. The course seems to be related to the age of the patient at diagnosis and the duration of a preleukemic phase. Presently, no therapies have demonstrated remissions for 5 years or more. The best outcomes, which still are very poor, are obtained with aggressive chemotherapy associated with radiotherapy followed by bone marrow transplantation.[86]

Conclusion

CD4/CD56 HN represents an anatomic and clinical entity that is relatively well-defined by its clinical, morphologic, and phenotypic features. The tumor's main characteristics are presented herein, but although considerable progress has been realized, many questions remain unresolved. PDC is currently the best candidate for the origin of the tumor cell based on our knowledge of DC differentiation patterns and markers. It is unclear what link there is with myeloid and NK-cell differentiation. Is it a primary skin disease? If not, what is the origin for its cutaneous tropism? The most important problem remains that of treatment. New therapeutic approaches need to be developed, including nontraditional therapies. Because these tumor cells strongly express the CD123 antigen (IL-3 α receptor), immunotherapies focused on CD123 or IL-3 might provide attractive possibilities.

From the [1]Centre de Pathologie, and Department of Pathology, Centre Hospitalo-Universitaire, Dijon, France; and the Departments of [2]Dermatology and [20]Pathology, Henri Mondor Hospital, Créteil, France; [3]Dermatology, Leiden University Medical Center, Leiden, the Netherlands; [4]Dermatology and [5]Pathology, Haut Lévêque Hospital, Pessac, France; [6]Dermatology-Cancerology, St André Hospital, Bordeaux, France; [7]Pathology, Vrije Universiteit Medical Center, Amsterdam, the Netherlands; [8]Pathology and [9]Dermatology, Charles Nicolle Hospital, Rouen, France; [10]Dermatology, Pasteur Hospital, Colmar, France; [11]Pathology and [12]Dermatology, Trousseau Hospital, Tours, France; [13]Dermatology, Clemenceau Hospital, Caen, France; [14]Pathology, Institut Gustave Roussy, Villejuif, France; [15]Pathology, Maison Blanche Hospital, Reims, France; [16]Dermatology, Robert Debré Hospital, Reims, France; [17]Dermatology, Bocage Hospital, Dijon, France; [18]Pathology and [19]Dermatology, Hotel Dieu, Clermont-Ferrand, France; and [21]Pathology and Pediatrics, 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, BP 189, 21000 Dijon, France.

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