# *Immunohistochemical Studies Using Monoclonal Antibodies on Lymph Nodes From Patients With Mycosis Fungoides and Sézary's Syndrome*

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**Using an indirect immunoperoxidase technique and a panel of monoclonal antibodies with well-defined specificities, the authors studied the distribution of lymphoid and nonlymphoid cells in the T-cell areas of both involved and uninvolved lymph nodes from patients with mycosis fungoides (MF) and Sézary's syndrome (SS) and dermatopathic lymph nodes from patients with generalized benign skin disease. The distribution of the different T-cell subsets, HLA-DR$^+$ interdigitating cells and OKT6$^+$ Langerhans cells, in the paracortical areas of MF lymph nodes showing features of dermatopathic lymphadenopathy with early involvement, as assessed after conventional histologic examination, was similar to that of dermatopathic MF lymph nodes without early involvement and lymph nodes from patients with generalized benign skin disease, indicating that these studies do not provide additional criteria for the early diagnosis of MF involvement. MF lymph nodes showing partial or complete obliteration of the normal architecture tended to have lower numbers of HLA-DR$^+$ interdigitating cells and OKT6$^+$ Langerhans cells, but showed increased numbers of blast cells, part of which had lost their mature helper-T-cell phenotype. These differences between the early and advanced stages of lymph node involvement by MF were analogous to those observed in the different stages of cutaneous involvement, as described previously. The lymph nodes from patients with SS were diffusely infiltrated by neoplastic T cells that had retained their mature helper-T-cell phenotype (Leu-1$^+$, 3a$^+$, 4$^+$), contained very low numbers of Leu-2$^+$ T-cells and relatively few HLA-DR$^+$ interdigitating cells and OKT6$^+$ Langerhans cells. These different staining patterns in MF and SS lymph nodes may reflect different pathogenetic mechanisms. (Am J Pathol 1985, 120:46–54)**

MYCOSIS FUNGOIDES (MF) and Sézary's syndrome (SS) are related T-cell lymphomas that clinically originate in the skin. The study of these lymphomas has been facilitated by the development of monoclonal antibodies reactive with distinctive T-cell differentiation antigens. Application of these monoclonal antibodies on tissue sections or cell suspensions has demonstrated that the neoplastic cells in these lymphomas express the phenotype of mature helper T-cells.[1–3] With the use of immunoperoxidase or immunofluorescence techniques on frozen *skin* sections, the distribution of lymphoid and nonlymphoid cells in the different clinical stages of MF and SS has been studied extensively.[4,5] In contrast, immunologic studies on *lymph nodes* from patients with MF and SS are few and have only been performed on cell suspension.[1,6] Although studies on cell suspensions may provide valuable information on lymph nodes diffusely infiltrated by neoplastic cells, they have limited value in the study of lymph nodes in which (part of) the normal architecture is preserved, as in most lymph nodes involved by MF.[7] In the study of lymph nodes from patients with MF and SS immunohistochemical studies on frozen tissue sections may be more rewarding not only because of their possible diagnostic value, eg, in demonstrating early lymph node involvement by MF, which may be extremely difficult by conventional histology alone,[8] but even more as these studies provide an unique opportunity to investigate the topological relationships between different cell populations, which may result in a better understanding of the pathogenetic mechanisms operative in these lymph

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nodes. The latter seems important because recent studies on lymph nodes from patients with MF and SS have demonstrated histologic differences between these two diseases which may reflect different pathogenetic mechanisms.[9]

For these reasons we have investigated the distribution of the lymphoid and nonlymphoid cells in the T-cell areas of both dermatopathic lymph nodes from patients with generalized benign skin disease and the involved and noninvolved lymph nodes from patients with MF and SS using an indirect immunoperoxidase technique and a series of monoclonal antibodies with well-defined specificities.

## Materials and Methods

### Patients

From 15 patients with MF, 3 with SS, and 4 with generalized benign skin disease (atopic dermatitis or psoriasis) peripheral lymph nodes were available for this study. The diagnosis MF was based on clinical and histologic criteria.[10] The patients with SS showed a pruritic infiltrated erythroderma, lymphadenopathy, and the presence of hyperconvoluted lymphoid cells (Sézary cells) in the skin, lymph nodes, and peripheral blood.

Histologically the lymph nodes from the patients with MF were classified according to the criteria of Scheffer et al.[7] In this classification four categories of lymph node involvement by MF are recognized: I), dermatopathic lymphadenopathy (DL) with cerebriform mononuclear cells (CMCs) not larger than those in dermatopathic control lymph nodes from patients with unrelated disease; II) DL with CMCs larger than those in the control lymph nodes (these Category II lymph nodes are considered to represent early involvement by MF); III) and IV) partial or total replacement or the normal lymph node architecture by atypical lymphoreticular tissue, respectively (Figure 1). From the 15 MF lymph nodes, 2 were classified into Category I, 4 into Category II, 3 into Category III, and 6 into Category IV. In 2 of the 6 lymph nodes from Category IV large areas almost entirely consisted of large cells with strongly basophilic cytoplasm resembling immunoblasts, and a diagnosis of T-immunoblastic lymphoma (T-IBL) can therefore be made. Another of these Category IV MF lymph nodes revealed large collections of histocytic cells with lobulated nuclei and ample cytoplasm, which were localized predominantly within, but also outside, the sinuses. In the vicinity of these cells large clusters of eosinophils were observed. Histologically, the lymph nodes from the patients with SS were diffusely infiltrated by large numbers of CMCs, which were larger than those in control lymph nodes, providing a rather monotonous histologic picture (Figure 2). One of these lymph nodes obtained from a patient with very early disease still showed some features of DL, ie,

