Differentiation and Clonality of Lesional Lymphocytes in Pityriasis Lichenoides Chronica

Sherry Shieh, MD; Debra L. Mikkola, MS; Gary S. Wood, MD

Background: Pityriasis lichenoides chronica (PLC) and pityriasis lichenoides et varioliformis acuta (PLEVA) are benign T-cell diseases that share several overlapping clinicopathologic features, leading many to believe that they exist as a spectrum rather than as single entities. Previous molecular studies have shown that PLEVA is a clonal lymphoproliferative disorder. To further characterize the immunohistologic features of PLC and to determine whether PLC demonstrates clonality, we studied 6 cases of PLC using a frozen section–immunoperoxidase technique and polymerase chain reaction/denaturing gradient gel electrophoresis.

Observations: All 6 cases showed a mild to moderate superficial and deep perivascular infiltrate composed predominantly of CD4+ T cells, admixed with Langerhans cells and macrophages; most were associated with an HLA-DR+ epidermis. Three of 6 cases involved monoclonal T-cell receptor gamma (TCRg) gene rearrangements detected by Vg1-8/Jg1-2 and Vg9/Jg1-2 primers.

Conclusions: Our findings enhance existing data showing that PLC shares many immunohistologic features with PLEVA and indicating that PLC is frequently a clonal T-cell disease. This provides further evidence that PLC and PLEVA are interrelated processes within the larger group of T-cell lymphoproliferative disorders.

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Pityriasis lichenoides chronica (PLC) is a benign, acquired, idiopathic dermatosis characterized by recurrent crops of scaling papules, which may resolve spontaneously over weeks to months or follow a more indolent course.1 Histologically, PLC exhibits a superficial perivascular lymphohistiocytic infiltrate, parakeratosis, vacuolization of basal cells, exocytosis, mild extravasation of erythrocytes, and scattered necrotic keratinocytes.2 Pityriasis lichenoides chronica is considered by many to lie at one end of a clinicopathologic spectrum with pityriasis lichenoides et varioliformis acuta (PLEVA) at the opposite end.1,3-4 The 2 processes are strikingly similar, with the exception that PLEVA demonstrates a more abrupt onset with vesiculopustular lesions, more widespread microscopic epidermal destruction, and a predominance of CD8+ rather than CD4+ T lymphocytes.

On another level, PLC and PLEVA are grouped within the parapsoriasis family of skin disorders, which also includes large-plaque parapsoriasis, small-plaque parapsoriasis, and lymphomatoid papulosis (LyP). These individual disorders display many overlapping features and some may coexist or occur sequentially.5-6 In recent years, all members of the parapsoriasis group, with the exception of PLC, have been reported to demonstrate dominant T-cell receptor clonality.7-13 The close relationship between PLC and PLEVA would predict that PLC is also a T-cell lymphoproliferative disorder. To test this hypothesis and to more completely define the clinical, histologic, and immunologic characteristics of PLC, we analyzed 6 cases of PLC with immunohistochemical techniques and molecular biology assays of gene rearrangement.

REPORT OF CASES

The clinical characteristics of 6 patients with PLC are summarized in Table 1. Age of onset ranged from 33 to 64 years, and there was no significant predilection in regard to sex or race. Most patients presented with generalized, erythematous, scaly papules distributed predominantly on the trunk and extremities. Case 5 included hypopigmented macules, a common presentation in black skin. Some patients were asymptom-
MATERIALS AND METHODS

CASE SELECTION

Six patients with PLC, who were seen in the Department of Dermatology at Case Western Reserve University, Cleveland, Ohio, between 1989 and 1999, were selected by chart and slide review (paraffin sections were stained with hematoxylin-eosin). Eligibility for inclusion in the study was based on a combination of clinical and histologic features typical of PLC and the availability of fresh-frozen tissue for immunohistologic and molecular biology analyses.

IMMUNOHISTOLOGIC METHODS

We used a standard panel of antibodies specific for T cells, T-cell activation and proliferation, Langerhans cells, and macrophages. Acetone-fixed cryostat sections of lesional skin were stained with a 3-stage monoclonal antibody–biotin-avidin immunoperoxidase technique, as described in an earlier report.14

ANALYSIS OF T-CELL RECEPTOR (TCRγ) GENE REARRANGEMENTS

Genomic DNA was obtained either from frozen samples or extracted de novo with a standard phenol-chloroform extraction protocol. Subsequently, a 2-step polymerase chain reaction (PCR) was performed.15 In the first reaction, 2 µg of DNA was hybridized with 5-µmol/L of an oligonucleotide consensus primer for Vγ1-8 or Vγ9 and Jγ1/2 and catalyzed by 0.5 µL of Taq polymerase within a 100-µL buffer system. In the second reaction, 10 µL of DNA product from the first reaction was hybridized with 40 µmol of nested primers per liter to enhance specificity. Finally, the amplified PCR products were separated by denaturing gradient gel electrophoresis (DGGE) on a polyacrylamide gel containing a 30% to 60% urea-formamide gradient, stained with ethidium bromide solution, and interpreted as either monoclonal if 1 or more discrete bands appeared.

