Association of Lymphomatoid Granulomatosis With Epstein-Barr Viral Infection of B Lymphocytes and Response to Interferon-α2b

By Wyndham H. Wilson, Douglas W. Kingma, Mark Raffeld, Robert E. Wittes, and Elaine S. Jaffe

Lymphomatoid granulomatosis (LYG) is an angiodestructive lymphoproliferative disorder (LPD) often involving the lungs. Its etiology is uncertain, but a number of previous studies had suggested it is a T-cell LPD associated with Epstein-Barr virus (EBV). Because of the similarity between LYG and nasal angiocentric lymphoma, the term angiocentric immunoproliferative lesion was proposed for both entities. Optimal therapy is unknown, but chemotherapy is often used. We studied four patients with LYG over a 5-year period. Biopsy samples were analyzed by immunohistochemistry, EBV in situ hybridization, and for Ig heavy-chain (IgH) gene rearrangements. Clinically, we assessed EBV serology, lymphocyte subsets, and the efficacy of interferon-α2b (IFN-α2b). All biopsy samples showed an exuberant T-cell infiltrate with scattered atypical large B cells. Double labeling showed EBV in the B cells but not T cells. Clonal IgH gene rearrangements were detected in 2 of 3 patients studied, 1 of whom had three distinct clones, and light-chain restriction showed two clones in an additional patient. All patients had positive EBV serologies and markedly abnormal lymphocyte subsets. With IFN, 3 patients are alive and disease free at 36, 43, and 60 months; 1 patient achieved a partial response for 16 months but discontinued therapy and died with lymphoma. These results indicate that LYG is a T-cell–rich EBV-associated B-cell LPD in which the infiltrating T cells are numerous but reactive. IgH gene rearrangements may be polyclonal, monoclonal, or oligoclonal. Its association with immune defects suggests it is related to posttransplant LPD. However, LYG and nasal angiocentric lymphoma are distinct entities and should no longer be included together under the term angiocentric immunoproliferative lesion. IFN is effective therapy and should be studied further.

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CASE REPORTS

Patient 1. A 21-year-old man presented with cough and nodular infiltrates on chest x-ray (CXR), and a left open-lung biopsy showed LYG grade I (Table 1). Computed tomography (CT) revealed pericardial, mediastinal and hilar adenopathy, and lung infiltrates. Head CT and bone marrow (BM) biopsies specimens were normal, there were no constitutional symptoms, and the cerebral spinal fluid (CSF) showed polymorphic lymphoid cells with negative cytology. Chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) was administered for six cycles with resolution of all abnormalities. Three months later, the pulmonary nodules reappeared and a new 1.5-cm hepatic lesion was found. Repeat open-lung biopsy showed LYG grade I in the right middle lobe and grade II in the right lower lobe. BM biopsy, CSF cytology, blood chemistry, and complete blood count (CBC) were normal. IFN was begun at a dose of 10 million units (MU) subcutaneously (sc) three times per week (TIW). Approximately 5 weeks later, all lesions had decreased in size, and by 3 months a CT scan showed that the hepatic lesion had resolved and the pulmonary nodules had resolved or regressed to less than 5 mm. Because of fatigue, the IFN dose was reduced to 7 MU after 12 months of therapy. IFN was discontinued after 40 months of therapy, and the patient is in CR 20 months since drug discontinuation.

Patient 2. A 53-year-old woman presented with fevers and a left middle lobe infiltrate on CXR (Table 1). CT showed multiple

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hepatic lesions, a right renal mass, and two small left renal lesions. The right kidney was resected and pathologically showed LYG grade I. BM biopsy specimens, blood chemistry, and CBC were normal. IFN was begun at 5 MU sc TIW. CT evaluation 14 weeks later showed resolution of all hepatic and renal lesions. The IFN dose was reduced to 7.5 MU after 6 months, and then to 5 MU after 12 months of therapy because of fatigue and headaches. IFN was discontinued 24 months after beginning therapy, and the patient remains in CR 19 months since drug discontinuation.