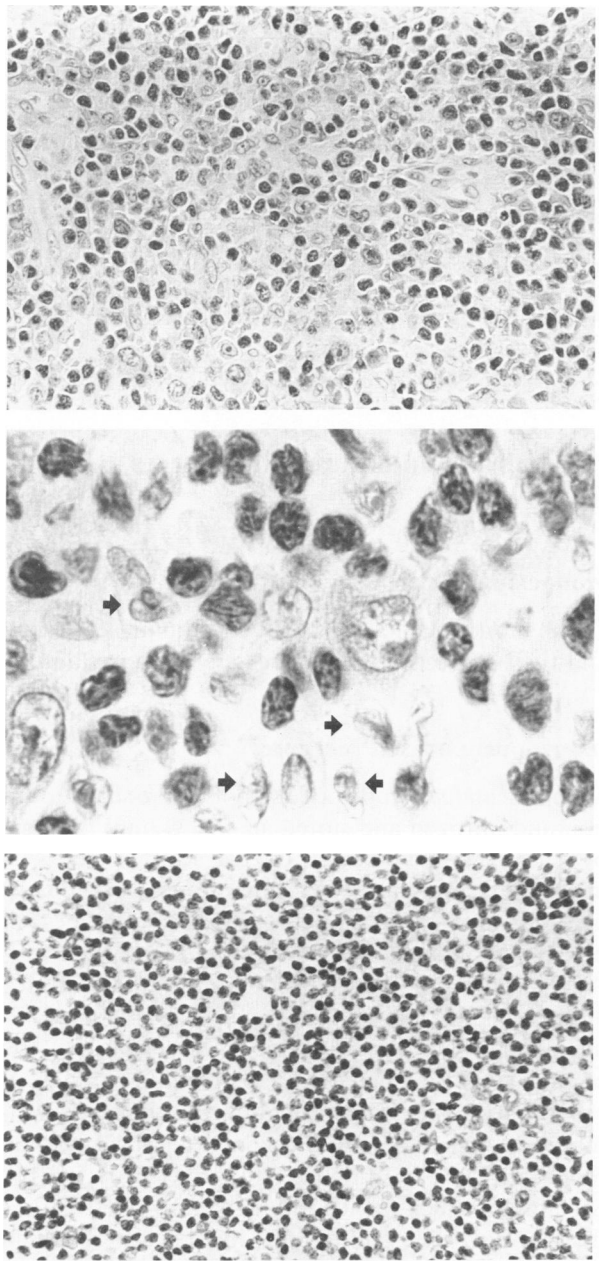



**Figure 1**—Lymph node section from a patient with MF (Category III). **A**—Note the mixed infiltrate with large hyperchromatic CMCs, many histiocytic cells, and blast cells. (×250) **B**—At higher magnification many large CMCs with convoluted and indented nuclei, polymorphous interdigitating reticulum cells (*arrowheads*), and large blast cells can be seen. (×650) **Figure 2**—Lymph node section from an SS patient, showing a rather monotonous infiltration with CMCs and relatively few nonpolymorphous IDCs. (×250)

Table 1—Antibodies and Their Specificity

| Antibody | Source* | Specificity |
|---|---|---|
| Leu-1 | BD | 95% of human thymocytes, 95% of peripheral T-lymphocytes, most sIg+ B-CLL cells, no normal B lymphocytes[1] |
| Leu-2a | BD | Suppressor/cytotoxic T-cell subset[12] |
| Leu-3a | BD | Helper/inducer T-cell subset[13]; weak intracytoplasmic staining of macrophages and Langerhans cells[14] |
| Leu-4 | BD | 80–95% of peripheral T-lymphocytes; 65–85% of thymocytes |
| HLA-DR | BD | B-lymphocytes, monocytes/macrophages, activated T-lymphocytes[15] |
| OKT6 | Ortho | 70% of thymocytes[16]; epidermal Langerhans cells[17] |
| OKT9 | Ortho | Transferrin receptor; activated and/or proliferating cells[18] |
| OKT10 | Ortho | (Pro)thymocytes, activated T and B cells[19]; plasma cells, follicular center cells[20] |
| B1 | CC | All B-lymphocytes; no plasma cells[20,21] |
| Anti-DRC (R4/23) | DAKO | Dendritic reticulum cells[22] |

* BD, Becton–Dickinson, Sunnyvale, California; Ortho, Ortho Diagnostics, Raritan, New Jersey; CC, Coulter Clone, Hialeah, Florida; DAKO, Dakopatts, Copenhagen, Denmark.

enlarged paracortical areas with an increase in histiocytic cells.

