The Immunologic and Clinicopathologic Heterogeneity of Cutaneous Lymphomas Other Than Mycosis Fungoides

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Twenty-one cases of non-Hodgkin's lymphoma with cutaneous involvement, other than mycosis fungoides, were evaluated immunologically, histologically, and clinically. Ten patients presented with skin disease alone, seven with concurrent cutaneous and extracutaneous disease, and four with extracutaneous disease only. Twenty of the 21 cases were nonepidermotropic tumors and were equally likely to express B or T phenotypes. None of the cases expressed a true histiocytic phenotype. Almost all cases expressed la and class I HLA determinants. Immunophenotypes were stable regardless of time interval, therapy, or body site sampled in seven of eight patients studied serially. In contrast to mycosis fungoides, the T lymphomas exhibited noncerebriform cytology, tumor Ia expression, lack of mature helper T-cell phenotype, nonepidermotropic histology, a tendency for marrow involvement, and presented as nodules rather than patches or plaques. Since each T lymphoma expressed an abnormal but uniform T-cell phenotype other than mature cytotoxic/suppressor or helper, the neoplastic population could be distinguished from reactive T cells. Reactive elements averaged one-third of the cellular infiltrates and were mainly T cells and macrophages. Langerhans cells were generally normal in number and distribution. Several histopathologic subtypes were identified with diffuse large cell lymphomas, including immunoblastic lymphomas, comprising 71% of cases (15/21). Prediction of the immunophenotype based on cytologic criteria was correct in 67% of cases (14/21). All errors occurred among the 13 high-grade lymphomas. Survival data were consistent with those of prior studies that have indicated that clinical course is dependent on stage and histologic subtype. Non-Hodgkin's cutaneous lymphomas constitute an immunologically, histologically, and clinically heterogeneous group of neoplasms.

ALTHOUGH PRIOR WORK has extensively documented the T-cell nature of mycosis fungoides and its leukemic variant, Sézary's syndrome, there are few immunologic or clinicopathologic studies of other cutaneous lymphomas. Moreover, in the few available studies, it is difficult to compare conclusions because of variations in case selection criteria, histopathologic classification, extent of staging investigations, therapy, and immunologic phenotyping techniques. Available data does, however, indicate that among patients presenting with cutaneous non-Hodgkin's lymphoma, the most common histopathologic subtype is diffuse large cell, including immunoblastic, lymphoma. Immunologic marker studies have disclosed both T- and B-cell cases. In addition, it appears that patients with low-grade histopathologic subtypes of lymphoma and with disease limited to the skin at diagnosis have a significantly better freedom from relapse at 5 yr compared to patients presenting with high-grade lymphomas and extracutaneous involvement.

Patients with cutaneous involvement by non-Hodgkin's lymphomas, other than mycosis fungoides, can be divided into three groups: those presenting with cutaneous disease alone, those presenting with concurrent cutaneous and extracutaneous disease, and those presenting with extracutaneous disease who subsequently develop skin involvement. In the current investigation, we focus on immunohistologic and clinicopathologic studies of each of these types of cutaneous lymphoma and document their immunologic, histologic, and clinic heterogeneity.

MATERIALS AND METHODS

Histopathologic Evaluation

A consecutive series was compiled of patients with cutaneous involvement by lymphoma, without leukemic involvement at presentation, who had tumor biopsies accessioned in the Laboratory of Tissue Immunodiagnosis at Stanford University. Representative paraffin sections from each biopsy, corresponding to the tissues studied by immunohistologic means, were reviewed independently by one of the authors (J.S.B.). Classification was performed according to the working formulation of non-Hodgkin's lymphomas and the modified Rappaport classification. In addition, an attempt was made to predict the immunophenotype of each case by employing the morphological criteria of Lukes and Collins. Classification was performed without knowledge of the original histologic diagnosis or the immunologic phenotype. Additional relevant extracutaneous biopsies were also reviewed. Hematoxylin and eosin stains were examined for each case, as well as special stains in selected cases, including periodic acid-Schiff (PAS), reticulin, methyl green pyronin (MGP), and naphthol AS-D chloroacetate esterase (NASDCA).

