

Primary Central Nervous System Posttransplant Lymphoproliferative Disorders

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Abstract

Posttransplant lymphoproliferative disorders (PTLDs) represent a spectrum ranging from Epstein-Barr virus (EBV)-driven polyclonal lymphoid proliferations to EBV+ or EBV- malignant lymphomas. Central nervous system (CNS) PTLDs have not been characterized fully. We reviewed the clinical, radiologic, and pathologic features of 12 primary CNS PTLDs to define them more precisely. Patients included 10 males and 2 females (median age, 43.4 years) who were recipients of kidney (n = 5), liver (n = 2), heart (n = 2), peripheral blood stem cells (n = 2), or bone marrow (n = 1). All received immunosuppressive therapy. CNS symptoms developed 3 to 131 months (mean, 31 months) after transplantation. By neuroimaging, most showed multiple (3 to 9) intra-axial, contrast-enhancing lesions. Histologic sections showed marked expansion of perivascular spaces by large, cytologically malignant lymphoid cells that were CD45+, CD20+, EBV+ and showed light chain restriction or immunoglobulin gene rearrangement. In distinction to PTLDs in other organ systems, CNS PTLDs were uniformly high-grade lymphomas that fulfilled the World Health Organization criteria for monomorphic PTLDs. Extremely short survival periods were noted for each CNS PTLD that followed peripheral blood stem cell transplantation. Survival of others with CNS PTLD varied; some lived more than 2 years.

Pathologic lymphoid proliferations that arise after organ transplantation have been recognized for more than a quarter century.¹⁻⁶ As currently defined by the World Health Organization (WHO), posttransplant lymphoproliferative disorders (PTLDs) are lymphoid proliferations or lymphomas that develop in immunosuppressed recipients of solid organ or bone marrow allografts. They are best considered as a spectrum of disease ranging from early, Epstein-Barr virus (EBV)-driven polyclonal proliferations to malignant lymphomas that can be EBV+ or EBV-. The vast majority are of the B-cell phenotype; rare T-cell PTLDs have been described.^{1,3,5,7-11} Patient outcome generally depends on the histologic grade, organ sites involved, tumor burden, and response to therapy.^{5,12,13}

The incidence of PTLDs in the transplantation population has been estimated at less than 2%, with slightly higher rates in the pediatric population.^{7,14,15} Patients undergoing heart-lung or liver-bowel transplantation are at highest risk (5%). Risk is lower following liver, cardiac, and bone marrow allograft (1%-2%) and is lowest after kidney transplantation (<1%).⁷

The anatomic distribution of PTLDs varies with patient age and the type of immunosuppressive therapy. Childhood PTLDs often involve lymphoid tissues including lymph nodes and adenoids and arise in the abdomen (64%), thoracic cavity (50%), and head and neck (25%).^{14,15} PTLDs in adults tend to localize to the liver, lung, lymph nodes, and gastrointestinal tract.⁷ In most cases, the transplanted organ is involved. PTLDs that arise following azathioprine-based immunosuppressive therapies are more common in the allograft and also might involve the central nervous system (CNS); those that follow FK-506- or cyclosporine-based

regimens most frequently involve lymph nodes and the gastrointestinal tract.^{13,16,17}

Among CNS disorders after transplantation, PTLDs follow cerebrovascular disease and infection in frequency. CNS PTLDs were seen in 2% to 7% of brains in the largest autopsy series of posttransplant patients (which most likely overestimates the incidence of clinical disease).^{18,19} Partly owing to their rarity, the spectrum of pathologic features of CNS PTLDs has not been characterized fully, nor has their range of biologic behavior. Case reports and small series seem to indicate that CNS PTLDs are more aggressive as a group than PTLDs involving other organ systems. Recognizing CNS PTLDs and distinguishing them from other nontransplant primary CNS lymphomas is critical because therapeutic options and clinical outcomes can vary substantially.^{20,21} We describe the features of 12 primary CNS PTLDs with the aim of better characterizing their clinical, radiographic, and pathologic features and distinguishing them from other primary CNS lymphomas.

