Primary Cutaneous γ/δ T-Cell Lymphoma Presenting as Disseminated Pagetoid Reticulosis

Emilio Berti, Amilcare Cerri, Stefano Cavicchini, Domenico Delia, Davide Soligo, Elvio Alessi, and Ruggero Caputo

Istituto di Clinica Dermatologica Prima e Dermatologia Pediatrica and Istituto di Scienze Medice (DS), University of Milan and Istituto di Ricovero Cura a Carattere Scientifico Ospedale Maggiore di Milano; and Istituto Nazionale Tumori (DD), Milan, Italy

The first case of primary γ/δ cutaneous T-cell lymphoma (CTCL) with a fatal outcome is reported. The patient had the clinical and histopathologic features of disseminated pagetoid reticulosis, a rare form of CTCL characterized by a strong epidermotropic lymphoid infiltrate. Extensive immuno-cytochemical studies showed that the neoplastic cells were almost exclusively localized in the epidermis, expressed the γ/δ variant of the T-cell receptor ($CD3^+$, TCR-δ-1^+) and were $CD5^+$, $CD7^+$, $CD27^+$, $CD29^+$, $CD43^+$, $CD44^+$, $CD45^+$, $CD45RA^+$, $CD54^+$, $CD69^+$, but $\beta F1^-$, $Ti\gamma a^-$, $BB3^-$, $A13^-$, $CD2^-$, $CD4^-$, $CD8^-$, $CD11a^-$, $CD49d^-$, $CD25^-$, $CD30^-$, and $HLA\text{-}DR^-$. A comparison of our results with those of the literature, which have not included γ/δ T-cell receptor analysis, suggests that some reported cases of pagetoid reticulosis may have phenotypes similar to our case. Electron microscopy studies demonstrated that the γ/δ T lymphocytes were villous, containing dense and multivesicular bodies, and formed close contacts with the surrounding keratinocytes, suggesting that these cells should have a role in the skin-associated lymphoid tissue. The proliferating cells in our case might represent the neoplastic counterpart of the recently reported $CD2^-$ subset of normal human peripheral blood γ/δ T lymphocytes. *J Invest Dermatol 96:718–723, 1991*

Two different forms of pagetoid reticulosis have been recognized: the benign localized type, first described by Woringer-Kolopp in 1939 [1], presenting with a slow developing cutaneous hyperkeratotic plaque and the disseminated type, reported by Ketron and Goodman in 1931 [2], showing erythematosquamous psoriasiform patches, nodules, and ulcerated skin tumors, and usually having a worse prognosis [3].

The T-lymphocytic nature of the pagetoid reticulosis neoplastic cells has been recently demonstrated by immunophenotypic studies [4]. On the basis of these data, most authors consider pagetoid reticulosis a variant of mycosis fungoides. However, in contrast with mycosis fungoides and other CTCL, the neoplastic T-cell infiltrate expressed a double negative $CD3^+$, $CD4^-$, $CD8^-$, or a suppressor-cytotoxic $CD3^+$, $CD8^+$, $CD4^-$ phenotype in about 50% of the reported cases [5].

Molecular analysis was also available in one case of the localized form (with a $CD3^+$, $CD4^+$ phenotype) and revealed clonal rearrangements of the β and γ chains of the T-cell receptor (TCR) [6].

Recently, a small subset of T lymphocytes presenting similar phenotypes ($CD3^+$, $CD4^-$, $CD8^-$ or $CD3^+$, $CD4^-$, $CD8^+$) and bearing the γ/δ variant of the TCR has been detected and characterized, using specific monoclonal antibodies in mouse [7], avian [8], and human normal and pathologic tissues [9,10]. We report the clinical, histopathologic, immunologic, and ultrastructural features of a patient with disseminated pagetoid reticulosis in whom the epidermotropic T-cell infiltrate showed a double negative $CD3^+$, $CD4^-$, $CD8^-$ phenotype and expressed the γ/δ variant of the TCR (TCR-1).