Immunohistologic Methods

Representative portions of fresh surgical biopsies received in cold normal saline were snap-frozen, cryostat-sectioned, and briefly acetone-fixed as previously described. The specificity of the murine hybridoma monoclonal anti-human antibodies employed in this study are summarized in Table 1. In situ immunologic phenotyping was performed with a three-stage immunoperoxidase technique employing unconjugated monoclonal antibody as the first
stage, followed by biotinylated F(ab')2, fragments of purified goat anti-mouse IgG (heavy and light chains) (Tago, Inc., Burlingame, CA), followed by avidin-horseradish peroxidase (Vector Laboratories, Inc. Burlingame, CA). In all cases, immunoglobulin phenotyping was performed with monoclonal antibodies directed against kappa, lambda, and mu. B-cell cases were further studied with monoclonal antibodies directed against gamma and delta and/or with goat anti-human whole antisera directed against IgG, IgD, and IgA. These antisera were detected with a horseradish peroxidase conjugate of swine anti-goat immunoglobulin (Tago, Inc., Burlingame, CA). In all cases, immunoglobulin phenotyping was performed with monoclonal antibodies directed against kappa, lambda, and mu. B-cell cases were further studied with monoclonal antibodies directed against gamma and delta and/or with goat anti-human whole antisera directed against IgG, IgD, and IgA. These antisera were detected with a horseradish peroxidase conjugate of swine anti-goat immunoglobulin (Tago, Inc.). All cases were tested for reactivity with 63D3 (anti-monocyte/macrophage). Cases 9, 11, 15, 19, and 20 were also tested for reactivity with 61D3 (anti-monocyte/macrophage). Reagent titers and methodology were identical to those previously described. Controls included cross-comparisons between the staining patterns of first-stage reagents of similar isotype, staining with one or more stages deleted, the substitution of first-stage reagents with others devoid of specificity for the target antigens, and staining of normal lymphoid tissues compared to staining of lymphomatous tissues. The criteria for assessing immunophenotype were straightforward, since virtually all tumor cells within a biopsy were either reactive or unreactive with a particular antibody.

Clinical Evaluation

Clinical evaluation included history and physical examination, hemogram, and chest x-ray in all patients. Lymphangiography and/or computerized abdominal tomography was performed in 19 of 21 patients and percutaneous bone marrow biopsies were obtained in 20 patients. Staging laparotomies were performed in two patients. Additional studies included cerebrospinal fluid analysis in three patients and technetium bone scans in two patients. The patients were staged in general accordance with the Ann Arbor system.

RESULTS

Clinical Features at Presentation

The 21 patients, 9 females and 12 males, ranged in age from 4 to 74 yr. None had evidence of leukemic involvement. Based on the presence of cutaneous and/or extracutaneous involvement at the time of initial evaluation, the patients were retrospectively placed into three groups: primary cutaneous lymphoma (10 patients), concurrent cutaneous and extracutaneous lymphoma (7 patients), and secondary cutaneous lymphoma (4 patients) (Table 2). All patients were asymptomatic at presentation. Skin lesions were most commonly red to violaceous nodules. No anatomic site was predominantly involved. Four of ten patients with primary cutaneous lymphoma had skin lesions in multiple sites.

Five of seven patients presenting with concurrent cutaneous and extracutaneous lymphoma had generalized dermal involvement. Patient 12 had mediastinal and bone marrow disease. All patients in this group had peripheral lymphadenopathy, except patient 13, who had central nervous system and testicular involvement. Patient 15 was in the second trimester of pregnancy when she developed left axillary adenopathy and involvement of the axillary skin. Patient 17 developed multiple subcutaneous nodules, pulmonary nodules, and extensive adenopathy while receiving cyclosporine and prednisone to prevent cardiac transplant rejection. Of the four patients who developed secondary cutaneous involvement, patient 18 originally presented with lymphoma limited to the breast and patient 20 with a nasopharyngeal mass. The other two patients had advanced disease at diagnosis.