Materials and Methods

We reviewed 12 cases of CNS PTLDs from our files from January 1, 1990, through December 31, 2002. In all cases, the diagnosis of CNS PTLD was established in the absence of clinical or radiologic evidence of PTLD in any other organ system. Clinical data were obtained by review of medical records and included patient demographics, features of the underlying disease necessitating the transplant, type of transplant, immunosuppressive therapy, latency from transplantation to the development of the CNS PTLD, symptoms referable to PTLDs, treatment of PTLDs, and clinical follow-up. All available neuroradiologic studies, including computed tomography and magnetic resonance imaging, were reviewed to document the number, location, size, and characteristics of the CNS lesions.

Brain biopsy specimens or tissue samples derived from postmortem examination were fixed in 10% buffered formalin, routinely processed, paraffin embedded, sectioned at 4 to 6 μ m, and stained with H&E. Reticulin stains were applied to selected cases. Immunohistochemical analysis was performed on formalin-fixed, paraffin-embedded tissue samples with primary antibodies directed at CD45 (monoclonal, dilution 1:80; DAKO, Carpinteria, CA), CD20 (monoclonal, dilution 1:80; DAKO), CD19 (polyclonal, dilution 1:100; DAKO), CD79a (monoclonal, dilution 1:160; DAKO), CD3 (polyclonal, dilution 1:80; DAKO), κ light chain (polyclonal, dilution 1:4; Ventana Medical Systems, Tucson, AZ), λ light chain (polyclonal, dilution 1:4; Ventana Medical Systems), and collagen type

IV (monoclonal, dilution 1:40; DAKO). The antigen-antibody reactions were detected using the avidin-biotin-peroxidase complex method and visualized using 3,3'-diaminobenzidine as the chromogen. Standard positive control samples were used throughout, and normal serum served as the negative control sample. In some cases, clonality was assessed via immunoglobulin gene rearrangement by Southern blot analysis.

EBV status was assessed by in situ hybridization for EBV-encoded small RNA (DAKO) and/or immunohistochemical analysis for EBV nuclear antigen (DAKO) and latent membrane protein-1 (DAKO).

PTLDs in this series were classified as polymorphic PTLDs (P-PTLDs) or monomorphic PTLDs (M-PTLDs) according to WHO criteria.⁷ P-PTLDs have been defined as atypical lymphoid infiltrates that are destructive of the underlying tissues and composed of a heterogeneous cell population containing the full range of B-cell maturation, from a prominent plasmacytic infiltration with no atypia to proliferations composed of immunoblasts with focal or diffuse areas of necrosis. In contrast, M-PTLDs are composed of large, transformed, blastic cells with prominent nucleoli and basophilic cytoplasm. These tumors are monoclonal by light chain restriction or EBV studies. By these definitions, most M-PTLDs would be classified as large B-cell lymphomas under the revised European-American Lymphoma classification.^{3,7,22}

Results

Clinical Features

The clinical features of our 12 cases are listed in **Table 1**. CNS PTLDs occurred in 10 males and 2 females, ranging in age from 1 to 80 years (median, 43.4 years). The organs transplanted included kidney (5 cases), liver (2 cases), heart (2 cases), peripheral blood stem cells (2 cases), and bone marrow (1 case). Medical conditions underlying the requirement for organ transplantation were varied.

All patients received immunosuppressive therapy following transplantation. Therapies included tacrolimus (6 cases), prednisone (9 cases), cyclosporine (4 cases), azathioprine (3 cases), mycophenolate (4 cases), methylprednisolone (1 case), daunorubicin (1 case), vincristine (1 case), asparaginase (1 case), cytarabine (1 case), melphalan (1 case), and muromonab-CD3 (1 case).

The latency between transplantation and development of CNS PTLDs ranged from 3 to 131 months (mean, 31 months). During this period, comorbid conditions included cardiovascular disease; viral, fungal, and bacterial infections; graft-vs-host disease; diabetes mellitus; renal failure; and