CASE REPORT

A man, aged 65, presented with a cutaneous eruption, characterized by several erythemato-squamous patches and plaques, nodules, and ulcerated painful tumors in different sites on the body (Fig 1). He had had the eruption for 1 year; other past medical history was negative and physical examination of the patient was unremarkable. At admission, complete blood cell counts, bone marrow aspirate and biopsy, and computed tomography scans of the thorax and abdomen showed no abnormalities. Normal percentages of $CD4^+$ and $CD8^+$ T-cell subsets and B cells were found in the peripheral blood; the TCR-δ-1^+ lymphocytes accounted for 4% of peripheral blood mononuclear cells and were not detectable in the bone marrow aspirate. The patient's serum was negative for anti-HTLV1 antibodies and dosages of the sIL-2 receptor and sTNF-α were in the normal range. On the basis of the clinical and laboratory findings re-

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Reprint requests to: Dr. Emilio Berti, Associate Professor of Dermatology, Istituto di Clinica Dermatologica Prima, University of Milano, Via Pace 9 20122 Milano, Italy.

Abbreviations:
AIM: activation inducer molecule
APAAP: alkaline phosphatase anti-alkaline phosphatase complexes
APC: antigen-presenting cells
CD: clusters of differentiation of human leukocyte antigens
CTCL: cutaneous T-cell lymphoma
ICAM: intracellular adhesion molecules
LCA: leukocyte common antigen
LFA: leukocyte function–associated antigen
MoAb: monoclonal antibodies
MHC: major histocompatibility complex
PUVA: psoralen and ultraviolet A
s-IL2: soluble interleukin 2 receptor
s-TNFα: soluble tumor necrosis factor α
TCR: T-cell receptor
TEM: transmission electron microscopy
VLA: very late antigen
WBC: white blood cells

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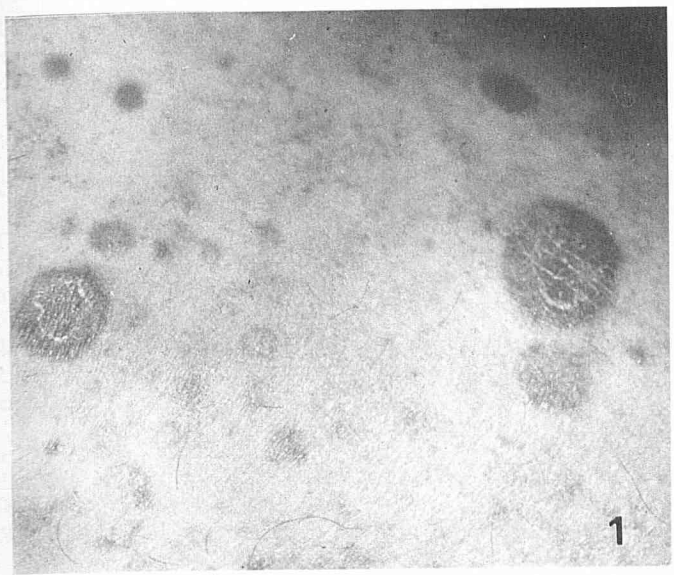

Figure 1. Clinical findings: erythematosquamous patches and plaques on the back.

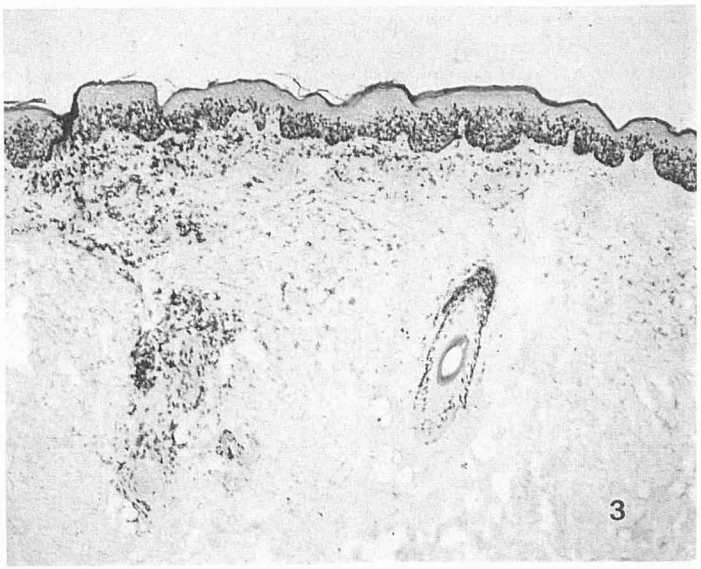

Figure 3. Immunohistochemical findings. A strong epidermotrophic γδ T cell infiltrate is well evident after labeling with TCR δ1 MoAb. Magnification ×25.

ported below, a diagnosis of disseminated pagetoid reticulosis was made.