### Monoclonal Antisera

The monoclonal antisera used in the present study and their respective specificities are listed in Table 1.

### Immunoperoxidase Procedures

Representative lymph node samples were snap-frozen in liquid nitrogen and stored at −70 C until the time of study. Six-micron-thick cyostat sections were air-dried with a ventilator, fixed in acetone at room temperature for 10 minutes, washed three times in phosphate-buffered saline (PBS), and incubated with the monoclonal antibodies at appropriate dilutions for 30 minutes at room temperature in a humidified atmosphere. After three additional washes in PBS, the sections were incubated with peroxidase-conjugated rabbit anti-mouse immunoglobulin (Dakopatts, Denmark) diluted 1:40 with PBS containing 20% normal human serum for 30 minutes, and washed again in PBS. Sections were then stained with a solution of 0.05% 3,3′-diaminobenzidine and 0.015% hydrogen peroxide in Tris-HCl buffer for 5 minutes at room temperature and rinsed quickly in distilled water. Finally, the sections were counterstained with Mayer's hematoxylin, dehydrated in a graded series of alcohol solutions, and mounted in malinol.

The percentages of positive cells were estimated semiquantitatively by two investigators (R.W., C.M.). The mean of at least 5 high-power fields (400×) was taken as the final value.

## Results

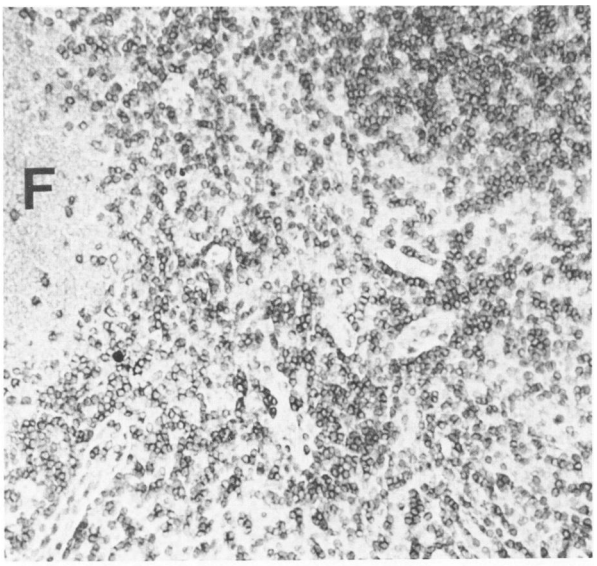
### Mycosis Fungoides

Identical staining patterns were observed in the dermatopathic lymph nodes from the patients with generalized benign skin disease and the MF lymph nodes showing features of DL without (Category I) or with (Category II) early involvement. In the enlarged paracortical areas about 90% of the lymphoid cells were reactive with Leu-1 and Leu-4, between 10% and 30% with Leu-2a, and 60–80% with Leu-3a (Figure 3). Numerous large interdigitating cells (IDCs) showing a strong intracytoplasmic staining with HLA-DR and a weak intracytoplasmic staining with Leu-3a were observed, either scattered between the lymphoid cells or forming large clusters (Figure 4). The large majority of the lymphoid cells appeared negative when stained with HLA-DR. Although the HLA-DR$^+$ interdigitating cells often occupied 50% or more of the surface area of the enlarged T-cell compartments, they constituted no more than 25–30% of the total number of cells in these areas. The ratio between Leu-1$^+$ or Leu-4$^+$ T-cells and HLA-DR$^+$ interdigitating cells in these lymph nodes was approximately 2–3:1. About 20–40% of the HLA-DR$^+$ IDCs was strongly reactive with OKT6 (Figure 4). These cells are considered to represent Langerhans cells that have migrated from the skin to the regional lymph node.

Staining with OKT10 showed clusters of strongly positive plasma cells in the subcapsular and medullary areas. In some lymph nodes a weak, rather diffuse staining was observed in the germinal centers of the secondary follicles. OKT10$^+$ cells were occasionally observed in the paracortical areas and probably represent plasma cells. The T cells in the paracortical areas appeared nonreactive with OKT10.

