A Long-Term Clinicopathologic Survey of Patients With Jessner's Lymphocytic Infiltration of the Skin

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Skin biopsies from 6 patients with Jessner's lymphocytic infiltration (JLI) were studied using monoclonal antibodies in peroxidase staining, on some occasions combined with [3H]thymidine incorporation visualized by autoradiography. Ninety-one ± two percent of all inflammatory mononuclear cells in situ were T11-positive T lymphocytes, whereas B lymphocytes were few. Forty-nine ± nine percent of cells were la-positive, suggesting involvement of T cells in the local pathogenetic mechanisms, but interleukin-2 receptor-carrying cells as well as [3H]thymidine-incorporating cells accounted for less than 2% of all inflammatory cells, suggesting that T blasts account for only a small minority. Similarly, PCA-1 plasma cells were few in situ, there was no immunoglobulin or complement deposition at the dermal-epidermal junction and serum antinuclear and anti-DNA antibodies as well as complement levels were normal, and no visceral involvement was revealed during the survey period. According to our findings, JLI of the skin seems to be sufficiently distinctive to be appreciated as an entity. T lymphocytes in JLI do not seem to proliferate in the site of inflammation but are merely accumulated from the circulation. J Invest Dermatol 89:205–208, 1987

Patients and Methods

Patients Six patients with JLI with a longstanding history were enrolled in the study. The clinical and laboratory data of the patients studied are given in Table 1. Clinically the lesions appeared as well-demarcated, peripherally expanding, pink or red smooth papules, plaques, or nodules in the face, neck, arms, chest, or back. Repeated serologic studies showed no antinuclear or anti-DNA antibodies (single-stranded, double-stranded), and the serum complement component C3 and C4 levels were in a normal range. Because the histology of the lesions in DLE, PLE, and JLI may resemble each other, one part of the biopsy specimens was processed for routine H & E staining in order to verify the correct diagnosis of JLI. The routine histology revealed normal epidermis, whereas dense accumulations of uniform small lymphocytes were occupying much of the dermis, extending occasionally into the subcutis. The infiltrates were mostly located in the perivascular or periadnexal areas. Histocyte and plasma cells were also present in some specimens. The densities of the cellular infiltrates of the patients were comparable. All patients showing follicular hyperkeratosis or atrophy were excluded. Only patients with recurrent lesions healing without sequelae were included in the study group. Skin biopsies from the patients were always taken from active lesions. A part of the biopsy specimen was snap-frozen in liquid nitrogen and stored at −70°C until processing. Direct immunofluorescence using a standard technique showed no deposition of immunoglobulin or complement in the clinically involved skin. None of the patients fulfilled the American Rheumatism Association 1982 criteria for SLE [6]. Two patients complained about photosensitivity. However, phototesting with a supraerythemal dose of UV radiation (Philips TL 20W/08 black light tubes) proved normal. The mean follow-up time for the study group at the time for biopsy was 7.6 years (range 2–15 years). During the follow-up period no transformations into lymphoproliferative malignancies were recorded and, in spite of sometimes extensive lymphocytic infiltrates, no germinal centers were observed histopathologically.

Lymphoprep (specific gravity 1.078 g/liter) density gradient
isolation (350 g, 40 min, +22°C) was used to obtain peripheral blood mononuclear cells from heparinized venous blood diluted 1:1 with RPMI 1640 from 4 patients with JLI and from 4 normal healthy controls. The cells were washed, and cytosin preparations (1 × 10^6 cells/slide) were made and air-dried before subsequent immunostaining.

**Immunohistochemistry** Immediately after removal, punch biopsy samples 3–4 mm in diameter were put in RPMI 1640 containing 3 g/glucose, 30 g/mL RPMI, 20 g/mL L-glutamine, 1.5 g/mL sodium bicarbonate, 2% heat-inactivated fetal bovine serum (1:5,000), 1% streptomycin, 1% penicillin, 1% nonessential amino acids, 20 g/mL HEPES buffer, and 20 g/mL trypsin inhibitor for 30 min in a cold (4°C) aqueous solution containing 3 g/100 mL trypsin in trypsin inhibitor. Biopsy samples were put in OCT compound (Lab-Tek Products, Division of Miles Laboratories, Naperville, Illinois) and frozen in liquid nitrogen before being transferred to a cryostat. Cryostat sections (6 μm) were placed on glass slides treated with 3% formaldehyde and air-dried before sub- stantial immunostaining.

**Radiochemical Centre, Amersham, U.K.), incubated for 4 h at +37°C in 5% CO2 in air [7], and then embedded and frozen in OCT compound (Lab-Tek Products, Division of Miles Laboratories, Naperville, Illinois).**

**RESULTS**

The staining and slide controls showed the specificity of the staining, demonstrating that the inhibition of endogenous peroxidase was successful.