Histopathology

Fifteen of the 21 cases (71%) were classified as diffuse large cell ("histiocytic") lymphoma (Table 2).
Table 2. Clinical, Histopathologic, and Immunologic Features of 21 Patients With Cutaneous Lymphoma

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at Diagnosis</th>
<th>Primary Site(s)</th>
<th>Histology</th>
<th>Immuno-phenotype:</th>
<th>Stage</th>
<th>Skin Site(s) at Presentation</th>
<th>Primary Therapy*</th>
<th>Site(s) of First Relapse</th>
<th>Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>4/ F</td>
<td>Marrow†</td>
<td>LB</td>
<td>B(T)</td>
<td>IE</td>
<td>Scalp</td>
<td>CT</td>
<td>Marrow</td>
<td>D⁺ 24</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>42/ F</td>
<td>Eyelid</td>
<td>LC, (DHL)</td>
<td>B(B)</td>
<td>IE</td>
<td>Eyelid</td>
<td>XRT</td>
<td>—</td>
<td>A⁰ 65</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>39/ F</td>
<td>Subcutis</td>
<td>LC, (DHL)</td>
<td>B(B)</td>
<td>IE</td>
<td>Thigh</td>
<td>XRT</td>
<td>Subcutis</td>
<td>A⁺ 47</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>16/ F</td>
<td>Skin</td>
<td>IB, mln (DHL)</td>
<td>T(T)</td>
<td>IE</td>
<td>Thigh</td>
<td>XRT</td>
<td>Skin, marrow</td>
<td>A⁺ 35</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>71/M</td>
<td>Skin†</td>
<td>IB, mln (DHL)</td>
<td>T(T)</td>
<td>IE</td>
<td>Lower leg</td>
<td>XRT</td>
<td>Skin</td>
<td>D⁺ 25</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>57/M</td>
<td>Skin†</td>
<td>IB, pc (DHL)</td>
<td>T(B)</td>
<td>IE</td>
<td>Thorax</td>
<td>S</td>
<td>Skin</td>
<td>A⁰ 59</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>68/M</td>
<td>Skin†</td>
<td>IB, cc (DHL)</td>
<td>T(B)</td>
<td>IV</td>
<td>Face, arms, thorax</td>
<td>CT</td>
<td>(Progression) D⁺ 23</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>58/M</td>
<td>Skin†</td>
<td>IB, pc (DHL)</td>
<td>T(B)</td>
<td>IV</td>
<td>Neck, thigh</td>
<td>XRT</td>
<td>Skin</td>
<td>A⁰ 71</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>38/M</td>
<td>Skin†</td>
<td>SNC, (DUL)</td>
<td>T(B)</td>
<td>IV</td>
<td>Leg, arms, thorax</td>
<td>CT</td>
<td>(On therapy) A⁺ 17</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>63/M</td>
<td>Skin†</td>
<td>SL, pc (DLWD)</td>
<td>T(B)</td>
<td>IV</td>
<td>Face, ears</td>
<td>CT</td>
<td>(On therapy) A⁺ 15</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>17/F</td>
<td>Skin†</td>
<td>LB</td>
<td>T(T)</td>
<td>IV</td>
<td>Arms, buttock, breast</td>
<td>CT</td>
<td>(Progression) D⁺ 13</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>34/M</td>
<td>Skin†</td>
<td>LB</td>
<td>T(T)</td>
<td>IV</td>
<td>Thorax</td>
<td>CT</td>
<td>—</td>
<td>A⁰ 12</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>50/M</td>
<td>Skin†</td>
<td>LC, (DHL)</td>
<td>B(T)</td>
<td>IV</td>
<td>Abdomen, thigh</td>
<td>CT</td>
<td>Skin</td>
<td>D⁺ 48</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>27/M</td>
<td>Skin†</td>
<td>LC, (DHL)</td>
<td>B(B)</td>
<td>IV</td>
<td>Thorax, scalp</td>
<td>CT</td>
<td>—</td>
<td>A⁰ 17</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>27/F</td>
<td>Skin†, **</td>
<td>LC, (DHL)</td>
<td>N</td>
<td>IIE</td>
<td>Axilla</td>
<td>XRT</td>
<td>(Progression) A⁺ 9</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>60/M</td>
<td>Skin node</td>
<td>IB, pm (DHL)</td>
<td>T(T)</td>
<td>IV</td>
<td>Face, abdomen</td>
<td>CT</td>
<td>—</td>
<td>A⁺ 27</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>40/M</td>
<td>Node†</td>
<td>IB, pm (DHL)</td>
<td>B(T)</td>
<td>IV</td>
<td>Multiple</td>
<td>A</td>
<td>(Progression) D⁺ 1</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>74/F</td>
<td>Skin†</td>
<td>LC, (DHL)</td>
<td>B(B)</td>
<td>IE</td>
<td>—</td>
<td>XRT</td>
<td>Multiple</td>
<td>D⁺ 15</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>58/F</td>
<td>Skin†</td>
<td>IB, pm (DHL)</td>
<td>N(T)</td>
<td>IE</td>
<td>—</td>
<td>CT</td>
<td>Skin</td>
<td>D⁺ 28</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>58/F</td>
<td>Nasal sinus</td>
<td>IB, mln (DHL)</td>
<td>T(T)</td>
<td>IE</td>
<td>—</td>
<td>XRT</td>
<td>Skin</td>
<td>D⁺ 16</td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>55/M</td>
<td>Node†, **</td>
<td>M (DML)</td>
<td>B(B)</td>
<td>IV</td>
<td>—</td>
<td>IFN</td>
<td>Nodes</td>
<td>A⁰ 65</td>
</tr>
</tbody>
</table>

