Primary Cutaneous CD8-Positive Epidermotropic Cytotoxic T Cell Lymphomas

A Distinct Clinicopathological Entity with an Aggressive Clinical Behavior

Emilio Berti,* Dario Tomasini,[†]
Maarten H Vermeer,[‡] Chris JLM Meijer,[‡]
Elvio Alessi,* and Rein Willemze[‡]

From the Institute of Dermatologic Science and IRCCS Ospedale Maggiore, Milan, Italy; the Department of Dermatology,[†] Ospedale Busto Arsizio, Italy; and the Departments of Dermatology and Pathology,[‡] Free University Hospital, Amsterdam, The Netherlands*

Cutaneous T cell lymphomas (CTCL) generally have the phenotype of CD3+, CD4+, CD45RO+ memory T cells. CTCL expressing a CD8+ T cell phenotype are extremely rare and ill-defined. To elucidate whether these CD8+ CTCL represent a distinct disease entity, the clinical, histological, and immunophenotypical features of 17 CD8+ CTCL were reviewed. None of the 17 cases expressed markers characteristic of natural killer cells or γ/δ T cells. Nine of 17 cases showed the characteristic clinical and histological features as well as clinical behavior of well defined types of CTCL, such as mycosis fungoides (2 cases), pagetoid reticulosis (2 cases), lymphomatoid papulosis (2 cases), and CD30+ large T cell lymphoma (2 cases), all of which usually express a CD4+ T cell phenotype, and 1 case of subcutaneous panniculitis-like T cell lymphoma. The other 8 cases formed a homogeneous group showing a distinctive set of clinicopathological and immunophenotypical features, not consistent with that of other well defined types of CTCL. Clinical characteristics included presentation with generalized patches, plaques, papulonodules, and tumors mimicking disseminated pagetoid reticulosis; metastatic spread to unusual sites, such as the lung, testis, central nervous system, and oral cavity, but not to the lymph nodes; and an aggressive course (median survival, 32 months). Histologically, these lymphomas were characterized by band-like infiltrates consisting of pleomorphic T cells or immunoblasts, showing a diffuse infiltration of an acanthotic epidermis with variable degrees of spongiosis, intraepidermal blistering, and necrosis. The neoplastic cells showed a high Ki-67 proliferation index and expression of

CD3, CD8, CD7, CD45RA, β F1, and TIA-1 markers, whereas CD2 and CD5 were frequently lost. Expression of TIA-1 pointed out that these lymphomas are derived from a cytotoxic T cell subset. The results of this and other studies reviewed herein suggest that these strongly epidermotropic primary cutaneous CD8+ cytotoxic T cell lymphomas represent a distinct type of CTCL with an aggressive clinical behavior. (Am J Pathol 1999, 155:483–492)

Recently, the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Group proposed a new classification for primary cutaneous T (CTCL) and B (CBCL) cell lymphomas.¹ This classification is based on a combination of clinical, histological, immunohistochemical, and genetic criteria and contains a number of well defined entities as well as some provisional forms. Well defined entities within the CTCL group include classical mycosis fungoides (MF), follicular MF, pagetoid reticulosis, Sézary's syndrome (SS), CD30+ primary cutaneous large T cell lymphomas (PC-LCL) and CD30– PC-LCL. Together they constitute about the 96% of CTCL in the Dutch registry.¹ In the overwhelming majority the neoplastic T cells have the phenotype of resting or activated CD4+ memory T cells (CD45RO+, CD29+). However, rare cases of CD8+ CTCL, with the clinicopathological features of MF or pagetoid reticulosis,^{2–9} were also reported. In 1980, Jensen¹⁰ described a fulminant MF-like case in which the neoplastic T lymphocytes were CD8+. Since that initial report, other aggressive cases have been reported.^{11–18} However, because of the small number and the heterogeneity in clinical presentation and course of the cases published so far, CD8+ CTCL were not included as a separate group in the EORTC classification for primary cutaneous lymphomas.

