CNS Lymphoma: A Practical Diagnostic Approach

Caterina Giannini, MD, PhD, Ahmet Dogan, MD, PhD, and Diva R. Salomão, MD

Abstract

The concept and understanding of central nervous system (CNS) lymphoma have greatly evolved in the past few years. Better characterization of a number of lymphoproliferative neoplasms through clinical, immunophenotyping, and molecular studies is reflected in a much more complex WHO Classification of Tumours of Hematopoietic and Lymphoid Tissue. The term “primary CNS lymphoma” is now restricted to primary diffuse large B-cell lymphoma confined to the CNS (and/or to the eye) that occurs in immunocompetent patients. Many other lymphoma subtypes, some of which are primary or exclusive to the CNS, such as lymphomas of the dura and immunodeficiency-associated lymphomas, are excluded from this definition. We describe the clinical and morphologic features of a diverse group of lymphomas occurring in the CNS, including primary CNS lymphoma, primary vitreoretinal lymphoma, lymphomatosis cerebri, Epstein-Barr virus–associated lymphoproliferative disorders, low-grade B-cell lymphoma, T-cell lymphoma, anaplastic large cell lymphoma, intravascular large B-cell lymphoma, and Hodgkin lymphoma. The purpose of this review is to provide a practical approach to the diagnosis of an often-challenging entity, focusing on how to maximize the use of small tissue biopsies and prevent diagnostic traps, which we have encountered with similar cases. Clinical, radiologic, and histologic examples are presented.

Key Words: CNS, Large B-cell lymphoma, Primary CNS lymphoma, Retina, Vitreous.

INTRODUCTION

Malignant lymphoma can occur in the central nervous system (CNS) in the absence of involvement elsewhere at the time of diagnosis or as secondary involvement in the setting of systemic lymphoma. The most common morphology in both primary and secondary CNS lymphomas is that of a diffuse large B-cell lymphoma (DLBCL), but a variety of lymphomas, including low-grade B-cell lymphomas and T-cell lymphoma, can affect the CNS. According to the most recent WHO Classification of Tumours of Hematopoietic and Lymphoid Tissue (1), the term “primary CNS lymphoma” (PCNSL) should be reserved for primary DLBCL of the CNS, a rare parenchymal brain lymphoma confined to the CNS (and/or to the eye) occurring in immunocompetent patients (2). A variety of other lymphomas, which may also manifest primarily or exclusively in the CNS, such as lymphomas of the dura and immunodeficiency-associated lymphomas, are excluded from this definition. Intravascular large B-cell lymphoma (IVLBCL), also a rare form of disseminated B-cell lymphoma characterized by selective growth of lymphoma cells within small vessels/capillary lumina, can also present clinically with a predominant neurologic variant secondary to CNS involvement (1).

With rare exceptions, histopathologic diagnosis is mandatory in planning appropriate treatment, which typically consists of systemic chemotherapy with or without whole brain radiotherapy. Diagnosis is most often obtained using stereotactic needle biopsy. Because most lesions are located deep into the brain, stereotactic needle biopsy is the standard diagnostic procedure for patients with suspected CNS lymphoma. In contrast to other brain tumors, virtually all review articles and national or international guidelines recommend that efforts at PCNSL resection not be undertaken (3). The US National Comprehensive Cancer Network guidelines suggest biopsy using the least invasive approach (referring to a specialized center if stereotactic biopsy is not available) when cerebrospinal fluid (CSF) examination (if safe) and eye examination fail to yield the diagnosis (http://www.nccn.org/professionals/physician_gls/pdf/cns.pdf). This traditional view that the extent of resection has no prognostic impact and may even be detrimental is based on a small number of retrospective studies (4–7) and has only recently been challenged (3).

In our experience, biopsy has been highly successful in diagnosing CNS lymphoma, but obtaining a definitive diagnosis may be challenging for a variety of reasons. The primary goal of this review is not to present an in-depth discussion of all types of lymphoma that may affect the CNS. Rather, we share our practical diagnostic approach, largely through a series of cases that we have encountered in our clinical in-house and consultation practice and that illustrate the difficulties and potential pitfalls in diagnosing CNS lymphoma, and offer suggestions as to how to handle those difficult cases. We will largely concentrate on lymphomas that primarily involve the neuraxis rather than the leptomeninges or dura.

