Junctional CD8+ Cutaneous Lymphomas With Nonaggressive Clinical Behavior

A CD8+ Variant of Mycosis Fungoides?

Reinhard Dummer, MD; Jivko Kamarashev, MD; Werner Kempf, MD; Andreas C. Haffer, MD; Monika Hess-Schmid, MD; Genter Burg, MD

Objective: To evaluate the clinical and prognostic features in primary cutaneous CD8+ T-cell lymphomas, which are rare and considered to be aggressive cutaneous lymphoproliferative disorders.

Design: Single-center retrospective study.

Setting: Lymphoma clinic (referral center) of a university hospital.

Patients: Three patients presented with CD8+ cutaneous lymphoma characterized by a patchlike pattern and hyperpigmentation.

Results: Histological analysis revealed a CD3+, CD8+ small-cell infiltrate showing a remarkable affinity to the dermoepidermal junction zone. Clonality for the T-cell receptor γ chain was detected by polymerase chain reaction followed by denaturing gradient gel electrophoresis. The clinical presentation lasted several years (6 and 9 years, respectively) before the correct diagnosis was made. Treatment with nontoxic approaches (UV-B and local steroids) was successful. Aggressive clinical behavior was not observed.

Conclusions: Our 3 cases of junctional CD8+ cutaneous T-cell lymphomas were characterized by hyperpigmentation and nonaggressive clinical behavior. This type of lymphoma, which can be considered a CD8+ mycosis fungoides variant, must be distinguished from other types of cutaneous CD8+ lymphomas so that overtreatment can be avoided.

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Most cutaneous T-cell lymphomas (CTCLs) have the phenotype of T-helper memory lymphocytes (CD3+, CD4+, and CD45R0+).1,2 Only a minority of cases present with other phenotypes, such as CD3+, CD4+, CD8+, or CD3+CD83+,4 or with the spectrum of CD56+ lymphomas.5,7 The primary cutaneous lymphomas with the phenotype of cytotoxic/suppressor (CD8+) T cells have been of significant interest in the recent literature.8,12 The detailed analysis of histological and clinical features in several cases has led to the conclusion that CD8+ T-cell lymphomas represent a distinct type of CTCL with an aggressive clinical behavior.4,12

Within the last 3 years, we have seen 3 cases that have fulfilled the criteria of a CD8+ epidermotropic T-cell lymphoma with a remarkable affinity of the CD8+ cells to the dermoepidermal junction zone. The patients in all 3 cases presented with hyperpigmented lesional skin. In 2 cases, the period between the appearance of the first skin symptoms and the diagnosis was extremely long (6 and 9 years, respectively). None of the patients developed progressive disease during the observation period.

RESULTS

The clinical presentations of the patients are summarized in Table 1 and shown in Figure 1. All 3 patients were in good condition and free of general symptoms. The lesions, which were confined to the trunk and the proximal aspect of the extremities, consisted of discrete, reddish brown patches, several centimeters in diameter, with minimal desquamation. The hyperpigmented aspect of the patches was prominent in all 3 patients and was not associated with a particular phenotype (Table 1). In 2 patients, the lesions were asymptomatic. Patient 2 had an 8-year history of severe pruritus and urticaria factitia, both
PATIENTS AND METHODS

PATIENTS AND STAGING PROCEDURES

Our study included 3 patients who were seen in the outpatient lymphoma clinic of the Department of Dermatology, University of Zurich, Zurich, Switzerland. The patients underwent a clinical examination, routine blood cell counts and chemistry studies, chest x-ray radiographic investigation, and ultrasound examination of the abdomen and lymph nodes. Also, serological immunoparameters were investigated, and a fluorescent activated cell sorter was used to analyze circulating peripheral blood lymphocytes.

HISTOPATHOLOGIC EXAMINATION

Each patient underwent a biopsy at first presentation. Skin sections were partly fixed in paraffin and partly snap frozen for molecular biological analysis. Paraffin-embedded material was extensively studied using a panel of monoclonal antibodies (Table 1). Immunoreactivity was visualized using a standard alkaline phosphatase, anti-alkaline phosphatase technique (Dako Diagnostics AG, Zug, Switzerland).11

MOLECULAR BIOLOGICAL ANALYSIS

Snap-frozen material was used to extract DNA. Using previously described primers, the T-cell receptor γ chain locus was amplified, and denaturing gradient electrophoresis was used to detect clonal populations.14-17

EPSTEIN-BARR VIRUS IN SITU HYBRIDIZATION

In situ hybridization for Epstein-Barr virus RNA was performed using a commercial kit and an Epstein-Barr virus–encoded small nuclear RNA probe (Dako Diagnostics AG).

Table 1. Clinical Presentation and Outcome of the 3 Patients

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Skin Type</th>
<th>Time Between First Notice of Skin Lesions and Diagnosis (TNM Stage at Diagnosis)</th>
<th>Differential Diagnosis Before Histological Investigation</th>
<th>Clinical Course During Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/66</td>
<td>III</td>
<td>6 y (IB)</td>
<td>Morphea, chronic eczema</td>
<td>UV-B narrowband therapy resulting in complete remission; relapse: UV narrowband therapy resulting in complete remission; follow-up: 40 mo</td>
</tr>
<tr>
<td>2/M/42</td>
<td>IV</td>
<td>9 y (IB)</td>
<td>Ashy dermatosis, lichen planus, chronic eczema</td>
<td>PUVA + interferon alfa, PUVA + retinoid therapy resulting in partial remission; follow-up: 22 mo</td>
</tr>
<tr>
<td>3/F/45</td>
<td>II</td>
<td>10 mo (IB)</td>
<td>Chronic eczema, lichen sclerosus et atrophicus, morphea</td>
<td>Local corticosteroid therapy resulting in partial remission; follow-up: 14 mo</td>
</tr>
</tbody>
</table>

*PUVA indicates psoralen–UV-A.