Table 1
Clinical Features of Patients With Central Nervous System PTLDs

No./ Sex/Age(y)	Transplanted Organ	Underlying Disorder	Immunosuppressive Drugs	Latency (mo)*	Comorbid Diseases	PTLD Therapy	Follow-up
1/M/1	Liver	Biliary atresia and cirrhosis	FK-506, prednisone	3	Seizure disorder	Multiagent chemotherapy; prednisone	Remission, 62 mo
2/M/80	Liver	Cryptogenic cirrhosis	Mycophenolate	74	CRF, CMV colitis	Megestrol	AWD, 11 mo
3/M/19	Kidney	Obstructive uropathy	FK-506, azathioprine, prednisone	37	Congenital unilateral kidney	XRT, CTL infusion, rituximab, prednisone	Remission, 14 mo
4/M/63	Kidney	FSGS	FK-506, prednisone	17	Hypertension, CHF, AS, CAD, hypercholesterolemia	XRT infusion, prednisone	Remission, 23 mo
5/F/22	Kidney	Renal dysplasia	Cyclosporine, mycophenolate, prednisone	23	Hypertension	Methylprednisolone, XRT	AWD, 24 mo
6/M/50	Kidney	PCKD	FK-506, prednisone	131	Hypertension, chronic sinusitis, SCC, bronchiectasis	XRT, rituximab	Remission, 12 mo
7/M/59	Kidney	Glomerular disease	Cyclosporine, muromonab-CD3, azathioprine, prednisone	6	Hypertension, gout, acute rejection	Azathioprine, cyclosporine	DOD, 2 mo 13 d
8/M/51	PBSC	AML; PML	Daunorubicin, cytarabine	3	GVHD	Prednisone, dapsone, cyclosporine	DOD, 1 mo
9/M/51	PBSC	Multiple myeloma	Melphalan, mycophenolate, methylprednisolone	11	GVHD	Methylprednisolone, mycophenolate	DOD, 1 wk
10/M/6	Bone marrow	Lymphoblastic leukemia	Prednisone, vincristine, asparaginase	23	Fungal infection	Untreated	DOD, 22 mo
11/F/59	Heart	Ischemic cardiomyopathy	Cyclosporine, mycophenolate, prednisone	12	Cryptococcal meningitis, CMV retinitis, type 2 diabetes mellitus	Methotrexate, leucovorin	DOD, 1 mo
12/M/60	Heart	Ischemic cardiomyopathy	Azathioprine, prednisone, cyclosporine, tacrolimus	32	PUD, hypertension, gout, CRF, hearing loss	Methotrexate, cytarabine, thiotepa, XRT	LFU

AML, acute myelogenous leukemia; AS, aortic stenosis; AWD, alive with disease; CAD, coronary artery disease; CHF, congestive heart failure; CMV, cytomegalovirus; CRF, chronic renal failure; CTL, cytotoxic T-lymphocyte; DOD, died of disease; FSGS, focal segmental glomerulosclerosis; GVHD, graft-vs-host disease; LFU, lost to follow-up; PBSC, peripheral blood stem cells; PCKD, polycystic kidney disease; PML, promyelocytic leukemia; PTLD, posttransplant lymphoproliferative disorder; PUD, peptic ulcer disease; SCC, squamous cell carcinoma; XRT, radiation therapy.

* From transplantation until the development of the central nervous system PTLD.

seizures. CNS PTLD was the first manifestation of PTLD for all patients included in the study. There was no clinical or radiologic evidence of other organ involvement at the time of diagnosis of the CNS PTLD. In the 4 cases that included a postmortem examination, PTLD was not noted in any other organ systems, including the allograft.

Therapy was not initiated for 1 patient because the diagnosis of CNS PTLD was not established until the post-mortem examination (case 10). In the remaining 11 cases, PTLDs were treated with therapies that included the following: corticosteroids (6 cases), radiation therapy (5 cases), cytotoxic T-lymphocyte infusion (2 cases), cyclosporine (2 cases), anti-CD20 antibodies (ie, rituximab, 2 cases), methotrexate (2 cases), leucovorin (1 case), cytarabine (1 case), azathioprine (1 case), megestrol (1 case), thiotepa (1 case), dapsone (1 case), and mycophenolate (1 case) (Table 1).

Five patients died of CNS PTLDs at periods of 1 week (case 9), 1 month (cases 8 and 11), 2 months and 13 days (case 7), and 22 months (case 10) after diagnosis. Of the 3 patients who died with the shortest intervals following

PTLDs, 2 had undergone peripheral blood stem cell transplantation. Four patients recovered, and their CNS PTLDs were in complete remission at 12, 14, 23, and 62 months. Two patients remained alive with disease at 11 and 24 months. One case was lost to clinical follow-up.