In the present study we discuss the clinical, histological, immunohistochemical, and molecular features of 17

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Address reprint requests to Berti Emilio, M.D., Associate Prof. of Dermatology, Institute of Dermatologic Sciences, Ospedale Maggiore Policlinico-IRCCS, Via Pace 9, 20122, Milan, Italy. E-mail: paceskin@imiucca.csi.unimi.it or berti@jupiter.augustea.it

Table 1. Clinical Parameters of Evaluated Cases

Case	G/A	St	Type of lesion	SR	Involvement	Treatment	Progression	Outcome, follow-up
1	F/58	IIB	patches, plaques, papulo-nodules, tumors, necrotic lesions	Y	widespread	IFN- α -nr, PUVA -nr, CHOP -nr	skin, oral mucosa, syst. involv., CNS	DOD, 39 m
2	M/33	IIB	patches, plaques, papulo-nodules, tumors, necrotic lesions	N	widespread	PUVA -pr, IFN- α -nr, TSEBT -nr, CHOP -nr	skin, oral mucosa, syst. involv.	DOD, 34 m
3	F/81	IIB	patches, plaques, papulo-nodules, tumors, necrotic lesions	Y	widespread	PUVA -nr, IFN- α -nr	skin, syst. involv.	DOD, 14 m
4	M/53	IIB	patches, plaques, papulo-nodules, tumors, necrotic lesions	N	widespread	PUVA -nr, RT -nr	skin, syst. involv., CNS	DOD, 27 m
5	M/39	IIB	patches, plaques, papulo-nodules, tumors, necrotic lesions	Y	widespread	PUVA -nr, IFN- α -nr, TSEBT -nr, CHOP -nr, MINE -nr	skin, oral mucosa, testis, syst. involv.	DOD, 36 m
6	M/31	IIB	patches, plaques, papulo-nodules, tumors, necrotic lesions	N	widespread	IFN- α -nr, Promace-Cytabom+BMT -nr, TSEBT -nr	skin, syst. involv.	DOD, 20 m
7	F/65	IIB	patches, plaques, papulo-nodules, tumors, necrotic lesions	N	widespread	MTX -nr, TSEBT -pr, RT -pr	skin, syst. involv.	DOD, 50 m
8	M/59	IIB	annular plaques, nodules	N	widespread	RT -pr, CHOP -pr	skin, syst. involv.	DOD, 28 m
9	F/55	IIA	patches, plaques, necrotic lesions	Y	widespread	PUVA -cr, IFN- α -nr, CHOP -nr, end MTX -nr	skin, oral mucosa, syst. involv., CNS	DOD, 124 m
10	M/52	IA	patches, papulo-nodules	Y	right arm, lower limbs	PUVA -pr	none	AWD, 23 m
11	M/89	IB	annular patches	Y	locoregional (gluteal)	PUVA -pr	none	AWD, 61 m
12	M/73	IIB	subcutaneous nodules	N	widespread	CHOP -cr	none	ADF, 72 m
13	F/72	IB	papules, nodules	Y	isolated (arms)	PUVA -pr	none	AWD, 30 m
14	M/62	IA	nodulo- verrucous lesions	N	locoregional (hands, feet)	PUVA -cr	none	ADF, 180 m
15	F/24	IB	papules	Y	locoregional (arms)	PUVA -pr	none	AWD, 24 m
16	F/6	IA	papulo-nodules	Y	isolated (lower limbs)	none	none	AWD, 13 m
17	M/60	IA	nodules	Y	isolated (trunk, face)	surgical excision -cr	none	AWD, 55 m

St, stage; G, gender; A, age; SR, spontaneous regression of lesions; Y, yes; N, no; Involvement, extension of skin involvement at the time of first diagnosis; F, female; M, male; nr, not responsive; pr, partial response; cr, complete response; PUVA, psoralene plus UVA rays; IFN- α , interferon- α ; TSEBT, total skin electron beam therapy; RT, local radiotherapy; end MTX, endoteleal methotrexate; CHOP, cyclophosphamide adriamycin vincristine prednisone; MINE, mesna iphosphamide mitoxantrone etoposide; Promace-Cytabom, methotrexate adriamycin cyclophosphamide etoposide cytarabine vincristine prednisone bleomycin; syst. involv., systemic involvement; CNS, central nervous system; DOD, dead of disease; AWD, alive with disease; ADF, alive, disease free; m, months.

cases of CD8+ CTCL. To characterize the derivation and functional status of the CD8+ neoplastic T cells, they were further investigated for the presence of cytotoxic proteins such as perforin (PF), granzyme-B (g-B), and T-intracytoplasmic antigen (TIA)-1/granule membrane protein (GMP)-17.¹⁹⁻²² In $\gamma\delta$ + T cells and natural killer (NK) cells these cytotoxic proteins (CGPs) are expressed irrespective of their functional state.²³ In $\alpha\beta$ + cytotoxic T cells (CTL) TIA-1/GMP-17 is expressed constitutively,²¹ whereas PF and g-B are detectable at protein level only after antigenic stimulation.^{24,25}

The ultimate goal of our study was to find out whether distinct clinicopathological entities could be recognized in this group of CD8+ CTCL.