The patient was treated by PUVA (Psoralen and ultraviolet A) therapy (3–4 times/week for 6 weeks) and most of the cutaneous lesions disappeared, except for the ulcerated nodules, which remained unchanged. A few days after completion of this therapy, the patient developed oropharyngeal candidiasis, hyperpyrexia, and the clinical and radiological signs of progressive respiratory failure due to either a mycotic infection or a lymphomatous lung infiltration. The patient was readmitted to our hospital where physical examination showed weight loss and arrhythmia. Laboratory investigations demonstrated an elevated erythrocyte sedimentation rate, neutrophilic leukocytosis (21,000 WBC/mm³), hematuria, and albuminuria. Microbial cultures were negative, except for the isolation of Candida glabrata from the mouth and of staphylococcus aureus from skin lesions. The patient was treated with antibiotics and antimycotic drugs, but died of cardiac failure 3 d after admission. No postmortem examination was done.

TISSUE STUDIES

Biopsy specimens obtained from two cutaneous lesions were either routinely processed for light and electron microscopy, or frozen in liquid nitrogen for immunohistochemical studies or enzymatically digested by incubation for 30 min at 37°C in a 0.25% Trypsin solution (GIBCO, Grand Island, NY) to obtain dermoepidermal separation and epidermal cell suspension.

The monoclonal antibodies (MoAb) used in this study and specific for the cluster differentiation antigens (CD) were obtained as undiluted ascites from the IVth International Workshop on Human Leukocyte Differentiation Antigens [11]. β-F1 [12] (specific for the β chain of TCR-2), TCR-δ-1 [13], and δ-TCS1 [14] (specific for the δ chain of TCR-1) MoAb were purchased from T Cell Science

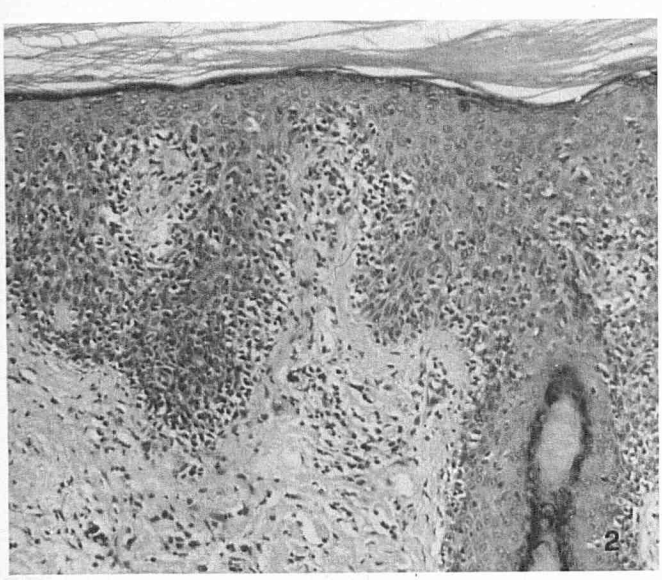

Figure 2. Histopathologic findings. Many lymphoid cells, with abundant clear cytoplasm and infiltrating the basal and suprabasal layers of the epidermis, are evident. Magnification ×100.

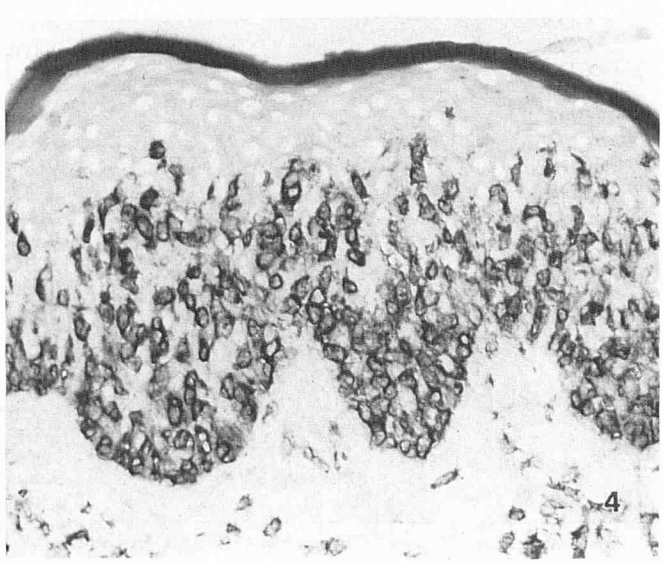

Figure 4. Immunohistochemical findings. All intraepithelial lymphocytes were strongly labeled by anti-CD3 (UCHT1) MoAb; the dendritic morphology of some neoplastic cells is evident. Magnification ×200.