**Patient 3.** A 16-year-old boy presented with weight loss, cough, a 2.5-cm right upper-lobe pulmonary nodule, and skin macules (Table 1). A right open-lung biopsy sample showed LYG grade I and a skin biopsy specimen was consistent with this diagnosis. CT showed no other disease sites, and BM biopsy samples, blood chemistry, and CBC were normal. IFN was begun at 10 MU sc TIW. Repeat chest CT 13 weeks later showed resolution of some nodules and decrease of others. One year after beginning IFN, the chest CT showed vague but stable scattered irregularities. At this time, the patient stated he had only administered one or two weekly injections over the past few months, and, 2 months later he discontinued therapy. Seventeen months after beginning IFN, he developed fever, rash, subcutaneous nodules, and a debilitating 10% weight loss, rash, subcutaneous nodules, and a debilitating lower extremity sensory and motor neuropathy (Table 1). CT showed bilateral pulmonary nodules and effusions, splenomegaly, and peritoneal ascites. Blood tests showed an elevated lactate dehydrogenase of 358 UL, transaminases one to two times normal, hypercalcemia of 2.7 mmol/L, white blood cell (WBC) count 3,300 cells/µL, and erythrocyte sedimentation rate (ESR) 53 mm/h. A BM biopsy sample showed focal aplasia, acalciagin and intravenous Ig (IVIg) begun for presumptive acute EBV infection. He died 4 weeks later with multiple cerebral hemorrhages, and a postmortem exam showed extensive LYG grade III.

**Patient 4.** A 28-year-old man presented with fevers, malaise, 10% weight loss, rash, subcutaneous nodules, and a debilitating lower extremity sensory and motor neuropathy (Table 1). CT showed bilateral pulmonary nodules and effusions, splenomegaly, and peritoneal ascites. Blood tests showed an elevated lactate dehydrogenase of 558 UL, transaminases one to two times normal, hypercalcemia of 2.7 mmol/L, white blood cell (WBC) count 3,300 cells/µL, and hemoglobin 11 G/dL. A BM biopsy sample showed focal aplasia without LYG. Nerve conduction studies were consistent with axonal degeneration and brain magnetic resonance imaging was normal. CSF showed an elevated protein of 63 mg/dL, and marked lymphocytosis with a small monoclonal population of λ-expressing plasmacytoid B cells consistent with LYG grade I. An open-lung biopsy specimen showed LYG grade II, and a skin biopsy sample was consistent with LYG grade I. IFN was begun at 10 MU sc TIW and escalated to 20 MU over the next 3 months. By the first month of therapy, constitutional symptoms had resolved and the skin lesions and CXR improved. On the third month, a CT showed an increased left lung mass. A fine-needle aspiration showed a granulomatous process with budding yeasts consistent with cryptococcus and no LYG. IFN was increased to 25 MU and a CT 6 months later showed minimal residual scarring. One year after beginning therapy, several new skin nodules were noted. IFN was increased to 30 MU, and they resolved. IFN was subsequently increased to 40 MU. The leptomeningeal disease resolved over the first 4 months of IFN therapy, but stable mild distal parasthesias remained. Thirty-six months after beginning IFN, the patient has no evidence of disease and continues on therapy.

**MATERIALS AND METHODS**

Light microscopy, immunohistochemistry and EBV EBERI in situ hybridization. Tissue was fixed in either formalin or B5, embedded in paraffin, sectioned, and stained with hematoxylin and eosin (H&E). Formalin-fixed paraffin-embedded tumor sections were immunophenotyped with an avidin-biotin-peroxidase method using monoclonal antibodies (MoAbs): L26 (CD20; Dako, Carpenteria, CA); anti-CD3 (Dako); and A6 (CD45RO; Zymed, San Francisco, CA). The percent of T (CD3+, A6+) and B (L26+) lymphocytes were estimated and reported as 1+ (0% to 25%), 2+ (26% to 50%), 3+ (51% to 75%), or 4+ (76% to 100%). Tissue sections were also analyzed for EBV by EBV-encoded small nuclear RNA1 (EBER1) in situ hybridization. The immunophenotype of the EBV-infected cells was determined by combined immunohistochemistry (L26, A6, CD3) and EBV EBER1 in situ hybridization.

Biopsy specimens involved by LYG were subclassified in the present study based on a modification of a previously published grading scheme for AIL. Grade I lesions contained a mixed polymorphous infiltrate without large transformed or atypical lymphoid cells. Grade II lesions contained a polymorphous infiltrate, but there were scattered large and atypical transformed cells admixed. Grade III lesions fulfilled criteria for malignant lymphoma, and were polymorphous and composed of a predominance of large transformed cells. The infiltrates in all biopsies were angiocentric and angiodestructive. However, necrosis was minimal to absent in grade I lesions but was more prominent in grade II and III lesions.

