γδ T-Cell Lymphoma of the Skin

A Clinical, Microscopic, and Molecular Study

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**Background:** Only a few cases of primary γδ cutaneous T-cell lymphoma (CTCL) have been reported. We encountered 3 cases of this rare condition.

**Objectives:** To characterize γδ CTCL by clinical, microscopic, and molecular methods and to investigate the role of Epstein-Barr virus (EBV) infection in its pathogenesis.

**Design:** Patients were evaluated by clinical examination, and biopsy specimens of lesional skin were examined by light microscopy and immunohistochemistry. Polymerase chain reaction amplification for T-cell receptor γ gene rearrangements and in situ hybridization for EBV were performed on 3 biopsy specimens.

**Setting:** National Institutes of Health, a tertiary referral center.

**Patients:** Individuals with a clinical and histologic diagnosis of primary γδ CTCL.

**Outcome Measures:** Clinical, light microscopic, and immunohistochemical features, and the presence of T-cell rearrangement and EBV RNA in biopsy specimens.

**Results:** Patients exhibited multiple plaques, tumors, and/or subcutaneous nodules primarily distributed over the extremities. Individuals exhibited an aggressive clinical course with resistance to multiagent chemotherapy and radiation. Microscopic examination revealed epidermotropism in 2 cases, a dermal infiltrate in all 3 cases, and subcutaneous involvement in 1 case. Immunohistochemical studies showed the presence of CD3+ TCRγδ in 3 patients, CD8+ in 1, and CD4+, CD20+, CD56+, and βF1+ in none. All 3 cases exhibited an activated cytotoxic T-cell phenotype positive for T-cell intracellular antigen 1, perforin, and granzyme B. A clonal T-cell receptor γ chain gene rearrangement was detected in all 3 cases by polymerase chain reaction. In situ hybridization was negative for EBV sequences in all 3 cases.

**Conclusion:** γδ Cutaneous T-cell lymphomas are EBV-negative lymphomas that express a mature cytotoxic phenotype and have an aggressive clinical behavior.

Arch Dermatol. 2000;136:1024-1032

For editorial comment see page 1052
PATIENTS AND METHODS

The diagnosis of γδ CTCL was made on 6 biopsy specimens from 3 patients during the period from July 1997 to January 1999. Skin lesions were classified as plaques, tumors, or subcutaneous nodules based on their clinical appearance. All cases were retrieved from the files of the National Cancer Institute, Bethesda, Md. Clinical evaluation documented primary cutaneous disease without evidence of systemic spread within 1 year of diagnosis. Routine morphological studies were done on 4-µm-thick sections stained with hematoxylin-eosin. Sections from biopsy specimens were reviewed by 3 of the authors (J.R.T., E.S.J., and M.B.) for the presence of epidermotropism, angioinvasion, rimming of fat spaces, cytologic atypia, karyorrhexis, and foamy histiocytes. We classified cases by the pattern of lymphomatous involvement as epidermotropic, dermal, or subcutaneous. The serological result was negative for human lymphotropic virus type 1 (HTLV-1) for all 3 patients.

IMMUNOPEROXIDASE STAINS

Antigen retrieval was performed as previously described.17 Staining was performed on an automated immunostainer (Ventana Medical Systems Inc, Tucson, Ariz). Immunoperoxidase stains were done using the following antibody panel: CD3, CD8, and L26 (Dako Corp, Carpinteria, Calif); Leu 22 (Becton Dickinson, Mountain View, Calif); CD4, CD30, CD56, and CD57 (Novocastra Laboratories Ltd, Newcastle Upon Tyne, England); βF1 and TCRβ (T Cell Diagnostics Inc, Woburn, Mass); perforin (Kamiya, Tukwila, Wash); and TIA-1 and granzyme B (Coulter Immunology, Hialeah, Fla). Staining for TCRβ was done in frozen sections.

TCRγ GENE REARRANGEMENT

Deoxyribonucleic acid was extracted and purified from frozen and formalin-fixed paraffin-embedded tissue by standard phenol-chloroform methods.18 Polymerase chain reaction (PCR) amplification for TCRγ gene rearrangement was performed as previously reported.19 Briefly, 2 sets of consensus primers that anneal to the TCRγ variable (V) and joining (J) regions were used in separate reactions to amplify the genomic DNA. The PCR products were separated by 16% nondenaturing polyacrylamide gel electrophoresis, and the bands were visualized by staining with ethidium bromide. The expected molecular weight of the appropriate PCR products ranged from 65 to 90 base pairs. Consensus primers to the V and J regions of the immunoglobulin heavy chain (IgH) gene were used to amplify the genomic DNA for analysis of B-cell clonality as previously described.20 The expected molecular weight of the appropriate PCR products ranged from 70 to 120 base pairs.