Radiologic and Pathologic Features

The radiologic and pathologic features of our cases are listed in **Table 2**. By neuroimaging that included magnetic resonance imaging or computed tomography scan, CNS PTLDs were seen as multiple, contrast-enhancing, intra-axial lesions in 10 of 12 cases and as solitary lesions in the remaining 2 cases **Image 1**. In all cases, the lesions were associated with extensive peritumoral edema. CNS parenchymal lesions were distributed in highest frequency in the cerebral hemispheres (44/54 [81%]), brainstem (8/54 [15%]), and cerebellum (2/54 [4%]). In the cerebral hemispheres, lesions were most common in the cortex and white matter (18/54 [33%] each), basal ganglia (7/54 [13%]), and corpus callosum (1/54 [2%]). No spinal cord involvement was noted in the 12 cases.

Table 2
Radiologic and Pathologic Features of Central Nervous System PTLDs*

Case No.	Neuroimaging		Immunophenotype	EBV Status
	Topography of Lesions	No. of Lesions		
1	Cerebrum, basal ganglia, cerebellum	7	CD19+, CD20+, CD22+, λ+	+ (EBER)
2	Frontal, parietal, temporal lobes	4	CD20+, increased MIB-1, κ+	+
3	Basal ganglia, frontoparietal lobes	3	CD20+, λ+	+ (EBER)
4	Frontal gray-white matter junction	8	CD20+, CD79a+	+ (EBER)
5	Pons, corpus callosum, occipital, parietal lobes	9	CD20+	+ (EBER)
6	Pons	1	CD20+, CD30+, EBV-LMP-1+	+ (LMP-1)
7	Parietal lobe	1	CD20+, CD30+, immunoglobulin rearrangement	+ (EBNA/LMP-1)
8	Forebrain white matter	3	CD20+, κ+	+
9	Parietal, temporal lobes	5	CD20+, λ+	+
10	Cerebral hemispheres, pons	4	CD20+, λ+	+ (LMP-1)
11	Cerebral hemispheres, basal ganglia	6	CD20+, κ+	-
12	Cortical and brainstem lesions	3	CD20+, CD79a w+	+ (LMP-1)

EBER, Epstein-Barr virus–encoded small RNA; EBNA, Epstein-Barr virus nuclear antigen; EBV, Epstein-Barr virus; LMP-1, latent membrane protein-1; PTLD, posttransplant lymphoproliferative disorder; w, weak staining.

* The histologic diagnosis for all cases was monomorphic PTLD.

All cases were classified pathologically as M-PTLDs as defined by WHO criteria. These were composed almost entirely of large, transformed cells with large, irregular nuclei, prominent nucleoli, and increased mitotic activity (Image 2A), (Image 2B), and (Image 2C). In all lesions, tumor cells showed a perivascular distribution and grew with a concentric, laminar pattern away from the central vessel. Between cell layers, the stroma was highlighted by reticulin stains or by immunohistochemical analysis for collagen IV (Image 2D). In the majority of cases, transmural invasion of blood vessel walls by tumor cells was seen. Both sheet-like growth of tumor cells and infiltration of CNS parenchyma by

individual tumor cells were typical (Image 2C). Necrosis was a common feature and occupied from 30% to 90% of the submitted specimen. In the background of these lesions were scattered small lymphocytes.

By immunophenotype, all tumors were CD20+ (Image 2E). Three tumors so tested showed expression of additional B-cell markers (CD19, CD22, or CD79a). The T-cell marker CD3 demonstrated admixed lymphocytes in the background. Results from immunohistochemical analysis for light chains were available for 7 cases. Among these, all 7 were light chain–restricted, 3 for κ and 4 for λ. Of 12 tumors, 11 showed evidence of EBV infection within tumor cells (Image 2F).