Incubation of tissue sections with OKT9 showed peripheral staining of most of the cells of the germinal centers, whereas the cells of the mantle zone were unstained. Scattered in the germinal centers, large cells showing cytoplasmic extensions, probably representing tingible-body macrophages, intensely stained with OKT9. A similar type of staining was observed in sinus histiocytes. In the paracortical areas small numbers of both nonlymphoid cells, often with a dendritic or stellate appearance and probably representing inter-

3A

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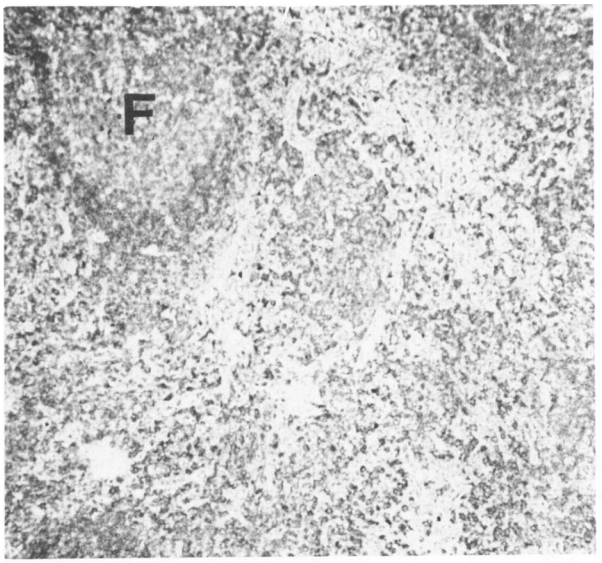


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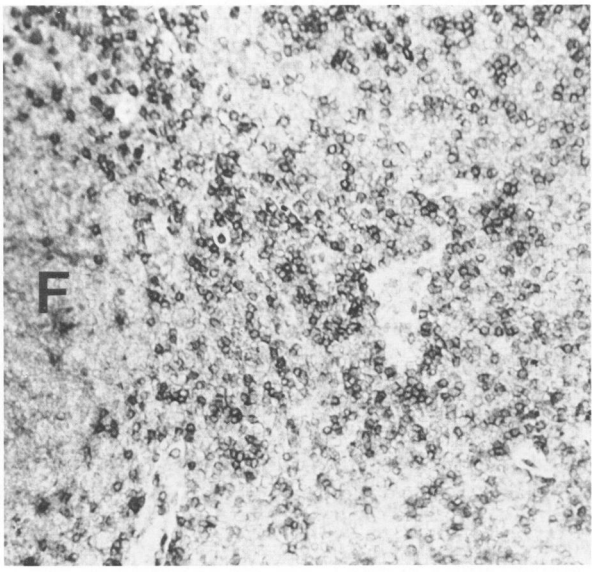


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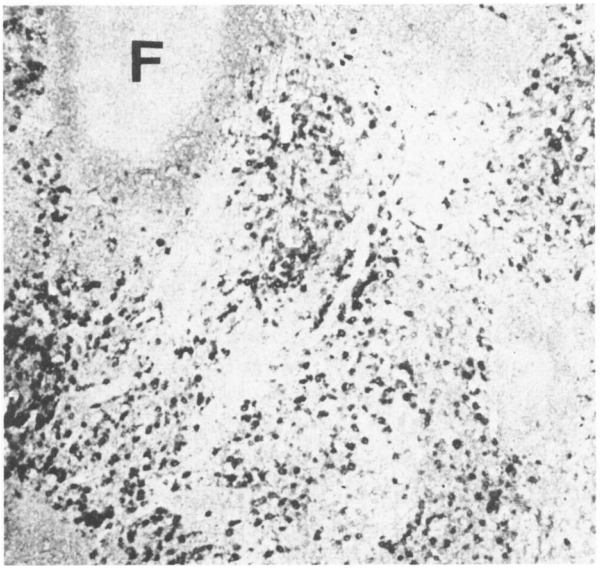


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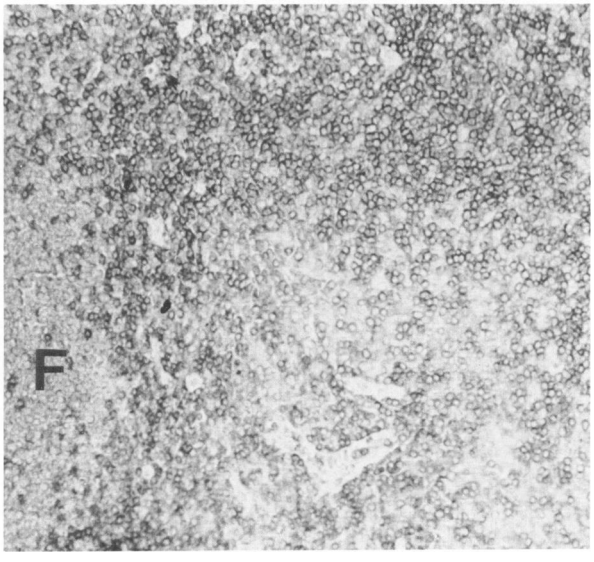
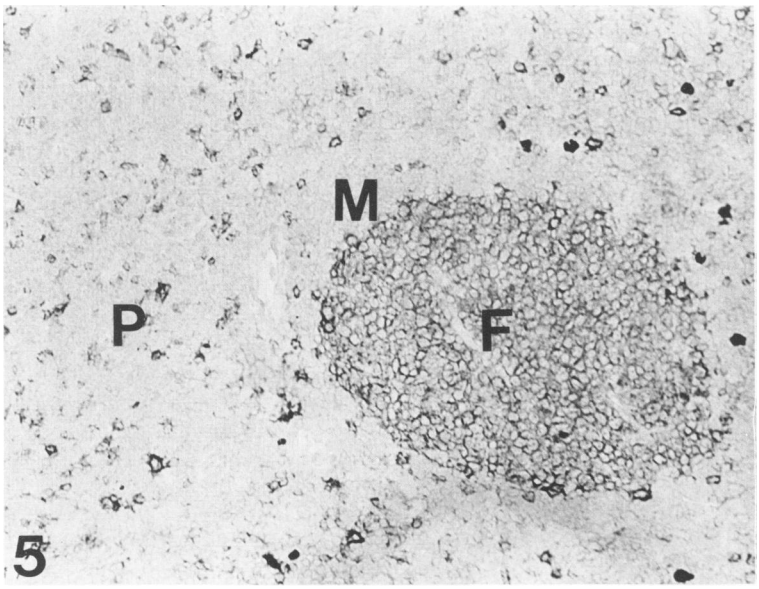



