Angiocentric Immunoproliferative Lesions: A Clinicopathologic Spectrum of Post-Thymic T-Cell Proliferations

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Twenty-three patients with angiocentric immunoproliferative lesions (AILs) including angiocentric lymphoma were evaluated clinically and pathologically. Pathologic subclassification performed without knowledge of the clinical outcome divided the cases into three histologic grades on the basis of cellular atypia and degree of inflammatory lesions (AILs) including angiocentric lymphoma. Ill. That tumor also demonstrated a clonal rearrangement of the Tβ gene. Progression to malignant lymphoma following initial immunosuppressive therapy with cyclophosphamide and prednisone occurred in three of nine patients with grade I lesions and four of six patients with grade II lesions. The supervening lymphomas were usually refractory to subsequent aggressive chemotherapy, with only one patient achieving a complete remission. In contrast, seven of eight patients with grade III lesions achieved a complete remission with aggressive combination chemotherapy, two of whom also received supplemental radiation therapy. These studies support the concept that the AILs represent a spectrum of post-thymic T-cell proliferations. The single most important prognostic indicator for ultimate survival is achievement of an initial complete remission. Patients treated initially with conservative chemotherapy may be compromised in their ability to achieve a complete remission if they progress to a higher grade lesion.

LIEBOW ET AL described lymphomatoid granulomatosis as an angiocentric and angiodestructive lymphoreticular proliferation involving predominantly the lungs, but also involving other extranodal sites such as upper respiratory tract, skin, kidneys, peripheral nervous system, and CNS. Although they considered the process to be nonneoplastic and granulomatous, resembling Wegener's granulomatosis, progression to lymphoma occurred in 13% of their initial series. Even without overt progression to what would consider lymphoma, the 5-year survival was <50% in those patients treated with corticosteroids or other conservative management.

DeRemee et al pointed out the morphologic and clinical similarities between polymorphic reticulosis (or midline malignant reticulosis) and lymphomatoid granulomatosis. Both lesions have similar histologic features and represent an angiocentric and angiodestructive lymphoreticular proliferation. The investigators concluded that both diseases represented the same process.

Thirty patients with angiocentric immunoproliferative lesion (AIL) was coined by Jaffe and Costa and Martin as an alternative to both lymphomatoid granulomatosis and polymorphic reticulosis. The term was desirable because it conveyed both the proliferative character of the lesion as well as its cytologic composition. In addition, it referred to the angiocentricity of the process, which is such a unique and distinctive part of the lesion. Lymphoreticular proliferations that were cytologically malignant were observed presenting with similar clinical features to both lymphomatoid granulomatosis and polymorphic reticulosis, and exhibiting a similar angiocentric and angiodestructive character. These were termed angiocentric lymphomas, and it was hypothesized that these represented the end point in the morphologic spectrum of AILs and were part of a single clinicopathologic entity.

Questions have persisted as to whether AILs are neoplastic at onset. Katzenstein et al noted that the prognosis in lymphomatoid granulomatosis inversely correlated with the number of large atypical lymphoid cells. This observation is comparable with the clinical experience with follicular lymphoma, a low grade B-cell neoplasm. Nevertheless, some patients with AILs attain a complete remission after treatment with only cyclophosphamide and prednisone, and thus, patients with AIL do not invariably progress.

In this study we have further addressed the question of the utility of histologic grading in AILs as a guide to clinical management. In addition, we performed immunophenotypic analysis on all cases with fresh tissue to determine both the immunologic phenotype of the proliferating cells, and features that might be suggestive of malignancy based on immunologic phenotype. Finally, molecular genetic analysis was performed in one case to determine if indeed the proliferation was clonal.