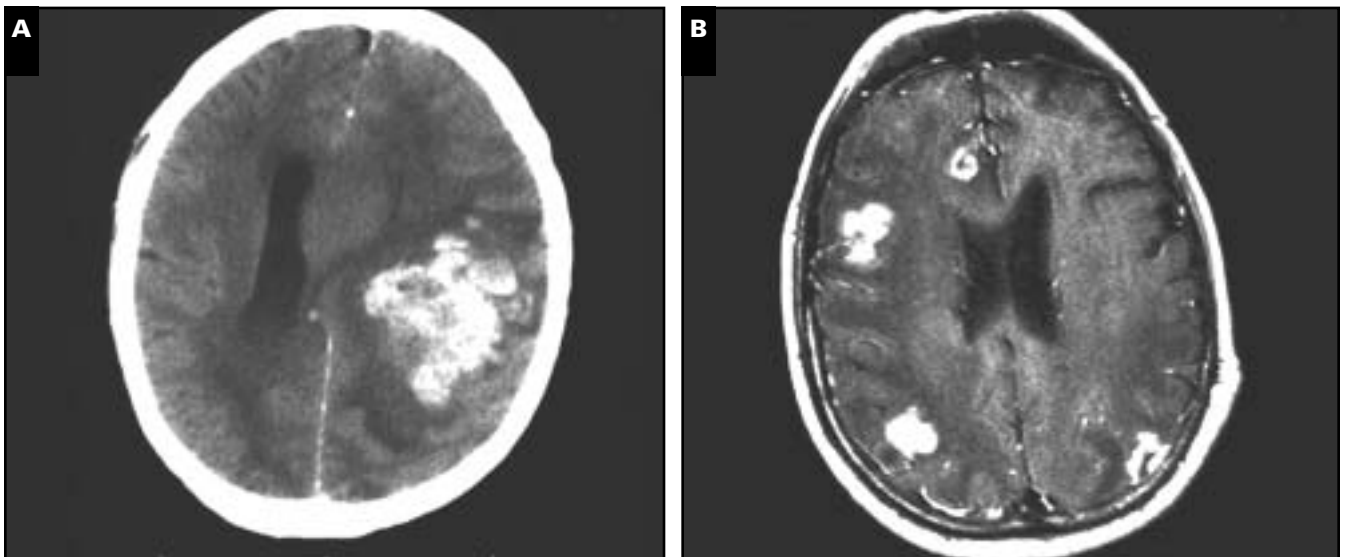


Image 1 Neuroimaging of central nervous system posttransplant lymphoproliferative disorders (CNS PTLDs). **A** (Case 7), Computed tomography scan demonstrating a solitary, contrast-enhancing mass centered in the left parietal lobe with extensive peritumoral edema and midline shift. **B** (Case 2), More often, CNS-PTLDs were multifocal, as seen in the axial magnetic resonance image. Four discrete contrast-enhancing lesions are seen in the left and right cerebral hemispheres

