American Journal of Pathology, Vol. 155, No. 2, August 1999

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, βF1, 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, Jensen[10] 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

Accepted for publication April 28, 1999.

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, endotecal 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 γδ+ T cells and natural killer (NK) cells these cytotoxic proteins (CGPs) are expressed irrespective of their functional state.[23] In αβ+ 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 γδ T-lymphocytes (TCR-δ1), 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

	Genotype		Histological features								
Case no.	TCR-γ chain	EBV	Band-like lichenoid	Epidermotropism	Spongiosis blistering	Acanthosis-hyperkeratosis	Keratinocyte necrosis	Appendages involvement	Angiocentrism	Subcutis 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-μm-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 δG-9[25] recognizing PF, and clone GrB-7[26] 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
TCRβ*	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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/βF1 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, Hieleah, 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/δG9*=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, -βF-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 nongermline 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 protocol[30] 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 erythemato-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

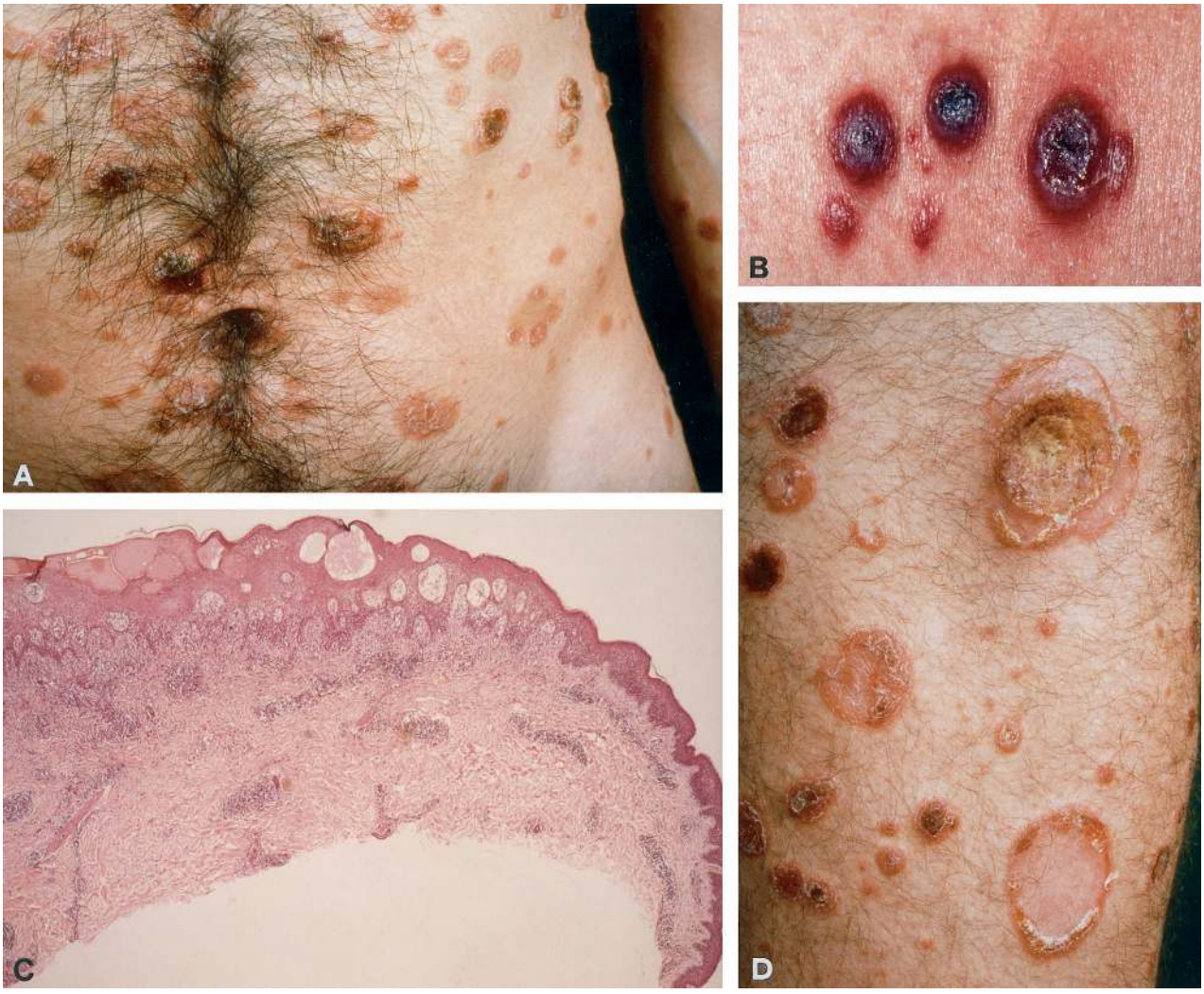

Figure 1. A: Clinical features of case no. 6: widespread eruption of patches, plaques, and papulonodular verrucous and hemorrhagic lesions. B: Clinical features of case no. 2: typical hemorrhagic and necrotic evolution of some lesions. C: Histology (H&E; original magnification, ×2.5) of case no. 2: a perivascular and periadnexal, 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 βF-1/TCR-β+, 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.

