Atypical Lymphoproliferative Diseases

Timothy Greiner (Chair), James O. Armitage, and Thomas G. Gross*

This review addresses the clinical presentation, pathology, and therapy of several uncommon lymphoid proliferations. Because these lymphoproliferations span the characteristics of reactive polymorphous proliferations to clonal malignant neoplasms, they are often difficult to diagnose and treat effectively.

In Section I, Dr. Greiner describes the pathology of the spectrum of atypical lymphoid disorders including Castleman’s disease, angioimmunoblastic lymphadenopathy, lymphadenopathy in autoimmune diseases, posttransplant lymphoproliferative disorders, and X-linked lymphoproliferative disorder. The relationship to Epstein-Barr virus (EBV) and human herpesvirus-8 (HHV-8) is discussed, and molecular diagnostic assays and principles for obtaining proper diagnostic evaluation are emphasized.

In Section II, Dr. Armitage presents a practical approach to the management of Castleman’s disease. The discussion includes the importance of confirmation of the histological diagnosis and careful staging evaluation, therapeutic options, and the increased risks for infection and lymphoma. The appropriate roles of surgical excision, corticosteroids, and combination chemotherapy are addressed along with alternative strategies such as anti-interleukin-6 and bone marrow transplantation.

In Section III, Dr. Gross reviews the treatment of EBV-associated lymphoproliferative disorders in primary immunodeficiencies and in post-transplant patients. He gives an update on the recent molecular discoveries in X-linked lymphoproliferative disorder. Preliminary results of a phase II trial of low-dose cyclophosphamide in posttransplant lymphoproliferative disorders and the use of GM-CSF as preemptive therapy are presented.

Lymphoid tissues have limited ways of generating a histologic response to an agent. These include follicular hyperplasia, plasmacytosis, eosinophilia, proliferation of immunoblasts, T-zone expansion and sinus histiocytosis. There is no unifying system for classifying atypical lymphoproliferations (ALP) that predicts whether a patient will have a self limited illness or one that will eventually result in lymphoma or death. Significant subgroups of patients present with unusual clinical features; however, their biopsies may result in pathologic diagnoses of “atypical lymphoid proliferation or hyperplasia.” Lymph nodes with ALP are defined as containing a distorted or effaced architecture, but the histology falls short of the criteria for malignancy. The infectious causes of lymphadenopathy are listed in Table 1 because they are occasionally mistaken for malignancy (e.g. toxoplasmosis as marginal zone lymphoma, or necrotizing lymphadenitis of cat scratch fever as Hodgkin’s disease). Some disorders present with clinical features such as generalized lymphadenopathy that initially suggest a malignant process but are found to have lesions with characteristic histologic features that correlate with a benign outcome. Many of these uncommon lymphoproliferations are related to an abnormal immune response to some inciting stimulus. Some ALP may result in the death of the patient, either by progression to malignancy or by damage to the immune system. Accurate diagnosis requires careful correlation of immunohistologic, karyotypic, virologic, and genotypic analyses with the clinical findings, previous medications, and family history. A list of underlying conditions and causes of atypical lymphoproliferations is given in Table 1. The purpose of this

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our experience is that a background level of 1–5 EBV cells per high power field are seen. Elderly patients, malnourished patients, and those with cancer also develop EBV-associated atypical lymphoproliferation as a result of a secondary immunodeficiency.2,6 In fulminant infectious mononucleosis (FIM), extensive infiltration by polyclonal T and B cells in varying degrees of transformation occurs in lymphoid and parenchymal organs. Extensive T cell and histiocytic reactions in FIM are common along with hemophagocytosis.4,7 Unusual cases of EBV infection develop clonal T cell proliferations with EBV integrated into the genome.

Medication-Associated Atypical Lymphoproliferations

Diphenylhydantoin (dilantin) causes lymph node pathology that is similar to that in infectious mononucleosis, with a florid follicular hyperplasia or paracortical expansion by a polymorphous immunoblastic infiltrate.8,9 The immunoblastic proliferation can be sometimes mistaken for lymphoma. Other findings include focal necrosis and Reed-Sternberg-like cells. There have been reports of Hodgkin’s disease and non-Hodgkin’s lymphoma in association with dilantin therapy.9 Other hyperplastic lymphoid responses to drugs have been reported, including dermatopathic lymphadenitis in association with carbamazepine.10 The immunosuppressive drugs, including cyclosporine, steroids, antilymphocyte globulin, and tacrolimus, are associated with EBV-positive lymphoproliferations.

Autoimmune Disorders

Disorders of immune regulation have an increased prevalence of lymphoid neoplasia, such as in collagen-vascular disease (i.e. rheumatoid arthritis).11,12 Patients with rheumatoid arthritis have a 5-fold increase in the rate of spontaneously transforming B cell clones in vitro. This is thought to be due to a specific defect in T cell inhibition of EBV-induced lymphocyte proliferation.13 While immunosuppressed during methotrexate or azathioprine therapy, these patients may develop atypical lymphoid hyperplasia and non-Hodgkin’s lymphoma.14-16 Case reports describe spontaneous resolution of lymphoma upon discontinuation of methotrexate therapy.15,16 Individuals with Sjögren’s syndrome have a 44-fold increased risk of developing lymphoma.17 Patients with systemic lupus erythematosus may develop necrotizing lymphadenopathy during exacerbations of the disease. Occasionally lymph node biopsy findings, including a polymorphous infiltrate, plasma cells, arteriolitis, focal necrosis, and hematoxylin bodies, help suggest the presence of lupus. Immunophenotyping the tissue biopsy appears to provide no assistance in distinguishing lupus-associated

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<td>Kikuchi’s Disease</td>
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Abbreviation: EBV, Epstein-Barr virus associated

review is to describe the pathology of selected entities and provide focused discussions on the therapy of Castleman’s disease and Epstein-Barr virus (EBV)-related lymphoproliferations in immunodeficiency conditions.