MATERIALS AND METHODS

Patient population. The study group represented 23 patients referred to either the Laboratory of Immunoregulation, National
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Institute of Allergy and Infectious Disease, or the Medicine Branch, National Cancer Institute. All patients had a confirmed diagnosis of an AIL or angiocentric lymphoma according to the criteria described below. Patients initially diagnosed as having lymphomatoid granulomatosis were treated as previously described with oral cyclophosphamide, 2 mg/kg of body weight per day, together with daily prednisone, 1 mg/kg/d. Five patients initially diagnosed as having angiocentric lymphoma were treated with aggressive combination chemotherapy: C-MOPP in two patients, ProMACE-MOPP in one, and ProMACE-CytaBOM in two. The patients received radiation therapy to residual disease following completion of their chemotherapy. Two patients felt to have angiocentric lymphoma on review had received cyclophosphamide and prednisone. One additional patient with angiocentric lymphoma received azathioprine, cyclophosphamide, and prednisone before referral to the National Institutes of Health. He was subsequently treated with C-MOPP, but failed to respond and is the one patient with a grade III lesion who has died.

**Clinical evaluation.** The clinical course was analyzed with particular attention to the following features: time interval from onset of symptoms to biopsy; time interval from onset of symptoms to treatment; response to initial therapy; relapse-free survival; survival; current clinical status and treatment; and sites of involvement at presentation and sites of involvement at relapse.

**Pathologic analysis.** Pathologic analysis was performed without knowledge of the clinical outcome. Initial diagnostic biopsies obtained before treatment as well as all subsequent surgical pathology material was reviewed. The lesions were classified according to the degree of cytologic atypia, described in detail below, based on the degree of cytologic atypia in the lymphoid cells and the extent of the inflammatory background.

**Immunophenotypic analysis.** Portions of biopsy specimens were snap frozen in a mixture of 2-methylbutane and dry ice and embedded in OCT (Miles Labs, Naperville, IL). Frozen material was stored in the vapor phase of liquid nitrogen until processed for phenotypic analysis. Air dried acetone fixed frozen sections were stained with the avidin-biotin-complex immunoperoxidase method as previously described. Phenotypic analysis was performed with the following panel of monoclonal antibodies: Leu1 (CD5), Leu4 (CD3), Leu3a (CD4), Leu2a (CD8), Leu8, Leu7, Leu11 (CD16), HLA-DR (Becton-Dickinson, Sunnyvale, CA), T11 (CD2), T6 (CD1), T9, B1 (CD20), B4 (CD19) (Coulter Monoclonal Antibodies, Hialeah, FL), 3A1 (CD7) (ATCC, Rockville, MD), anti-TAC (CD25) (a gift from Dr Thomas Waldmann, NCI), and immunoglobulin light and heavy chains: kappa, lambda, G, A, M, and D.

**Molecular genetic analysis.** High molecular weight DNA was extracted from a frozen tissue block of case no. 6 by a standard proteinase K/RNase chloroform-phenol technique and subjected to restriction endonuclease digestion, Southern transfer, and probed with genomic clones of human immunoglobulin Jλ, Jκ, Cλ, Cκ, and a cDNA of the T-cell receptor beta subunit constant region (Cβ) as detailed in a previous report.

**RESULTS**

**Pathologic evaluation.** Twenty-three patients were entered in the study. Nine patients were classified as having grade I lesions, six as grade II, and eight as grade III (angiocentric lymphoma).

Grade I lesions consisted of an angiocentric and angiodestructive lymphoid proliferation in the lung or any other anatomic site. Both small arteries and veins were involved. The infiltrates were composed of a polymorphic infiltrate of lymphocytes, plasma cells, and histiocytes, with or without eosinophils (Fig 1). Large lymphoid cells or immunoblasts were infrequent, and if present, did not demonstrate cytologic atypia. The small lymphocytes had condensed nuclear chromatin and minimal nuclear irregularities. Necrosis was usually not seen in grade I lesions.

Grade II lesions consisted of a polymorphous angiocentric and angiodestructive lymphoid infiltrate. Most of the lymphoid cells were small, but in contrast to grade I lesions, some cytologic atypia in small lymphoid cells was evident (Fig 2). Occasional large lymphoid cells or immunoblasts were present but these too failed to demonstrate marked cytologic atypia. A polymorphous inflammatory background was present, comparable with grade I. Necrosis was more commonly seen in grade II lesions.