PRIMARY CNS LYMPHOMA

Primary CNS lymphoma is rare, representing less than 1% of all non-Hodgkin lymphomas (NHLs) and approximately 2% of all primary brain tumors (8). Primary CNS lymphoma...
occurs at all ages, with a predominance of patients in their 60s or 70s and with a slight male predominance, with a male-to-female ratio of 3:2. Most patients (50%-80%) present with focal neurologic deficits that are related to the location of the lesions. Approximately 60% of patients with PCNSL present with single or multiple intraparenchymal supratentorial lesions, whereas 13% of PCNSLs primarily involve the posterior fossa, and only a minority of cases present primarily with diffuse leptomeningeal involvement. Indeed, leptomeningeal presentation should prompt workup for a systemic lymphoma. Imaging characteristics are often suggestive of the diagnosis. Lesions are typically symmetric, located in the deep periventricular white matter with occasional subependymal extension, many times involving the corpus callosum. Signal characteristics on magnetic resonance imaging (MRI) are also quite typical, with isointense or hypointense T2 signals and associated restricted diffusion due to their cellular nature. They avidly and homogenously enhance after the administration of contrast, with variable perilesional edema (Fig. 1a).

Primary CNS lymphoma is a highly aggressive lymphoma associated with poor prognosis (median survival, 9 months).

Primary CNS lymphoma is a DLBCL with large blastoid cells, pleomorphic nuclei, and single or multiple distinct nucleoli (immunoblasts and centroblasts) (Figs. 1b, c). Tumor cells show a differentiation state corresponding to late germinal center exit B-cells (9) and, as such, express specific proteins that can be exploited as diagnostic markers (Figs. 1d–f, 2). In addition to the expression of pan-B cell markers, including CD19, CD20, and CD79a, lymphoma cells express BCL6 (although often only focally) and MUM1 (>90%) in most cases (Figs. 2a–f). Expression of proteins associated with plasma cell differentiation (CD38, CD138) is absent. Tumor cells may also express CD10 (10) and BCL2, which is not related to the differentiation (CD38, CD138) is absent. Tumor cells may also express CD10 (10) and BCL2, which is not related to the t(14;18)(q32;q21) translocation (1).

In most cases, the diagnosis of CNS lymphoma, even with the limited tissue sample often provided by stereotactic needle biopsy, is straightforward. In our practice, we find reliable and cost-effective method for providing a definitive diagnosis, a first-line diagnostic approach based on hematox- ylin and eosin (H&E) findings, in conjunction with CD3 and CD20 immunostains. We reserve additional studies only for selected cases depending on morphologic, clinical, and imaging features. Immunohistochemical classifiers, including the original Hans classifier, based on CD10, BCL6, and MUM1 (11) and the more recent ones, which include a larger number of markers especially of germinal center B-cells (12), have long been used in nodal DLBCL as surrogates of gene expression profiling to distinguish 2 basic subgroups: the “activated B-cell” and the “germinal center B-cell type,” which have significantly different clinical courses and prognoses (13, 14). The rationale for this distinction in PCNSL, based on nodal DLBCL profile, has been doubted given the fact that gene expression profiling has shown PCNSL to be segregated over the entire spectrum of DLBCL (10), and no evidence of distinctive subgroups in PCNSL has been found in accordance with clinical observations (15). In addition, classifying PCNSL as a germinal center B-cell type does not have treatment implications. BCL6 protein expression, the marker that has been most extensively studied as a possible stratification factor for PCNSL, also seems to be very problematic given the fact that it is frequently expressed in PCNSL, with most cases showing more than 50% to 60% BCL6-positive cells (15). Flow cytometry, a technique that has become essential for the diagnosis of many hematologic malignancies in routine clinical practice, has a very limited role in PCNSL, largely restricted to the analysis of CSF and mostly for staging and long-term follow-up of PCNSL patients rather than for primary diagnosis (15, 16). A variable number of reactive small T lymphocytes accompany PCNSL, with some cases showing only scattered T lymphocytes and others showing a large number of lymphocytes, nearly obscuring lymphoma cells. In a recent study, the presence of reactive perivascular T-cell infiltrates has been shown to be associated with significantly better overall survival, particularly among patients treated with high-dose methotrexate chemotherapy (17).