Epstein-Barr Virus

A frequent cause of atypical lymphoproliferations in immune suppressed patients is EBV activation.2,13 Immune suppression allows the escape of EBV-infected B cells and results in a polymorphous lymphoproliferation of small B cells, plasmacytoid cells, and immunoblasts, similar to that seen in infectious mononucleosis in immunocompetent individuals.3 In situ hybridization of EBV-encoded RNA (EBER) sequences in lymph nodes will demonstrate 5- to 10-fold more EBV-positive cells in lymphoid tissues of human immunodeficiency virus (HIV)-infected patients compared to lymphoid tissue in normal patients (0–1 EBV infected cell per high power field). In posttransplant patients, our experience is that a background level of 1–5 EBV cells per high power field are seen. Elderly patients, malnourished patients, and those with cancer also develop EBV-associated atypical lymphoproliferation as a result of a secondary immunodeficiency.2,6 In fulminant infectious mononucleosis (FIM), extensive infiltration by polyclonal T and B cells in varying degrees of transformation occurs in lymphoid and parenchymal organs. Extensive T cell and histiocytic reactions in FIM are common along with hemophagocytosis.4,7 Unusual cases of EBV infection develop clonal T cell proliferations with EBV integrated into the genome.

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Autoimmune Lymphoproliferative Syndrome

Clinical manifestations
Autoimmune lymphoproliferative syndrome (ALPS) is a recently described entity in which patients develop generalized lymphadenopathy, hepatosplenomegaly, hypergammaglobulinemia, B cell lymphocytosis and autoimmune characteristics. The autoimmune manifestations include hemolytic anemia, Guillain-Barré syndrome, urticarial rash, glomerulonephritis, and idiopathic thrombocytopenic purpura. Presentation usually occurs in the first two years of life. Radiologically, the masses appear hyperechoic as in reactive lymphadenopathy.

Pathology
The pathology of this disorder is characterized by an expansion of double negative T cells (CD4-, CD8-) in the paracortical regions of the lymph nodes. These are accompanied by a polymorphous infiltrate composed of plasma cells, small lymphocytes, and immunoblasts, which may resemble posttransplant lymphoproliferative disorder, as the immunoblastic proliferations can be extensive. Florid follicular hyperplasia is frequently present; however, in some cases follicular involution as seen in Castleman’s disease has been reported. Both reduced apoptosis and an increased percentage of proliferative cells are seen. Histocytes containing cellular debris are frequently absent.

Etiology
The etiology of the lymphadenopathy in most patients with ALPS is related to an impairment of apoptosis due to inherited heterozygous mutations in the fas gene (tumor necrosis factor receptor gene superfamily member 6-TNFRSF6, CD95, APO-1, APT-1), which is referred to as ALPS type I. Rare cases have been described of ALPS type II (mutations in caspase 10) and type III, wherein no mutation has been identified, however a functional deficiency of fas-mediated apoptosis has been observed. Rare patients have developed T cell rich B cell large cell lymphoma and nodular lymphocyte predominant Hodgkin’s disease. A monoclonal expansion has reportedly resolved spontaneously in a patient after antibiotic therapy. A diagnosis of lymphoma should be made cautiously in these patients as in other patients with an immunodeficiency syndrome.

Dysproteinemia

Clinical presentation
Patients with angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) have been described with generalized lymphadenopathy, hepatosplenomegaly, hypergammaglobulinemia, skin rashes, fevers, and increased infections. Night sweats, weight loss, and antibody-mediated anemia may occur. The Coombs’ test is frequently positive and occasionally a small monoclonal protein may be identified. Mortality has been reported as high as 60%, usually due to infections despite treatment with chemotherapy regimens. The etiology of the AILD is unknown. Association with previous medications such as antibiotics and anticonvulsants and viral infections has been reported.

Pathology
The key features of the lymph node pathology in the AILD are prominent arborizing vasculature, immunoblasts and polymorphic mixtures of plasma cells and large numbers of eosinophils. The lymph node architecture is effaced, frequently with loss of the usual germinal centers, although exceptions occur. Proliferations of medium to large T cells with clear cytoplasm are characteristically seen along vessels consistent with peripheral T cell lymphoma, along with distorted proliferations of dendritic cells admixed with small B cells. A hyperimmune reaction to a medication must be ruled out when the diagnosis is considered.

Molecular and cytogenetics
Clonal T cell gene rearrangements are present in many cases, supporting the concept that AILD is a peripheral T cell lymphoma in most cases. When cases with clonal populations are demonstrated by gene rearrangements or cytogenetic abnormalities the proposed WHO classification system designates these AILD patients as having peripheral T cell lymphoma, angioimmunoblastic type. This is in keeping with Frizzera’s previous recommendations that the term AILD should be reserved for those cases without molecular or cytogenetic abnormalities. While most rearrangements are in T cell receptor beta-chain gene (TCRβ) (80%), immunoglobulin heavy chain gene rearrangements have been seen (5–10%). Both TCRβ and immunoglobulin gene rearrangements are found in about 10% of cases. Occasionally there have
been cases of B cell lymphomas described in a previous background of AILD. Trisomies of chromosome 3, 5, and X are the most frequent chromosomal aberrations in AILD; however, other abnormalities are also seen.32,37,38

**Recent findings**

Foss et al have described the presence of increased vascular endothelial growth factor (VEGF) by mRNA in situ hybridization in peripheral T cell lymphomas, AILD type.40 They have hypothesized that increased VEGF in fibroblasts is associated with the hypervascularity present in the lymphoid tissue. It is not observed in normal germinal centers. Increased expression of tumor necrosis factor α and interleukin (IL)-6 may help explain the T cell proliferation and hypervascularity.40 Increased levels of fas protein have been observed in the serum of patients with peripheral T cell lymphoma, AILD type, compared to normal controls and patients with other tumors.41