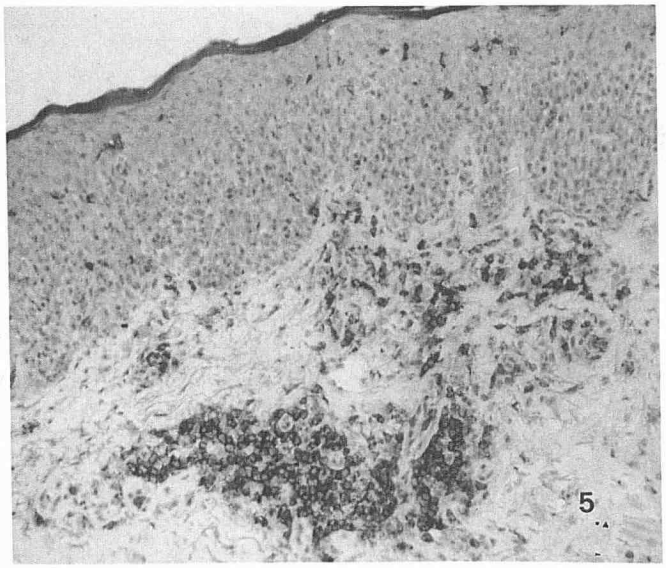

Figure 5. Immunohistochemical findings. Intraepithelial lymphocytes were unstained using anti β-F1 MoAb, recognizing the β chain of the TCR-2; note the labeling of some T cells in the superficial dermis. Magnification $\times 100$.

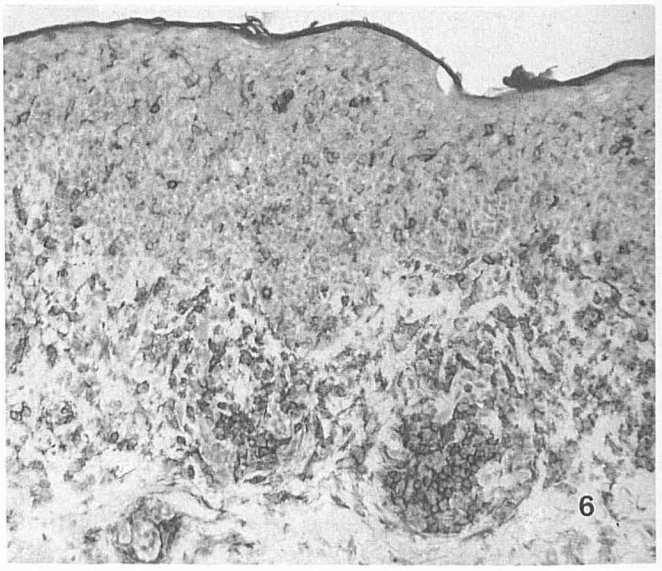

Figure 6. Immunohistochemical findings. CD4-stained (MoAb Leu3a) reactive T lymphocytes and monocytic-macrophagic elements in the superficial dermis, whereas only dendritic cells showing distribution and morphology of Langerhans cells were positive in the epidermis. Magnification $\times 100$.

Table I. Immuno-Reactivity of Intraepithelial Atypical Lymphocytes[a]