Grade III lesions, also termed angiocentric lymphomas, were felt to be malignant lymphomas on cytologic grounds, based on the monomorphism of the infiltrate and the marked cytologic atypia present in both small and large lymphoid cells (Fig 3). Particular attention was paid to the angiocentric component of the lesion, where a polymorphous inflammatory background was usually inconspicuous. At the periphery of the lesions an inflammatory component was sometimes observed. Necrosis was usually prominent. The malignant lymphomas were further subclassified according to the Working Formulation based on the cytologic subtype as follows: diffuse, mixed small and large cell type (six patients), diffuse, large cell type (one patient), and diffuse, large cell immunoblastic type (one patient).

Pathologic sites of involvement at presentation are summarized in Table 1. There were no differences in anatomic distribution of disease according to histologic grade and all patients presented with extranodal disease. Lung was the most frequent site of involvement with 13 of the 23 patients having pulmonary involvement. Lymph node involvement was conspicuous by its absence.

**Differential diagnosis.** Although grossly the pulmonary lesions of AIL may resemble Wegener's granulomatosis (WG), the histologic distinction from WG is usually straightforward. Multinucleated giant cells or true granulomas are not a feature of AILs, and in this regard, the term lymphomatoid granulomatosis was a misnomer. In comparison with AIL, lymphoid cells are relatively sparse in WG, and neutrophils are much more prevalent. The necrosis of AIL is usually coagulative in character, whereas in WG abundant cellular and nuclear debris is present, presumably secondary to the prominent neutrophilic infiltrate.

The distinction of angiocentric lymphoma from other aggressive lymphomas in extranodal sites, such as the lung, may sometimes be subtle. The aggressive lymphomas of the Working Formulation (large cell, immunoblastic, and small non-cleaved) may often be associated with spontaneous necrosis. However, in those lesions the necrosis usually does not show a vascular distribution. In angiocentric lymphoma the necrosis appears secondary to obstruction of arterial lumina, and areas of viable tumor may often be identified surrounding infiltrated and destroyed blood vessels. Occasionally other non-Hodgkin's lymphomas may show subendothelial infiltration of arteries and veins. However, permeation and infiltration of the vascular wall is usually not
apparent, this being a constant feature of angiocentric lymphoma. Cytologically the angiocentric lymphomas demonstrate greater nuclear pleomorphism with marked variation in cell size and shape, in comparison with the more monomorphic character of large cell and small non-cleaved cell lymphomas.

Clinical course. Seven of nine patients with grade I lesions achieved an initial complete remission with cyclophosphamide and prednisone. Five of the seven patients required no additional treatment. Two of the seven progressed to lymphoma at 2 and 4 years after diagnosis, respectively (Table 2). The two patients who failed to achieve an initial complete remission progressed rapidly and died with disease. One of those patients developed a hemophagocytic syndrome and died within 3 months of diagnosis. At autopsy he was found to have widespread malignant lymphoma subclassified as large cell immunoblastic type.

Three of the six patients with grade II lesions achieved an initial complete remission. Four of the six progressed to malignant lymphoma with a median time to progression of 12 months. Only one patient progressing to lymphoma...
Fig 2. Angiocentric immunoproliferative lesion. Grade II. (A) Infiltrate is polymorphous, but some lymphocytes show cytologic atypia. Lymphoid cells are admixed with histiocytes and plasma cells (arrow). Occasional mitotic figures are seen (curved arrow). (B) Grade II lesion involving the skin. The infiltrate is in the deep dermis and subcutaneous tissue. The infiltrate retains its polymorphous character.

Achieved a complete remission with aggressive combination chemotherapy. That patient died of gastric carcinoma after being in complete remission for 6 months. No evidence of lymphoma was found at postmortem examination.