**Castleman’s Disease**

The atypical lymphoproliferative disorder commonly termed Castleman’s disease was described in 1956.42 This syndrome has been called by a variety of names including giant lymph node hyperplasia, angiofollicular lymph node hyperplasia, angiomatous lymphoid hamartoma, lymph nodal hamartoma, and lymph node hyperplasia of Castleman.43

**Clinical Presentation**

Clinical manifestations of Castleman’s disease can vary from a localized mass to a systemic disorder with widespread adenopathy, fevers, autoimmune manifestations, and recurring infections. The disease may remit, be chronic and nonprogressive, or be rapidly fatal. The median age of patients who develop the disorder is similar to malignant lymphoma, being 64 years in one series of 38 patients.44 There appears to be a male predominance. Systemic symptoms such as fever, night sweats, and weight loss are seen in the majority of patients. Pooled data from several series found the following physical findings: Peripheral lymphadenopathy was seen in 100% of the patients, abdominal adenopathy in 53%, and mediastinal adenopathy in 47%. Seventy-nine percent had spleenomegaly and 63% hepatomegaly. Edema or pleural effusions were seen in 48% of the patients, and skin rashes in 37%. Twenty-four percent of the patients had neurologic findings including peripheral neuropathy and, rarely, central nervous system involvement by the disease process. Laboratory results in patients with Castleman’s disease typically include anemia, elevated sedimentation rate, hypoalbuminemia and polyclonal hypergamma-globulinemia. Severe autoimmune cytopenias and symptoms of glomerular injury such as proteinuria and renal insufficiency are seen occasionally.

**Pathology**

The histological diagnosis of Castleman’s disease is not trivial and the accuracy of the diagnosis has not been tested. Localized cases are frequently subdivided into the hyaline-vascular (90%) and plasma cell (10%) subtypes.45 The criteria for histological diagnosis of the hyaline-vascular subtype of Castleman’s disease includes the presence of shrunken or “burned out” germinal centers, with paradoxical concentric expansion of the mantle zones with an “onion skin” pattern. A single vessel is usually seen extending from the germinal center. Eosinophilic material or hyalinization is present in variable amounts around the vessels. Vascularity is increased in the interfollicular regions.43-45 The plasma cell variant is largely composed of extensive proliferations of plasma cells in the interfollicular regions with follicles maintained. Other causes of these findings such as human immunodeficiency virus, other infections, or autoimmune disease must be ruled out prior to the diagnosis of Castleman’s disease.43-45 Studies of clonality in Castleman’s disease have shown that most patients have a polyclonal lymphoproliferative process.40 The development of monoclonality might represent transformation to a malignant lymphoma as immunohistochemical and gene rearrangement studies have identified clonal cell populations in some cases of multicentric Castleman’s disease.47,48

**Etiology**

The etiology of Castleman’s disease is unknown. Hypotheses for its development have included infection, autoimmunity, and disordered cytokine regulation causing lymphoproliferation. The cytokine IL-6 seems to be central to the progression of Castleman’s disease in at least some cases.49 Increased expression of the gene coding for IL-6 has been demonstrated in Castleman’s disease, and retroviral transduction of the gene into mice has reproduced the symptoms and histologic findings.50 Recently it has been shown that humanized anti-IL-6 receptor antibody can ameliorate the symptoms of the disease as well as can antibodies directed at IL-6 itself.51,52 Castleman’s disease has been associated with infection by the human herpesvirus-8 (HHV-8; Kaposi’s sarcoma-associated herpesvirus) in the multicentric form of Castleman’s disease in 25% of cases, but not with the more common subtypes.53 We did not observe HHV-8 in a small series of pediatric cases of multicentric disease.54 This infection appears to be causally related to the overproduction of IL-6.

**Therapeutic approach**

Almost all patients with Castleman’s disease will require therapy. Patients with peripheral, localized masses can be treated with excision.55 Patients in whom the disease is localized but not amenable to surgery can be success-
fully treated with radiotherapy.\textsuperscript{56} Patients with disseminated disease can sometimes be successfully treated with corticosteroids. Patients who do not respond to corticosteroids have been treated with combination chemotherapy regimens utilized for lymphoma. However, the risk from death from infection is significant. Other treatments have included retinoic acid,\textsuperscript{57} humanized anti-IL-6 receptor antibodies,\textsuperscript{53} anti-IL-6 antibodies and bone marrow transplantation.\textsuperscript{58,59}

A practical approach to patients with Castleman’s disease involves confirmation of the histological diagnosis and a careful staging evaluation. If the disease is truly localized, then surgery or radiotherapy can be curative. In patients with more widespread disease, a trial with corticosteroids appears to be indicated. If the patient achieves a complete remission on doses of 60-100 mg of prednisone daily, the drug should be slowly tapered off over weeks to a few months. Some patients will achieve a durable remission. Patients who relapse after months or years of remission can be retreated with corticosteroids. Patients who have failed to respond, or who relapse promptly, have a serious disorder. Another biopsy to confirm the diagnosis might be appropriate. In a young patient who has persisting, symptomatic Castleman’s disease, autologous bone marrow transplantation might be considered. Combination chemotherapy with regimens such as cyclophosphamide, vincristine, and prednisone (CVP) has been utilized, but is associated with considerable risk for serious infection. However, this treatment should probably be offered to patients with progressive but otherwise unresponsive disease.