CD #	MoAb/Sources[b]	Antigen Distribution	% Stained Cells and Intensity
CD1a	MT102	Cortical thymocytes, APC	Neg
CD1c	L161	Same as above + B cell subset	Neg
CD2	Leu5 (BD)	Pan-T lymphocytes	Neg
CD3	UCHT1	Pan-T lymphocytes	100% S
CD4	Leu3a (BD)	Helper T lymphocytes	Neg
CD5	Leu1 (BD)	Pan-T lymphocytes + B cell subset	40% W
CD7	Leu9 (BD)	Pan-T lymphocytes	70% S
CD8	Leu2a (BD)	Suppressor-cytotoxic T lymphocytes	Neg
CD11a	MHM24	LFA-1, lympho-monocytes	Neg
CD14	My4	Monocytes-macrophages	Neg
CD18	MHM23	LFA-1 β, lympho-monocytes	Neg
CD22	Leu14 (BD)	Pan-B lymphocytes	Neg
CD25	IL-2R (BD)	Activated lymphocytes	Neg
CD27	OKT17	T lymphocytes, plasmacells	40% W
CD29	4B4	VLA β, widely expressed	100% S
CD30	Ber-H2	Reed-Sternberg cells, activated by lymphocytes	Neg
CD43	MT1	T lymphocytes, myelo-monocytes	30% M
CD44	F10.44.2	Homing receptor, widely expressed	100% S
CD45	9.4	LCA, panleukocyte	100% S
CD45RA	4KB5	LCA, B cell restricted	100% S
CD45RO	UCHL-1	LCA, T cell restricted + monocytes	Neg
CD49d	B-5G10	VLA-4, lympho-monocytes	Neg
CD54	RR1/1	ICAM-1, widely expressed	50% W
CD69	FN61	AIM, activated lympho-monocytes	70% S
CD70	Ki-24	Reed-Sternberg cells, activated lymphocytes	Neg
	HLA-DR (BD)	MHC Class II, B lymphocytes, APC	Neg
	Ki-67 (Dako)	Proliferating cells	20% W
	S-100[c] (Dako)	S-100 protein, APC	Neg
	Leu8 (BD)	Homing receptor, T and B lymphocytes	Neg
	Ber-Act8[d]	Activated intraepithelial T lymphocytes	Neg
	TCRdelta-1 (TCS)	Pan-gamma-delta T Lymphocytes	100% S
	TiyA[e]	Pan-gamma-delta T lymphocytes	Neg
	delta-TCS1 (TCS)	Subset of gamma-delta T-cells (BB3 −)	Neg
	A13[f]	Same as above	Neg
	BB3[g]	Subset of gamma-delta T cells (delta TCS1 −)	Neg
	beta-F1	Pan alfa-beta T lymphocytes	Neg

[a] S, strong; M, medium; W, weak. If not otherwise indicated, reagents were obtained from the 4th International Workshop on Leukocyte Antigens. BD = Becton Dickinson, Mountain View, CA. TCS = T Cell Science, Cambridge, MA. C = Coulter Immunology, Hialeah, FL. Dako = Dakopatts, Glostrup, DK.

[b] MoAb recognizing CD1b, CD6, CD11b, CD11c, CD15, CD16, CD17, CD19, CD20, CD21, CD23, CD26, CD28, CD34, CD56, and CD68 were also tested and found negative.

[c] Polyclonal rabbit antiserum.

[d] Analogous to HML1 (provided by H. Stein, Frei University, Berlin).

[e] Provided by T. Hercend.

[f] Provided by L. Moretta.

[g] Provided by S. Ferrini.

(Cambridge, MA). The MoAb A13 [15], and BB3 [16] (specific for complementary subsets of peripheral γ/δ T lymphocytes) were a kind gift of Dr. L. Moretta and Dr. S. Ferrini (Istituto Nazionale Tumori, Genoa, Italy). Anti-TiγA [17] was a kind gift of Dr. T. Hercend (Institute Gustave-Roussy, Villejeuif, France).

Immunohistochemical stains were performed on 4-μm-thick cryostat skin sections, dried overnight, fixed 10 min in acetone, incubated with the different MoAb at 1:400 (ascites) or 1:20 (β-F1, TCR-δ-1, δ-TCS1) dilution, and processed with an alkaline phosphatase anti-alkaline phosphatase method (APAAP) [28], using a commercial kit (Dakopatts, Glostrup, Denmark).

For transmission electron microscopy (TEM), small fragments of skin biopsies were fixed in Karnovsky's solution and in 1% OsO_4 for 2 h. After dehydration in alcohol and propylene oxide, the specimens were embedded in Epon 812 mixture.

The immunofluorescence analysis of epidermal cell suspensions was performed using an EPICS-C flow cytofluorimeter (Coulter Electronics, Hialeah, FL). ELISA Kits were used to detect anti-HTLV-1 antibodies (Du Pont de Nemour, Geneva, Switzerland), sTNF-α, and sIL-2R (T Cell Science) in the patient's serum.

RESULTS

Light microscopy examination of two skin biopsies showed an epidermis infiltrated by small to medium-sized, atypical, lymphoid cells with abundant clear cytoplasm and a centrally located round or oval hyperchromatic nucleus with a prominent nucleus (Fig 2). A few atypical lymphoid cells were also present around the vessels in the upper part of the dermis.