Materials and Methods

Patients

The study described 17 patients with a CD8+ CTCL registered in the files of the Institute of Dermatological

Sciences of the University and IRCCS (Milan, Italy) and of the Dutch Cutaneous Lymphoma Working Group (Amsterdam, The Netherlands). Only one of these cases was previously reported.² Criteria for inclusion were 1) presentation with skin lesions and no evidence of extracutaneous disease at the time of diagnosis, 2) expression of CD8 antigen together with other T-cell-associated antigens by the neoplastic T cells, 3) negative staining for mAbs against NK cells (CD16, CD56, CD57) and $\gamma\delta$ T-lymphocytes (TCR- δ 1), and 4) HIV negativity and absence of any immunosuppression. Staging procedures, including routine blood counts and chemistry, chest radiograph, computed abdominal tomography, and bone marrow biopsy and aspirates had failed to demonstrate other than cutaneous disease. Clinical records and follow-up data were obtained from patients' charts. Clinical parameters evaluated were age, gender, extent of disease, type of skin lesions at presentation, spontaneous regression, progression of disease, treatment, and follow-up (Table 1).

Table 2. Histological and Molecular Parameters of Evaluated Cases

Case no.	Genotype		Histological features								
	TCR- γ chain	EBV	Band-like	Spongiosis	Acanthosis-	Keratinocyte	Appendages	Subcutis			
			lichenoid	Epidermotropism	blistering	hyperkeratosis	necrosis	involvement	Angiocentrism	involvement	Cytomorphology
1	R	-	+	++	+	+	++	++	-	+	PTL s/m - BT
2	R	-	++	++	++	++	+	+	+	+	IB
3	R	-	+	++	-	+	++	++	-	+	PTL s/m - BT
4	ND	ND	+	+	+	+	+	+	-	+	PTL s/m - BT
5	R	-	+	+	-	++	++	++	+	+	PTL s/m - BT
6	R	-	++	++	++	++	+	++	+	-	PTL m/l
7	R	-	+/-	++	++	+	+/-	+	+/-	+	PTL m/l
8	R	-	+/-	++	++	+	+/-	+	+	+	PTL m/l
9	R	-	+	+	-	-	++	-	+	+	PTL s/m - BT
10	R	-	-	-	-	-	-	+/-	-	-	PTL m
11	GL	-	+/-	++	-	+	-	-	-	-	PTL s/m
12	R	-	-	-	-	-	-	-	-	+	PTL m/l
13	R	-	-	+/-	-	-	-	-	-	-	PTL m/l
14	ND	ND	+/-	+	-	++	++	+/-	-	-	PTL s/m
15	R	-	+/-	+	-	+	+	+/-	+	-	PTL s/m
16	R	-	-	-	-	-	-	-	+	+	PTL m/l
17	R	-	+/-	+/-	-	+	-	-	+	-	PTL m/l

TCR, T cell receptor; EBV, Epstein-Barr virus genome (using nested PCR and (only for cases no. 7 and 8) EBER RISH); -, absent; +/-, slight; +, moderate; ++, intense; PTL s/m-m/l, pleomorphic small/medium-medium/large size; IB, immunoblastic; BT, blastic transformation; R, rearranged; GL, germline; ND, not determined.

Pathology

Skin biopsies obtained from each patient both at onset and, whenever possible, during progression of disease were reviewed. Skin sections had been fixed in 10% buffered formalin or Bouin's liquid and embedded in paraffin; 3- μ m-thick sections were stained with hematoxylin/eosin (H&E) and Giemsa stain. Histological parameters evaluated are presented in Table 2.