Although primary CNS presentation of systemic NHL is very rare, staging of all patients first diagnosed as having lymphoma in the CNS is mandatory to exclude this possibility. In our practice, slit-lamp eye examination, postion emission tomography scan, bilateral bone marrow aspirate and biopsy, CSF examination (if safe to perform), lactic dehydrogenase, and human immunodeficiency virus tests are routinely performed in patients presenting with CNS lymphoma, whereas spinal MRI, testis ultrasound, and chest/abdomen/pelvis computed tomography may be performed in selected patients (Dr B.P. O’Neill, personal communication). Primary CNS lymphoma and secondary CNS involvement by systemic DLBCL cannot be distinguished simply on the basis of their morphology and immunophenotype, although CD10 expression, particularly in association with a relatively low Ki67 labeling index (<50%), should prompt an intense search of primary extracerebral DLBCL or follicular lymphoma (15). Central nervous system involvement in systemic NHL occurs infrequently (approximately 4% of cases) and may occur either at the time of primary treatment or at relapse. The risk of CNS relapse is low (2%-3%) or high (>15%), depending on lymphoma histology (low vs high grade), primary site (e.g., testis is high risk), and treatment (CNS prophylaxis) (18).

**PRIMARY VITREORETINAL LYMPHOMA**

Intraocular lymphoma is also rare, accounting for less than 1% of all NHLs (19). It represents a diverse group of hematologic malignancies involving different tissues within the eye (e.g., iris, ciliary body, choroid, vitreous, and retina), each with different morphologic, immunophenotypic, genetic, and clinical features (20, 21) on the basis of which it should be classified (22). Among these, primary vitreoretinal lymphoma (PVRL), characterized by vitreous and/or retinal lymphomatous infiltration, is considered a subset of PCNSL (1). Similar to PCNSL, PVRL is an aggressive lymphoma. Treatment of PVRL can induce remission, but disease relapses are common and cure is rare. Approximately 15% to 25% of patients with PCNSL develop vitreoretinal involvement in the course of their disease (23), and brain involvement is present and/or develops in 56% to 90% of patients with PVRL (24), ultimately causing an unfavorable outcome. The largest reported series of primary intraocular lymphoma cases included 83 immunocompetent patients assembled from 16 centers in 7 countries as a result of a
A 71-year-old woman presented with cognitive decline. (A) Magnetic resonance images, including T1 (left), FLAIR (middle), and T1 postcontrast (right) sequences, demonstrated an avidly enhancing mass with moderate surrounding edema involving the deep white matter of the left parietal lobe and the splenium of the corpus callosum. (B, C) Primary CNS lymphoma cells diffusely infiltrate the parenchyma (B) and show a characteristic angiocentric pattern (C). (D, E) Anti-CD20 immunohistochemistry highlighted the large lymphoma cells (D) in comparison with the small infiltrating CD3-positive reactive T lymphocytes (E). (F) Variable numbers of KP1-positive macrophages. Original magnification: (B, D–F) 200×; (C) 400×.
multi-institutional international collaboration (24). In these patients, the disease was confined to the eyes at diagnosis, with no evidence of brain, systemic, or spinal cord lymphoma; their symptoms were typical of vitreoretinal involvement (i.e. blurred vision, decreased visual acuity, and floaters). The median age of these patients at diagnosis was 63 years (range, 24–85 years); women represented 57% of patients. Similar to PCNSL patients, patients with PVRL have a limited life expectancy, with the median progression-free and overall survival at 29.6 and 58 months, respectively, regardless of treatment type (24). In this study, the diagnosis was made via vitrectomy in 74 (89%) cases, via choroidal/retinal biopsy in 6 (7%) cases, and via ophthalmic slit-lamp examination in 3 (4%) cases. Of these last 3 patients, 1 was subsequently diagnosed via positive CSF cytology, and 2 underwent brain biopsy at the time of tumor progression.