Seven of eight patients classified as grade III (angiocentric lymphoma) are alive and in remission. One patient had progressive malignant lymphoma and died at 10 months with widespread disease and a hemophagocytic syndrome. Six patients achieved an initial complete remission, and one had an initial partial remission. The one partial remission became
a complete remission with radiation therapy for persistent local disease in the ethmoid sinus. One patient achieving an initial complete remission has relapsed in a previously involved site, and achieved a second complete remission following radiation therapy. The seven responding patients with grade III lesions are in complete remission at 15, 29, 48, 84, 96, 132, and 144 months. Of the patients with angiocentric lymphoma, four presented with head and neck manifestations and four with pulmonary disease. Skin was involved in three of eight cases. Three of the patients had neural involvement at some point.

Most patients had symptoms present from several months to several years before diagnosis. The median interval from symptoms to diagnosis was 1 year. All patients with short antecedent histories had some long-term history of sinusitis, allergy, or epistaxis. The interval from initial symptoms to diagnosis ranged from several days to, in one patient, nearly 40 years. This latter patient had symptoms of multiple sinus infections, nasal discharge, and sinus headaches since childhood and ultimately presented with an angiocentric lymphoma in the palate and ethmoid sinuses.

**Immunophenotypic and molecular genetic evaluation.** Immunophenotypic studies performed on lesions from six patients (Table 3) demonstrated a mature (post-thymic) T-cell phenotype in all, usually with a predominance of CD4-positive cells (Fig 4). Abnormalities of antigenic expression were seen only in one grade III case, which presented as malignant lymphoma. The infiltrating T cells were CD2 and CD7 positive. Most, but not all, expressed the pan-T-cell antigens CD3 and CD5. However, the cells failed to express the subset antigens CD4 and CD8. In the three grade I and grade II cases studied, and in the two angiocentric lymphomas arising in patients with previous grade I and II disease, the proliferating cells expressed all mature T-cell antigens: CD3, CD5, CD7, and CD2. In all lesions B cells were sparse, and when present were polyclonal with expression of both k and lambda light chains.

Southern blot analysis performed on genomic DNA from the one grade III case studied demonstrated clonality on the basis of a single rearrangement of the T-cell antigen receptor beta chain gene. Southern blot analysis with all immunoglobulin probes demonstrated germline configurations and no rearrangements were detected.

**DISCUSSION**

This study supports the concept that AILs and angiocentric lymphomas represent a single clinicopathologic entity with varying degrees of clinical aggressiveness. Moreover, it demonstrates that histologic criteria are useful in the subclassification of angiocentric immunoproliferative lesions and can be predictive of clinical course. The most important prognostic indicator for long-term survival is achieving an initial complete remission. Moreover, patients with both low grade (grades I and II) and high grade (grade III) disease appear capable of achieving a complete remission that is durable, if appropriately treated.

Five of nine patients with grade I lesions and three of six with grade II lesions are alive with no evidence of disease following initial conservative therapy with low-dose cyclophosphamide and prednisone. However, of the seven patients with grade I and II lesions who progressed to angiocentric lymphoma, only one achieved a complete remission when treated for lymphoma. That one patient died in complete remission at 6 months with metastatic gastric carcinoma. While the risk of progression to lymphoma appears relatively low in grade I lesions (three of nine), the risk appears greater in grade II lesions (four of six). Moreover, the time to progression is considerably shorter in the grade II patients (median 12 months as opposed to a median of 23 months) although considerable overlap is present. Although the data are suggestive of prognostic differences between patients with grade I and II disease, the numbers in each group are small and confirmation of these results awaits further study. In view of the fact that 45% of the grade I and II patients