**General Treatment Approaches**

**Antiviral therapy**

The use of specific anti-viral agents such as acyclovir or ganciclovir may reduce viral replication and thereby limit the number of infected B cells, and may be useful in prophylaxis or pre-emptive therapy.\textsuperscript{61,62} There is some evidence in the SCID mouse that neutralizing anti-EBV antibodies may be effective in treating EBV-LPD.\textsuperscript{61} The efficacy of antiviral therapy in treating EBV-LPD is controversial because it is seldom used without other intervention, e.g. reduction of immunosuppression, but there is little risk of toxicity, and generally antiviral therapy is included as part of the treatment.\textsuperscript{61,62,64-66} However, if viral replication that is lytic to the infected B cells is suppressed, B cell proliferation could theoretically be enhanced.

**Interferon-\textalpha\textsuperscript{} (IFN-\textalpha\textsuperscript{})**

IFN-\textalpha\textsuperscript{} has been used successfully to treat EBV-LPD in both primary and post-transplant patients.\textsuperscript{65-69} IFN-\textalpha\textsuperscript{} may have antiviral, anti-B cell proliferative, and/or T cell-enhancing effects. IFN-\textalpha\textsuperscript{} can be marrow suppressive, increasing the risk of secondary infection, and theoretically may increase the risk of organ rejection or GVHD.

**Local cytotoxic therapy**

In post-transplant patients with localized disease, surgical resection of the mass and/or radiotherapy can be very effective.\textsuperscript{65,69} The toxicity depends on the location of the EBV-LPD. Success of this approach necessitates that there be no disseminated disease and that the patient has the ability to rapidly develop an EBV-CTL response to
control the latent infection.

Monoclonal antibodies

Anti-B cell antibodies have been used successfully to treat EBV-LPD. Although this approach does not stimulate EBV-CTL specifically, there is always a risk of developing GVHD organ rejection and loss of the graft. In primary immunodeficient patients and many BMT patients, the patient does not have enough T cell immunity for this approach to be effective. Infusion of donor lymphocyte (DLI) has been successful in BMT patients, but the donor must be EBV seropositive and possess memory EBV-CTL. To reduce the risk of GVHD and enhance efficacy, EBV-specific CTL generated ex vivo have been used successfully in preventing and treating EBV-LPD. Again, ex vivo generation of EBV-CTL is generally performed with EBV-seropositive donors to expand memory CTL. Ex vivo generation of EBV-CTL from EBV naive individuals can be achieved, but is technically more difficult. The issue of using DLI in an organ transplant recipient is complex and currently is not commonly used. The disadvantages of EBV-specific CTL or adoptive T cell therapy are that most centers do not have the technical capability to produce EBV-specific CTL. Also, it takes several weeks to generate EBV-specific CTL ex vivo, so one must either have a strategy for initial therapy or prospectively produce EBV-specific CTL for patients prior to developing EBV-LPD. The problem with the latter strategy is that even for the highest risk populations, the incidence of EBV-LPD is about 30%, making this strategy quite expensive.

Cytotoxic therapy

Cytotoxic chemotherapy has been used successfully for EBV-LPD. This approach is cytotoxic to proliferating B cells and is immunosuppressive enough to treat and/or prevent GVHD or organ rejection. For patients with concurrent rejection and EBV-LPD, chemotherapy offers the best control of both processes. For the rare patient who develops an abnormal T cell as well as B cell response, chemotherapy has been the only successful therapy. However, conventional doses for the treatment of non-Hodgkin’s lymphoma (NHL) in both primary immunodeficient and posttransplant patients, appear to result in more end organ toxicity and susceptibility to infection. In addition, conventional dosed chemotherapy theoretically may also inhibit the development of EBV-CTL.

Pre-emptive therapy

Management of posttransplant cytomegalovirus (CMV) disease that includes prophylaxis against infection, early detection, and pre-emptive therapy is an attractive approach for posttransplant EBV-LPD (PTLD). The role of antiviral prophylaxis with acyclovir or ganciclovir is controversial, since most patients are receiving antiviral therapy when PTLD develops. Since EBV cannot be cultured, polymerase chain reaction (PCR) of the blood is used to detect infection or reactivation, and semi-quantitative determination of EBV DNA in peripheral blood, i.e. viral load, appears to correlate with EBV-LPD and is useful in following “high-risk” patients. Compared to institutional historical data, the use of pre-emptive antiviral therapy with ganciclovir and/or high-EBV titer immunoglobulin (e.g., Cytogam) has been reported to be effective in preventing EBV-LPD in the organ transplant patient. PTLD has developed despite this pre-emptive approach, and to date there are no randomized trials to demonstrate its efficacy. However, many centers have adopted this approach as standard care in their organ and BMT patients. The use of anti-CD20 antibody as pre-emptive therapy is attractive but there has not been any experience reported.

Enhancement of EBV-CTL

To date there are no effective vaccines for EBV. The next best strategy would be to use agents, e.g. cytokines, at the earliest time of infection before B cell proliferation becomes clinically significant. GM-CSF can augment a primary immune CTL response to a neoantigen and has been used as a vaccine adjuvant to enhance T cell responses against viruses and cancer. Therefore, we hypothesized that using GM-CSF preemptively, when patients first become EBV PCR positive, can enhance EBV-CTL immunity specifically and decrease the incidence of PTLD without increasing risk of organ rejection or GVHD. A phase I trial using GM-CSF in BMT patients has demonstrated that it was well tolerated and did not increase GVHD. We have treated four patients, all T cell-depleted, matched unrelated donor marrow recipients, with GM-CSF when they became EBV PCR positive, developed symptoms (fever, fatigue and/or nausea/
vomiting), and had atypical lymphocytes present on peripher al smear. The median time post-transplant when GM-CSF was started was 52 days (48–70 days). Median EBV DNA levels at time of treatment were 325 copies/µg of DNA (10–500 copies). Median time to resolution of all symptoms was 15 days (7–20 days) and clearing of atypical lymphocytes was 15 days (7–32 days). Median time to EBV PCR negativity was 23 days (7–32 days). Three patients remain without EBV-LPD or symptoms, one patient later developed grade IV GVHD requiring antithymocyte globulin (ATG) therapy and intensification of immunosuppression and subsequently developed EBV-LPD. A trial in high-risk BMT and liver transplant recipients using GM-CSF as pre-emptive therapy is in progress.