**Figure 3**—MF lymph node (Category II). Serial sections stained with Leu-1 (**A**), Leu-2a (**B**), and Leu-3a (**C**). (× 125) **A**—Many of the lymphoid cells in the paracortical area are reactive with Leu-1. Unstained areas represent clusters of IDCs. Note some Leu-1⁺ T cells in the primary follicle (*F*). **B**—A few lymphoid cells are reactive with Leu-2a antiserum. The positive cells are scattered, forming small clusters. **C**—Most lymphoid cells are stained with Leu-3a antiserum. In contrast to the Leu-2a⁺ cells, these Leu-3a⁺ cells tend to form large aggregates. **Figure 4**—MF lymph node (Category II). Serial sections stained with anti-HLA-DR antiserum (**A**) and OKT6 antiserum (**B**). (× 50) **A**—In the paracortical area large numbers of IDCs show an intracytoplasmatic staining with anti-HLA-DR. Note positive staining of both the mantle and the center of the secondary follicle (*F*) with this antiserum. **B**—This section shows the presence of a considerable number of dendritic OKT6⁺ cells, which are considered to represent Langerhans cells. There is no staining of the follicular compartment (*F*).



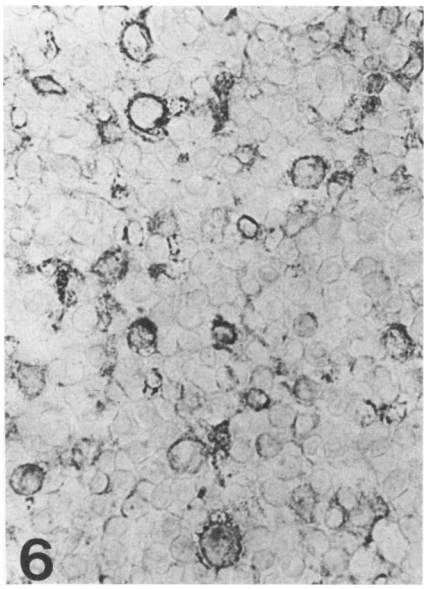




**Figure 5**—Staining pattern of a dermatopathic control lymph node with OKT9. Most of the cells of the follicle center (*F*) show peripheral staining, whereas the cells of the mantle zone (*M*) are unstained. In the paracortical area (*P*) scattered lymphoid and dendritic OKT9$^+$ cells can be observed. (×100) **Figure 6**—MF lymph node (Category III). Increased numbers of OKT9$^+$ cells, including large blast cells. (×250)

digitating reticulum cells, and small and large lymphoid cells (5% or less) were stained with OKT9 (Figure 5).

Lymph nodes from MF patients showing partial (Category III) or complete (Category IV) obliteration of the normal lymph node architecture tended to have lower numbers of HLA-DR$^+$ IDCs and OKT6$^+$ cells (Table 2). Moreover, these lymph nodes contained varying numbers of blast cells, a proportion of which did not stain with Leu-1, Leu-4, and/or Leu-3a. However, the immunohistochemical differences between these lymph nodes—except for the T-IBL nodes—and MF lymph nodes showing features of DL were gradual and not consistent. In one of these Category IV lymph nodes large accumulations of histiocytic cells were found within as well as outside the sinuses. These cells showed an intracytoplasmic staining with OKT6, HLA-DR, and Leu-3. Additional enzyme histochemical and ultrastructural studies demonstrated ATPase activity and the presence of Birbeck granules in these cells, indicating that they represent Langerhans cells. Staining with OKT10 in these Category III and Category IV lymph nodes was identical to that described for the dermatopathic MF