Immunohistochemistry

Immunohistochemical stainings were performed in all cases on paraffin-embedded tissues and, in 15 of 17 cases, on frozen tissue sections by using the panel of antibodies shown in Table 3. Three mAbs were used to detect CGPs: clone 2G9 identifying TIA-1/GMP17 protein,²¹ clone δ G-9²⁵ recognizing PF, and clone GrB-7²⁶ specific for g-B. A standard alkaline-phosphatase anti-

Table 3. Immunohistochemistry

Case no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
TCR β *	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
bcl-2	+	+	+	+	+	+	+	+	+	+	+	+	-	NT	+	+	-
CD45RA	+	+	-	+	+	+	+	+	-	-	+	-	-	NT	+	-	-
CD45RO	-	-	-	-	-	-	-	-	+	+	-	+	+	NT	-	+	+
CD1a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CD2	-	-	+	NT	+	-	-	-	+	+	+	+	-	NT	+	+	+
CD3	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CD4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CD5	+	-	-	NT	-	-	-	+	-	-	+	+	-	NT	+	-	-
CD7	+	-	+	NT	+	+	+/-	+/-	+	-	+	+	-	NT	+	+	-
CD8	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CD25	+	-	-	NT	-	-	NT	NT	-	-	-	-	-	NT	-	-	-
CD30	-	-	-	-	-	-	-	-	-	-	-	-	+	NT	-	-	+
TIA-1	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-
Gr-B	-	+	-	-	-	-	-	+	+	-	+	+	-	-	-	-	-
Perforin	-	+	-	-	-	-	NT	+	+	-	+	+	-	-	-	-	-
CLA	-	-	-	NT	-	-	+/-	-	+/-	+	+	+	+	NT	-	+	+
EMA	-	+/-	-	-	+	+/-	-	+/-	+/-	-	-	-	-	-	-	-	-
CD103	+	-	-	NT	-	-	-	-	-	-	+	-	-	NT	-	-	-
Mib-1* [†]	2	3	2	2	2	3	2	3	2	1	1	2	3	1	2	1	3

NT, not tested; +, positive; -, negative; +/-, only part of the neoplastic cells are stained.

Monoclonal antibodies for which reactivity was also tested on paraffin-embedded tissue specimens. mAbs legend: TCR- β / β F1 from T-Cell Science, Cambridge, MA; bcl-2/clone 124*, CD3* polyclonal, CD8/144B*, CD30/Ber-H2*, EMA* from Dako, Glostrup, Denmark; CD45RA/F8-11-13*, CD45RO/A6*, CLA/HECA-452, CD103/HML-1 from V Workshop on Human Leukocytes Differentiation Antigen, Boston, MA; CD1a/010*, Ki-67/Mib-1*, 2G9/TIA-1* from Coulter-Immunotech, Hialeah, FL; CD5/Leu-1*, CD8/Leu-2a, CD4/Leu-3a, CD2/Leu-5b, CD7/Leu-9, CD25/IL-2R from Becton-Dickinson, Mountain View, CA; CD2/AB75*, CD4/IF6* from Novocastra, Newcastle, UK, Granzyme-B/GrB-7*=Sambio, Amsterdam-Uden, The Netherlands; Perforin/ δ G9*=Ancell, Bayport, MN.

[†]Mib-1/Ki-67 nuclear reactivity of neoplastic cells. 1, less than 10%; 2, 10-30%; 3, more than 30%.

alkaline-phosphatase (APAAP) (Dako, Glostrup, Denmark) technique, according to the method of Cordell,²⁷ was performed. Microwave cooking technique was according to previously described method,²⁸ using EDTA buffer, pH 8.0, for antigen retrieval on paraffin sections before incubation with mAbs (anti-CD2, -CD3, -CD4, -CD5, -CD8, -CD30, -g-B, -PF, - β F-1/T-cell receptor (TCR)- β , -BCL-2, and -Ki-67). For CGPs staining was considered positive when more than 50% of tumor cells showed cytoplasmic granular positivity for specific mAbs. Proliferation index (Ki-67) was evaluated by a semiquantitative method.

Molecular Biology

TCR gene rearrangement was evaluated in 15 of 17 cases by a polymerase chain reaction assay coupled with nondenaturing polyacrylamide gel electrophoresis according to a method previously described.²⁹ The amplification of the TCR- γ chain locus V-J junctional region was performed by using the oligonucleotide specific primers for J1/2 coupled with V2a, V9, and V10.

Fifteen microliters of amplified material were then run overnight on 12% nondenaturing polyacrylamide gel electrophoresis in Tris-borate-EDTA buffer at 70V. Heteroduplex patterns were finally revealed by ethidium bromide staining. The presence of a nongerm line band, compared with previously identified positive and negative controls, was indicative of rearrangement of TCR- γ chain.