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The other patient showed a rearrangement of Vγ 1-8 and Jγy 1-2. Peripheral blood mononuclear cells did not contain clonal populations according to the results of polymerase chain reaction–denaturing gradient gel electrophoresis in cases 1 and 2; however, an identical clonal T-cell rearrangement was detectable in samples of skin and blood in case 3. The results of Epstein-Barr virus RNA in situ hybridization were negative in all 3 cases.

**CLINICAL COURSE**

In all 3 cases, the disease had a benign chronic course and was controlled with nontoxic and conservative therapy, including antihistamines, topical corticosteroids, and UV-B or psoralen–UV-A. The lesions in cases 1 and 2 responded to these mild therapies. The recalcitrant pruritus in case 2 posed a significant therapeutic problem. Different modalities, including a combination of psoralen–UV-A and systemic retinoids, with or without interferon alfa, were used to try to relieve the pruritus, without success. The overall duration of disease has been lengthy in patients 1 (9 years) and 2 (10 years), with no sign of progression or extracutaneous involvement. During the 10 months of follow-up in case 3, the clinical presentation of the disease has improved with local steroid treatment (betamethasone, 3-5 times a week).

**COMMENT**

Cutaneous T-cell lymphomas with a suppressor/cytotoxic (CD8+) phenotype are rare lymphoproliferative disorders. They are not categorized separately by recent lymphoma classifications. We report 3 cases of CD8+ CTCL. All 3 cases were diagnosed as low-grade lymphomas because of the clinical features, the course of the disease, and the findings of histological and molecular biological analysis. All of them showed clonality on polymerase chain reaction–denaturing gradient gel electrophoresis and a junctional homing preference for small-cell CD8+ T lymphocytes. Therefore, all 3 cases fulfilled the criteria for CD8+ epidermotropic cytotoxic T-cell lymphomas as defined in an earlier publication, as well as for CD8+ patch-stage mycosis fungoides.

All 3 patients had more or less extensively hyperpigmented, flat skin lesions, resulting in the clinical differential diagnosis of superficial morphea, lichen sclerosus et atrophicus, or ashy dermatosis. In 2 cases, it was several years before the correct diagnosis was finally made.

In lymphoproliferative disorders, the clinical features might be helpful in making the correct diagnosis. We encourage additional studies to see whether hyperpigmentation is more frequent in CD8+ CTCL, as the bruise-like, contusiforme appearance, which we described previously and which has been observed by other investigators, is a common feature in CD56+ natural killer cell lymphomas.

After diagnosis, our patients clearly responded to mild and nonaggressive treatment, including the use of local steroids, psoralen–UV-A, retinoids, and UV-B pho-

Figure 1. Clinical presentation in cases 1 (A), 2 (B), and 3 (C), characterized by extended hyperpigmented patches.
by any antipruriginous agent. This clinical behavior is in contrast to that described by Berti et al,4 who reported an aggressive course and median survival time of 32 months in 17 cases. In 2 of our cases, the disease course was protracted over 9 and 10 years, respectively, and in all 3 cases, there was no tendency for extracutaneous involvement, which agrees with the chronic subtype reported by Agnarsson et al in 1990.10 All 3 of our cases showed a CD7 loss, similar to Agnarsson and colleagues’ cases. In view of the clinical descriptions in earlier publications, we are convinced that this variant of CD8+ lymphoma might also have been noticed earlier by other groups.

Because of the clinical presentation and the benign behavior in our 3 cases, we think that this type of CD8+ T-cell lymphoma has to be differentiated from other cytotoxic lymphoproliferations, as it appears to have a good prognosis, similar to patch-stage mycosis fungoides. It remains to be determined whether the expression of CD8 by the tumor cells has any prognostic implications at all. However, today, there is a tendency toward aggressive treatment of CD8+ lymphomas, which is not always justified. Therefore, all physicians involved in the care of patients with CTCL have to be aware that CD8+ positivity alone has no clear prognostic value.

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Corresponding author and reprints: Reinhard Dummer, MD, Department of Dermatology, University Hospital, Gloriastrasse 31, CH-8091 Zürich, Switzerland (e-mail: dummer@derm.unizh.ch).

Table 2. Immunohistochemistry Results on Paraffin-Embedded Tissue*

<table>
<thead>
<tr>
<th>Antigen (CD Cluster)</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3 Epidermis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dermis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD4 Epidermis</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dermis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD7 Epidermis</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dermis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD8 Epidermis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dermis</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CD20</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CD21</td>
<td>–</td>
<td>–</td>
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</tr>
<tr>
<td>CD30</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CD45RO Epidermis</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dermis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD56</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CD68</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CD79A</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TIA-1 Epidermis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dermis</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Plus sign indicates more than 80% of cells positive; minus sign, more than 80% of cells negative.
REFERENCES


A symposium will be held on the clinical management of epidermolysis bullosa (EB) in children and adults on November 7 through 8, 2002, at The Institute of Child Health, 30 Guilford St, London WC1N 1EH, England. All individuals and multidisciplinary teams who care for patients with EB are invited. The meeting is sponsored by DEBRA UK. Those interested in participating should contact DEBRA UK, DEBRA House, 13 Wellington Business Park, Dukes Ride, Crowthorne, Berks RG14 6LS, England; phone: 0044-7779-221909; fax 0044-1344-762777 (e-mail: sue.glazier@btinternet.com).