Ig gene rearrangement. DNA was extracted from paraffin tissue and subjected to polymerase chain reaction (PCR) using consensus primers directed at the variable (V) and joining (J) region of the Ig heavy chain. VJ PCR products were analyzed on a 20% polyacrylamide gel. A clonal B-cell population was reported if a prominent band was observed on the gel. Alternatively, if a series of bands were observed, imparting a ladder appearance, the biopsy sample was reported as polyclonal. Positive and negative controls accompanied each PCR analysis.

**RESULTS**

Viral serology. EBV serology is shown in Table 2. In cases 1 and 4, pretreatment EBV IgG titers were positive,
and in case 2, serology performed 21 months after beginning treatment was positive. However, in case 3 EBV IgG titers were initially negative but acutely converted when the patient developed progression to LYG grade III. None of two additional patients tested had significant EBV IgM levels, and a heterophile test was negative in cases 3 and 4. In no case was there clinical evidence of acute EBV infection within the previous year. Cytomegalovirus IgM and IgG titers were undetectable before treatment in cases 1, 3, and 4.

**Immunological characteristics.** We performed lymphocyte subset analysis from the peripheral blood in all patients, and assessed other indices of immune function in individual patients (Table 3). Total T cells (CD3) were severely decreased in 3 patients and moderately decreased in 1 patient, whereas CD4 cells were moderately to severely decreased in 3 patients. Unexpectedly, all patients had moderately to severely depressed CD8 cells. Natural killer (NK) and total T cells were also reduced, but less so compared with other T-cell subsets. Serial subset analyses were performed in two patients. In one patient, no significant change occurred between pretherapy and after 2 years of IFN therapy, whereas in the other patient, the CD4 and CD8 subsets increased from abnormal to near normal over a 16-month period.

Case 3 had a history of recurrent oral candidiasis for 3 years before developing LYG, suggesting preexistent immunodeficiency, but was reactive to candida and mumps skin tests. However, no other patients had a history of recurrent or opportunistic infections which suggested a clinically significant underlying immunodeficiency. Case 4 was anergic to tetanus, purified protein derivative (PPD), and mumps skin tests at the time of diagnosis. Quantitative immunoglobulins, obtained in cases 3 and 4 at diagnosis and in case 1 after therapy, were normal.

**Light microscopy.** A diagnosis of LYG was established from pulmonary lesions in three patients and a renal lesion in one patient (Table 4). All showed an angiocentric and angiodestructive infiltrate, fulfilling the criteria for LYG (Fig 1A). Necrosis was seen in biopsy specimens classified as grade II or III, but not in those classified as grade I, and some blood vessels showed fibrinoid change and necrosis of the vessel walls. There was a predominant lymphocytic infiltrate with an admixture of histiocytes and plasma cells. Grade II lesions contained scattered large lymphoid cells, most conspicuously surrounding areas of necrosis.

Two cases had cutaneous involvement. Skin biopsy specimens were initially interpreted as showing Lichen sclerosis et Atrophicus, and Lichenoid and Granulomatous dermatitis, respectively, but, in the setting of LYG, were considered consistent with LYG grade I. Histologically, both contained a perivascular and periadnexal lymphoid infiltrate, but without atypical cells, angioinvasion, or angiodestruction. A soft-tissue mass from case 4 showed features of LYG grade II with necrosis and scattered large lymphoid cells. Lymphoid infiltrates consistent with LYG grade I were identified in the liver of case 2 and in the CSF of case 4. In case 2, there was progression of LYG from grade I to grade III over the disease course. The grade III lesion contained a monomorphic, cytologically malignant, population of large lymphoid cells and was classified as a diffuse large cell lymphoma (Fig 1C).

**Immunohistochemical analysis and EBV EBER 1 in situ hybridization.** All biopsy samples classified as either LYG grade I or II contained a predominantly T-cell infiltrate (CD3+, A67+) (Table 4 and Fig 1A). The number of B-cells (L26+ [CD20]) and EBV-infected cells correlated with the grade of the lesion. Those classified as grade I contained absent or few B cells and no EBV-infected cells, whereas biopsy specimens classified as grade II contained from 1-50 EBV+ cells per high-powered field (hpf) and increased numbers of small and large B cells. In all four cases, EBV was exclusively confined to B cells, as demonstrated by combined immunohistochemistry and in situ hybridization (Fig 1B). In case 4, there was evidence of proliferation of two different B-cell clones. An open-lung biopsy sample showed numerous plasmacytoid immunoblasts with a κ/λ