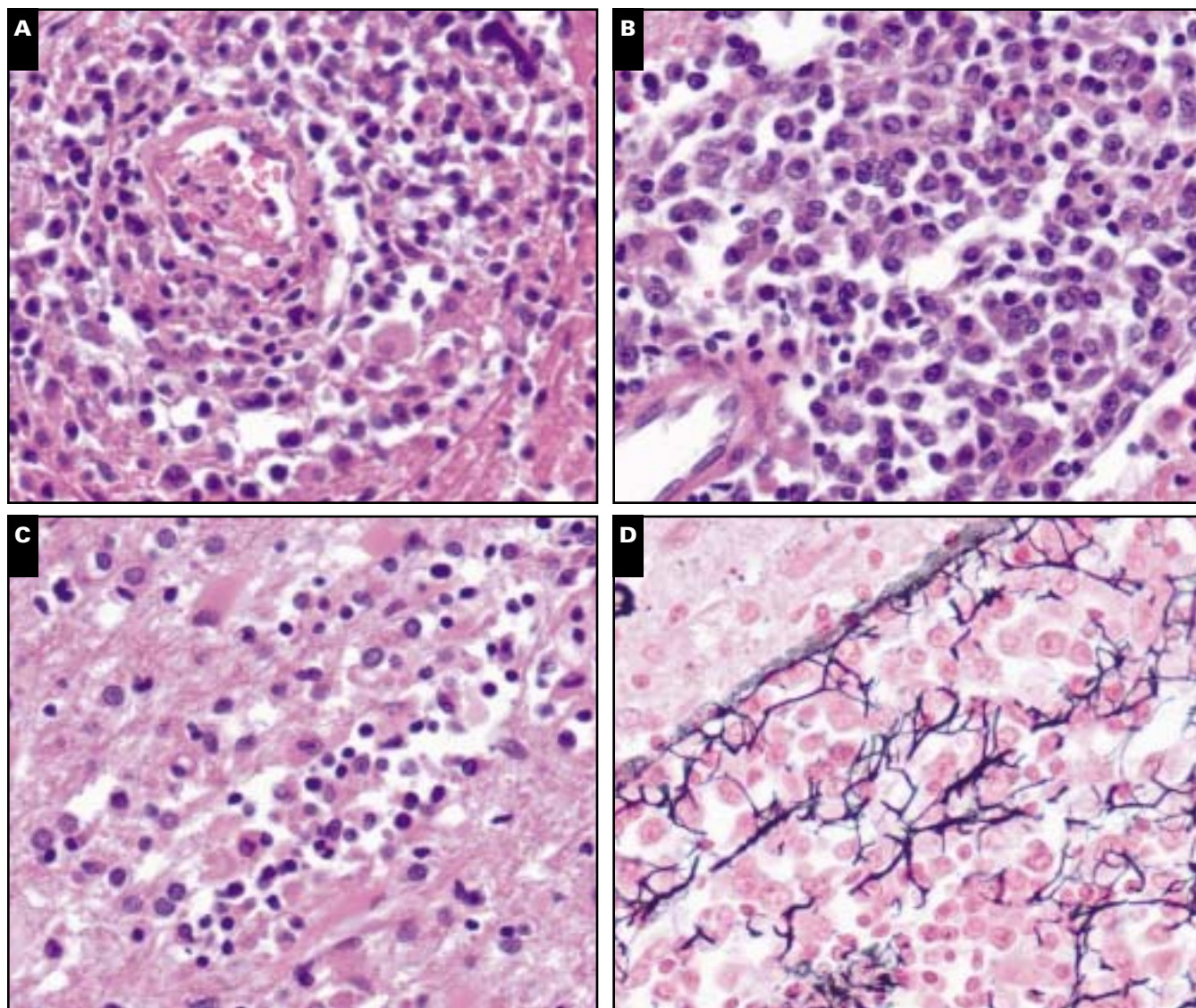


Image 2 Histopathologic and immunohistochemical features of central nervous system posttransplant lymphoproliferative disorders (CNS PTLDs). **A** and **B**, Tumor cells of CNS-PTLDs grow primarily around small and medium-sized intraparenchymal blood vessels and expand the perivascular spaces (**A**, H&E, $\times 10$; **B**, H&E, $\times 40$). **C**, In other regions, neoplastic cells can be seen infiltrating CNS structures and associated with reactive astrocytes (H&E, $\times 40$). **D**, The concentric, laminar growth of CNS-PTLDs around blood vessels can be detected by stains for reticulin (reticulin, $\times 40$).

Discussion

PTLDs are clinically and morphologically heterogeneous lymphoid tumors, their common elements being a history of organ transplantation and immunosuppression.^{3,7,21,23} These lesions arise most often in the allograft, but also frequently affect other organs, including the gastrointestinal tract, lung, lymph nodes, and bone marrow.^{3,7,12,14,24} Although their occurrence in the brain is relatively rare, it is critical for the pathologist to distinguish them from other CNS lymphomas and lymphoid proliferations. This is especially true for CNS PTLDs: the brain was

the first and only manifestation of PTLID in all patients in this study. Since immunosuppressive therapy is highly relevant to the pathogenesis of PTLIDs, treatment of these disorders nearly always involves its reduction.^{23,25,26}

Our review of 12 cases suggests that CNS PTLIDs are monomorphic by WHO criteria and have histopathologic features similar to the diffuse large cell lymphomas that occur in the HIV-infected population and elderly people—so-called primary CNS lymphoma (PCNSL). CNS PTLID and PCNSL are aggressive, large cell lymphomas, nearly always with a B-cell phenotype. Both have a marked predisposition to grow within perivascular spaces, to invade