Primary vitreoretinal lymphoma is also typically a DLBCL characterized by large atypical lymphocytes with high nuclear-cytoplasmic ratio, irregular nuclear membrane, coarse chromatin, and scant cytoplasm (Fig. 3). In view of its rarity, very few studies describing the immunophenotype of intraocular lymphoma are available (25, 26). In the study by Raparia et al (26), which included 16 patients, 11 of which were diagnosed as having DLBCL, only a limited panel of antigens (CD19, CD20, CD5, CD10, and κ/λ light chains) was examined by flow cytometry. The study by Coupland et al (25) included 8 intraocular lymphoma cases (and 42 cases of PCNSL), including 2 enucleated eyes and 6 chorioretinal biopsies examined with a wider panel of antibodies, including antibodies to CD3, CD20, CD10, PAX5, MUM1, BCL6, IgL, and IgH, among others. Similar to PCNSL, intraocular lymphoma demonstrates an immunophenotype consistent with mature B-cells that have undergone germinal center reaction (25).

Vitreous aspiration biopsy is the preferred diagnostic method for PVRL; however, its sensitivity has varied greatly in different studies (26, 27). Multiple diagnostic procedures may be necessary before a definitive diagnosis is achieved, particularly in cases with few neoplastic cells intermixed with reactive cells (28) or in cases where neoplastic cells are markedly degenerated (26). The presence of vitreous cells on
slit-lamp examination (Fig. 3a) in an older patient with persistent symptoms of uveitis, associated with the finding of retinal and subretinal infiltrates on optical coherence tomography, is virtually diagnostic of PVRL (19). In patients with associated CNS lesions, a diagnostic vitrectomy and/or retinal biopsy, in addition to CSF cytology, may prevent further need for a stereotactic brain biopsy prior to treatment.

Secondary involvement of the eye by a systemic DLBCL is rare and usually presents with choroidal infiltrates in the late stages of the disease. In a recent study, ocular involvement in systemic lymphomas was found in some cases to be limited to vitreoretinal involvement, therefore mimicking PVRL (29). Similar to what occurs in the CNS, rare intraocular T-cell lymphomas with exclusive vitreoretinal involvement have been reported, most likely representing secondary intraocular involvement (26, 30).

**FIGURE 3.** Primary vitreoretinal lymphoma. (A) A 67-year-old woman with complaints of blurred vision and floaters underwent slit-lamp examination, which revealed the presence of vitreous aggregates. (B, C) This was followed by a vitreous aspiration biopsy that demonstrated a cellular specimen with few preserved large atypical lymphocytes (B), which were CD20-positive (C). (D) A 79-year-old woman with a history of progressive visual loss evolving to severe ocular pain and blindness underwent eye enucleation. This revealed extensive retinal and subretinal infiltrates with large atypical lymphocytes totally effacing the retinal architecture. The asterisk demarcates the subretinal space, indicating the retinal pigment epithelium superiorly and the Bruch membrane inferiorly. (E) The neoplastic cells are CD20-immunopositive; the choroid is not immunostained. Original magnification: (B) 400×; (C) 600×; (D, E) 200×.

**DIAGNOSTIC CHALLENGES IN PCNSL**

Diagnostic challenges in reaching a diagnosis of PCNSL may arise in a variety of situations. By far, the most common diagnostic challenge is the ability to reach a definitive diagnosis when corticosteroids have been administered prior to the biopsy; however, other challenges, including limited biopsy sample size and occurrence of unusual growth patterns such as “lymphomatosis,” are not uncommon.