EBV IN SITU HYBRIDIZATION

The RNA in situ hybridization technique has been described previously.21 Briefly, 5-µm-thick sections of paraffin-embedded tissue were prepared on silanated slides. Tissue sections were deparaffinized, rehydrated, permeabilized with Trion X-100, and digested with proteinase K (10 µg/mL). Riboprobes were applied in a 50% formamide hybridization buffer, and the slides were hybridized overnight. Following posthybridization washes, antidigoxigenin alkaline phosphatase antibody conjugate was applied to each slide. Then the slides were washed and placed into a color-developing solution consisting of nitroblue tetrazolium and X-phosphate. The reaction was stopped by washing the slides in an appropriate buffer. The slides were counterstained with eosin and coverslips were applied.

The integrity of the RNA in each tissue section was evaluated with a digoxigenin-labeled riboprobe directed at an abundant cellular RNA polymerase II transcript, U6. Sections showing hybridization signal with the U6 probe were determined to be adequate for analysis with the EBER1 probe. The EBV EBER1 riboprobe was prepared as previously described.21 Slides prepared from a paraffin-embedded tissue block containing metastatic nasopharyngeal carcinoma to lymph node were used as positive controls.

RESULTS

CLINICAL FEATURES

The clinical features are summarized in Table 1. There were 3 men (2 whites and 1 African American) ranging from 46 to 74 years of age. The dermatologic lesions were varied, and in some patients, more than one type of lesion was seen. All patients had a few scaly plaques that clinically resembled mycosis fungoides (MF) (Figure 1). Two individuals exhibited multiple dermal pink to plum-colored tumors, some of which were ulcerated and covered with hemorrhagic crust (Figure 1). Two individuals exhibited painful indurated nodules and tumors, some of which healed with an atrophic scar and postinflammatory hyperpigmentation (Figure 1). All individuals exhibited painful indurated nodules and tumors, some of which were ulcerated and covered with hemorrhagic crust (Figure 1).

None of the patients exhibited peripheral blood, hepatosplenic, or bone marrow involvement. None of the patients developed hemophagocytic syndrome. All 3 individuals exhibited an aggressive clinical course with resistance to multiagent chemotherapy and radiation (Table 1). At the time of this report, patient 3 was alive with residual disease. Initially, he was treated with cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone and then with multiple doses of interferon alpha and isotretinoin. At the time of this report, he was being treated with intravenous 7-hydroxystauosporine (UCN-01), a tyrosine kinase inhibitor.

HISTOLOGIC FEATURES

The histologic features are summarized in Table 1. Several distinct patterns were noted. Moreover, different biopsy specimens from the same patient often exhibited different histologic patterns. Biopsy specimens from 2 patients showed a dense bandlike lymphocytic infiltrate in the papillary dermis with marked epidermotropism with little to no spongiosis in the epidermis, slight psoriasiform epidermal hyperplasia, and compact hyperkera-
totic scale (Figure 2, A and B). Lymphocytes within the epidermis were present both as small aggregates and as individual cells along the epidermal side of the dermal epidermal junction. However, pagetoid spread was not present. Cytologically, the abnormal lymphocytes were medium sized with dense clumped chromatin and irregular but not cerebriform nuclear contours. In 2 biopsy specimens from 2 patients, the lymphocytic infiltration was present in the reticular dermis, separated from the uninvolved epidermis by a grenz zone (Figure 2, C). Patient 3 showed a combined pattern of epidermotropism, dermal and focal subcutaneous tissue involvement with neoplastic cells (Figure 2, D). There was an extensive nodular dermal infiltrate that extended into the subcutaneous tissue. However, this patient's specimen did not show the typical rimming of fat spaces, karyorrhexis, and foamy histiocytes present in subcutaneous panniculitis-like T-cell lymphoma (SPTCL).