Additionally, 15 of 17 cases were analyzed for the presence of Epstein-Barr virus (EBV)-1 genome respectively with nested polymerase chain reaction in 13 cases and by *in situ* hybridization (ISH) in the remaining two (cases no. 7 and 8). Specific oligonucleotide primers targeted to EBNA-2 gene were used according to a published protocol³⁰ and 1 mg DNA was tested for each specimen. Amplified products were resolved by standard horizontal agarose gel electrophoresis and visualized by W-light exposure after ethidium bromide staining. ISH to detect the presence of EBV small encoded RNA (EBER) was performed on formalin-fixed, paraffin-embedded sections of tumoral lesions. Briefly, a cocktail of fluorescein isothiocyanate (FITC)-labeled EBER-1 and EBER-2 was used (Dako, Glostrup, Denmark). The RNA-ISH protocol was performed according to a previously published method.³¹ To evaluate the specificity of the signal, paraffin-embedded tissue sections were treated with 2Q-1-DNase (Pharmacia, Uppsala, Sweden) or hybridized with irrelevant anti-sense or sense RNA probes according to standard procedures. A known EBV-positive tumor served as positive control.

Results

Clinical Findings (Table 1)

Our group included 7 females and 10 males with a median age of 53 years (range, 8–91 years). Patients no. 1–8 showed similar clinical presentation and course,

suggesting they can be recognized as a distinct group. These patients showed a generalized eruption of erythematous-scaling patches, plaques, and verrucous or hemorrhagic papulonodular and tumoral lesions (Figure 1, a and b, and Table 1), sometimes showing a spontaneous central resolution (Figure 1d). Specific involvement of the oral cavity was observed during the course of the disease in cases no. 1, 2, and 5. Follow-up data for patients no. 1–8 showed metastatic involvement of the testis (no. 6), lung (no. 4), and central nervous system (CNS) (no. 1 and 4), sparing of lymph nodes, and a rapidly fatal course with a mean survival time of 32 months. In patients no. 1–8, despite the therapeutic regimens used, only partial remission with short disease-free periods were achieved. Furthermore, at relapse, all patients showed signs of progressive disease, and in 3 of 8 cases (no. 2, 3, and 6) worsening of the disease was observed during interferon- α (IFN- α) or photochemotherapy (PUVA) treatment. In none of the cases was the development of the CD8+ CTCL preceded by long-standing precursor lesions as commonly seen in MF. One patient (no. 1) had a history of nodular sclerosis Hodgkin's disease, stage IIA, 6 years before the appearance of a CD8+ cutaneous lymphoma. She was treated with polychemotherapy and local radiation therapy with a good result and no relapse of Hodgkin's disease.

In addition to these 8 cases, the other cases presented with the clinical and histological features characteristic of other types of CTCL, such as pagetoid reticulosis (2 cases), MF (2 cases), lymphomatoid papulosis (LyP) (2 cases), CD30+ PC-LCL, and panniculitis-like subcutaneous T cell lymphoma (SC-TCL) (1 case). The clinical behavior of these CD8+ CTCL was very similar to that reported for CD4+ cases (see Table 2). Only case no. 9 showed a peculiar if not distinct clinical course (see Discussion).

Histology (Table 2)

The histological features are summarized in Table 2. Cases with aggressive clinical behavior (no. 1–8) showed characteristic if not distinct histological features. Very early lesions showed intraepidermal pagetoid spreading of atypical lymphocytes. Fully developed lesions were characterized by a band-like/lichenoid infiltrate (Figure 1c) consisting of atypical small/medium (cases no. 1, 3, 4, and 5) and medium/large (cases no. 6–8) pleomorphic lymphocytes (Figure 2, a-c) or immunoblasts (case no. 2) (Figure 2d), with a diffuse infiltration of an acanthotic or hyperplastic epidermis (Figures 1c, 2a, and 2b). Intercellular edema, blistering, and necrosis were frequently detected in the central part of the lesion (Figure 1c), whereas a pagetoid spreading of lymphocytes at the border of the lesions was seen (Figures 1c and 2d). Extensive keratinocyte necrosis was observed only in cases no. 1 and 5 (Figure 2b). A diffuse epidermotropic infiltrate was observed also in tumoral stage (Figure 2, a and d). Sweat glands and hair follicles were frequently involved (Figure 1c), sometimes forming a lymphoepithelioid pattern (Figure 2c); a perivascular distribution of neoplastic cells (Figure 1c) without signs of