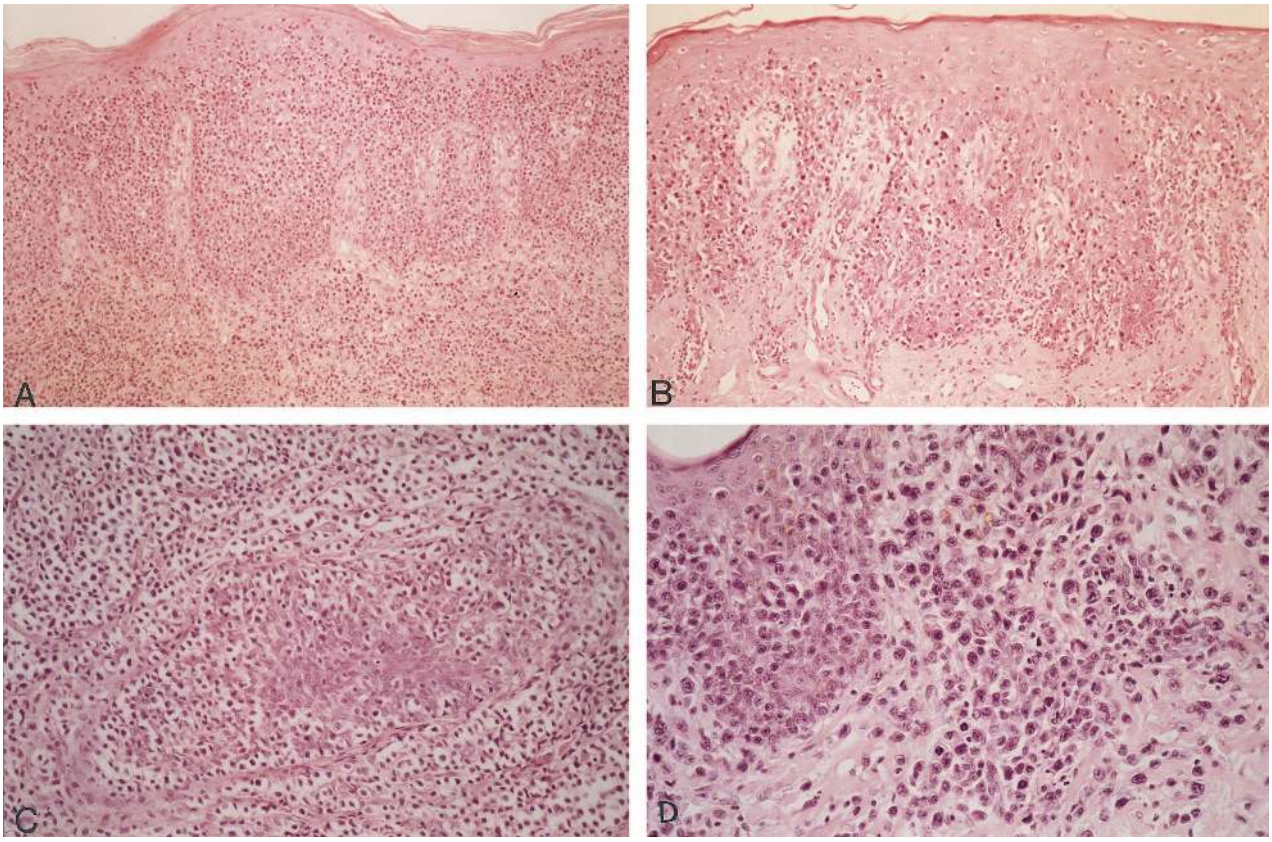

Figure 2. A: Histology (H&E; original magnification, ×100) of case no. 4: well developed nodular lesion. Note the diffuse pleomorphic strongly epidermotropic T cell infiltrate. B: Histology (H&E; original magnification, ×100) of case no. 1: early lesion. Note the intraepithelial pleomorphic atypical lymphoid infiltrate; the involved epidermis shows extensive keratinocyte necrosis. C: Histology (H&E; original magnification, ×200) of case no. 3: the strongly adnexotropic small- to medium-size pleomorphic lymphocytes show a lymphoepitheliod pattern. D: Histology (H&E; original magnification, ×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 lymphomas (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 βF1+, 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.