Primary Immunodeficiencies and EBV-LPD

General pathology

An increased incidence of lymphoproliferative disease is observed in individuals with inherited immunodeficiencies.64 The diagnosis of EBV-LPD can be difficult in these patients, who frequently have reactive lymphoid hyperplasia. As in post-transplant patients, demonstration of EBV in lesions is helpful in evaluating a lymphoid lesion but is not synonymous with EBV-LPD, since EBV-positive cells can be found in greater than normal numbers in benign nodes. Though most of the B cell lymphomas and Hodgkin’s disease have been found to be EBV positive, EBV is not found in all the lymphomas. Data from the Immunodeficiency Cancer Registry for lymphoproliferations are shown in Table 2.

Pathology in X-linked lymphoproliferative disease

X-linked lymphoproliferative disease (XLP) or Duncan’s disease illustrates the spectrum of lymphoproliferation that can occur in hereditary immune deficiencies, ranging from benign to fatal infectious mononucleosis to NHL or Hodgkin disease.2,60 Patients with FIM have a disseminated lymphoproliferation involving generalized lymphadenopathy, as well as multiple organ sites. These patients often present with hepatitis, fever and pancytopenia, similar to other lymphohistiocytic disorders, e.g. hemophagocytic lymphohistiocytosis (HLH) and the accelerated phase of Chediak-Higashi.4 Patients who develop malignant lymphoma usually present with discrete, often extranodal mass(es). Though large B cell lymphomas are the most frequent, Burkitt-like and T cell lymphomas and Hodgkin’s disease have also been observed.2,60 Surprisingly, the majority of lymphomas tested for the presence of EBV were negative.

Mutations of SH2D1A in XLP

The gene mutated in XLP has been identified as SH2D1A.87,90 The protein coded by SH2D1A is a small protein of about 100 amino acids, the majority being an SH2 domain, and is expressed in human T cells, fetal liver and spleen. The SH2D1A protein interacts with SLAM (signaling lymphocyte activating molecule) and presumably with other molecules required for controlling T cell response to EBV infection.90 Thirty-five kindreds from the XLP Registry were tested for mutations in SH2D1A, and 34 had detectable mutations.91 Twenty-eight different mutations were identified, but no correlation between genotype of SH2D1A and clinical phenotype or severity of disease could be found. Additionally, no mutations in SH2D1A were identified in 25 males with a phenotype reminiscent of XLP following EBV infection but no family history to support the diagnosis of XLP or in nine patients with chronic active EBV syndrome. These results demonstrate that SH2D1A mutations are diagnostic of XLP, but other defects may have

Table 2. Immunodeficiency Cancer Registry (ICR) cases: incidence of tumors and immunodeficiencies.64

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<th>Immunodeficiency</th>
<th>Median Age @ Diagnosis (yr.)</th>
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<th>Hodgkin’s Disease</th>
<th>Leukemia</th>
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<td>4 (9.5%)</td>
<td>5 (11.9%)</td>
<td>1 (2.4%)</td>
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<td>XLA</td>
<td>1.2</td>
<td>3 (14.3%)</td>
<td>7 (33.3%)</td>
<td>3 (14.3%)</td>
<td>7 (33.3%)</td>
<td>1 (4.8%)</td>
<td>21 (4.2%)</td>
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<td>20 (16.7%)</td>
<td>55 (45.8%)</td>
<td>8 (6.7%)</td>
<td>8 (6.7%)</td>
<td>29 (24.2%)</td>
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<td>IgA deficiency</td>
<td>9.4</td>
<td>8 (21.1%)</td>
<td>6 (15.8%)</td>
<td>3 (7.9%)</td>
<td>0</td>
<td>21 (55.3%)</td>
<td>38 (7.6%)</td>
</tr>
<tr>
<td>CD40 Ligand deficiency</td>
<td>7.8</td>
<td>0</td>
<td>9 (56.3%)</td>
<td>4 (25.0%)</td>
<td>0</td>
<td>3 (18.8%)</td>
<td>16 (3.2%)</td>
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<tr>
<td>Wiskott-Aldrich</td>
<td>6.2</td>
<td>0</td>
<td>59 (75.6%)</td>
<td>3 (3.8%)</td>
<td>7 (9.0%)</td>
<td>9 (11.5%)</td>
<td>78 (15.6%)</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>8.5</td>
<td>13 (8.7%)</td>
<td>69 (46.0%)</td>
<td>16 (10.7%)</td>
<td>32 (21.3%)</td>
<td>20 (13.3%)</td>
<td>150 (30.0%)</td>
</tr>
<tr>
<td>Other immunodeficiencies</td>
<td>4.0</td>
<td>1 (4.0%)</td>
<td>12 (48.0%)</td>
<td>1 (4.0%)</td>
<td>4 (16.0%)</td>
<td>7 (28.0%)</td>
<td>25 (5.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>7.1</td>
<td>46 (9.2%)</td>
<td>252 (50.4%)</td>
<td>43 (8.6%)</td>
<td>63 (12.6%)</td>
<td>96 (19.2%)</td>
<td>500 (100%)</td>
</tr>
</tbody>
</table>

Abbreviations: SCID, severe combined immunodeficiency; XLA, X-linked agammaglobulinemia; CVID, common variable immunodeficiency
identical manifestation with severe or fatal EBV infections. In the XLP Registry, 38 males (12.5%) have had no evidence of EBV infection at the time of first clinical manifestation. No difference at age of first manifestation, phenotypes or survival could be found between EBV- or EBV+ males with XLP. These results demonstrate that even in XLP, EBV is not the only etiologic trigger of lymphoproliferation.