Immunohistochemical staining of cryostat sections of the involved skin showed that the proliferating intraepithelial lymphocytes were positive for the TCR-δ-1 (Fig 3), CD3 (Fig 4), CD5, CD7, CD27, CD29, CD43, CD44, CD45, CD45RA, CD54, CD69, and Ki-67 MoAb, but were unreactive with β-F1 (Fig 5), CD2, CD4 (Fig 6), CD8, and other T- and B-cell-specific immunologic markers (Table I). The surrounding keratinocytes focally expressed the CD54 (ICAM-1) antigen but were negative for anti-MHC class II molecules. Reactive small lymphoid cells ($CD3^+$, $CD4^+$, $CD8^-$, β-$F1^+$) were seen in perivascular areas of the superficial dermis. An increased number of dendritic cells ($CD1a^+$, $CD1c^+$, $S100^+$, $CD4^+$, $CD14^{+/-}$, ICAM-$1^{+/-}$) and of monocytic-macrophagic elements ($CD1a^-$, $CD1c^-$, $S100^-$, $CD4^+$, $CD14^+$, ICAM-1^+) was found both in the epidermis and superficial dermis (Fig 6).

In perilesional apparently normal skin, only very few and scattered TCR-δ-1^+ lymphocytes were detected in the basal layer of the epidermis and in perivascular areas of the superficial dermis.

By TEM the atypical lymphoid cells of the epidermis presented an irregular, villous cytoplasmic membrane, frequently in close contact with other lymphoid cells and keratinocytes (Figs 7 and 8). The nuclei of the blastic cells were centrally located and roundish, with dispersed chromatin and often a large nucleolus; the cytoplasm contained many polyribosomes, a well developed Golgi apparatus, mitochrondria, dense bodies, coated vesicles, and filaments. More differentiated cells showed an indented nucleus, darker cytoplasm containing more intermediate-type filaments and few dense-cored granules (Figs 7, 8, and 8 inset).

Cell cultures and cloning of γ/δ T lymphocytes isolated from epidermal cell suspensions were unsuccessful.

DISCUSSION

To this date, the few reported TCR γ/δ^+ malignancies have been found among T-lymphoblastic lymphomas and leukemias [19-22]. In a recent study [23] using the TCR-δ-1 MoAb, 6 TCR γ/δ^+ cases were found in a large number of peripheral T-cell lymphomas including cutaneous T-cell lymphomas (CTCL). Remarkably, we found proliferation of γ/δ T lymphocytes in a case of CTCL, showing the clinical features of disseminated pagetoid reticulosis. All intraepithelial neoplastic lymphocytes were $CD3^+$, $CD4^-$, $CD8^-$,