IMMUNOGENOTYPING

Given in Table 3 and shown in the Figure are the results of molecular biology analysis of TCRγ gene rearrangements. Cases 2, 4, and 6 demonstrated a polyclonal pattern in PLC lesions. Results of PCR/DGGE with the Vγ1-8/Jγ1/2 primers revealed a rearrangement in case 5. Using the Vγ9/Jγ1/2 primers, a rearranged band appeared in cases 1 and 3. Of note, case 1 had 2 similarly rearranged bands from 2 different biopsy sites of PLC, indicating a common clonal origin.10

RESULTS

IMMUNOHISTOLOGIC CHARACTERISTICS

The results of immunophenotyping are summarized in Table 2 and support previous immunohistologic descriptions of PLC.14 All cases showed a mild to moderate superficial and deep perivascular infiltrate composed predominantly of a CD4+ T-cell infiltrate admixed with Langerhans cells and macrophages. The phenotype of T cells in the epidermis and dermis was similar. All lesional lymphocytes demonstrated greater than 50% expression of CD2, CD3, CD5, and Bcl-2 antigens. Staining for CD25 varied from 0% to 40% and for CD1a, from 10% to 40%. Most keratinocytes were HLA-DR+.

COMMENT

In this study, we evaluated 6 cases of PLC for immunophenotype and genotype using immunohistochemical methods and PCR/DGGE. Our results support existing data showing that PLC shares many clinicopathologic immunohistologic, and clonal characteristics with other benign cutaneous lymphoproliferative disorders, in particular PLEVA.17 Our current findings are fully consistent with the concept that PLC and PLEVA are two ends of the same disease spectrum.

Monoclonal T-cell rearrangements occurred in 3 of our 6 patients with PLC. This contrasts with an earlier study that compared the clonal relationship between 3 cases of PLEVA and 3 cases of PLC using a PCR assay that was unable to detect clonality in PLC.18

Interestingly, in both cases 3 and 6, MF preceded the diagnosis of PLC, supporting the observation that lymphoproliferative disorders often coexist. Although relatively uncommon, the coexistence of PLC and MF has been reported previously.19 The occurrence of this coexistence in 2 of our 6 patients probably reflects (like the diagnosis of breast cancer) referral bias to our cancer-oriented tertiary care center. In addition, PLC in case 3 was followed by LyP. Previous molecular studies showed LyP and early patch/plaque stage MF in the same individuals share a common clonal origin. In this study, however, lesions of PLC and MF displayed multiclonality. For example, in case 3, MF lesions showed rearrangements with Vγ1-8/Jγ1-2, while those of PLC showed rearrangements with Vγ9/Jγ1-2; there was no detectable rearrangement in the LyP lesion. The MF lesions of case 6 showed...
rearrangements with Vγ1-8/Jγ1-2, whereas the PLC lesions were polyclonal.

There is no reason to expect that shared clonality will always be a feature of patients with dual cutaneous lymphoproliferative disorders. For example, sometimes multiple samples from patients with a single disease such as MF do not show the same clonal pattern. The prevalence of dominant clonality in our PLC series was 50% regardless of whether the MF-associated cases 3 and 6 were included. Because even clear-cut MF shows clonality only about 80% of the time owing to technical limitations of the assays we used, a clonality rate of less than 100% was expected.