Table 2—Cellular Composition of T-Cell Areas in Dermatopathic Lymph Nodes From Patients With Generalized Benign Skin Disease (DL) and Lymph Nodes From Patients With Mycosis Fungoides (MF) and Sézary's Syndrome (SS)

| | n | T cell/IDC ratio* | T-lymphocytes | | | | HLA-DR$^+$ IDCs† | OKT6$^+$ LCs† |
|---|---|---|---|---|---|---|---|---|
| | | | Leu-1 | Leu-2a | Leu-3a | Leu-4 | | |
| DL | 4 | 2–3:1 | 4+ | 1+/2+ | 3+/4+ | 4+ | 2+ | 1+/2+ |
| MF, Category I | 2 | 2–3:1 | 4+ | 2+ | 3+/4+ | 4+ | 2+ | 1+/2+ |
| MF, Category II | 4 | 2–3:1 | 4+ | 1+/2+ | 3+/4+ | 4+ | 2+ | 1+/2+ |
| MF, Category III | 3 | 3–6:1 | 3+ | 1+ | 3+ | 3+/4+ | 1+ | 1+ |
| MF, Category IV | 4 | 4–6:1 | 3+ | 1+ | 3+ | 3+/4+ | 1+ | 1+ |
| T-IBL | 1 | — | 3+ | 1+ | 2+ | 3+ | — | — |
| T-IBL | 1 | — | — | — | 1+ | — | — | — |
| SS | 2 | 8–10:1 | 5+ | ± | 5+ | 5+ | 1+ | ± |
| SS | 1 | 5:1 | 4+ | ± | 4+ | 4+ | 2+ | 2+ |

Percentages are semiquantitatively estimated from the total number of cells in the T-cell areas: ±, <5%; 1+, 5–15%; 2+, 16–30%; 3+, 31–60%; 4+, 61–90%; 5+, >90%.

* Ratio between Leu-1$^+$ or Leu-4$^+$ T cells and HLA-DR$^+$ IDCs.

† IDCs, interdigitating reticulum cells; LCs, Langerhans cells.

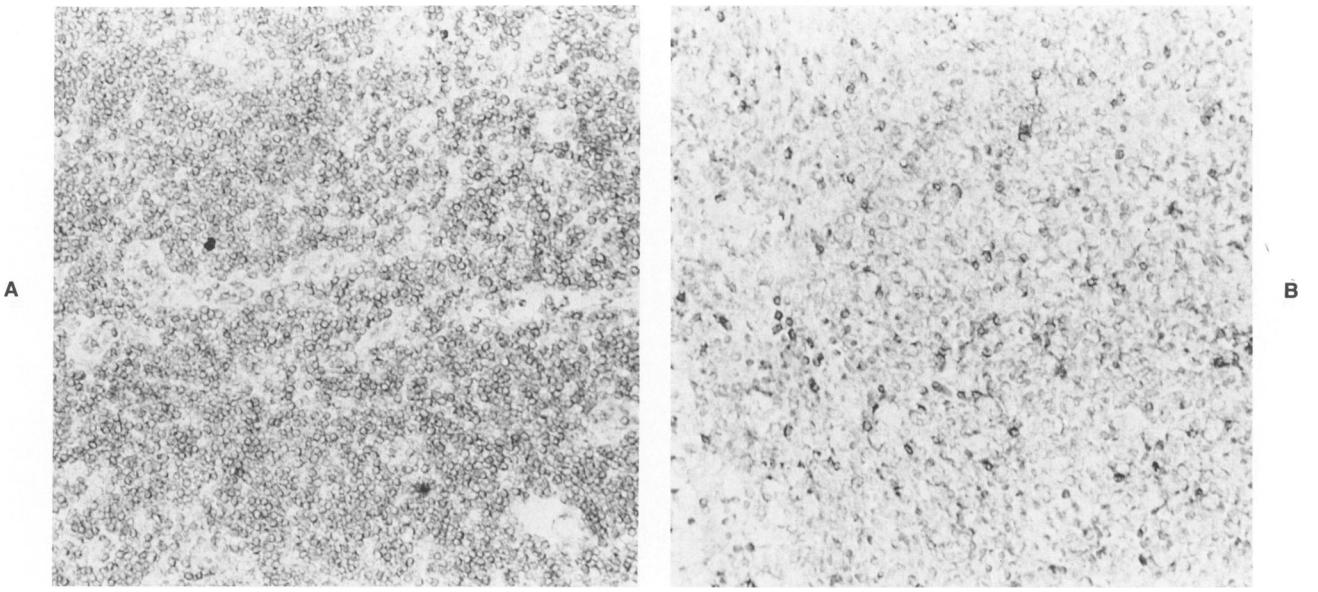



**Figure 7**—Lymph node section from a patient with SS showing (**A**) numerous Leu-3a$^+$ T cells and (**B**) few scattered Leu-2a$^+$ T cells. (×125)

lymph nodes. In two Category IV lymph nodes about 20% of the neoplastic lymphoid cells, including many blast cells, were reactive with OKT9 (Figure 6).

In one of the two T-IBLs approximately 50% of the blast cells were reactive with Leu-1 and Leu-4, and about 30% with Leu-3a. In the other T-IBLs a small proportion of the blast cells expressed HLA-DR and OKT10 antigens. The remainder of the blast cells in both cases were not stained by any of the antisera used. Both lymph nodes contained numerous HLA-DR$^+$ macrophages, which were strongly stained by acid phosphatase and $\alpha$-naphthyl acetate esterase. Cells reactive with OKT6 were not observed in these T-IBL lymph nodes.