**Table 1. Pathologic Sites of Involvement at Presentation**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Lungs</th>
<th>Skin</th>
<th>CNS</th>
<th>Nasopharynx</th>
<th>Lymph Node</th>
<th>Other</th>
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<tr>
<td>I</td>
<td>9</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>0</td>
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</tr>
<tr>
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<td>6</td>
<td>4</td>
<td>3</td>
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<tr>
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<td>8</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 2. Summary of Clinical Course**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Median Time from Diagnosis to Progression (mo)</th>
<th>CR*</th>
<th>Long-term Survival†</th>
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<tr>
<td>I</td>
<td>3/9</td>
<td>0/3</td>
<td>5/9</td>
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<tr>
<td>II</td>
<td>4/6</td>
<td>1/4</td>
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</tr>
<tr>
<td>III</td>
<td>NA</td>
<td>7/8</td>
<td>7/8</td>
</tr>
</tbody>
</table>

*Complete remission when treated for lymphoma.
†Alive with no evidence of disease (minimum 2 years).

**Table 3. Immunophenotypic Evaluation of Angiocentric Immunoproliferative Lesions**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Tissue</th>
<th>Diagnosis</th>
<th>CD2</th>
<th>CD3</th>
<th>CD5</th>
<th>CD7</th>
<th>CD4</th>
<th>CD8</th>
<th>Leu-8</th>
<th>CD16</th>
<th>Leu7</th>
<th>CD25</th>
<th>T9</th>
<th>CD1</th>
<th>Is</th>
<th>CD20</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lung</td>
<td>Grade I</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+/-</td>
<td>--</td>
<td>+</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>Skin</td>
<td>Grade II</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+/−</td>
<td>--</td>
<td>+</td>
<td>+/−</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>Lung</td>
<td>Grade II</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+/−</td>
<td>--</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>Lung</td>
<td>Grade III</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+/−</td>
<td>+/−</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>Skin</td>
<td>Grade III</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<td>--</td>
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<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>Palate</td>
<td>Grade III</td>
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<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+/−</td>
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<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
</tr>
</tbody>
</table>

Grading scheme quantitates percentage of lymphoid cells in the infiltrate expressing a particular antigen: −, <1%; +/−, 1%-5%; +, 6%-25%; ++, 26%-75%; ++++, >75%.

*Originally grade I, progressed to grade III.
†Originally grade II, progressed to grade III.
died from progressive disease when treated with cyclophosphamide and prednisone, a more aggressive therapeutic approach using combination chemotherapy, with or without radiation therapy, similar to that which was successful in patients with grade III lesions, may be appropriate. Such a treatment approach is currently under investigation at the National Cancer Institute.

The survival for patients presenting with angiocentric lymphoma was excellent in this study. Seven of eight patients are alive with no evidence of disease. While two of the seven achieved a complete remission with only cyclophosphamide and prednisone, five of seven received aggressive treatment, which included combination chemotherapy. In two patients, consolidative radiation therapy was necessary to achieve a complete remission for persistent localized disease following chemotherapy. Only the one patient who failed to achieve an initial complete remission has died of his disease.

The clinical behavior of the angiocentric immunoproliferative lesions, including angiocentric lymphoma, appears analogous in many respects to the follicular center cell

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Fig 4. Immunophenotypic characterization of an angiocentric immunoproliferative lesion. Grade I, involving the lung (ABC immunoperoxidase technique with methyl green counterstain). (A) Frozen section stained with Leu1 (CD5). Nearly all cells are strongly positive. A perivascular pattern of infiltration is evident. (B) Parallel frozen section stained with Leu2a (CD8). Approximately 20% of the lymphoid cells are Leu2a positive. (C) Parallel frozen section stained with Leu3a (CD4). The majority of the lymphoid cells are positive. Alveolar macrophages are also weakly stained.
lymphomas of the B-cell system. Follicular lymphomas of low histologic grade present with an indolent clinical course, and patients may survive for many years, with or without aggressive therapy. However, if histologic progression occurs to a diffuse lymphoma of mixed or large cell type, the disease is associated with a more aggressive clinical course. Paradoxically, the high grade follicular center cell lymphomas appear to be more responsive to aggressive combination chemotherapy. Patients who achieve an initial complete remission and sustain that remission for more than 2 years frequently are cured of their disease.