**CORTICOSTEROID EFFECTS**

Corticosteroids can have a profound apoptotic effect on lymphoma cells, causing them to disappear in a very short time interval (31), a phenomenon referred to as vanishing lymphoma (32). Steroid effect can be quite variable, with some cases showing scattered apoptotic bodies among tumor cells.
and with other cases showing numerous apoptotic bodies with no remaining intact diagnostic cells (Figs. 4a, e–f). In our experience, some of these cases, especially those demonstrating “florid apoptosis,” can be rescued from a diagnostic point of view by obtaining multiple levels from tissue blocks and preserving a few unstained sections at each level for confirmatory immunostains. One example is illustrated in Figures 4a to d. Once lymphoma cell debris has disappeared, only an extensive macrophage infiltrate, which closely mimics primary demyelination, remains (Fig. 5). Despite the similarities between the histopathologic features of treated lymphoma and demyelination, there are, in our experience, subtle differences that can provide clues to the correct interpretation of the biopsy. At times, a definitive diagnosis may have to be postponed until an additional biopsy has been obtained, as in the illustrated case (Figs. 5a–f vs h–j). Myelin loss is often marked but is typically not as sharply demarcated from the surrounding intact white matter as in classic active demyelination (Fig. 5a). Axons are also somewhat less preserved and not simply “spread apart” by infiltrating foamy macrophages, as in active demyelination (Figs. 5b, d). Their density is often decreased to some extent and, not infrequently, a number of axonal spheroids are present, consistent with axonal damage, a finding that is most unusual in primary demyelination. Although large atypical neoplastic B-cells disappear from the lesion, infiltrating small T lymphocytes are often moderately to highly numerous, and their distribution is often more diffuse than in demyelination, in which they are typically concentrated around perivascular spaces (Fig. 5f).

Despite the marked apoptotic effect, the impact of steroids on the diagnosis of PCNSL is highly variable; in many cases, a diagnosis can still be made even when steroids have been used (32–34). In our series of 109 PCNSL patients, 64% had received corticosteroids before biopsy, and most did not experience significant radiographic change or require a second biopsy for diagnosis. We had 13 patients (14%) in which a repeat biopsy was performed to reach the diagnosis; they included 8 patients who had received steroids and 5 patients who had not, a difference that was not statistically significant (34). Similar to our study, in a review of 58 PCNSL cases in immunocompetent patients, Haldorsen et al (33) found the first biopsy to be nondiagnostic in one third of patients younger than 65 years and in 4% of patients older than 65 years, with a median time of 100 days (range, 9–290 days) from the first biopsy to the final diagnosis in their series. Because only 22% of these patients had received corticosteroids before biopsy, they concluded that “the unfavorable effect of steroids on the yield of biopsy was not statistically significant in our small series (33).” In our series, we identified only 3 PCNSL patients with lesion regression, one of which was considered a “vanishing tumor,” supporting the view that true vanishing lymphoma is a rare phenomenon. We recommend that, when possible, corticosteroids be postponed until the biopsy has been obtained, but ultimately, the use of corticosteroids should be determined by the clinical circumstances and by necessity, rather than by the concern of obscuring PCNSL diagnosis. In cases in which contrast enhancement persists after administration of corticosteroids, a biopsy can still be performed with high diagnostic yield. Lastly, it is also important to recognize that the "vanishing phenomenon" is not necessarily pathognomonic for PCNSL. In their retrospective study evaluating the relationship of PCNSL and “vanishing tumors,” Bromberg et al