Table 1. Clinical Features of Cases of γ6 Cutaneous T-Cell Lymphoma in the Literature

<table>
<thead>
<tr>
<th>Patient No./</th>
<th>Age, y /</th>
<th>Sex</th>
<th>Lesions Distribution</th>
<th>Dermatologic Examination</th>
<th>Histologic Profile</th>
<th>Treatment†</th>
<th>Hemophagocytic Syndrome‡</th>
<th>Duration of Disease, Outcome§</th>
<th>Reference</th>
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<td>M</td>
<td>Plaques</td>
<td>Extremities</td>
<td>E</td>
<td>PUVA</td>
<td>No</td>
<td>48 mo, DOD</td>
<td>Present study</td>
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<td>2/74/M</td>
<td>74</td>
<td>M</td>
<td>Plaques, tumors, and nodules</td>
<td>Extremities and trunk</td>
<td>D</td>
<td>RT, IFN-α, IFN-γ, anti-Tac</td>
<td>No</td>
<td>8 mo, DOD</td>
<td>Present study</td>
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<td>69</td>
<td>M</td>
<td>Plaques, tumors, and nodules</td>
<td>Extremities</td>
<td>E, D, SC</td>
<td>CHOP, IFN-α, isotretinoin, and UCN-01</td>
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<td>Present study</td>
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<td>Tumors</td>
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<td>Prednisone, cyclophosphamide, adriamycin, vincristine, RT, and methotrexate</td>
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<td>Ralfkiaer et al, 1992</td>
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<td>PUVA, RT, vincristine, chlorambucil, prednisone, adriamycin, and cyclophosphamide</td>
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<td>Extremities</td>
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<td>Prednisone and CHOP</td>
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<td>CHOP and BMT</td>
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<td>PUVA</td>
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<td>Extremities</td>
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<td>Polychemotherapy and RT</td>
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<td>Extremity</td>
<td>E, D, SC</td>
<td>CHOP</td>
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<td>17 mo, DOD</td>
<td>Arnulf et al, 1998</td>
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<td>22/14/M</td>
<td>14</td>
<td>M</td>
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<td>SC</td>
<td>CHOP</td>
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<td>11 mo, AWD</td>
<td>Arnulf et al, 1998</td>
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<tr>
<td>23/41/M</td>
<td>41</td>
<td>M</td>
<td>Nodules</td>
<td>Extremity</td>
<td>E, D</td>
<td>CHOP</td>
<td>No</td>
<td>8 y, AWD</td>
<td>Arnulf et al, 1998</td>
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</tbody>
</table>

*E indicates epidermotropic; D, dermal; and SC, subcutaneous (extending into the subcutaneous tissue).
†PUVA indicates psoralen–UV-A; RT, radiation therapy; IFN, interferon; CHOP, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone; UCN-01, a 7-hydroxy analogue of staurosporine that is tyrosine kinase inhibitor; BMT, bone marrow transplant; THP-COP, pirarubicin, cyclophosphamide, vincristine, and prednisolone; and Pro-MACE-cytaBOM, prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide-cytarabine, bleomycin, vincristine, and methotrexate.
‡NA indicates not applicable.
§DOD indicates dead of disease; AWD, alive with disease; and CR, complete remission.
The lymphocytic infiltrate of all cases was composed of atypical cells with hyperchromatic and round to slightly irregular nuclei. Prominent nucleoli were noted, especially in biopsy specimens in which larger cells predominated. Scattered mitotic figures were present. In the Revised European-American Lymphoma (REAL) classification, these 3 cases would be best classified as peripheral T-cell lymphoma, unspecified; in the European Organization for Research and Treatment of Cancer (EORTC), they would fall within large cell CTCL, CD30-negative, and pleomorphic. Although some biopsy specimens from patient 3 had subcutaneous involvement, they did not fit the diagnosis of SPTCL in the REAL and the EORTC classifications.

**IMMUNOPHENOTYPE**

Data from immunohistochemical studies are summarized in Table 2. All 3 cases were positive for CD3. Two cases were CD4/CD8 double negative. One case expressed CD8 (Figure 3). All cases lacked natural killer (NK) cell markers, including CD56 and CD57. All cases were negative for all pan–B-cell markers tested (CD19, CD22, CD20, and CD79a). All 3 cases were positive for TCRβ by frozen-section immunohistochemical analysis and negative for TCRαβ (BF1) (Figure 3). All cases exhibited strong expression of TIA-1, perforin, and granzyme B, with granular cytoplasmic expression in most of the tumor cells (Figure 3).