*CT, chemotherapy (usually multiagent as indicated by tumor histologic subtype); XRT, radiation therapy (usually local orthovoltage irradiation); S, surgery; A, acyclovir; IFN, interferon.
†Working formulation with corresponding modified Rappaport classification in parentheses. LB, lymphoblastic; LC, large cell cleaved and noncleaved; DHL, diffuse "histiocytic" lymphoma; IB, large cell immunoblastic; mln, multilobated nuclei; pc, plasmacytoid; cc, clear cell; SNC, small noncleaved cell non-Burkitt's; DUL, diffuse undifferentiated lymphoma; SL, small lymphocytic; DLWD, diffuse well differentiated lymphoma; pm, polymorphous; M, mixed small cleaved and large cell; DML, diffuse mixed lymphocytic and "histiocytic" lymphoma.
‡All patients were asymptomatic when staged.
§D⁺, dead with disease; A⁰, alive without disease; A⁺, alive with disease.
§ Working formulation with corresponding modified Rappaport classification in parentheses. LB, lymphoblastic; LC, large cell cleaved and noncleaved; DHL, diffuse "histiocytic" lymphoma; IB, large cell immunoblastic; mln, multilobated nuclei; pc, plasmacytoid; cc, clear cell; SNC, small noncleaved cell non-Burkitt's; DUL, diffuse undifferentiated lymphoma; SL, small lymphocytic; DLWD, diffuse well differentiated lymphoma; pm, polymorphous; M, mixed small cleaved and large cell; DML, diffuse mixed lymphocytic and "histiocytic" lymphoma.
‖All patients were asymptomatic when staged.
§Prior therapy involving site biopsied identical to that listed in "primary therapy" column.
**Prior chemotherapy.
††Prior antidiotype monoclonal antibody therapy; N, non-T/non-B.

The remaining cases represented a variety of histopathologic types and included small (well differentiated) lymphocytic, diffuse mixed small cleaved, and large cell, lymphoblastic, and small noncleaved (undifferentiated) lymphoma. A follicular pattern was not observed in any skin biopsy.

The most common pattern of cutaneous involvement by lymphoma consisted of patchy, periadnexal infiltrates in the superficial dermis with coalescence of the lymphomatous aggregates in the deep dermis. The diagnostic areas of several cases exhibiting this pattern were observed only in the deep portions of the biopsy; a polymorphous cell population was encountered in the more superficial aspects of the dermis, and these areas were not diagnostic of lymphoma. In four cases, the lymphomas massively infiltrated the skin, obliterating the adnexae, while in three other cases, the lymphomas were confined to the periadnexal regions of the dermis. One additional lymphoma was observed only in the deep dermis and underlying subcutaneous tissues.
Biopsies of two cases were too superficial to establish a precise histologic pattern. Only in cases 9 and 15 was there an absence of a definite Grenz zone. Case 9 also exhibited focal epidermotropism.

**Immunohistopathology**

Thirty-one biopsies from 21 patients were studied with frozen section immunohistologic techniques. Approximately half of the biopsies were obtained prior to therapy, as detailed in Table 2. Regardless of tumor immunophenotype or histologic subtype, the neoplastic component averaged about 66%-75% of the total cellular infiltrate. Biopsies obtained after initiation of therapy generally contained fewer tumor cells than pretreatment biopsies.