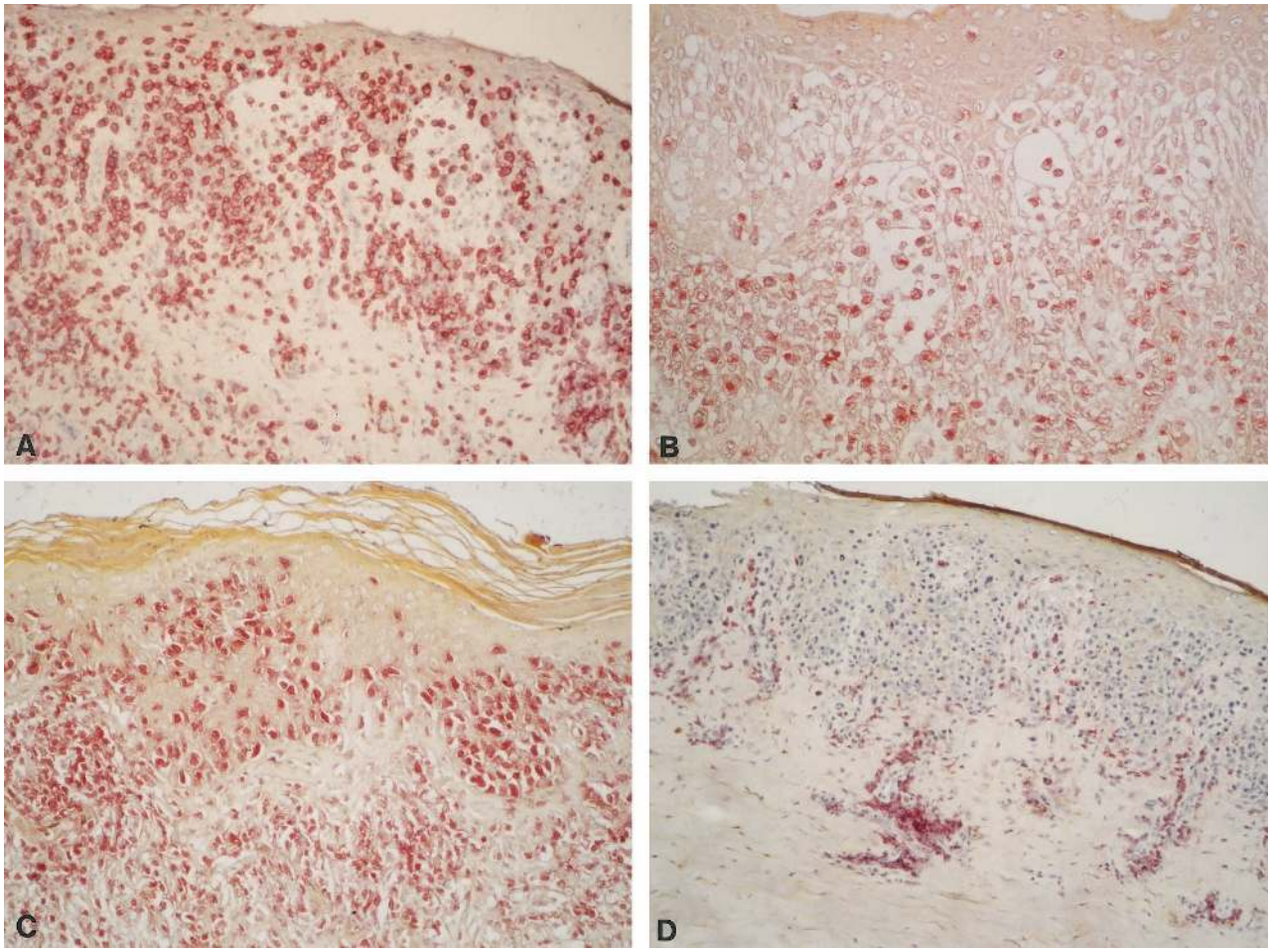

Figure 3. A: Immunohistochemistry (APAAP; original magnification, ×200) (Leu-2a/CD8-frozen section) of case no. 1: early erythemato-scaling lesion. Note in the superficial dermis many CD8+ strongly epidermotropic T lymphocytes. B: Immunohistochemistry (APAAP; original magnification, ×400) (TIA-1-paraffin 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, ×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, ×200) (Leu-5/CD2-frozen section) of case no. 1: early erythemato-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 al[15] 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 reported 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 phenotype[52–53] 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.

Acknowledgments

We thank Dr. M. Corbellino (Department of Infectious Disease, L. Sacco Hospital, Milan) for the virological studies, coworkers Drs. I. Decleva, M. Ghislanzoni, and L. Lupica for molecular analysis, Mrs. L. Venegoni and Dr. A. Piccolo for immunohistochemical analysis, and Profs. G. Galbiati and F. Allegra (Department of Dermatology of Monza and Parma) for permission to include the data for cases no. 1 and 3 in this manuscript.