### Sézary's Syndrome

In three lymph nodes from the patients with SS more than 90% of the lymphoid cells were reactive with Leu-1, Leu-4, and Leu-3a (Figure 7). Residual B-cell areas, as demonstrated by B1 and anti-DRC monoclonal antisera, were also diffusely infiltrated by these cells. The percentages of Leu-2a$^+$ cells were 5% or less (Figure 7). In one of the three SS lymph nodes the numbers of HLA-DR$^+$ IDCs and OKT6$^+$ Langerhans cells were almost the same as those in dermatopathic lymph nodes from patients with MF and patients with generalized benign skin disease. In the other two lymph nodes obtained from patients with more advanced disease, the numbers of HLA-DR$^+$ IDCs and OKT6$^+$ Langerhans cells were considerably less (see Table 2). In one of these two lymph nodes more than 80% of the lymphoid cells were reactive with OKT9 and OKT10 (Figure 8).

## Discussion

Recognition of lymph node involvement in MF is important, because it is associated with a poor prognosis and determines the choice of therapy.[23] However, histologic diagnosis of early lymph node involvement, ie, involvement without disturbance of the lymph node architecture, may be very difficult.[8] Recently, Scheffer et al[7] suggested a classification of lymph node involvement by MF into four categories and defined histologic criteria to differentiate between dermatopathic lymph nodes with and without early involvement by MF. The clinical relevance of this classification has been well established.[23]

In the present study we have investigated whether immunohistochemical studies employing a series of commercially available monoclonal antibodies may provide additional differential diagnostic criteria. However, the similarities in staining patterns between dermatopathic lymph nodes with early involvement by MF, as assessed by conventional histologic examination, and dermatopathic lymph nodes from MF patients without early involvement and from patients with generalized benign skin disease, indicate that these studies do not contribute to the diagnosis of early lymph node involvement.

Comparison between MF lymph nodes showing fea-

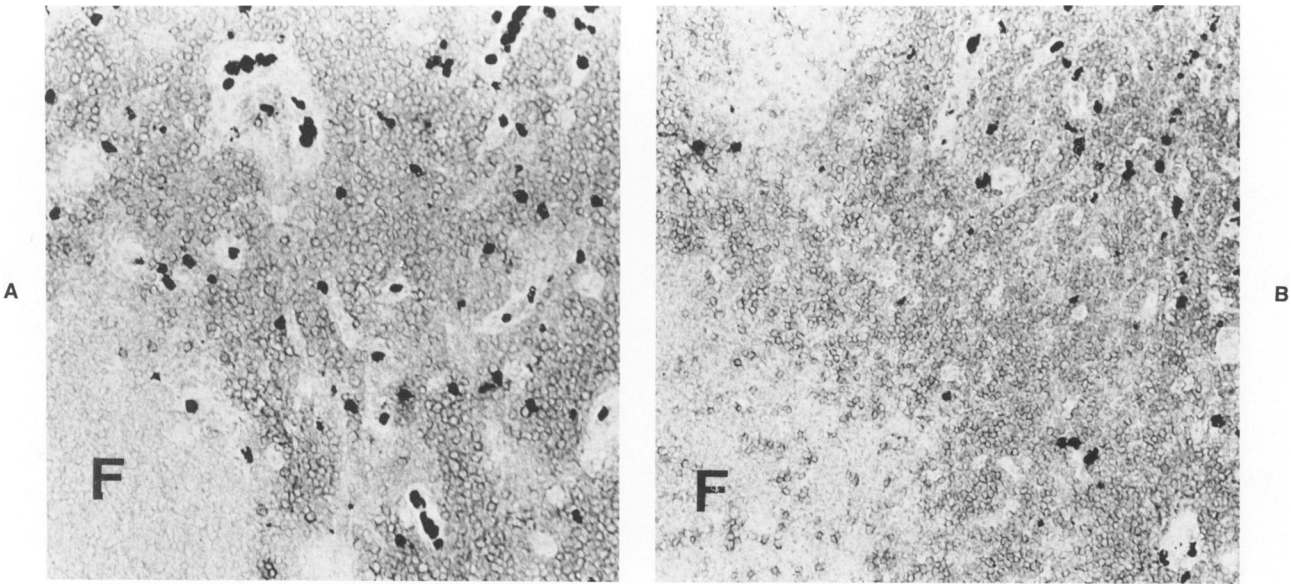



**Figure 8**—Serial sections from a SS lymph node stained with (**A**) OKT10 and (**B**) Leu-4, showing that the large majority of the cells in this lymph node represent activated T cells. The follicular center cells (*F*) stain very faintly with OKT10. (×125)