Most of the local lymphocyte infiltrates were located around postcapillary venules and consisted mainly of T lymphocytes. T8 cells outnumbered the T4 cells in local lymphocytic infiltrates with T4/T8 ratio of 0.9 ± 0.1. B lymphocytes and plasma cells were few in situ (Fig 1).

Although the proportion of major histocompatibility complex locus II coded la-antigen-positive cells was high in perivascular lymphocytic infiltrates (49 ± 9%) (Fig 1), there were only few (0.5 ± 0.1%) Tac-positive cells carrying interleukin-2 receptor (Fig 2a,b). The proportion of T9-positive cells carrying transferrin receptor as well as 4F2-positive cells carrying glycoprotein 40/80 was slightly higher (Table II). Most of the endothelial cells in the middle of the perivascular infiltrates were also la-positive.

**Table 1. The Clinical and Laboratory Data of the Patients Studied**

<table>
<thead>
<tr>
<th>Pr. No</th>
<th>Age at Time of First Examination (years)</th>
<th>Duration of the Disease (years)</th>
<th>Localization of Lesions</th>
<th>SR (mm/h)</th>
<th>Hb (g/dl)</th>
<th>ANA</th>
<th>α-DNA</th>
<th>C3 (g/l)</th>
<th>C4 (g/l)</th>
<th>IF</th>
<th>Treatment at Time of biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>9</td>
<td>Face, ears, back</td>
<td>139</td>
<td>9</td>
<td>Neg</td>
<td>Neg</td>
<td>0.66</td>
<td>0.23</td>
<td>Neg</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>15</td>
<td>Chest, neck</td>
<td>142</td>
<td>4</td>
<td>ND</td>
<td>ND</td>
<td>0.93</td>
<td>0.31</td>
<td>ND</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>12</td>
<td>Back, arms</td>
<td>126</td>
<td>16</td>
<td>Neg</td>
<td>Neg</td>
<td>ND</td>
<td>ND</td>
<td>Neg</td>
<td>Chloroquine, proguazone</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>3</td>
<td>Neck, back</td>
<td>137</td>
<td>24</td>
<td>Neg</td>
<td>Neg</td>
<td>0.73</td>
<td>0.24</td>
<td>Neg</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>2</td>
<td>Face</td>
<td>153</td>
<td>5</td>
<td>Neg</td>
<td>Neg</td>
<td>0.84</td>
<td>0.21</td>
<td>Neg</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>5</td>
<td>Chest, neck</td>
<td>185</td>
<td>8</td>
<td>Neg</td>
<td>Neg</td>
<td>ND</td>
<td>ND</td>
<td>Neg</td>
<td>None</td>
</tr>
</tbody>
</table>

**Abbreviations:** SR = erythrocyte sedimentation rate, Hb = serum hemoglobin concentration, ANA = antinuclear antibodies, α-DNA = anti-deoxyribonucleic acid antibodies, C3 = serum complement 3 (normal 0.55–1.20), C4 = serum complement 4 (normal 0.20–0.50), IF = immunofluorescence, ND = not done.

**Figure 1.** Histogram of the proportions of positively staining cells in [I] of the skin. Monoclonal antibodies used for staining are indicated on the x-axis.
The relatively low proportion of cells in situ expressing immunoreactive interleukin-2 receptor might have been due to blocking caused by receptor-bound interleukin 2. Because this should push the cells over the G1/S interphase, we studied the proportion of T cells synthesizing DNA in situ. However, only occasional [3H]thymidine-incorporating T blasts were observed in situ (Fig 3), suggesting that the low proportion of T cells carrying interleukin-2 receptor is not an artifact. The double labeling technique also showed that the majority of these T blasts carried the T4 glycoprotein.

**DISCUSSION**

Only occasional PCA-1 plasma cells were observed in JLI of the skin. There were no immunoglobulin or complement deposits at the dermal-epidermal junction either [9,10]. None of our patients during the follow-up developed any systemic symptoms or visceral involvement akin to those observed in SLE. Thus, there is little evidence for active involvement of B cell-mediated humoral immune response in the pathogenesis of JLI of the skin.

Some authors have classified JLI of the skin as a pseudolymphoma consisting exclusively of B lymphocytes [2]. However, according to our findings most of the mononuclear inflammatory cells do not carry markers typical of resting B lymphocytes or plasma cells but display T-lymphocyte markers. None of our patients developed a lymphoproliferative malignancy either. These findings refute the idea of JLI as a B cell-derived prelymphomatous condition.