References

1. Willemze R, Kerl H, Sterry W, Berti E, Cerroni L, Chimenti S, Diaz-Perez JL, Geerts ML, Goos M, Knobler R, Ralfkiaer E, Santucci M, Smith N, Wechsler J, van Vloten WA, Meijer CJ: EORTC classification for primary cutaneous lymphomas: a proposal from the cutaneous lymphoma study group of the european organization for research and treatment of cancer. Blood 1997, 90:354–371
2. Caputo R, Berti E, Monti M, Cavicchini S: A verrucoid epidermotropic OKT8-positive lymphoma. Am J Dermatopathol 1983, 5:159–164
3. Buechner SA, Winkelmann RK, Banks PM: T cells and T-cell subsets in mycosis fungoides and parapsoriasis. A study of 18 cases with anti-human T cell monoclonal antibodies and histochemical techniques. Arch Dermatol 1984, 120:897–905
4. Deneau DG, Wood GS, Beckstead J, Hoppe RT, Price N: Woringer-Kolopp disease (pagetoid reticulosis): four cases with histopathologic, ultrastructural, and immunohistologic observations. Arch Dermatol 1984, 120:1045–1051
5. Mackie RM, Turbitt ML: A case of pagetoid reticulosis bearing the cytotoxic suppressor surface marker on the lymphoid infiltrate: further evidence that pagetoid reticulosis is not a variant of mycosis fungoides. Br J Dermatol 1984, 110:89–94
6. Gonzalez M, Martin-Pascual M, San Miguel J, Caballero MD, Lopez Borrasca A: Phenotypic characterization of skin-infiltrating cells in pagetoid reticulosis by monoclonal antibodies. Acta Derm Venereol 1984, 64:421–424
7. Mielke V, Wolff HH, Winzer M, Sterry W: Localized and disseminated pagetoid reticulosis. Diagnostic immunophenotypical findings. Arch Dermatol 1989, 125:402–406
8. Smoller BR, Stewart M, Warnke R: A case of Woringer-Kolopp disease with Ki-1 (CD30)+ cytotoxic/suppressor cells. Arch Dermatol 1992, 128:526–529
9. Burns MK, Chan LS, Cooper KD: Woringer-Kolopp disease (localized pagetoid reticulosis) or unilesional mycosis fungoides? An analysis of height cases with benign disease. Arch Dermatol 1995, 131:325–329
10. Jensen JR, Thestrup-Pedersen K: Subpopulations of T lymphocytes in a patient with fulminant mycosis fungoides. Acta Derm Venereol 1980, 60:159–161
11. Bennett SR, Greer JP, Stein RS, Glick AD, Cousar JB, Collins RD: Death due to splenic rupture in suppressor cell mycosis fungoides: a case report. Am J Clin Pathol 1984, 82:104–109