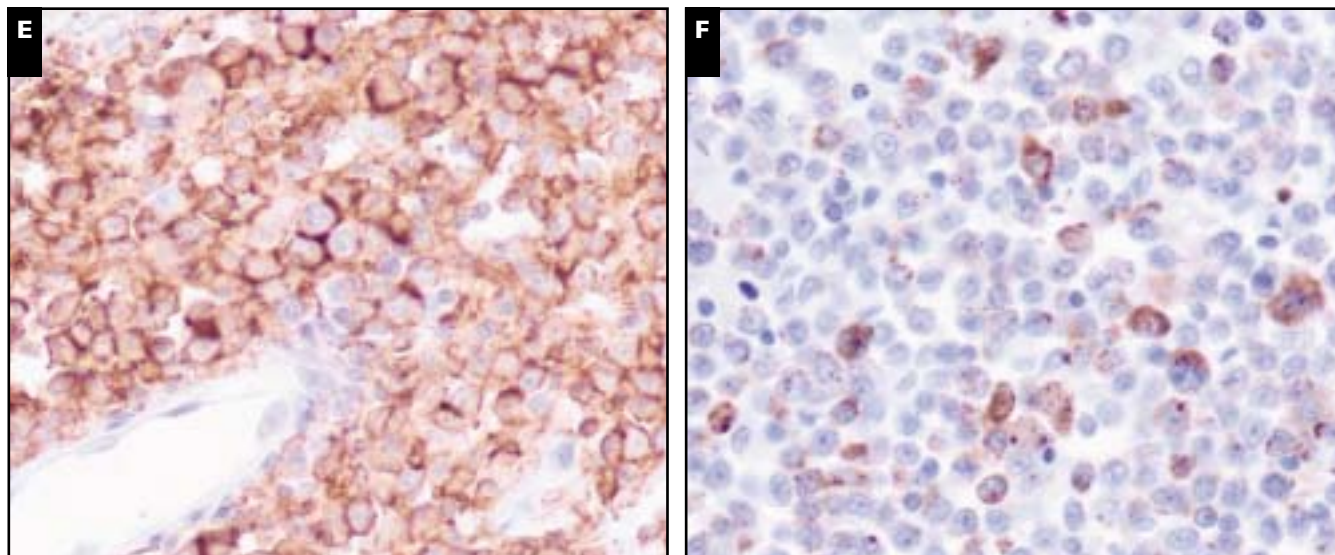


Image 2 (cont) **E** and **F**, Neoplastic cells are strongly positive for CD20, indicating a B-cell phenotype (**E**, CD20, $\times 40$) and are positive for Epstein-Barr virus in the majority of cases (**F**, immunohistochemical analysis for latent membrane protein-1, $\times 40$).

vascular walls, and to display a concentric, laminar pattern around central vessels that can be highlighted by stains for reticulin or collagen IV. PCNSLs and CNS PTLDs also are similar in their ability to infiltrate CNS parenchyma, and both typically demonstrate extensive necrosis. Similar to CNS PTLDs, the PCNSLs that arise in the HIV-infected population are EBV+. PCNSLs that arise in elderly people usually do not show evidence of EBV expression.²⁷⁻²⁹

The distinction between PCNSLs and monomorphic CNS PTLDs lies in the clinical history, response to therapy, and clinical outcomes. The requirement for transplantation—solid organ or bone marrow allograft—together with posttransplant immunosuppression is absolute for the diagnosis of PTLDs. The majority of PTLDs in other organ sites occur within 1 to 4 years after transplantation, with slightly shorter latency periods after azathioprine therapy.^{1,3,7,23} Similar latency periods (3-131 months) were seen for PTLDs that arose in the CNS.

The majority of CNS PTLDs were multifocal on neuroimaging studies, often with large numbers of discrete, contrast-enhancing masses. When the lesions of CNS PTLDs were multiple, the number varied from 3 to 9, and most were confined to the supratentorial compartment. In 4 cases, both infratentorial and supratentorial lesions were seen. The solitary lesions (cases 6 and 7) involved the pons and the parietal lobe, respectively. In contrast, PCNSLs can be solitary or multifocal, depending mostly on the immunologic status of the patient.³⁰ Up to 80% of PCNSLs that arise in immunocompromised patients are multifocal. In contrast, the majority of PCNSLs that arise in nonimmunocompromised patients are solitary.³¹⁻³⁴ Thus, neuroimaging features of CNS PTLDs overlap most with those of PCNSLs that

arise in immunocompromised patients. It has been suggested that PCNSL is a “whole brain” disease, with diffuse involvement of CNS structures manifesting as solitary or multiple masses on neuroimaging, and the same may be true of CNS PTLDs.³² Most neuroimaging studies of PCNSLs, as well as the clinical review of PTLDs by Phan et al,²⁵ have stressed the intimacy of these lymphomas with the ependymal lining and distribution in the periventricular region. Distinguishing the contrast-enhancing lesions of CNS PTLDs or PCNSLs from infection by neuroimaging is not always possible, and a tissue-based diagnosis usually is required.^{27,32,34}