Figure 1. A: Clinical features of case no. 6: widespread eruption of patches, plaques, and papulonodular verrucous and hemorrhagic lesions. B: Clinical features of case no. 2: typical hemorrhagic and necrotic evolution of some lesions. C: Histology (H&E; original magnification, $\times 2.5$) of case no. 2: a perivascular and perianal, lichenoid, strongly epidermotropic infiltrate in an acanthotic and hyperplastic epidermis with spongiosis, blistering, and necrosis. D: Clinical features of case no. 5: particularly of the papulonodular and verrucous lesions. Note the central resolution of some lesions.

angioinvasion and angiodestruction was seen; nerves were spared by infiltration. A variable number of reactive macrophages and dendritic cells, rare eosinophils, and plasma cells was observed. The other 9 cases showed the characteristic histological features of MF (nos. 9–10), pagetoid reticulosis (nos. 11 and 14), LyP (nos. 15 and 16), CD30+ PC-LCL (nos. 13 and 17), or panniculitis-like SC-TCL (no. 12).

Immunohistochemistry (Table 3)

The neoplastic cells showed a peripheral T cell phenotype (Table 3). The phenotypical profile of cases no. 1–8 was $\beta F-1/TCR-\beta+$, CD3+, CD8+ (Figure 3a), TIA-1/GMP17+ (Figure 3b), CD45RA+ (7/8) (Figure 3c), CD7+ (6/7). The pan T cell markers CD2 (Figure 3d) and CD5, granzyme-B, and perforin were expressed in only 2 cases; HECA 452 was negative in 7/8 cases and weak in case no. 8; all showed high proliferation index using Mib-1. The complete immunophenotype of the other 9

cases is also reported in Table 3. In contrast to the aggressive cases, neoplastic T cells of this last group were often CD45RO+ and HECA-452+. It is noteworthy that no significant differences were observed in the expression of GCPs between these two groups.

Molecular Biology (Table 2)

Successful amplification of DNA was obtained in 14 of 15 analyzed cases. Rearrangement of the TCR- γ gene by heteroduplex analysis was demonstrated in 13 cases, while only one case (no. 11) showed germline configuration of the TCR- γ gene (Table 2). It was not possible to evaluate the TCR- γ gene rearrangement in the archival cases, nos. 4 and 14. Nested polymerase chain reaction analysis for EBNA-2 genes yielded negative results in all of the tested cases. Neoplastic cells in case nos. 7 and 8 were negative by RISH for EBER-1/2.

Figure 2. A: Histology (H&E; original magnification, $\times 100$) of case no. 4: well developed nodular lesion. Note the diffuse pleomorphic strongly epidermotropic T cell infiltrate. B: Histology (H&E; original magnification, $\times 100$) of case no. 1: early lesion. Note the intraepithelial pleomorphic atypical lymphoid infiltrate; the involved epidermis shows extensive keratinocyte necrosis. C: Histology (H&E; original magnification, $\times 200$) of case no. 3: the strongly adnexotropic small- to medium-size pleomorphic lymphocytes show a lymphoepithelioid pattern. D: Histology (H&E; original magnification, $\times 200$) of case no. 2: well developed tumoral lesion. High magnification of the infiltrate shows perivascular, strongly epidermotropic immunoblasts in the superficial dermis.

Discussion

In the present study 17 CD8+ CTCL were evaluated to find out whether these cases should be considered as a distinct group of CTCL. Within this group 8 patients showed a distinctive combination of clinical, histological, and immunophenotypical features suggesting that they represent a distinct disease entity. Clinically, these 8 cases presented with generalized skin lesions including erythematous-scaling patches, plaques, and papulonodular hemorrhagic or verrucous lesions and tumors, frequent involvement of the oral mucosa, metastatic spread to unusual sites such as the testis, lungs, and CNS (but sparing of lymph nodes), and an unfavorable clinical behavior. None of the eight patients achieved complete remission, neither with conventional CTCL therapies like PUVA, IFN- α , and retinoids, nor with more aggressive treatments like total skin electron beam irradiation, polychemotherapy, or allogenic bone marrow transplantation (Table 1). All eight patients died with disseminated disease 14 to 50 months (median, 32 months) after diagnosis. Histologically, these cases showed a band-like, lichenoid, strongly epidermotropic lymphoid infiltrate involving the appendages, mimicking in some cases the lymphoepithelioid pattern observed in gastrointestinal lymphomas.³² Cytologically 4 cases were classified as small/medium size pleomorphic T cell lympho-