### Table 1. Clinical Characteristics of 6 Patients With PLC*

<table>
<thead>
<tr>
<th>Case No./Race/Sex</th>
<th>Age at Onset, y</th>
<th>Duration Prior to Study</th>
<th>Clinical Presentation</th>
<th>Other Diagnoses</th>
<th>Clinical Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/W/F</td>
<td>64</td>
<td>2 mo</td>
<td>Generalized, slightly burning, pink, scaly macules and papules and 1- to 2-cm thin plaques that developed after the diagnosis of breast cancer and a course of 5-fluorouracil and tamoxifen</td>
<td>Breast cancer, treated with tamoxifen; posttraumatic stress disorder</td>
<td>No response to topical and oral steroids; complete clearance at 5 mo with methotrexate (15 mg weekly); recent flare with cephalosporin, fluconazole, and tetanus shot</td>
</tr>
<tr>
<td>2/W/F</td>
<td>63</td>
<td>10 y</td>
<td>Few, asymptomatic, scattered, erythematous, slightly scaly papules on lower extremities and buttocks that developed after a course of conjugated estrogens</td>
<td>Breast cancer, status postmastectomy (after PLC); hypertension</td>
<td>Improvement with minocycline (50 mg twice daily); relapsing/remitting eruptions</td>
</tr>
<tr>
<td>3/W/M</td>
<td>35</td>
<td>10 y</td>
<td>Clusters of tender, 2-mm erythematous papules, with some scaling on distal upper and lower extremities that developed 10 y after the onset of mycosis fungoides</td>
<td>Mycosis fungoides stage IA while receiving topical nitrogen mustard; lymphomatoid papulosis (1 y after PLC); acute optic neuropathy; hypertension</td>
<td>No response to tetracycline (500 mg by mouth twice daily); relief with trimcinolone acetonide 0.1% cream; relapsing/remitting eruptions</td>
</tr>
<tr>
<td>4/B/F</td>
<td>37</td>
<td>3 y</td>
<td>Few, scattered, pruritic, 3- to 4-mm violaceous macules and papules on neck, trunk, and extremities</td>
<td>None</td>
<td>No response to isotretinoin; relief with 0.1% trimcinolone acetonide cream twice daily and ammonium lactate; relapsing/remitting eruptions</td>
</tr>
<tr>
<td>5/B/M</td>
<td>39</td>
<td>10 mo</td>
<td>Irregular, asymptomatic, 1- to 2-cm hypopigmented macules (some with crusting) on trunk and extremities</td>
<td>Hypertension</td>
<td>No response to oral steroids; trimcinolone acetonide 0.1% cream twice daily and ammonium lactate; relapsing/remitting eruptions</td>
</tr>
<tr>
<td>6/W/M</td>
<td>45</td>
<td>1 y</td>
<td>Diffuse, erythematous, slightly scaly papules on trunk and extremities that developed 2 y after remission of mycosis fungoides</td>
<td>Mycosis fungoides; dysplastic nevi; basal cell carcinoma</td>
<td>No response to trimcinolone acetonide 0.1% cream twice daily, skin barrier repair lipocream, calcipotriene ointment, and UV-A and UV-B; persistent eruption</td>
</tr>
</tbody>
</table>

*PLC indicates pityriasis lichenoides chronica.

### Table 2. Pityriasis Lichenoides Chronica: Immunophenotype of the Mononuclear Cell Infiltrate*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Pan-T Cell</th>
<th>Majority T Cell</th>
<th>T-Cell Subset</th>
<th>Interleukin 2 Receptor (CD25)</th>
<th>Class II Major Histocompatibility Complex (HLA-DR)</th>
<th>T-Cell Activation (CD38)</th>
<th>Proliferation (Any Cell) (MI-B1)</th>
<th>Antiapoptosis (Bcl-2)</th>
<th>Langerhans Cell (CD1a)</th>
<th>Macrophage (CD11c)</th>
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<tr>
<td>1</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>0/rare</td>
<td>O/rare</td>
<td>0/rare</td>
<td>+++</td>
<td>+</td>
<td>+</td>
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<tr>
<td>2</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>0/rare</td>
<td>O/rare</td>
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<td>+++</td>
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<td>+</td>
<td>0/rare</td>
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<td>0/rare</td>
<td>NT</td>
<td>0/rare</td>
<td>+++</td>
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</tbody>
</table>

*Semiquantitative grading scheme: a triple plus sign indicates ≥50%; a double plus sign, 20%-40%; a single plus sign, ≤10%; 0/rare, none or rare; and NT, not tested.

### Table 3. Pityriasis Lichenoides Chronica: Clonality of TCRγ Gene Rearrangements Detected by PCR/DGGE*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Vγ1-8/Jγ1-2</th>
<th>Vγ9/Jγ1-2</th>
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<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
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<tr>
<td>6</td>
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</table>

*PCR/DGGE indicates polymerase chain reaction/denaturing gradient gel electrophoresis; minus sign, negative findings; and plus sign, positive findings.
The detection of clonality is dependent on several factors including intact gene rearrangements, separate migration of clonal bands from the germline band, sensitivity of primer sets, and sampling error. For example, a false-negative finding results if a gene is rearranged but deleted or if a rearrangement occurs with alleles not detected by the primers used. Using primers targeted to the Vγ1-8, Vγ1-9, and JγP genes may enhance the detection of clonal rearrangements. Also, despite the high sensitivity of PCR/DGGE, sampling earlier or later lesions of PLC could yield differing infiltrate densities and account for differences in clonal detection rates.

The significance of clonality in PLC is not fully understood. Clonality does not seem to correlate with clinical outcome. Many cases of PLC are resolved, and only rare cases have been associated with a malignant lymphoma. Establishing the clonality of PLC allows us to further unify the members of the parapsoriasis group. Specifically, our findings reinforce the idea that PLC and PLEVA form a disease continuum and belong to the larger group of cutaneous T-cell lymphoproliferative disorders.

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REFERENCES