**Therapy**

Antiviral therapy has had little effect in the treatment of EBV-LPD in primary immunodeficiency. Three patients with antibody deficiencies but at least partial T cell immunity were treated successfully with antibody deficiencies but at least partial T cell immunity were treated successfully with αIFN. Though complete remissions can be achieved with chemotherapy, the outcome compared to immunocompetent patients with lymphoma has been poor. In 32 patients, treated for lymphoid malignancies and ataxia-telangiectasia (AT), the complete remission (CR) rate was 50% and median survival overall was about 6 months, and 32 months for those who achieved CR. Nineteen patients with primary immunodeficiency and NHL were treated with BFM NHL protocol regimens; 63% achieved a CR, and the 5-year disease-free survival (DFS) was 46%. In XLP, about 70% of boys achieved a CR with chemotherapy, but more than half relapsed. In contrast, non-immunodeficient children with NHL have a greater than 70% 5-year DFS. These poor outcomes are due to increased toxicity to chemotherapy, especially in AT patients, but also increased fatal infections and relapses, which can be of different clonal origin. As stated previously, successful treatment depends on controlling B cell proliferation and developing appropriate EBV-CTL immunity. Enhancing EBV-CTL immunity with αIFN or GM-CSF may be possible in certain B cell deficiencies and partial T cell deficiencies. However, in the majority of cases, the only way to develop appropriate T cell immunity against EBV and cure is to correct the underlying immune defect by allogeneic stem cell transplant, if a suitable donor can be identified. In the case of FIM, many treatments have been utilized, including antibiotics, steroids, IVIG, acyclovir, interferon (both α and γ), chemotherapy and/or cyclosporin. Since FIM is essentially indistinguishable from other hemophagocytosis syndromes, it is now recommended that patients receive chemotherapy with etoposide (VP-16) with steroids and/or cyclosporine. Approximately 75% will have a complete response, but relapse is common. Therefore, the recommended therapy for FIM after aggressive intervention with etoposide and immunosuppression is now to search for a suitable bone marrow donor, with allogeneic transplantation performed once the patient is stabilized.

**Secondary immunodeficiencies and EBV-LPD**

EBV-associated NHL is well described in the HIV/AIDS population, and will not be discussed here. Rarely, elderly patients, malnourished patients, and those with cancer develop EBV-associated atypical lymphoproliferation. Treatment of EBV-LPD in cancer patients can be quite successful, because removing the source of immunosuppression, i.e. discontinuing the chemotherapy, has little risk, and adding agents to enhance control of B cell proliferation and/or EBV-CTL immunity, e.g. IVIG, antivirals and/or αIFN adds little toxicity. The use of anti-B cell antibody therapy with discontinuation of chemotherapy is a particularly attractive approach, though there are no reported cases in the literature.

**Post-Transplant EBV-LPD**

**Clinical presentation**

PTLD represents a spectrum of clinically and morphologically heterogeneous lymphoid proliferations. EBV lymphoproliferative disease post transplant may manifest as isolated hepatitis, lymphoid interstitial pneumonitis or meningo-encephalitis or as an infectious mononucleosis (IM)-like syndrome with peripheral adenopathy, fever and/or hepatitis. Frequently, the definition of PTLD is limited to lymphomatous lesions (localized or diffuse) that are often extranodal (often in the allograft). Though less frequent, the most fulminant presentation of EBV-LPD in the post-transplant patient is as disseminated, systemic disease that clinically resembles septic shock.

**Pathology of PTLD**

Tissue biopsy should be performed for immunophenotyping the cell lineage and to identify clonality. In situ hybridization for EBV sequences is required since immunohistochemistry for latent membrane protein 1 will be negative in 25% of cases. Typically, the lymphoid tissue is composed of plasmacytoid B cells, with few T cells, and often regional areas of necrosis. Distinguishing between a polyclonal and a monoclonal PTLD often requires lymphoid receptor gene rearrangement analysis, since up to 50% of PTLDs do not express surface immunoglobulin. Peripheral blood will sometimes reveal circulating plasmacytoid lymphocytes or plasma cells.

These atypical lymphoproliferations can be aggressive with continued immunosuppression, even when polyclonal or oligoclonal, as defined by immunoperoxidase and gene rearrangement studies. The clonal ambiguity has led to difficulties in diagnosis. Early classifications of PTLD were proposed by Frizzera and Nalesnik. The most recent, by Knowles, describes three main subgroups: plasmacytic hyperplasias, polymorphous PTLDs, and monomorphic PTLDs, which include subtypes of...
lymphoma and multiple myeloma. The proposed WHO classification system retains the basic broad categories. The monomorphic PTLDs have a higher incidence of clonal heavy chain or light chain immunoglobulin gene rearrangements. The monomorphic PTLDs also have a low incidence of translocations and mutations in p53. While Cesarman described a poor prognosis when bcl-6 mutations are present in PTLD, we have observed no difference in outcome in the 32 patients studied at our institution (T. Greiner, unpublished data).

Polyclonal, oligoclonal or monoclonal proliferations may be observed, even within different lesions in the same patient. Though the majority of the lesions are EBV positive, occasionally B cell or Hodgkin’s disease will be EBV negative, especially if occurring late (more than 1 year post transplant). T cell NHL typically has a very late onset (median, 15 years post transplant), occurring most frequently in renal transplant patients.