Those grade I and grade II patients who progress after having achieved a complete remission or partial remission on cyclophosphamide and prednisone have a poor prognosis and are unlikely to achieve a complete remission with more aggressive therapy. This situation is also analogous to that observed in the low grade follicular lymphomas where initial conservative chemotherapy may compromise the ability of these patients to achieve a complete remission when they progress histologically. It is notable that at least some patients with low grade angiocentric immunoproliferative lesions are capable of achieving a sustained complete remission, in contrast to patients with follicular lymphoma who consistently relapse over time.

Additional evidence supporting the concept that the angiocentric immunoproliferative lesions represent a single clonologic entity comes from the immunophenotypic studies. The proliferating cells had mature T-cell characteristics in all cases studied. A predominance of CD4-positive or "helper" T cells was usually observed. Previous studies of both lymphomatoid granulomatosis and nasal lymphomas (consistent with angiocentric lymphomas) also have shown T-cell markers. However, the immunophenotypic studies are not helpful in resolving whether angiocentric immunoproliferative lesions are neoplastic at onset. In contrast to the B-cell system, where kappa and lambda light chain restriction can serve as markers of clonality, there are no easily available phenotypic markers for clonality in the T-cell system. A common feature observed in the peripheral T-cell lymphomas is abnormalities of antigenic phenotype, such as failure to express one or more of the usual pan-T-cell or subset antigens. The tumor cells from one case that presented as angiocentric lymphoma did demonstrate abnormalities of antigenic phenotype, comparable with that seen in T-cell lymphomas. However, the results for the remaining cases studied fail to provide supportive evidence for malignancy. Of the five grade I and grade II lesions studied, no phenotypic abnormalities were demonstrated and an admixture of both CD4- and CD8-positive cells was seen in biopsy specimens. Two of these cases had progressed histologically, and the lesions subjected to immunophenotypic analysis were classified as grade III (angiocentric lymphoma).

Molecular genetic analysis performed in one grade III lesion provided additional supportive evidence for its malignant nature. It demonstrated rearrangement of the T-cell receptor beta chain gene, a clonal marker seen in most T-cell malignancies. Unfortunately, no grade I or II lesions were available for molecular genetic analysis in this study. Future studies of these lesions should enable determination as to whether grade I and grade II lesions are clonal at presentation. Clonality would be strong presumptive evidence of malignancy in this clinical situation. Moreover, clonality may be a useful tool in determining which patients require initial aggressive therapy for grade I and grade II lesions, although clonality does not always correlate with malignant clinical behavior in lymphoproliferative disorders.

This study demonstrates that histologic grading is of value in the subclassification of AILs. Grade I lesions have a polymorphous cellular composition without any cytologic atypia. The histologic features of grade I lesions appear comparable in many respects with the benign lymphocytic angitis and granulomatosis of Saldana et al. Lesions with this histologic appearance appear cytologically benign and many such patients respond to conservative management with cyclophosphamide and prednisone. Grade II and grade III lesions appear more closely related and are more suggestive of malignancy on cytologic and histologic grounds. Cytologic atypia is more prominent and necrosis secondary to profound vascular involvement is more frequently observed. Grade II lesions are distinguished from grade III lesions by their more polymorphous cellular appearance. However, in other respects they are similar. We believe that grade II and grade III lesions are probably both malignant lymphoid proliferations. It is well recognized that the peripheral T-cell lymphomas commonly have an inflammatory background of plasma cells, eosinophils, and histiocytes. Thus, the polymorphous cellular composition of the grade II lesions does not rule out a neoplastic character. Whether or not grade II and III lesions should be separated in the future cannot be entirely resolved from this study. Clinically they appear quite comparable; in fact, the conservative therapy that patients with grade II lesions received in this study may have contributed to a relatively poor survival for this group (50%).

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