**MOLECULAR STUDIES**

All cases had rearrangement of the TCRγ gene by PCR. A representative polyacrylamide gel of 1 patient with multiple biopsy specimens is shown in Figure 4. Interestingly, patient 2 showed an IgH gene rearrangement in addition to showing rearrangement of the TCRγ gene (data not shown). The tumor cells were negative for EBV RNA transcripts in all 3 patients by in situ hybridization with the EBER1 probe. Adequate tissue RNA was present in all cases tested, as shown by strong in situ hybridization signals with the U6 riboprobe.
COMMENT

γδ T-cell lymphomas are rare. γδ T-cell malignancies have been found among T-cell lymphoblastic lymphoma/leukemia,24,25 hepatosplenic T-cell lymphomas,26 nasal NK/T-cell lymphoma,27 cutaneous mucosa–associated T-cell lymphoma,16 and SPTCL.14,28,29 Hepatosplenic T-cell lymphomas are nearly always of γδ T-cell origin, as opposed to other types of T-cell lymphoma, in which αβ T-cells usually predominate.

The γδ T-cell lymphomas can be related to different stages of T-cell functional maturity (Table 3). γδ T-cell lymphoblastic lymphoma/leukemia represents a neoplastic expansion of precursor γδ T cells. The existence of γδ T-cell lymphomas among lymphoblastic malignancies is not surprising, since rearrangement of the γδ TCR genes is an early event in T-cell differentiation.

Mature γδ T cells exhibit a cytotoxic T-cell phenotype. Therefore, it is not unexpected that mature γδ T-cell lymphomas share an expression of cytotoxic T-cell antigens. There are 2 major pathways by which cytotoxic T cells are able to induce apoptosis: secretion of perforin and granzymes and/or expression of Fas ligand on their surface.30 The neoplastic cells of hepatosplenic T-cell lymphoma are functionally immature γδ T cells, since they express TIA-1 but lack expression of perforin and granzyme B.25 In addition, they fail to induce apoptosis and necrosis, offering additional evidence of their functional immaturity and failure to release cytotoxic proteins. In the current study, the cells of primary γδ CTCL expressed TIA-1, granzyme B, and perforin, and demonstrated both apoptosis and necrosis. These results are in accordance with previous reports and the cytotoxic activity of normal γδ T cells. Mucosal/cutaneous γδ T-cell lymphomas represent a proliferation of functionally mature lymphocytes that express and release cytotoxic proteins, granzyme B, and perforin and that are capable of inducing cellular apoptosis and necrosis.14,16,28

Figure 2. Histologic findings of biopsy specimens: A, Low magnification shows an example of the mycosis fungoides–like pattern. There is psoriasiform epidermal hyperplasia and lymphocytic infiltrate in the dermis. B, High magnification of the biopsy specimen in A shows epidermotropism. There are small aggregates and individual atypical lymphocytes along the epidermal side of the dermal-epidermal junction. C, This biopsy specimen of the dermal pattern shows a lymphocytic infiltrate in the reticular dermis separated from the uninvolved epidermis by a grenz zone. D, This biopsy specimen of the combined pattern shows epidermal, dermal, and subcutaneous involvement.
Twenty-three cases of γδ CTCL have been described in the literature (Table 1), including 15 males and 8 females ranging from 13 to 82 years of age. A combined review of the literature and our cases indicates that 4 patients exhibited only plaques, 12 had nodules and/or tumors, and 7 exhibited plaques, nodules, and/or tumors. All patients had lesions on their extremities, and 11 patients also had lesions distributed over their trunk. Sixteen patients had progressive disease, with 12 individuals dead within 2 years of initial presentation, and all 16 individuals dead within 5 years. The histologic profile showed that 12 patients had epidermotropism, 18 exhibited dermal involvement, and 10 had subcutaneous involvement, usually with features resembling SPTCL. Four cases developed hemophagocytic syndrome, all who had subcutaneous involvement.

Table 2. Immunophenotype and Molecular Findings of 3 Patients With γδ Cutaneous T-Cell Lymphoma*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>CD3</th>
<th>CD4</th>
<th>CD8</th>
<th>CD56</th>
<th>CD30</th>
<th>TIA-1</th>
<th>Perforin</th>
<th>βF1</th>
<th>Granzyme B</th>
<th>TCRδ</th>
<th>TCR PCR</th>
<th>EBV ISH</th>
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<tr>
<td>1</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
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<td>+</td>
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</table>

* TIA-1 indicates T-cell intracellular antigen 1; TCR, T-cell receptor; PCR, polymerase chain reaction; EBV ISH, Epstein-Barr virus in situ hybridization; +, presence of antigen or molecular finding; and −, absence of antigen or molecular finding.