mas (PTCL), 3 as medium/large size PTCL, and one as immunoblastic T cell lymphoma. Unlike most cases of MF, epidermotropism was noted in all stages of the disease. When only these histological features are considered, differentiation between these aggressive CD8+ epidermotropic cytotoxic T cell lymphomas and other types of CTCL, such as transformed MF or pagetoid reticulosis, may be difficult or even impossible. However, when the clinical features, the proliferation index (Ki-67+), and the phenotypic profile are taken into account as well, these CD8+ epidermotropic cytotoxic T cell lymphomas can easily be recognized also in early stage. The neoplastic T cells had a characteristic β F1+, CD3+, CD8+, CD7+, CD45RA+, TIA-1/GMP-17+ immunophenotype, suggesting bona fide derivation from CD8+ cytotoxic T cell subset,³³ although only 3 cases also expressed PF and/or g-B (which are, for their well established biochemical role, more reliable markers of cells with activated cytotoxic function).^{24,25} The absence or the weak expression (case no. 8) of the cutaneous lymphocyte antigen, an epitope expressed by memory T lymphocytes (CD45RO+) in the context of P-selectin glycoprotein ligand-1/CD162 molecule,³⁴ and of the CD103/HML-1+ (specific homing of the intraepithelial lymphocytes of the gut, observed only in case no. 1), confirms that different mechanisms could play a role in this disease.

Figure 3. A: Immunohistochemistry (APAAP; original magnification, $\times 200$) (Leu-2a/CD8-frozen section) of case no. 1: early erythematous-scaling lesion. Note in the superficial dermis many CD8+ strongly epidermotropic T lymphocytes. B: Immunohistochemistry (APAAP; original magnification, $\times 400$) (TIA-1-paraffin section) of case no. 2: well developed nodular lesion. The intraepithelial neoplastic lymphocytes in a spongiotic and blistering area show strong cytoplasmic TIA-1 positivity. C: Immunohistochemistry (APAAP; original magnification, $\times 200$) (F8-11-13/CD45RA-paraffin section) of case no. 1: papulonodular lesion showing that the dermal and intraepithelial neoplastic lymphocytes uniformly express the CD45RA marker. D: Immunohistochemistry (APAAP; original magnification, $\times 200$) (Leu-5/CD2-frozen section) of case no. 1: early erythematous-scaling lesion showing that the epidermotropic neoplastic lymphocytes are CD2-, whereas perivascular reactive lymphocytes in the superficial dermis are clearly labeled.

Review of the few case reports and small series of patients with a CD8+ CTCL published thus far revealed cases with very similar clinicopathological features,^{15,18} including presentation with a generalized skin lesions that often mimic disseminated pagetoid reticulosis,³⁴ metastatic spread to unusual anatomical sites, such as the spleen,¹¹ lungs,^{13,14,17} liver,¹³ CNS,¹³ and oral cavity,^{15,18} but rarely to peripheral lymph nodes,¹⁵ unresponsiveness to or even worsening during specific CTCL treatment,^{15,16,18} and poor prognosis. The histological features of these cases, showing marked infiltration of medium/large pleomorphic T cells into an acanthotic epidermis with variable degrees of spongiotic alterations and blistering, are very similar to what we observed in our own cases. With respect to the immunophenotype, Agnarsson et al¹⁵ suggested that cases with fatal outcome were CD2- and CD7+. The loss of the CD2 pan T cell marker was also noted in other reported cases^{16,18} and was detected in 5 of 7 tested aggressive cases of our group. The CD7+ reactivity was detected in most of our CD8+ aggressive cases (7/8), but had been also re-

ported in several cases of extranodal lymphomas of NK or γ/δ T cell derivation,³⁶⁻⁴⁰ and also in our CD8+ pagetoid reticulosis, LyP, and MF-like cases (Table 3). Interestingly, we detected CD45RA positivity in 7/8 of the aggressive cases, although the last case was CD45RA-/RO- (Table 3). CD45RA expression has also been noted in other aggressive lymphoproliferative cutaneous disorders of γ/δ T cell derivation.⁴¹ The loss of leukocyte common antigen CD45 and their isoforms was previously reported on atypical lymphocytes in the localized and disseminated pagetoid reticulosis.⁴² Only Urrutia et al had used these markers and described a CD45RA-/RO- aggressive case.¹⁶

The results of our own study, as well as data available from the literature, strongly suggest that these strongly epidermotropic CD8+ CTCL represent an aggressive and distinct disease entity.