Incidence of PTLD

The incidence of PTLD depends on its definition. With the current rate of transplantation, it is estimated that there are 500–1500 new cases of PTLD a year in the US. The incidence ranges from 1–5% in “low-risk” procedures, e.g. renal, heart, liver and non-T cell-depleted bone marrow transplants, to 10–30% in the “high risk” procedures, e.g. lung, small bowel and T cell-depleted bone marrow transplants. Because of the increased incidence in children receiving organ transplantation, PTLD may soon become the one of the most common types of lymphoma in children in the US. Though pathogenesis and treatment strategies are similar for BMT and SOT recipients, there are enough dissimilarities that each will be discussed separately.

Risk Factors for PTLD

In addition to the type of organ received, additional risk factors for PTLD in the SOT include the frequency of rejection episodes requiring intensified immunosuppression, especially the use of T cell antibody therapy, EBV seronegative status at time of transplant, and younger age of recipients, especially less than 5 years of age at time of transplant. Over 90% of early (fewer than 6 months post transplantation) PTLDs are EBV positive, whereas late (more than 2 years) PTLDs tend to be EBV negative. The incidence of PTLD is highest in the first year after transplantation when EBV CTL immunity is lowest.

PTLD has been described following autologous BMT, but it is very rare. The estimated overall incidence of PTLD following allogeneic BMT is only 1-2%, but all allogeneic BMT recipients are at risk, even cord blood recipients. The most significant factors associated with increased risk of PTLD include the use of intensive immunosuppressive prophylaxis and therapy of GVHD, especially with anti-T cell agents, increased donor age, use of total body irradiation, recipient-donor HLA-incompatibility, or T cell depletion of the donor graft. The recipients of an HLA-mismatched, T cell-depleted graft have a risk as high as 15%. The method of T cell depletion may also contribute to the risk, with T cell-specific depletion methods having a higher risk than pan-lymphocyte depletion methods, e.g. CAMPATH or elutriation. The reason for this observation may be the added depletion of EBV-infected B cells from the donor graft by the latter methods. PTLD usually develops in donor cells and occurs within 6 months of BMT, before EBV-CTL immunity has developed.

Therapy of PTLD

The mortality of PTLD post-BMT is as high as 90%. Unlike PTLD in SOT recipients, withdrawal of immunosuppression is rarely successful. Antiviral therapy has been successful in some cases of IM-like disease or meningo-encephalitis, but not in PTLD that presents as a mass or disseminated disease. Chemotherapy, especially at standard doses for treating NHL, are usually poorly tolerated by BMT patients within 6 months post transplant. Therefore, immune therapy has been the most successful. Using αIFN, 40-50% of patient may achieve a complete remission (CR). DLI has been demonstrated to be successful in the treatment of PTLD post-BMT. However, severe GVHD has also been associated with DLI, and deaths due to a “shock-like syndrome” have been reported. DLI is not always successful at controlling PTLD. A recent study demonstrated only 2/7 patients with PTLD to be alive without disease following DLI; four patients died of progressive disease and one died of GVHD following CR. Ex vivo EBV-specific CTL has been shown to be effective as prophylactic, pre-emptive therapy and treatment for PTLD post-BMT. But as stated previously, this technology is not readily available in most centers. The use of anti-CD21 and anti-CD23 has been well tolerated, and 35% of patients reportedly achieved long-term survival—1/11 with monoclonal PTLD and 7/16 with polyclonal disease. Anti-CD20 is now available and being used as treatment with little reported toxicity and 8/9 patients treated have reportedly achieved a CR.

The approach most widely used as initial therapy of PTLD is reduction of immunosuppression. Many times this is sufficient to control the disease, especially in localized, polymorphic cases or cases that present like infectious mononucleosis, but patients who do not tolerate reduction of immunosuppression (i.e. graft rejection) or do not respond to immunosuppression reduction require more aggressive therapy and have a much poorer prognosis. Antiviral agents (acyclovir or ganciclovir) and/
or IVIG have been used extensively for prophylaxis and treatment of PTLD.\textsuperscript{61,62,65,85} The efficacy of antivirals and IVIG is difficult to assess because reduction of immune suppression is almost always initiated simultaneously.

Surgery and/or radiotherapy are very effective in curing localized disease, but this represents a small percentage of patients.\textsuperscript{65} Even PTLD with monomorphic, monoclonal or aggressive histology (i.e. Burkitt-like) can be cured by local therapy if localized. Davis, et al, reported CR in 8/14 such patients treated with IFN, and at 1 year all patients were disease free.\textsuperscript{68} Liebowitz et al reported a 83% response rate, but median survival was only 6 months due to relapse, infection and rejection.\textsuperscript{67} Fifty-five percent of patients treated with anti-CD21 and anti-CD23 were reported to be long-term disease-free survivors, including 8/18 with monoclonal and 5/9 with oligoclonal PTLD.\textsuperscript{70} The response rate to anti-CD20 has been reported to be 65%, with a relapse rate of 18%; 4% died of rejection and 12% died of infection.\textsuperscript{71}

For patients who fail to resolve the PTLD or develop rejection after reduction of immune suppression, cytotoxic chemotherapy is attractive since it will treat both processes.\textsuperscript{81} However, standard dose chemotherapy for treating NHL may be toxic for post-transplant patients and may theoretically inhibit EBV-CTL development.\textsuperscript{85,98} Therefore, we have been conducting a multicenter study using low-dose chemotherapy. Results of several series using chemotherapy, including our low-dose regimen, are summarized in Table 3 (Gross, unpublished data).\textsuperscript{81} The results with the low-dose approach appear to be at least as good as standard NHL chemotherapy; the regimen is immunosuppressive enough to prevent rejection in the majority of cases and to effectively treat PTLD with concurrent rejection. Of interest, patients receiving the low-dose chemotherapy develop EBV-CTL and achieve numbers higher than normal EBV-seropositive controls. It has been demonstrated that cyclophosphamide enhances T cell adoptive therapy in murine models, enhances CTL precursor frequency against vaccinated antigens, and by stimulating IFN production, induces proliferation and persistence of activated memory CTL against tumors.\textsuperscript{114}

We hypothesize that this regimen may enhance EBV-CTL generation by inducing endogenous IFN production while controlling B cell proliferation and preventing allograft rejection. In addition, this regimen is relatively cheap, accessible to all, easy to administer and safe (mostly given in an outpatient setting).