tures of DL (Categories I and II) and lymph nodes showing partial (Category III) or complete (Category IV) obliteration of the lymph node architecture revealed that the changes in the cellular composition of the paracortical areas in the different categories of lymph node involvement by MF are analogous to those observed in the different clinical stages of cutaneous involvement (premycotic or eczematous stage, plaque stage, tumor stage), which have been described previously.[5] In the premycotic and plaque stages of MF, which may be compatible with DL without and with early involvement, respectively, the dermal infiltrates show a predominance of cells with the phenotype of mature helper T cells and varying numbers of Leu-2a$^+$ T cells. In addition, there are increased numbers of OKT6$^+$ Langerhans cells, both in the epidermis and in the dermis. With progression of the disease (tumor stage in the skin, Categories III and IV of lymph node involvement), the percentage of Leu-2a$^+$ T cells, OKT6$^+$ Langerhans cells, and HLA-DR$^+$ IDCs tend to decrease, whereas an increasing number of blast cells, part of which are nonreactive with Leu-1, Leu-4, and/or Leu-3a, can be observed. In these advanced stages the percentages of Leu-4$^+$ T cells are generally higher than the percentages of Leu-1$^+$ and Leu-3a$^+$ T cells, which indicates that the antigens recognized by Leu-4 are less easily lost from the surface membranes than those reactive with Leu-1 and Leu-3a. The similarities in cellular composition between the different stages of skin and lymph node involvement by MF suggest that the pathogenetic mechanisms in the skin and lymph nodes of patients with MF are very similar.

The staining patterns observed in the three lymph nodes from patients with SS differed from those in the MF lymph nodes. These SS lymph nodes were diffusely infiltrated by neoplastic T cells, which had retained their mature helper-T-cell phenotype, and contained very few Leu-2a$^+$ T cells (5% or less) and relatively few HLA-DR$^+$ IDCs and OKT6$^+$ Langerhans cells. The T cell/IDC ratios were approximately 8–10:1 in the two lymph nodes from patients with advanced disease, but still 5:1 in the SS lymph node still showing remnants of DL.

Receptors for transferrin, recognized by OKT9 monoclonal antibody, are expressed by both normal and malignant proliferating cells.[18] Recent studies in patients with non-Hodgkin's lymphomas have demonstrated a relationship between the proportion of lymphocytes expressing transferrin receptors and the histologic grade of malignancy, and thus with prognosis.[24] In this study increased numbers of OKT9$^+$ lymphoid cells (up to 20%), including many blast cells, were observed in only two Category IV MF lymph nodes. In one of the SS lymph nodes approximately 80% of the neoplastic cells expressed both T9 and T10 antigens. In the other MF and SS lymph nodes the staining patterns with OKT9 and OKT10 were similar to those observed in the dermatopathic lymph nodes from patients with benign disease. Previous studies on lymph node suspensions from

patients with MF and SS have also demonstrated that the neoplastic cells in these diseases generally do not express T9 and T10 antigens.[1,6]

A remarkable finding was the presence of large aggregates of OKT6$^+$, HLA-DR$^+$, Leu-3a$^+$ Langerhans cells within as well as outside the sinuses of one of the MF lymph nodes. The localization of these cells suggests massive influx of Langerhans cells from the skin. Because of the presence of numerous eosinophils surrounding these Langerhans cell aggregates, the histologic picture of this lymph node resembled that of histiocytosis X. The intracytoplasmic staining with Leu-3a of both these cells and the large majority of the IDCs in all lymph nodes studied is consistent with previous studies on Leu-3a activity in histiocytosis X cells[25] and Langerhans cells.[14]

The data presented in this study confirm and extend the results of recent studies demonstrating histologic differences between MF and SS lymph nodes.[9] Clinically enlarged lymph nodes from patients with MF first show the characteristic histologic picture of DL (Category I). In the next stage (Category II) there is not only an increase in size and number of the CMCs, but there is also a marked polymorphism of the IDCs that may sometimes resemble Reed–Sternberg cells. In the subsequent stages the normal lymph node architecture is partially (Category III) or completely (Category IV) replaced by increasing numbers of atypical lymphoid cells, ie, large CMCs and/or blast cells that have often lost their mature helper-T-cell phenotype. In some lymph nodes, however, there is no proliferation of the lymphocytic cells, but of the histiocytic cells (IDCs), resulting in a histologic picture resembling that of Hodgkin's disease[9] or that of an interdigitating reticulum cell sarcoma.[26] These morphologic observations support the view that interactions between helper T cells and the antigen-presenting cells of the Langerhans cell/IDC series play a key role in the development of MF.[27] Unlike MF lymph nodes, lymph nodes from patients with SS generally do not show a considerable degree of DL. In most SS lymph nodes the normal lymph node architecture is rapidly overgrown by a rather monotonous proliferation of CMCs, which have retained their mature helper-T-cell phenotype. The IDCs in these lymph nodes are usually small and not polymorphous, and large numbers of blast cells, as in MF, are lacking. These histologic differences between MF and SS lymph nodes support the results of recent studies,[28] suggesting that different pathogenetic mechanisms are operative in the development of MF and SS, respectively.

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