The expression of TIA-1 molecules and CD45RA in these cases suggests derivation from CD8+ cytotoxic T cells. By investigating the expression of CGPs, the cytotoxic origin of a broad range of lymphoproliferative dis-

orders has been demonstrated.^{36-40,43-51} Interestingly, some of these disorders can involve the skin at both onset^{36-40,43-46,48} and relapse.^{36-40,43,46,49-51} Gastrointestinal cytotoxic T cell neoplasms have a very similar T cell phenotype,⁴⁷ whereas NK/T cell lymphomas of the nasal type are angiocentric and predominantly CD16+ and CD56+.³⁶⁻³⁹ Consistently, unlike nasal NK/T cell lymphomas, primary cutaneous epidermotropic CD8+ CTCL were not associated with EBV-1.

In addition to this well defined group of CD8+ CTCL, the other 9 CD8+ cases showed the clinical and histological features of well defined types of CTCL, included as separate entities in the EORTC classification for primary cutaneous lymphomas. This group included 2 cases with MF-like lesions, 2 cases of pagetoid reticulosis, 2 cases of LyP, 2 cases of CD30+ PC-LCL, and 1 case of panniculitis-like SC-TCL. Whereas SC-TCL may often have a CD8+ cytotoxic T cell phenotype⁵²⁻⁵³ and shows an aggressive clinical course, the other conditions normally have a CD4+ T cell phenotype. The specific phenotype is reported in Table 3; in contrast to patients no. 1-8, CD45RO and HECA-452 markers were frequently positive. The clinical presentation and behavior of these CD8+ cases was very similar, as reported for CD4+ cases.¹ Only one of these patients (no. 9) showed a bimodal clinical course. This patient presented with MF-like lesions in 1984 and PUVA treatment resulted in complete remission. However, after 8 years the disease relapsed, and the patient died in a short time of disseminated disease involving skin, oral mucosa, and CNS, similar to the CD8+ aggressive variant. In 7 of these 9 cases the neoplastic T cells expressed TIA-1, with simultaneous expression of g-B and PF in two of them, suggesting that most of these cases are also derived from cytotoxic CD8+ T cells.

Taken together, the results of this and other studies suggest that perhaps three aggressive groups of CTCL-expressing a CD8+ phenotype can be distinguished. First, we reported the existence of a strongly epidermotropic type, which demonstrates an aggressive clinical behavior and can be considered as a distinct type of CTCL. Second, recent studies suggest that most cases of panniculitis-like SC-TCL have a CD8+ cytotoxic T cell phenotype and should be considered, according to the REAL classification,⁵⁴⁻⁵⁵ as a distinct disease entity. Third, it is well known that CD8+ T cell lymphomas are reported in case of congenital or acquired immunodeficiency.⁵⁶ Additionally, well defined types of CTCL such as MF, pagetoid reticulosis, LyP, and CD30+ PC-LCL can demonstrate a CD8+^{2-9,57-58} rather than a CD4+ T cell phenotype in a minority of cases. Current evidence suggest that these CD8+ cases have the same clinical behavior and prognosis as the more common CD4+ cases.

Delineation of these aggressive groups of CD8 cytotoxic CTCL may have important therapeutic implications. Recent evidence suggests that most CD4+ CTCL, including classical MF, SS, and CD30+ lymphoproliferative disorders, may have a Th2-like cytokine profile.⁵⁹⁻⁶¹ This might explain why therapies that augment Th1 responses, like retinoids and IFNs, have a beneficial effect

on these conditions. It might be expected that the neoplastic cells in these CD8+ aggressive CTCL have a Th1-like (Tc1) cytokine profile (IL-2, IFN- γ , TNF- β). According to our data and some literature reports,^{15,16,18} treatment with Th1-augmenting therapies might be counterproductive and could result in deterioration rather than amelioration of the disease. Thus, the derivation of neoplastic clones from cells with different immunological functions must always be considered for a correct approach to these disorders and we suggest including CD8 and TIA-1 mAbs in the panel of reagents used for routine evaluation of primary CTCL to facilitate early recognition of CD8+ CTCL.

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