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**Table 2. EB Virus Serology**

<table>
<thead>
<tr>
<th>Case</th>
<th>Specimen Date</th>
<th>EBV CA* Titer</th>
<th>EBV CA Titer</th>
<th>EBVNA* Titer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12/90 (Pretherapy)</td>
<td>&lt;1:10 (neg)</td>
<td>1:40 (pos)</td>
<td>&gt;1:10 (pos)</td>
</tr>
<tr>
<td>2</td>
<td>3/94 (During therapy)</td>
<td>ND</td>
<td>1:60 (pos)</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>9/92 (Pretherapy)</td>
<td>ND</td>
<td>&lt;1:8 (neg)</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>3/94 (Posttherapy)</td>
<td>1:40 (pos)</td>
<td>1:60 (pos)</td>
<td>&lt;1:2 (neg)</td>
</tr>
<tr>
<td>5</td>
<td>1/93 (Pretherapy)</td>
<td>&lt;1:10 (neg)</td>
<td>1:60 (pos)</td>
<td>&gt;1:40 (pos)</td>
</tr>
</tbody>
</table>

* Antibodies to the EBV capsid antigen.
† EB Virus nuclear antigen.

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**Table 3. Lymphocyte Subset Analysis**

<table>
<thead>
<tr>
<th>Case</th>
<th>Specimen Date</th>
<th>Total T Cells CD3+/μL</th>
<th>CD4 Cells CD4+/μL</th>
<th>CD8 Cells CD8+/μL</th>
<th>Total NK Cells CD16 or CD56+/μL</th>
<th>Total B Cells CD19 or CD20+/μL</th>
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<tr>
<td>1</td>
<td>4/95 (Posttherapy)</td>
<td>555</td>
<td>416</td>
<td>147</td>
<td>122</td>
<td>139</td>
</tr>
<tr>
<td>2</td>
<td>12/84 (Posttherapy)</td>
<td>962</td>
<td>837</td>
<td>198</td>
<td>175</td>
<td>599</td>
</tr>
<tr>
<td>3</td>
<td>9/93 (During therapy)</td>
<td>607</td>
<td>383</td>
<td>145</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>1/94 (Pretherapy)</td>
<td>ND</td>
<td>1,151</td>
<td>451</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>5</td>
<td>1/93 (Pretherapy)</td>
<td>321</td>
<td>273</td>
<td>46</td>
<td>ND</td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>1/94 (During therapy)</td>
<td>260</td>
<td>221</td>
<td>39</td>
<td>35</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>3/95 (During therapy)</td>
<td>311</td>
<td>280</td>
<td>91</td>
<td>170</td>
<td>79</td>
</tr>
</tbody>
</table>

Normal* — 1,100-1,700 700-1,100 500-900 200-400 200-400

* Ranges based on analysis of 101 normal adults.
light chain ratio > 10:1, consistent with a κ-expressing B-cell clone; these B cells were EBV EBER1+. CSF cytology showed plasmacytoid cells positive for λ light chain, consistent with a λ-expressing B-cell clone; EBV EBER1 in situ hybridization was technically unsatisfactory.

Ig gene rearrangement. No monoclonal IgH gene rearrangements were detected in three separate lung biopsy samples from case 1 (Fig 2). In case 2, a monoclonal IgH gene rearrangement was detected in tissue from the kidney, but a liver biopsy specimen showed no clonal B-cell process, consistent with the immunohistochemistry that detected no EBV+ B cells. Autopsy tissue was only available for analysis in case 3. Two distinct monoclonal IgH gene rearrangements were detected in the liver and a third monoclonal IgH gene rearrangement was detected in the lung of this patient, while tissue from the brain was polyclonal.

DISCUSSION

Since its description some 23 years ago, both the etiology and optimal treatment for LYG have been uncertain. Immunophenotyping showed that the principal infiltrating cells were T cells, and its similarity to nasal angiocentric lymphoma (NAL) prompted the term AIL for both diseases. Consequently, treatment strategies for LYG and NAL have been similar. However, clinically there are important differences. NAL usually presents as an aggressive angiocentric T-cell lymphoma (AIL grade III) and requires combination chemotherapy, whereas LYG infrequently presents as grade III disease, so the necessity of combination chemotherapy is unclear. 2,7