Figure 3. Immunophenotypic findings (immunoperoxidase): This biopsy specimen with prominent epidermotropism shows many CD8+ cells in the epidermis and papillary dermis (A). The neoplastic cells have a cytotoxic phenotype and are positive for T-cell intracellular antigen 1 (B) and granzyme B (C). The neoplastic cells express T-cell receptor δ (D) (also shown at higher power [E]). Higher magnification shows lymphoma cells positive for perforin (F).
Immunohistochemical studies were indicative of a γδ T-cell origin in all cases. Most specimens stained were positive for TCR γ and negative for βF1 by frozen section immunohistochemical analysis, providing direct evidence of γδ T-cell origin. Twenty-one cases were CD4/CD8 double negative, the usual phenotype of γδ T cells. Two cases expressed CD8 (cases 1 and 15), a phenotype present in a minor population of γδ T cells in peripheral lymphoid tissue and in other reported cases of γδ T-cell lymphoma.

All patients in the current series presented with disease initially confined to the skin. A characteristic clinical feature was the presence of tumors or nodules, primarily affecting the extremities. This clinical feature should raise suspicion for the diagnosis of γδ CTCL. Clinically, all our patients had aggressive disease with poor response to therapy. At the time of this report, 2 patients had died of their disease within 4 years and 1 was alive with persistent disease.

In the current report, these 3 cases would be best classified as peripheral T-cell lymphoma, unspecified, according to the REAL Classification.22 We identified 3 histological patterns of involvement in the skin: epidermotropic, dermal, and subcutaneous. Usually more than 1 histological pattern was present in the same patient in different biopsy specimens. Two cases in this study showed an MF-like pattern with a bandlike lymphocytic infiltrate and epidermotropism in at least 1 biopsy specimen. Epidermal infiltration from mild epidermotropism to pagetoid reticulosis-like has been reported previously in some cases of γδ CTCLs.3 Patient 3 presented with dermal nodules that extended into the subcutis, but other biopsy specimens exhibited dermal plaques and epidermotropism. Moreover, the subcutaneous component lacked the rimming of fat spaces, karyorrhexis, and foamy histiocytes typically seen in SPTCL. Therefore, while some cases of SPTCL have been reported to be of γδ origin, this case would not fall within that group.14-16,28 Moreover, the reported cases of γδ SPTCL differ from those of αβ phenotype in that pure subcutaneous involvement is usually not encountered and both dermal and/or epidermal involvement can be seen.15-20

Review of our cases and those previously reported suggests that γδ CTCL with epidermotropism is distinct from MF. In general, the clinical course of γδ CTCLs is more aggressive than classic MF. γδ Cutaneous T-cell lymphoma lacks the convoluted cerebriform lymphocytes present in MF. In addition, γδ CTCL exhibits extension to the subcutis, a feature usually absent in MF. In addition, lymphocytes in MF nearly always express CD4, a surface marker not present in γδ CTCL. Interestingly, γδ CTCLs share many common clinical and pathological features with epidermotropic suppressor/cytotoxic CTCLs,31-34 some of which have an αβ phenotype.32 However, none of our cases showed involvement of the oral cavity, palms, or soles, in contrast to cases described in prior reports.31-33 Whether the activated cytotoxic phenotype contributes to the aggressive clinical behavior remains to be determined. Nevertheless, many different types of lymphoma can express cytotoxic molecules, including anaplastic large cell lymphoma, nasal NK/T-cell lymphoma, and SPTCL.

Primary γδ CTCL can be distinguished from nasal NK/T-cell lymphoma, which involves the skin and subcutaneous tissue as a secondary site of involvement.27 Most cases of nasal NK/T-cell lymphoma fail to show clonal TCR gene rearrangement,27 in contrast to γδ CTCL. While nasal NK/T-cell lymphoma is always EBV positive,35 all our cases of primary γδ CTCL were EBV negative. Clinically, nasal NK/T-cell lymphoma commonly present with palatal or nasal destruction,27 features usually not observed in γδ CTCL.