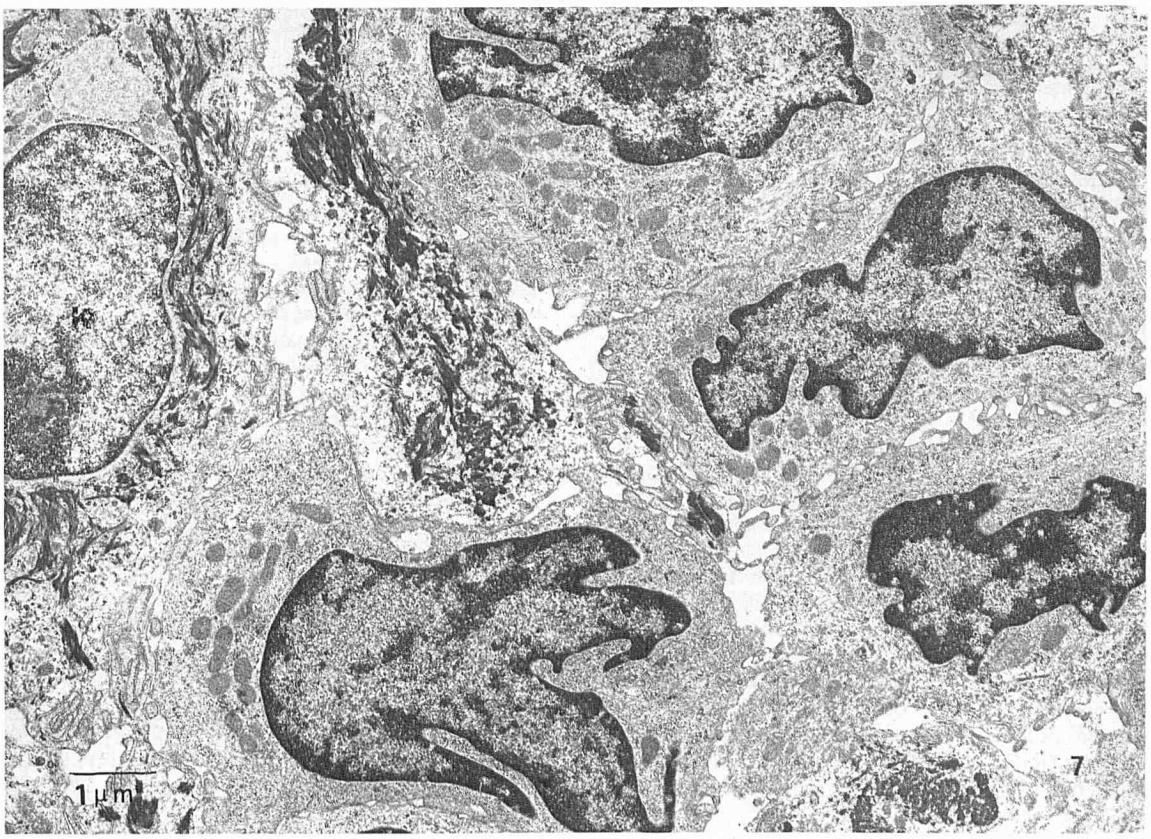

Figure 7. Low magnification showing several lymphocytes with indented nuclei and irregular villous membranes forming an abscess into the epidermis. K, keratinocytes. Magnification ×9800.

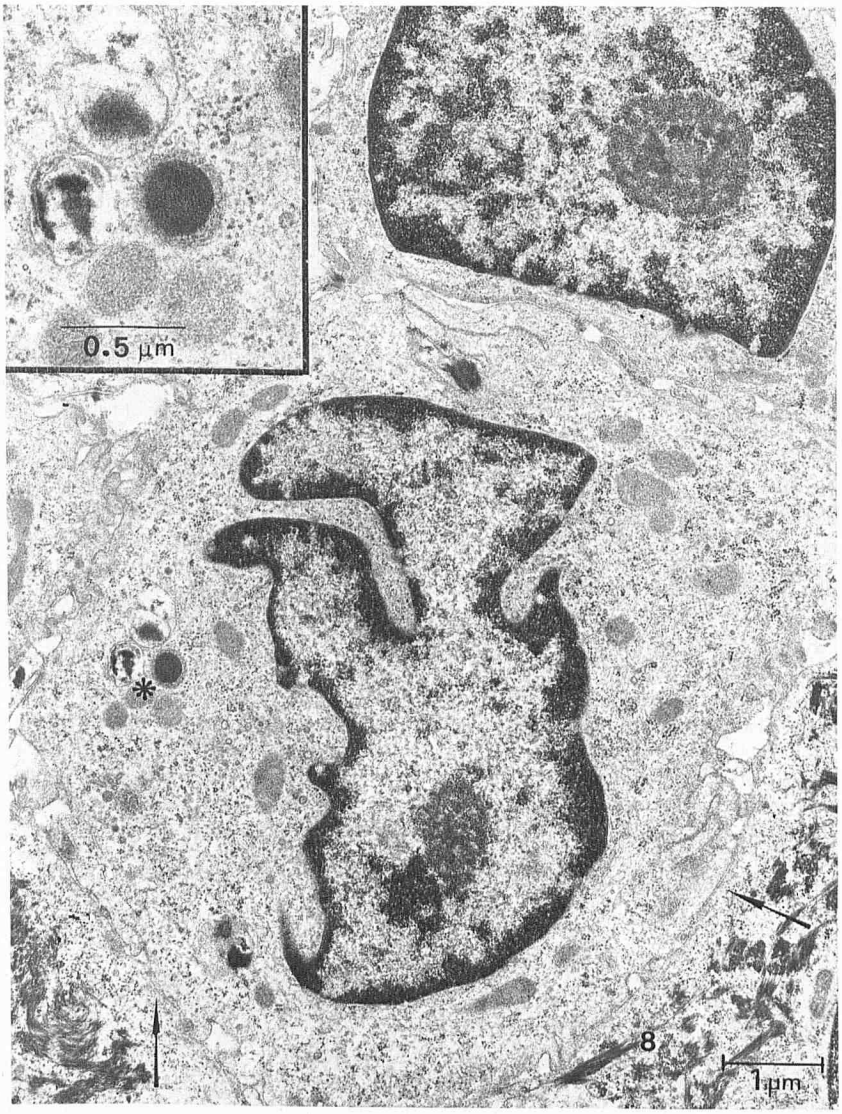

Figure 8. Electron microscopy. Higher magnification of a cell showing an indented nucleus and several cytotoxic bodies and dense-cored granules. *, *inset,* showing three dense-cored granules. Magnification ×13,500; *inset* ×32,000.