To address these questions, we studied the pathology of four patients with LYG. In all patients, we observed atypical medium to large B cells scattered in a background of T cells, and double-labeling showed localization of EBV sequences to the B cells. Interestingly, the number of EBV+ B cells/ hpf and the grade of lesion correlated (Table 4); EBV was undetectable in grade I lesions, and most prevalent in grade III lesions. IgH gene rearrangements were detected by PCR in 2 of 3 cases, and Ig light-chain restriction was found in a fourth case, indicating a clonal B-cell process in 3 of 4 patients. Of interest is case 3, who on autopsy had three different IgH gene rearrangements, and case 4, who had two different light-chain–restricted clones, indicating oligoclonal processes, an event that has been described after solid-organ transplantation.20

Many studies have failed to identify IgH gene rearrangements in patients with LYG. This may have been caused by the rarity of atypical B cells in the lesions, such as in grade I disease, and/or to the use of less sensitive Southern blot techniques. Alternatively, the EBV-infected B cells may be polyclonal, as suggested by our results in case 1. Moreover, many of the published reports are difficult to interpret because they included patients with both NAL and LYG.9,11,13 Nevertheless, a consistent finding has been the absence of either clonal TCR or IgH gene rearrangements in LYG or NAL.7,10

Multiple studies have demonstrated EBV sequences in LYG, but most have used Southern blot or PCR analysis without identifying the phenotype of the infected cell.9,13,22 Moreover, of the reports employing double-labeling techniques, most have studied NAL to the exclusion of cases fulfilling criteria for LYG, and thus showed EBV sequences in T or NK cells.23 However, a recent study of 10 cases of LYG by Guinee et al10 achieved results similar to those of the present report in which, using a double-labeling technique, EBV sequences were shown in the B cells of all cases, and these results have recently been confirmed.21,23

Based on our results, we hypothesized that LYG is an EBV B-cell LPD. Furthermore, the observation that LYG occurs in the setting of immunodeficiency and, like post-transplant LPD, is associated with EBV infection of B cells, suggested these entities are related. These observations also suggested that IFN might be effective because of its antiviral, antiproliferative, and/or immunomodulatory effects.24,25 We report here the favorable results with IFN in 4 patients with LYG, all of whom responded by 3 months. Three patients achieved CRs in a median of 3 months and remain disease free at a median (range) of 43 (36 to 60) months. Two of these patients achieved striking clinical benefit with IFN. Case 1 had developed progressive LYG after aggressive che-

Table 4. Pathologic, Immunophenotypic, and EBV EBER1 RNA In Situ Hybridization Results

<table>
<thead>
<tr>
<th>Case</th>
<th>Biopsy Site</th>
<th>Biopsy Date</th>
<th>Diagnosis</th>
<th>L26 (CD20) Positive Cells</th>
<th>CD3 and/or CD45RO Positive Cells</th>
<th>EBV EBER1</th>
<th>EBV+ and CD20</th>
<th>EBV+ and CD45RO/CD3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lung</td>
<td>12/27/90</td>
<td>LYG II</td>
<td>1+</td>
<td>4+</td>
<td>pos, 1-2/hpf</td>
<td>pos</td>
<td>neg</td>
</tr>
<tr>
<td>2</td>
<td>Kidney</td>
<td>6/2/92</td>
<td>LYG II</td>
<td>1+</td>
<td>4+</td>
<td>pos, &gt;50/hpf</td>
<td>pos</td>
<td>neg</td>
</tr>
<tr>
<td>3</td>
<td>Liver</td>
<td>6/2/92</td>
<td>c/w LYG I</td>
<td>1+</td>
<td>4+</td>
<td>neg</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>Lung</td>
<td>12/27/90</td>
<td>LYG II</td>
<td>1+</td>
<td>4+</td>
<td>pos, &gt;50/hpf</td>
<td>pos</td>
<td>neg</td>
</tr>
</tbody>
</table>

Abbreviations: c/w, consistent with; pos, positive; neg, negative; NS, not satisfactory; ND, not done; hpf, high-power field; 1+, 0% to 25%; 2+, 26% to 50%; 3+, 51% to 75%; 4+, 76% to 100%.