The tumor immunophenotypes are presented in Table 3. Nine patients had lymphomas expressing T-cell phenotypes. Eight different phenotypes were identified. While most cases expressed class I HLA, Ia, and L3B12 antigens, there was marked heterogeneity in the expression of T-cell differentiation antigens. Only case 16 expressed a phenotype recognized on a normal T-cell subset; however, even this helper T-cell phenotype was atypical in that Leu-1 and Leu-5 were very weakly expressed. No single T-cell surface antigen was present in every case, although Leu-3a was the most common (6 of 9 cases). In case 8, serial biopsies revealed two distinct phenotypes—initially Leu-2a /4 /5 with weak Leu-1 expression (skin), and 2.5 yr later, Leu-3a /4 /5 (skin and lymph node). In the other 7 cases in which multiple biopsies were studied, the phenotype was uniform.

Ten patients had lymphomas expressing B-cell phenotypes. The neoplastic nature of the tumor cells was deduced from light-chain restriction, and in case 21, from antiidiotypic staining. All 9 cases tested expressed B1. Eight of 10 cases expressed a single light chain and one or more heavy chains. Case 1, a convoluted lymphoblastic lymphoma, expressed the Ia /CALLA /mu /kappa /lambda phenotype characteristic of pre-B-cells. Case 17, an immunoblastic lymphoma, expressed Ia, CALLA, and B1 without immunoglobulin or T-cell antigens and was interpreted as a lesion of early B lineage. Case 18, a large cell lymphoma, weakly expressed Leu-1 in addition to immunoglobulin.

Two patients had lymphomas expressing a non-T/non-B phenotype. While expressing HLA, Ia and L3B12, these tumor cells were negative for T- and B-cell differentiation antigens, immunoglobulin, and CALLA. None of the lymphomas examined stained with 63D3 or 61D3, antibodies that define cells of monocyte/macrophage lineage.

Although highly variable in number, non-neoplastic elements averaged about one-third of the total cellular infiltrate and were composed predominantly of T cells and macrophages. T cells were of both helper and cytotoxic/suppressor phenotypes, generally in a ratio

| Table 3. Immunologic Phenotypes of 21 Cutaneous Lymphomas* |
|-----------------|-----------------|-----------------|-----------------|
| Patients        | Leu-1-7, 4H9    | HLA, Ia, L3B12  | Ig, B1†         | J5, 63D3‡       |
| T Cell (9)      |                 |                 |                 |                 |
| 16              | 1, 3, 4, 5      | +               | B1              |                 |
| 5               | 1, 4            | HLA             |                 |                 |
| 8               | 1, 2, 4, 5/3, 5 | +               |                 |                 |
| 6               | 3, 5            | +               |                 |                 |
| 4               | 3, 4H9          | +               |                 |                 |
| 9, 11           | 3               | +               |                 |                 |
| 12              | 4, 4H9          | L3B12           | B1              | J5             |
| 20              | 5, 4H9          | +               |                 |                 |
| B Cell (10)     |                 |                 |                 |                 |
| 17              | —               | +               | B1              |                 |
| 1§              | —               | +               | Mu              | J5             |
| 7, 10, 13       |                 | +               | Mu, kappa, B1   |                 |
| 3, 21           |                 | +               | Mu, lambda, B1  |                 |
| 18              | Leu-1           | +               | Mu, lambda, B1  |                 |
| 2               |                 | +               | Mu, gamma, kappa, B1 |         |
| 14              |                 | +               | Mu, alpha, kappa, B1 |     |
| Non-T/non-B (2) |                 |                 |                 |                 |
| 15, 19          | —               | +               |                 |                 |

*Virtually all tumor cells within a biopsy were either reactive (+) or unreactive (—) with each monoclonal antibody.
†All cases screened for B1, kappa, lambda, and mu. B cases subsequently screened for delta, gamma, and alpha.
‡Cases 9, 11, 15, 19, and 20 also 61D3 .
§Leu-6, 7. HLA, B1 and 63D3 not done. Ig data courtesy of M. Link et al. 34
||Leu-7 not done.
of 3:1. Since Leu-7+ cells were rare, natural killer cells were not a significant component of the host response. Eosinophils were usually sparse. B cells and plasma cells were absent or very rare. Ia+/T6+ Langerhans cells were generally normal or mildly increased in number within the epidermis and absent or rare within the dermis. Focal or diffuse epidermal intercellular staining for Ia, such as can be seen in mycosis fungoides, lichen planus, and lupus erythematosus, was only observed in 4 of 14 cases (8, 15, 18, and 20) and was associated with the greatest increase in epidermal Langerhans cells.