EBV-negative PTLD tends to occur late and require conventional NHL chemotherapy, and still has a poor prognosis.\textsuperscript{105,109-111} Hanson et al reported six patients with T cell PTLD, and none survived longer than 6 months despite aggressive chemotherapy.\textsuperscript{105} Dotti et al reported 15 patients with EBV-negative PTLD with a median survival of about 5 months and no survivors beyond 2 years.\textsuperscript{109} Leblond et al reported 11 EBV-negative PTLD patients with a median survival of 1 month, and only two survivors.\textsuperscript{111} Post-transplant Hodgkin’s disease also usually arises late, i.e. greater than 2 years post transplant, and conventional Hodgkin’s disease chemotherapy has been successful in treating these patients.\textsuperscript{112}

The use of adoptive T cell therapy in an organ transplant recipient is complex. First, cadaveric organs are most widely utilized; therefore, donor leukocytes are often not available. Second, as opposed to BMT, following organ

<p>| Table 3. Summary of results using chemotherapy to treat PTLD in solid organ transplant patients.\textsuperscript{81} |</p>
<table>
<thead>
<tr>
<th>Series</th>
<th>Regimen</th>
<th>No. Patients</th>
<th>CR Rate</th>
<th>Relapse Rate</th>
<th>Rejection Rate</th>
<th>Toxic Death*</th>
<th>1-Year DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swinnen, et al\textsuperscript{21}</td>
<td>ProMACE-CytaBOM</td>
<td>11</td>
<td>55%</td>
<td>0%</td>
<td>0%</td>
<td>27%</td>
<td>45%</td>
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<tr>
<td>Morrison, et al\textsuperscript{12}</td>
<td>CHOP +/- Bleo, COMLA, M-BACOD, VACOP-B, Ifos/VP-16/Dex</td>
<td>9</td>
<td>11%</td>
<td>0%</td>
<td>0%</td>
<td>NR</td>
<td>11%</td>
</tr>
<tr>
<td>Garrett, et al\textsuperscript{22}</td>
<td>CHOP</td>
<td>4</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
<td>25%</td>
<td>75%</td>
</tr>
<tr>
<td>Hayashi, et al\textsuperscript{23}</td>
<td>CY, Adria, VCR, MTX, AraC + IT, ABVD-MOPP\textsuperscript{**} (2 HD)</td>
<td>10</td>
<td>80%</td>
<td>10%</td>
<td>0%</td>
<td>0%</td>
<td>70%</td>
</tr>
<tr>
<td>Gross, et al</td>
<td>CY/Pred\textsuperscript{***}</td>
<td>35</td>
<td>83%</td>
<td>14%</td>
<td>11%</td>
<td>6%</td>
<td>81%</td>
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* Toxic deaths include death not due to progressive disease while on therapy
** For two patients with Hodgkin’s disease
*** CY (600mg/m\textsuperscript{2}) + Prednisone x 5 days every 3 weeks

Abbreviations: ProMace-CytoBOM, prednisone, vincristine (VCR), doxorubicin (Adria), methotrexate (MTx), cytosine arabinoside (Ara-C), bleomycin (Bleo), cyclophosphamide (Cy), etoposide (Vp16); CHOP, Cy, Adria, VCR, prednisone; COMLA, Cy, VCR, MTx, Leukovorin, Ara-C; M-BACOD, MtX, Bleo, Cy, VCR, dexamethasone (Dex); VACOP-B, Vp6, Adria, Cy, VCR, Bleo; Ifos, Ifosfamide; IT, intrathecal; CR, complete remission; DFS, disease-free survival
transplant the EBV-LPD cells are usually of recipient origin, so the immunologic recognition, specificity and efficacy of donor leukocytes is uncertain. Third, the use of closely matched relatives’ leukocytes runs the risk of both rejection and GVHD. And finally, the ex vivo generation of EBV-specific CTL used clinically has generally utilized only EBV-seropositive donors, which represents expansion of memory EBV-specific CTL. The highest risk individuals are EBV-seronegative individuals, and generation of EBV-specific CTL from an EBV-naïve individual, though possible, is technically challenging. There is one report of infusion of ex vivo generated EBV-specific T cells in a lung recipient with PTLD, which was well tolerated and effective. Though promising, this approach remains prohibitive for most centers due to cost and the high level of technology required.

EBV-LPD is a growing problem due to increasing numbers of transplant recipients. Due to the wide spectrum of clinical and pathologic presentations and many biases of the “best” therapy for EBV-LPD, there has been little progress in the understanding of critical factors in its pathogenesis. There are immense data on risk factors but still little understanding about the biologic factors that predict response to therapy. EBV-LPD develops in patients with a wide range of inherited immune defects. With the identification of the genetic defects in inherited immunodeficiencies, we should learn much about how the immune system functions and the elements required to prevent and to control EBV and LPD, as well as lymphoproliferations in general. The use of cDNA microarray technology offers us a powerful tool for advancing our understanding of the pathogenesis of EBV-LPD as well as providing better prognostication for response to therapy. Collaborative multicenter randomized trials are desperately needed to advance our therapeutic options and improve outcome in this patient population.

REFERENCES
95. Malatack JJ, Gartner JC, Urbach AH, et al. Orthotopic liver transplantation, Epstein-Barr virus, cyclosporine, and lympho-