12. Jimbow K, Maeda K, Ito Y, Ishida O, Takami T: Heterogeneity of cutaneous T-cell lymphoma: phenotypic and ultrastructural characterization of four unusual cases. Cancer 1985, 56:2458–2469
13. Ohkohchi K, Aiba S, Tagami H: OKT8-reactive cell mycosis fungoides. Arch Dermatol 1986, 122:20–22
14. Fujiwara Y, Abe Y, Kuyama M, Arata J, Yoshino T, Akagi T, Miyoshi K: CD8+ cutaneous T-cell lymphoma with pagetoid epidermotropism, and angiocentric, and angiodestructive infiltration. Arch Dermatol 1990, 126:801–804
15. Agnarsson BA, Vonderheid EC, Kadin EM: Cutaneous T cell lymphoma with suppressor/cytotoxic (CD8) phenotype: identification of rapidly progressive and chronic subtypes. J Am Acad Dermatol 1990, 22:569–577
16. Urrutia S, Piris MA, Orradre JL, Martinez B, Cruz MA, Garcia-Almagro D: Cytotoxic/suppressor (CD8+, CD4-) cutaneous T-cell Lymphoma with aggressive course. Am J Dermatopath 1990, 12: 603–606
17. Marti RM, Estrach T, Palou J, Urbano-Ispizua A, Gratacos J, Cervera R, Feliu E, Grau JM, Mascaro JM: Specific cutaneous lesions in a CD8+ peripheral T-cell lymphoma. Int J Dermatol 1992, 31:624–628
18. Quarterman MJ, Lesher JL, Davis LS, Pantazis CG, Mullins S: Rapidly progressive CD8-positive cutaneous T-cell lymphoma with tongue involvement. Am J Dermatopathol 1995, 17:287–291
19. Zalman LS, Martin DE, Jung G, Muller-Eberhard HJ: The cytolytic protein of human lymphocytes related to the ninth component (C9) of human complement: isolation from anti-CD3-activated peripheral blood mononuclear cells. Proc Natl Acad Sci USA 1987, 84:2426–2429
20. Hudig D, Ewoldt GR, Woodard SL: Proteases and lymphocyte killing mechanisms. Curr Opin Immunol 1993, 5:90–96
21. Anderson P, Nagler-Anderson C, O'Brien C, Levine H, Watkins S, Slayter HS, Blue ML, Schlossman SF: A monoclonal antibody reactive with a 15-kd cytoplasmic granule-associated protein defines a subpopulation of CD8+ T lymphocytes. J Immunol 1990, 144:574–582
22. Medley QG, Kedersha N, O'Brien S, Tian Q, Schlossman SF, Streuli M, Anderson P: Characterization of GMP-17, a granule membrane protein that moves to the plasma membrane of natural killer cells following target cell recognition. Proc Natl Acad Sci USA 1996, 93: 685–689
23. Koizumi H, Liu CC, Zheng LM, Joag SV, Bayne NK, Holoshitz T, Young JD: Expression of perforin and serine esterases by human γ/δ T cells. J Exp Med 1991, 173:449–502
24. Liu CC, Rafii S, Granelli-Piperno A, Trapani JA, Young JD: Perforin and serine esterase gene expression in stimulated human T cells. Kinetics, mitogen requirements, and effects of cyclosporin A. J Exp Med 1989, 170:2105–2118
25. Smyth MJ, Ortaldo JR, Shinkai YI, Yagita H, Nakata M, Okumura K, Young HA: Interleukin 2 induction of pore-forming protein gene expression in human peripheral blood CD8+ T cells: J Exp Med 1990, 171:1269–1281