**Predictability of Immunophenotype Based on Morphology**

The predictability of the immunophenotype employing cytologic criteria was correct in 14 of 21 (67%) of our cases (Table 2). The highest accuracy was encountered among the low and intermediate grade lymphomas, including the large follicular center cell cases. All seven of these cases forecast to represent B-cell lymphoma expressed B-cell phenotypes. In contrast, assessment of the immunophenotype by morphology was accurate in only 6 of 13 high-grade lymphomas (46%). Immunoblastic, lymphoblastic, and small noncleaved cell lymphomas comprised this group. Inaccuracy was most noticeable among the large cell, immunoblastic lymphomas in which the predictions were in error in 5 of 9 cases. An exception to the unpredictability of the immunophenotype among the large cell immunoblastic lymphomas was encountered in three cases with large multilobated nuclei similar to those previously described. The T-cell immunophenotype was correctly forecast. Other errors encountered among the high-grade lymphomas included one of three lymphoblastic lymphoma cases proven to be pre-B-cell in phenotype, and the single case of small noncleaved (undifferentiated) lymphoma, which was the only epidermotropic tumor in our series and expressed a T-cell phenotype (Fig. 1). No specific histologic pattern of nonepidermotropic cutaneous lymphoma correlated with a specific immunophenotype.

**Clinical Course**

All patients, except 4 and 9, were treated at Stanford. Initial therapy is summarized in Table 2. Patient 6 was treated with total body electron beam irradiation. Patients 11 and 12 with lymphoblastic lymphoma received intensive chemotherapy with central nervous system prophylaxis. Leukemic involvement developed in patient 1 at initial relapse and preterminally in patients 4 and 11. Circulating tumor cells were not immunophenotyped.

Seven of 10 patients with primary cutaneous lymphoma are alive, 3 in complete remission, with a median survival of 25 mo. The predominant site of initial relapse or progression was cutaneous. The marrow was involved at initial relapse in patients 1 and 4 and at subsequent relapse in patient 5. The primary large cell lymphoma subgroup, including immunoblastic lymphoma, had a relatively favorable course. Median survival was 47 mo, with patients 2, 6, and 8 in complete remission at 65, 59, and 71 mo respectively, the latter two after salvage combination chemotherapy for cutaneous relapse.

Four of 7 patients presenting with concurrent cutaneous and extracutaneous lymphoma are alive, 3 in complete remission. The median survival of this group was 13 mo. The skin was a major site of progression and relapse. Patient 11 had progressive skin disease with subsequent marrow involvement. Only 1 of 4 patients with secondary cutaneous lymphoma (patient 21) is alive at current follow-up. He is in complete remission 18 mo following treatment with antidiotype monoclonal antibody. There was no significant correlation between immunophenotype and clinical course within any of the 3 patient groups.

**DISCUSSION**

The data indicate that non-Hodgkin's cutaneous lymphomas are immunologically, histologically, and clinically heterogeneous. Correlations among histology, immunologic phenotype, and clinical presentation are given in Table 4. The morphological characteristics of the lymphomas in this study were similar to those previously reported. Diffuse large cell lymphomas, including immunoblastic lymphomas, comprised the majority of our cases (71%). T, B, and non-T/non-B phenotypes were identified. Primary cutaneous lymphomas were equally likely to express T or B phenotypes.

Prior studies of cutaneous lymphoma have indicated that clinical course is dependent on histologic subtype and stage. Table 2 shows trends in survival that are consistent with this view. The patients presenting with cutaneous lymphoblastic lymphoma had clinical features in common with other lymphoblastic lymphoma patients. One also presented with mediastinal and marrow disease, while the others developed subsequent marrow involvement. Median survival was 24 mo. The patients with primary cutaneous large cell lymphoma, including immunoblastic lymphoma, had a relatively favorable median survival (47 mo) compared to that of the large cell lymphoma subgroup presenting with concurrent cutaneous and extracutaneous involvement (17 mo). Similarly, among the 17 patients presenting with cutaneous lymphoma, the
immunoblastic (high-grade) large cell lymphoma subgroup showed poorer survival (median 27 mo) than did the nonimmunoblastic (intermediate grade) large cell lymphoma subgroup (median 47 mo).