* Autopsy sites analyzed for EBV: lung, liver, brain; autopsy sites involved by LYG: lung, heart, stomach, small intestine, liver, pancreas, kidneys, testis, lymph nodes, and brain.
Fig 1. (A) Case 1 lung biopsy sample shows an angiocentric and angioinvasive proliferation of predominantly small T-cells (anti-CD3 stain not shown) (H&E stain; original magnification × 400). (B) Case 1 lung biopsy sample shows rare large EBV-infected B cells by combined anti-CD20 immunohistochemistry (brown stain, membrane) and EBV EBER1 in situ hybridization (purple stain, nuclear) (original magnification × 1,000). (C) Case 3 autopsy lung specimen shows an angiocentric lymphoma with numerous B cells (anti-CD20 stain not shown) infected with EBV (EBER1 in situ hybridization, purple stain, nuclear, original magnification × 1,000).
motherapy, and achieved a durable CR with IFN. Case 4 was previously untreated but had multiple poor prognostic features, including splenomegaly, pancytopenia, and neurological manifestations, which are associated with greater than 90% mortality. One patient achieved a partial response with IFN, but, after discontinuing his own therapy, developed an aggressive EBV+ B-cell lymphoma. It is worth noting that the age of our patients (3 were < 30 years old) is significantly lower than the mean of approximately 50 years reported in other series.

However, younger age has been associated with a worse outcome, suggesting that the age distribution of our patients might be expected to be associated with a poorer response to IFN.

From this study, we cannot be certain of the optimal dose, schedule, or duration of IFN. However, over the study course the IFN dose ranged from 5 to 40 MU sc TIW. Our target starting dose was 10 MU, although one patient began at 5 MU because of a poor performance status. Three patients achieved their responses at doses ≥ 10 MU, whereas one patient was escalated to 40 MU when he had reappearance of a single skin nodule. Although responses to IFN were rapid, we treated all patients for at least 2 years; shorter treatment times may be equally effective.

Because of the association of LYG with EBV, we measured and found serologic evidence of EBV exposure in all patients; none had clinical or serologic evidence of acute EBV infection at initial presentation (Table 2). Of particular interest was case 3, who initially had a negative EBV capsid antigen IgG serology, but on disease progression, developed serologic evidence of an acute EBV infection. For several reasons, we believe it likely that this patient was unable to initially mount an EBV immune reaction, possibly because of an underlying immunodeficiency. We attempted to confirm the presence of EBV EBER1 by in situ hybridization and EBV EBNA 2 by PCR in the initial tissue from this patient, but were unsuccessful because of degraded DNA. However, the EBV EBER1 results from the present study as well as the study by Guinee et al., strongly indicate an etiologic role for EBV in LYG. Furthermore, tissue subsequently obtained from this patient was strongly EBV EBER1+. Thus, it appears less likely that the patient’s initial LYG was not associated with EBV and that an acute EBV infection triggered development of LYG grade III.

We examined lymphocyte subsets at various times during our patient’s treatment courses and found a profound depression in CD8 cells in all patients, and a profound depression in CD4 cells in two patients (Table 3). Furthermore, case 3 had preexistent oral candidiasis and case 4 was anergic to common antigens, also indicating T-cell deficits. We believe it likely that these immunologic deficits were preexistent, and placed these patients at risk for LYG. Indeed, LYG occurs with increased frequency in patients with immunodeficiencies such as those with HIV infection, and T-cell deficits persisted in the three patients who achieved CRs in this study. These results suggest the possibility that such patients have a quantitative and/or qualitative deficit in (CD8) cytotoxic T lymphocytes necessary for immune surveillance of EBV.

The similarities between LYG and PTLPD have potential therapeutic implications. In PTLPD, therapy consists of reducing immunosuppression and/or use of antivirals. Current approaches for LYG include prednisone, chemotherapy, and/or radiotherapy with variable results. Although reduction in immunosuppressive therapy is usually not an option in LYG, the success of this approach in PTLPD, and the poor results obtained with chemotherapy, suggest that immunomodulation and/or antivirals may be the best initial therapy for LYG. Indeed, the gratifying results we achieved with IFN in a limited number of patients suggest it is a promising therapeutic approach.

We believe the results presented here, in addition to those of Guinee et al., indicate that LYG and NAL are biologically and clinically distinct, and thus should no longer be included together under the term AIL. Furthermore, these results suggest that although LYG and PTLPD have similarities, the immune response appears to be different. Indeed, a distinguishing pathologic feature of LYG is the exuberant T-cell reaction and vasculitis, whereas in typical PTLPD most cells are plasmacytoid B cells with few T cells. Thus, to provide descriptive terms more consistent with their bio-
ogy, we propose T-cell-rich EBV-associated B-cell lymphoproliferative disorder (T-RELD) for LYG, and T-cell poor EBV-associated B-cell lymphoproliferative disorder (T-PELD) for PTLPD.

REFERENCES

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