26. Kummer JA, Kamp AM, van Katwijk M, Brakenhoff JP, Radosevic K, van Leeuwen AM, Borst J, Verweij CL, Hack CE: Production and characterization of monoclonal antibodies raised against recombinant human granzyme A and B and showing cross reactions with the natural proteins. J Immunol Methods 1993, 163:77–83
27. Cordell JL, Falini B, Erber WN, Grosh AK, Abdulaziz Z, MacDonald S, Pulford KA, Stein H, Mason DY: Immunoenzymatic labeling of monoclonal antibodies using immune complexes of alkaline phosphatase and monoclonal anti-alkaline phosphatase (APAAP complexes). J Histochem Cytochem 1984, 32:219–229
28. Cattoretti G, Pileri S, Parravicini C, Becker MH, Poggi S, Bifulco C, Key G, D'Amato L, Sabattini E, Feudale E, Reynolds F, Gerdes J, Rilke F: Antigen unmasking on formalin-fixed, paraffin-embedded tissue sections. J Pathol 1993, 171:83–98
29. Bottaro M, Berti E, Biondi A, Migone N, Crosti L: Heteroduplex analysis of T-cell receptor γ gene rearrangements for diagnosis and monitoring of cutaneous T-cell lymphomas. Blood 1994, 83:3271–3278
30. Lin JC, Lin SC, De BK, Chan WC, Evatt BL: Precision of genotyping of Epstein-Barr virus by polimerase chain reaction using three gene loci (EBNA-2, EBNA-3C and EBER): predominance of type A virus associated with Hodgkin's disease. Blood 1993, 81:3372–3381
31. Jiwa NM, Kanavaros P, van der Valk P, Walboomers JM, Hortsman A, Vos W, Mullink H, Meijer CJ: Expression of c-myc and bcl-2 oncogene products in Reed-Sternberg cells independent of presence of Epstein-Barr virus. J Clin Pathol 1993, 46:211–217
32. Isaacson PG: Gastrointestinal lymphoma. Hum Pathol 1994, 25: 1020–1029
33. Hamann D, Baars PA, Rep MH, Hooibrink B, Kerkhof-Garde SR, Klein MR, van Lier RA: Phenotypic and functional separation of memory and effector human CD8+ T cells. J Exp Med 1997, 186:1407–1418
34. Fuhlbrigge RC, Kieffer JD, Armerding D, Kupper TS: Cutaneous lymphocyte antigen is a specialized form of PSGL-1 expressed on skin-homing T cells. Nature 1997, 389:978–981
35. Ketron LW, Goodman MH: Multiple lesions of skin apparently of epithelial origin resembling clinically mycosis fungoides: report of a case. Arch Dermatol Syph 1931, 24:758–777
36. Jaffe ES, Chan JK, Su IJ, Frizzera G, Mori S, Feller AC, Ho FC: Report of the workshop on nasal and related extranodal angiocentric T/Natural killer cell lymphomas: definitions, differential diagnosis and epidemiology. Am J Surg Pathol 1996, 20:103–111
37. Nakamura S, Suchi T, Koshikawa T, Kitoh K, Koike T, Komatsu H, Iida S, Kagami Y, Ogura M, Katoh E, Kurita S, Suzuki I, Kobashi Y, Yamabe H, Hirabayashi N, Ueda R, Takahashi T: Clinicopathologic study of CD56 (NCAM)-positive angiocentric lymphoma occurring in sites other than the upper and lower respiratory tract. Am J Surg Pathol 1995, 19:284–296