Regardless of phenotype, the cutaneous lymphomas studied exhibited certain common immunologic features (Table 3). With one exception, all lymphomas were class I HLA\(^+\). This contrasts with one study of three diffuse histiocytic lymphomas that found them to be HLA\(^-\).\(^3\) Except for two T lymphomas, all cases were Ia\(^+\). This contrasts with mycosis fungoides, which generally expresses an Ia\(^+\) helper T phenotype.\(^5\) In the eight cases in which more than one biopsy was studied, the tumor phenotype remained
constant irrespective of time interval, therapy, or body site sampled, except in patient 8 as described above.

Since no single T-cell differentiation antigen, including Leu-5 (SRBC receptor), was expressed by all T tumors (Table 3), a panel of anti-T monoclonals is necessary for accurate recognition of T-lineage differentiation. Mature T-cell phenotypes, including the Ia^a, often strongly Leu-L helper T phenotype characteristic of mycosis fungoides, were not expressed by the T lymphomas. Instead, as shown in Table 3, the T lymphomas expressed uniform but unusual phenotypes that differed from those of reactive T cells of Leu-1^+ /2^/4^/5^ cytotoxic/suppressor phenotype or Leu-1^+ /3^/4^/5^ helper phenotype. These reactive cells were readily distinguished from the neoplastic cells (Fig. 1D). Thus, although there is currently no uniform immunologic marker of T-cell tumor clonality analogous to the immunoglobulin light chain or idiotype restriction of B lymphomas, the homogeneous expression of atypical phenotypes by many T lymphomas affords an indirect way of identifying the neoplastic T-cell population.

As calculated from Table 2, the overall predictability of the immunophenotype employing morphological criteria was 67%. Inaccuracies were due to the poorer correlation between actual and predicted phenotypes among the high-grade lymphomas (46%). A prediction accuracy of 61% was recently reported for 29 cases of diffuse aggressive non-Hodgkin's lymphoma.39 While several prior studies,5,7,10-13 and data from patient 9 indicate that epidermotropic lymphomas are characteristically T-cell lesions, the remaining nonepidermotropic lymphomas in this study were equally likely to express B or T phenotypes (Tables 2-4). It is evident that, while trends may exist in the association of a particular lymphoma histology with a particular phenotype,22,23 morphology cannot reliably be employed to predict phenotype, especially among the high-grade lymphomas.9 Since none of the cases expressed a true histiocytic phenotype, the term “large cell lymphoma” is preferable to “histiocytic lymphoma” in describing cutaneous lymphomas comprised of large cells.

The high proportion of reactive T cells and macrophages in several biopsies implies that morphology alone may not always be adequate for distinguishing lymphoma cells from inflammatory elements. For example, the scalp biopsy from patient 21 was interpreted as extensive dermal involvement by lymphoma (diffuse mixed small cleaved and large cell type), when in actuality less than one-fourth of the cells reacted with antidiotype antibody. Larger cells tended to stain as tumor or macrophages and smaller cells as T cells. Nuclear irregularity is a well-known feature of T cells in certain inflammatory disorders, such as dermato-
We have observed other cases, including large cell lymphoma patients 13 and 20 in this study, wherein the lymphoma cells in some biopsies comprised only a minority of the total cellular infiltrate. These findings imply that some tumors diagnosed as mixed lymphomas may actually represent large cell lymphomas with an exuberant host response. They also indicate that the presence of a heterogeneous cellular infiltrate has limited value as a criterion favoring the diagnosis of cutaneous pseudolymphoma over lymphoma.

A comparison of this study to similar studies of mycosis fungoides reveals considerable heterogeneity among the cutaneous lymphomas, much of which is maintained within the T-cell lymphoma subset (Table 5). The current T-cell cases presented as skin nodules rather than patches or plaques. Four of them involved the marrow. None of them expressed a mature helper T-cell phenotype, and most were Ia-. None of these features is typical of mycosis fungoides. While the term “cutaneous T-cell lymphoma” (CTCL) has often been used almost synonymously for mycosis fungoides and its leukemic variant, Sézary’s syndrome, this study demonstrates the immunologic, histologic, and clinical heterogeneity that exists among cutaneous lymphomas with T-cell phenotypes.

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The immunologic and clinicopathologic heterogeneity of cutaneous lymphomas other than mycosis fungoides

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