We have previously reported, using histochemical α-naphthyl acetate esterase (ANAE) staining, that most of the inflammatory cells in JLI belong to the T-cell series [4]. This was confirmed by Willemze et al [3] who used T cell-specific monoclonal antibodies. They further proposed JLI of the skin to be not a B-cell but a T-cell lymphoproliferative disease. Based on histochemical ANAE staining, however, this seems improbable: although resting T lymphocytes display ANAE [11], T blasts do not [12]. Our present results on low interleukin-2 receptor expression as well as the low proportion of DNA-synthesizing T cells in situ further suggest that JLI is not a local T-cell lymphoproliferative disease.

As for the activation of T-cell-mediated cellular response, our findings show a high proportion of Ia (HLA-DR)-positive cells in the lymphocytic infiltrate around postcapillary venules, quite different from that reported by Willemze et al [13], who could not find any Ia-positive cells in JLI. Several previous studies have shown that the local lymphocytes in various disease conditions characterized by mononuclear cell infiltrates are active participants in the local pathogenetic mechanisms based on the relatively high expression of Ia antigen [14]. However, recent studies comparing in vitro and in vivo activated lymphocytes have shown that most of the in vitro activated Ia-positive T lymphocytes are blast cells, whereas most of the in vivo activated T lymphocytes are small lymphocytes [15]. This may also explain our own observation of a high proportion of Ia-positive but a low proportion of Tac-positive and proliferating T cells. As for the role of Ia on T cells, it might be associated with lymphocyte homing receptors [16] responsible for their interaction with the high endothelial cells and thus their accumulation into inflammation sites. This is supported by our finding that most of the endothelial cells in the middle of the inflammatory perivascular infiltrations were also

**Table II.** Comparison of the Mononuclear Cell Phenotypes Between Jessner’s Lymphocytic Infiltration (JLI) and Peripheral Blood (PB) of the Patients (% ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>TLL</th>
<th>T4</th>
<th>T8</th>
<th>M1</th>
<th>B</th>
<th>Ia</th>
<th>Tac</th>
<th>T9</th>
<th>4F2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissues</td>
<td>91 ± 2°</td>
<td>40 ± 3</td>
<td>49 ± 4°</td>
<td>5 ± 1°</td>
<td>5 ± 0.3</td>
<td>49 ± 9°</td>
<td>0.5 ± 0.1</td>
<td>7 ± 2°</td>
<td>10 ± 2°</td>
</tr>
<tr>
<td>PB of the patients</td>
<td>77 ± 2</td>
<td>48 ± 3</td>
<td>29 ± 4</td>
<td>22 ± 2</td>
<td>2 ± 0.4</td>
<td>4 ± 1</td>
<td>0.6 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>PB of the controls</td>
<td>72 ± 4</td>
<td>47 ± 4</td>
<td>25 ± 1</td>
<td>17 ± 3</td>
<td>3 ± 1</td>
<td>3 ± 0.2</td>
<td>0.2 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>2 ± 0.1</td>
</tr>
</tbody>
</table>

°p < 0.01 (Mann-Whitney test); there were no significant differences between the PB of JLI patients and normal healthy controls.
Figure 3. The low proportion of interleukin-2 receptor-carrying lymphocytes might have been due to the blocking of immunoreactive epitopes by receptor-bound interleukin 2. This was refuted by [3H]thymidine incorporation/autoradiography combined with T-cell staining using T1 antibodies in avidin-biotin-peroxidase complex staining; in spite of good penetration of [3H]thymidine (proliferating epidermal basal cells are marked with large arrow), only occasional [3H]thymidine-incorporating T blasts (small arrow) were observed in situ. Original magnification × 400.

Ia-positive. However, the exact relationship of Ia and Hermès-1 (involved in high endothelial venule recognition) expression during different phases of the T-cell cycle is not yet known [16].

Upon activation, during the G1 phase of the cell cycle T lymphocytes acquire interleukin-2 receptor on their surface [17]. In the presence of interleukin 2, a soluble T-cell growth factor, these activated T cells will be further pushed into the S phase of the cell cycle. The number of cells in the S phase of the cell cycle was low based on a double labeling technique combining autoradiography with immunoperoxidase staining. The scarcity of [3H]thymidine incorporating blasts confirms the impression obtained using analysis of interleukin-2 receptor expression. It also suggests that the low interleukin-2 receptor expression observed in situ is not due to blocking of the receptors by receptor-bound interleukin 2.

Our findings suggest that, although the diagnosis of JL of the skin cannot be made on the basis of any single clinical or histopathologic observation, some cases in a long-term follow-up seem to be sufficiently distinctive to be regarded as a separate disease entity. We did not find evidence of activation of the B-cell-mediated humoral arm in this disease, and the local T cells, although Ia-positive, did not display interleukin-2 receptor and, accordingly, only a few DNA-synthesizing blasts were present in situ.

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REFERENCES