38. Emile JF, Boulland ML, Haioun C, Kanavaros P, Petrella T, Delfau-Larue MH, Bensussan A, Farcet JP, Gaulard P: CD5- CD56+ T-cell receptor silent peripheral T-cell lymphomas are natural killer cell lymphomas. Blood 1996, 87: 1466–1473
39. Macon WR, Williams ME, Greer JP, Hammer RD, Glick AD, Collins RD, Cousar JB: Natural killer-like T-cell lymphomas: aggressive lymphomas of T-large granular lymphocytes. Blood 1996, 87:1474–1483
40. Cooke CB, Krenacs L, Stetler-Stevenson M, Greiner TC, Raffeld M, Kingma DW, Abruzzo L, Frantz C, Kaviani M, Jaffe ES: Hepatosplenic T-cell lymphoma: a distinct clinicopathologic entity of cytotoxic γ/δ T-cell origin. Blood 1996, 88:4265–4274
41. Berti E, Cerri A, Cavicchini S, Delia D, Soligo D, Alessi E, Caputo R: Primary cutaneous γ/δ T-cell lymphoma presenting as disseminated pagetoid reticulosis. J Invest Dermatol 1991, 96:718–722
42. Sterry W, Hauschild A: Loss of leucocyte common antigen (CD45) on atypical lymphocytes in the localized but not disseminated type of pagetoid reticulosis. Br J Dermatol 1991, 125:238–242
43. de Bruin PC, Kummer JA, van der Valk P, van Heerde P, Kluin PM, Willemze R, Ossenkoppele GJ, Radaszkiewicz T, Meijer CJ: Granzyme B-expressing peripheral T-cell lymphomas: neoplastic equivalents of activated cytotoxic T cells with preference for mucosa-associated lymphoid tissue localization. Blood 1994, 84:3785–3791
44. Foss HD, Anagnostopoulos I, Araujo I, Assaf C, Demel G, Kummer JA, Hummel M, Stein H: Anaplastic large-cell lymphomas of T-cell and null-cell phenotype express cytotoxic molecules. Blood 1996, 88:4005–4011
45. Matutes E, Coelho E, Aguado MJ, Morilla R, Crawford A, Owusu-Ankomah K, Catovsky D: Expression of TIA-1 and TIA-2 in T cell malignancies and T cell lymphocytosis. J Clin Pathol 1996, 49:154–158
46. Krenacs L, Wellmann A, Sorbara L, Himmelmann AW, Bagdi E, Jaffe ES, Raffeld M: Cytotoxic cell antigen expression in anaplastic large cell lymphomas of T- and null-cell type and Hodgkin's disease: evidence for distinct cellular origin. Blood 1997, 89:980–989
47. Daum S, Foss HD, Anagnostopoulos J, Dederke B, Demel G, Araujo I, Rieken EO, Stein H: Expression of cytotoxic molecules in intestinal T-cell lymphomas. The German study group on intestinal non-Hodgkin lymphoma. J Pathol 1997, 182:311–317
48. Kummer JA, Vermeer MH, Dukers D, Meijer CJ, Willemze R: Most primary cutaneous CD30-positive lymphoproliferative disorders have a CD4-positive cytotoxic T-cell phenotype. J Invest Dermatol 1997, 109:636–640
49. Chan JK, Sin VC, Ng CS, Lau WH: Cutaneous relapse of nasal T-cell lymphoma clinically mimicking erythema multiforme. Pathology 1989, 21:164–168
50. Chan JK, Tsang WY, Lau WH, Cheung MM, Ng WF, Yuen WC, Ng CS: Aggressive T/natural killer cell lymphoma presenting as testicular tumor. Cancer 1996, 77: 1198–1205