© 2014 American Association of Neuropathologists, Inc.
FIGURE 5. Primary CNS lymphoma with steroid effect. A 62-year-old man presented with progressive memory decline and increasing headache, prompting MRI, which demonstrated a large enhancing temporal lobe mass suspected to represent a glioblastoma. He received a 3-week course of Decadron to reduce swelling in anticipation of surgery. While on steroids, his headache and cognitive symptoms significantly improved. On the day of surgery, a repeat MRI demonstrated that the tumor had shrunk dramatically, prompting modification of the surgical plan to stereotactic biopsy. (A-G) The biopsy was not diagnostic. The biopsy core (A) demonstrated an area of pallor on H&E stain (left core), corresponding to an area of myelin loss (LFB/PAS stain, second core from left) and, to a lesser extent, axonal loss (neurofilament stain, second core from right). In this area, macrophages were numerous (H&E; B, C, and KP1 immunostain; A, right core; and G). Axon density was decreased, and there were scattered axonal spheroids (D). No large B-cells were observed on CD20 immunostain (E), whereas CD3 immunostain highlighted the presence of a moderate number of T lymphocytes (F). A descriptive diagnosis was made, and the possibility of "treated/vanishing" lymphoma was raised. The patient did well for approximately 3 months; his memory started declining again at that time. Magnetic resonance imaging demonstrated recurrence of the temporal lobe mass, prompting a new stereotactic biopsy. (H-J) The new stereotactic biopsy was diagnostic of PCNSL (H, H&E; I, CD20; J, CD3). Original magnification: (A) 1.25×; (B, D, E-G, I, J) 200×; (C, H) 400×.
(32) identified 12 patients, 5 of whom subsequently received a diagnosis of PCNSL, whereas the remaining had a number of diagnoses, including demyelinating disease, infarct, sarcoidosis, and renal cell carcinoma.

**STEREOTACTIC BIOPSY SAMPLES**

When lymphoma is suspected clinically, the preferred diagnostic approach is stereotactic biopsy, generally MRI-guided. It is the least invasive biopsy with a low complication rate. Typically, neurosurgeons in our practice quote the patients the following: temporary worsening, 5%; permanent worsening, 1%; 30-day mortality largely caused by hemorrhagic complications, less than 1% (35–37). Stereotactic biopsy allows surgeons to reach deep-seated lesions, which are challenging to approach otherwise, making it the ideal diagnostic technique for lymphoma. The size of the sample obtained with this technique is usually limited, and all efforts should be made to preserve material for diagnosis. An optimal and tissue-sparing technique for intraoperative examination of stereotactic biopsies is the preparation of cytologic smears. This allows a thorough evaluation of each core while preserving its integrity for permanent section evaluation. We use this proactive careful approach in all stereotactic biopsies because many factors (e.g. location of the lesion or unexpected bleeding) may limit the number of obtainable cores, often in an unpredictable manner, as in the case illustrated in Figures 6a, c.

The cytologic features of lymphoma are distinctive. Typically, lymphoma has a noncohesive, relatively monomorphous appearance, with cells showing large generally “naked” nuclei, round to notched, and often prominent nucleioli (Fig. 6d). Although markedly reactive astrocytes, with their characteristic stellate appearance, are often present in the background, the fibrillarity typical of glial neoplasms is absent. Macrophages can be present in the background, usually as a few scattered cells. Marked macrophage infiltrates are observed in steroid-treated cases in which only rare viable tumor cells may remain. Although, in most cases, intraoperative diagnosis can be reasonably certain in previously treated cases, intraoperative assessment may be limited simply to “extensive macrophage infiltrate with scattered atypical cells.” Similar to glial tumors, CNS lymphoma can also be very heterogeneous, and assessment of the permanent paraffin-embedded sections may be very challenging, depending on the extent of involvement of tissue cores. In cases clinically suspicious for lymphoma in which the first level is nondoniagnostic, similar to what we recommend for corticosteroid-treated cases demonstrating extensive apoptosis, we also routinely obtain multiple levels from tissue blocks, maintaining a few unstained sections at each level for confirmatory immunostains. This practice has been very rewarding in more than 1 case (Fig. 6e). A special intraoperative challenge is presented by the involvement of the cerebellum, where recognizing tumor cells, especially when scant in number, among cerebellar granular cells may be nearly impossible (Fig. 6f).