The histopathologic features of PTLDs in most organs vary from plasmacytic hyperplasia to P-PTLD to M-PTLD.^{1-3,7,13,14,21,23,35} In contrast, all of the cases of CNS PTLD in the present study were M-PTLD, with no cases representing plasmacytic hyperplasia or P-PTLD. Moreover, all of the CNS PTLDs described recently by Phan et al²⁵ (who used the revised European-American Lymphoma classification) most likely would be classified as M-PTLD by current WHO criteria. Reasons for the predominance of M-PTLDs in the CNS are not clear. The disease might remain in a subclinical phase for a longer period in the CNS, with detection and diagnosis occurring only once it has progressed to M-PTLD. Alternatively, the CNS might be an immunologically privileged site in which EBV infection can drive neoplastic progression more efficiently. In either case, all CNS PTLDs reported to date have been aggressive lesions and, as a group, are highly overrepresented by M-PTLDs.

PTLDs involving organ systems other than the brain have variable outcomes, depending on the histopathologic grade, tumor burden, organ sites involved, and response of

the lesion to reduction of immunosuppressive therapy. Lower clinical stage PTLDs have less aggressive clinical courses, especially in the case of plasmacytic hyperplasia. Higher stage disease and more aggressive clinical behavior are associated with M-PTLDs.^{1,3,7,35} The overall mortality for PTLDs is 60% in solid organ recipients and 80% in bone marrow allograft recipients.⁷ Since most CNS PTLDs are monomorphic, aggressive B-cell lymphomas that involve an organ critical for life, it might be expected that patients would have short survival periods. Indeed, the prognosis with other aggressive lymphomas of the CNS is dismal. Life expectancy for patients with PCNSL, anaplastic large cell lymphoma of the brain, or intravascular lymphoma is typically less than 1 year, often with extremely short survival periods. PCNSL usually is responsive to corticosteroids in the short term but is not curable.^{27,29} Other lower grade forms of lymphoma that involve the CNS less frequently, ie, secondary involvement by systemic lymphoma, occasionally might be amenable to therapy.^{7,20,29}

We found that survival periods varied substantially in patients with CNS PTLDs. At least in some instances, survival for more than a year is possible. Four patients with CNS PTLDs recovered with decreased immunosuppression, having no evidence of disease at 12, 14, 23, and 62 months. Two patients remained alive with stable disease at 11 and 24 months. The longer survival of patients with CNS PTLD than other forms of primary CNS lymphomas is a notable and distinguishing feature. Prolonged survival most likely is related to tumoral response to the reduction of immunosuppressive therapy in patients with CNS PTLD. Such therapeutic modulation of immunosuppression is not as readily achieved in most other patients with high-grade, EBV-driven lymphomas of the CNS.

Although we had only a small number of patients in the present study, survival did not seem to correlate significantly with patient age. Rather, we found that survival depended on other factors such as type of transplant and likely depended on response to reduced immunosuppression. Among the 5 patients who died of disease, the 2 patients who underwent peripheral blood stem cell transplantation had the shortest survival periods (1 month or less). PTLDs that arise following peripheral blood stem cell transplantation have been shown to be derived from allografted stem cells. T-cell depletion and HLA mismatch of the allograft are risk factors for developing PTLD after hematopoietic stem cell transplantation. Recipients frequently have a rapidly fatal clinical course that is believed to be due to a lack of T-cell response to EBV.^{7,23,26}

Thus, the spectrum of PTLDs that arise in the CNS seems to be skewed strongly by an overrepresentation of M-PTLD compared with P-PTLD or plasmacytic hyperplasias. These EBV+, aggressive B-cell lymphomas have many neuroimaging and pathologic similarities to PCNSLs that arise in the

immunocompromised population but are distinguished from them by the clinical history of transplantation and therapeutic immunosuppression. The extremely short survival periods for some patients with CNS PTLDs following peripheral blood stem cell transplantation and the possibility of longer survival in patients with CNS PTLD following solid organ transplantation might be distinguishing features.

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