51. Takeshita M, Kimura N, Suzumiya J, Ohshima K, Kikuchi M, Watanabe R, Okamura T, Goto H: Angiocentric lymphoma with granulomatous panniculitis in the skin expressing natural killer cell and large granular T-cell phenotypes. Virchows Arch A 1994, 425:499–504
52. Kumar S, Krenacs L, Medeiros J, Elenitoba-Johnson KS, Greiner TC, Sorbara L, Kingma DW, Raffeld M, Jaffe ES: Subcutaneous panniculitic T-cell lymphoma is a tumor of cytotoxic T-lymphocytes. Hum Pathol 1998, 29:397–403
53. Salhany KE, Macon WR, Choi JK, Elenitsas R, Lessin SR, Felgar RE, Wilson DM, Przyblski GK, Lister J, Wasik MA, Swerdlow SH: Subcutaneous panniculitis-like T-cell lymphoma: clinicopathologic, immunophenotypic, and genotypic analysis of α/beta and γ/delta subtypes. Am J Surg Pathol 1998, 22:881–893
54. Harris NL, Jaffe ES, Stein H, Banks PM, Cleary ML, Delsol G, De Wolf-Peters C, Falini B, Gatter KC, Grogan TM, Isaacson PG, Knowles DM, Mason DY, Muller-Hermelink HK, Pileri SA, Piris MA, Ralfkiaer E, Warnke RA: A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994, 84:1361–1392
55. Jaffe EF, Krenacs L, Raffeld M: Classification of T-cell and NK-cell neoplasms based on the REAL classification. Ann Oncol 1997, 8 Suppl 2:17–24
56. Burns MK, Cooper KD: Cutaneous T-cell lymphoma associated with HIV infection. J Am Acad Dermatol 1993, 29:394–399
57. Beljaards RC, Meijer CJ, Scheffer E, Toonstra J, van Vloten WA, van der Putte SC, Geerts ML, Willemze R: Prognostic significance of CD30 (Ki-1/Ber-H2) expression in primary cutaneous large-cell lymphomas of T-cell origin: a clinicopathologic and immunohistochemical study in 20 patients. Am J Pathol 1989, 135:1169–1178
58. Kikuchi A, Sakuraoka K, Kurihara S, Akiyama M, Shimizu H, Nishikawa T: CD8+ cutaneous anaplastic large-cell lymphoma: report of two cases with immunophenotying, T-cell-receptor gene rearrangement and electron microscopic studies. Br J Dermatol 1992, 126: 404–408
59. Vowels BR, Lessin SR, Cassin M, Jaworsky C, Benoit B, Wolfe JT, and Rook AH:Th2 cytokines mRNA expression in skin in cutaneous T-cell lymphoma. J Invest Dermatol 1994, 103:669–673
60. Dummer R, Heald PW, Nestle FO, Ludwig E, Laine E, Hemmi S, Burg G: Sézary syndrome T-cell clones display T-helper 2 cytokines and express the accessory factor-1 (interferon-γ receptor β chain). Blood 1996, 88:1383–1389
61. Asadullah K, Docke WD, Volk HD, Sterry W: Cytokines and cutaneous T-cell lymphomas. Exp Dermatol 1998, 7:314–320