and strongly reactive with TCR-δ-1 MoAb, a pan γ/δ T-cell marker; moreover, the unreactivity with MoAb δ-TCS1, A13, BB3, and TiγA, specific for different subsets of γ/δ T lymphocytes, indicated that our case did not express the Vγ9/JP rearrangement of the variable γ chain and the VδAB12 and VIDP2/Jδ rearrangements of the δ chain [24].

The ultrastructural examination of our case demonstrated that the atypical lymphoid cells had a villous, elongated morphology, a roundish or indented nucleus, and contained dense-cored bodies; similar features were reported in mouse thy$^+$ dendritic cells of the epidermis [25,26].

Immunophenotypic data obtained in this case deserve further discussion. Interestingly, several molecules normally involved in T-cell interactions, adhesion, and spreading, such as CD2, CD4, CD8, CD11a [27], CD49d (VLA-4) [28], and Leu 8 [29], were not expressed on these cells, except for CD44 (HERMES-1) [30]. The absence of this repertoire of receptors in a CTCL with a well-defined tropism for epidermis, but without visceral involvement, suggests that these molecules have no role, at least in this case, in the activation and dissemination of proliferating γ/δ T lymphoid cells.

The classical T-activation antigens, CD25, CD30, CD70, and HLA-DR, were not expressed in our case; in contrast, the newly defined activation-inducer molecule CD69 [11] was expressed in the proliferating cells.

Another interesting issue concerns the secretory activity of the neoplastic cells. In fact, the keratinocytes of lesional skin did not express class II determinants, as usually happens in CTCL, and only focally showed ICAM-1 reactivity in the suprabasal layers of the epidermis. Langerhans cells, labeled with anti-S100, CD1a, CD1c, and HLA-DR markers, were increased in the superficial dermis and in the upper part of the epidermis, but did not express lymphokine-inducible markers, such as CD23 [31].

The phenotypic data of some reported cases of pagetoid reticulosis,which did not include the TCR-1 or TCR-2 analysis, are in many respects similar to those described in this study, suggesting that they could also represent proliferations of γ/δ T lymphocytes. In fact, the double negative CD4$^-$ and CD8$^-$ or the CD3$^+$, CD8$^+$, CD4$^-$ suppressor-cytotoxic phenotypes were found, respectively, in 2 of 13 and in 4 of 13 cases studied. The CD2 pan-T-cell antigen was negative in two of three reported cases of disseminated pagetoid reticulosis. Moreover, in one case of disseminated pagetoid reticulosis, the positivity of the neoplastic cells for the CD45RA-4KB5 marker, as in our case, was demonstrated [5].

Taken together, our phenotypic data (positivity of the TCR-δ-1 marker, negativity of TiγA, A13, δ-TCS1, and BB3 (MoAb) seem to favor clonality, although molecular studies are needed to more directly address this question. In addition, these results show for the first time that disseminated pagetoid reticulosis

can be caused by an intraepithelial proliferation of γ/δ T lymphocytes.

The distribution of γ/δ T lymphocytes in normal human skin [32,33] has been recently reported. A $CD2^-$, $CD3^+$, $CD4^-$, $CD8^-$, subset of TCR-δ-1^+ peripheral blood T lymphocytes, which may represent the normal counterpart of the neoplastic cells of our case, has recently been identified and functionally characterized in normal and pathologic conditions [34,35].

Our data on a CTCL and the cases reported by Falini [22] and Gaulard [23] provide evidence that subsets of γ/δ T cells may migrate to the skin compartment of the immune system, with a preferential intraepithelial homing (Fig 3). ICAM-1 expression but not class II molecules cold then be induced in the surrounding keratinocytes. Moreover, the close apposition between γ/δ T-lymphoid cells and keratinocytes found at ultrastructural examination strongly suggest that these cells should have a role in the skin-associated lymphoid tissue, more than being only occasional bystanders.

Further investigations on a large number of patients are needed to better define the involvement of the γ/δ T-cell subsets in pagetoid reticulosis and in other cutaneous T-cell lymphomas.

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