The role of EBV in the pathogenesis of γδ T-cell lymphomas has been questioned and appears to correlate with the site of involvement.16 In this study, in situ hybridization for EBV RNA was performed in 3 biopsy specimens, but no evidence of EBV was found. Our data and

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**Figure 4.** T-cell receptor-γ gene rearrangement by polymerase chain reaction. Representative gels of multiple biopsy specimens of patient 2 are shown here. The positive band of an appropriate molecular weight for a T-cell receptor-γ gene rearrangement is indicated in lanes Bx 1 and Bx 2 (biopsy 1 [Bx 1]) and biopsy 2 (Bx 2) of patient 2). MW indicates standard molecular weight marker; N-C, negative control samples to which no template was added; C, show the banding patterns of the positive control samples of a CEM cell line; and bp, base pairs.

**Table 3. The Relation of γδ T-Cell Neoplasms to Different Stages of T-Cell Function**

<table>
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<th>Type</th>
<th>TCRγ</th>
<th>TdT</th>
<th>CD8</th>
<th>TIA-1</th>
<th>Perforin</th>
<th>Granzyme B</th>
<th>T-Cell Stage</th>
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<td>γδ T-cell lymphoblastic</td>
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<td>Immature</td>
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<td>lymphoma/leukemia</td>
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<tr>
<td>Hepatosplenic γδ T-cell</td>
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<td>Functionally immature</td>
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<tr>
<td>lymphoma</td>
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<tr>
<td>Cutaneous/mucosal γδ T-cell</td>
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<td></td>
<td></td>
<td>Functionally mature</td>
</tr>
</tbody>
</table>

* TCR indicates T-cell receptor; TdT, terminal deoxynucleotidase; TIA-1, T-cell intracellular antigen 1; +, presence of protein; and −, absence of protein.
previous reports\textsuperscript{26} suggest that EBV does not play a major role in the development of primary \( \gamma \delta \) CTCL.

Patient 2 manifested some novel clinical and molecular features. This individual had an idopathic CD4 deficiency (human immunodeficiency virus type 1 [HIV-1] and HTLV-I) and a history of systemic Mycobacterium avium-intracellulare infection. Recent studies reported that \( \gamma \delta \) T cells participate in the immune response to mycobacterial infections.\textsuperscript{36,37} Chronic antigen exposure has been associated with a dysregulation of the immune response. It is possible that an impaired immune response in association with chronic antigenic stimulation could have favored the proliferation of reactive \( \gamma \delta \) T cells. Indeed, expansion of \( \gamma \delta \) T cells has been found in autoimmune diseases, such as celiac sprue and rheumatoid arthritis.\textsuperscript{38,39} A disturbance of normal immune signals that more mature cells possess. Normally, in mature T and B cells, the production of immunoglobulin T-cell lymphoma.\textsuperscript{16,17} Lineage fidelity at the genotypic level is exceedingly rare in mature lymphoid neoplasms, in contrast to precursor lymphoid malignancies.\textsuperscript{18} The dual rearrangements of the IgH and TCR genes could represent different populations of B and T cells within the same lesion. However, the strong intensity of the rearranged IgH band seen by gel electrophoresis, coupled with the finding that far less than 1% of the cells stained as B cells with CD20, favors a dual genotype in the malignant T-cell population. In immature, precursor lymphoid lesions, such as lymphoblastic lymphomas, it has been postulated that cells lack gene rearrangement termination signals that more mature cells possess. Normally, in mature T and B cells, the production of immunoglobulin or TCR molecules constitutes a stop signal.\textsuperscript{42} Most of the reported bigenotypic cases have been associated with immunodeficiency, most notably HIV infection, suggesting that an underlying immunodeficiency may play a critical role in the development of the disordered differentiation of these dual genotypic lymphomas. Thus, it is of interest that our sole bigenotypic case initially presented with a systemic \( M \) avium-intracellulare infection before the development of the cutaneous lymphoma. However, he was HIV and HTLV-1 negative.

In conclusion, \( \gamma \delta \) CTCL can exhibit diverse histological patterns, often in the same patient, including epidermotropism, dermal and subcutaneous involvement. Our data and reports in the literature suggest that \( \gamma \delta \) CTCLs are EBV-negative clonal lymphomas that express a mature cytotoxic phenotype with frequent necrosis and/or apoptosis. \( \gamma \delta \) CTCL has preferential involvement of the extremities with necrotic tumors and subcutaneous nodules, and an aggressive clinical course. Because of the poor clinical outcome, early diagnosis and aggressive therapy are indicated in these patients.

Accepted for publication February 29, 2000.

We thank Harry Shaeffer, John Crawford, Mary King, and Rick Dryfuss for their excellent photography.

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