**LYMPHOMATOSIS CEREBRI**

*(A PATTERN OF PCNSL)*

Primary CNS lymphoma can present with widespread and diffuse infiltration of the cerebral white matter by individual lymphoma cells without the formation of a discrete tumor mass, an unusual PCNSL pattern often referred to as “lymphomatosis cerebri.” The term was coined by Bakshi et al (38) in analogy to what is observed in classic examples of gliomatosis cerebri, a rare diffusely infiltrative glioma that also presents with extensive involvement of the brain in the absence of a mass lesion. Although less than 20 cases of PCNSL with features of lymphomatosis cerebri in immunocompetent patients have been reported, mostly as single case reports (39–51) or small series of 2 to 3 cases (38, 52), this pattern is not rare in clinical practice. Personality change and subacute cognitive impairment/dementia are the most common presenting symptoms, in association with imaging of diffuse leukencephalopathy in both hemispheres and a lack of enhancement on postcontrast images. This pattern is very unusual compared with the most common imaging pattern, which raises a high suspicion for a PCNSL diagnosis even before a tissue diagnosis is obtained. It is, however, a very important pattern to recognize because the diagnosis of PCNSL may not be entertained by the pathologist in these cases. Figure 7 illustrates a challenging example of an 80-year-old woman who presented with anxiety, spells of perioral numbness, left hand tingling, aphasia, and diffuse symmetric hyperreflexia. Preoperative MRI showed extensive confluent T1 hypointense and T2 hyperintense lesions in the white matter of the parieto-occipital lobes with minimal enhancement, raising a wide differential diagnosis, including gliomatosis cerebri and, less likely, lymphoma (Fig. 7a). Despite the H&E appearance showing mild hypercellularity with a number of cells with nuclei, which, at first, may suggest an infiltrating glioma, scant large atypical lymphoma cells diffusely infiltrated the biopsy sample (Figs. 7b, c). The large lymphomatous cells were highlighted by the CD20 immunostain (Fig. 7d), whereas a low number of small reactive CD3-positive T lymphocytes were present in the underlying parenchyma (Fig. 7e).

**EPSTEIN-BARR VIRUS-ASSOCIATED LYMPHOPROLIFERATIVE DISORDERS**

Epstein-Barr virus (EBV)-associated lymphoid proliferations are a well-recognized complication of both congenital and acquired systemic immunosuppression and vary from polymorphic lymphoplasmacytic proliferation to frank lymphoma (53). Although they can occur in any anatomic site, they seem to have a predilection for extranodal locations, particularly for immune-privileged sites such as the CNS (54). Central nervous system lymphomas developing in immunocompromised individuals are typically B-cell neoplasms, mostly DLBCL, and are EBV-positive (>95% vs 0%–20% in immunocompetent patients). The frequency of CNS DLBCL, originally the most common primary brain tumor in AIDS patients and largely responsible for the increase in CNS lymphoma in the immunocompromised population, has decreased dramatically with highly active antiretroviral therapy (HAART) and is now stable. Iatrogenic immunosuppression is today a well-recognized and important risk factor for DLBCL, although its frequency is not well known and is difficult to determine. Clinically, the most common association is with organ transplantation (i.e. posttransplant lymphoproliferative
A 20-year-old immunocompetent man presented with fatigue, double vision, intermittent headache, and gait unsteadiness. He was found to have an enhancing third ventricular mass that markedly decreased in size with 5 days of dexamethasone (initially given intravenously then orally). His symptoms virtually disappeared. After 3 weeks off steroids, despite remaining asymptomatic, the mass started growing again, (A, right) and a new lesion appeared in the cerebellum, abutting the ventricle (A, left). The cerebellar lesion was chosen as a biopsy target because it was a new lesion and was in a less critical location. After a few nondiagnostic biopsy cores had been taken, the biopsy was aborted because of bleeding (B). A single diagnostic cluster of lymphoma cells was found on permanent sections in the last core taken, largely blood (C). The cells were positive for CD20 (inset) and PAX5 (not shown), consistent with a DLBCL. The immunostains were obtained on unstained slides (which had been ordered up front), whereas no residual tumor remained on recuts of the blocks. This spared the patient the need for a second biopsy, avoiding the chance of another bleed at a more critical site. He received aggressive treatment of PCNSL, including chemotherapy, salvage radiotherapy, and autologous stem cell transplant, and was free of the disease 4 years and 2 months from the biopsy. (D) Cytology of CNS lymphoma. (E) In a patient with a history of systemic DLBCL presenting with a brain lesion suspicious for CNS recurrence, this small focus of DLBCL was identified in the deep levels of an “at first nondiagnostic biopsy” (CD20 stain is illustrated in the inset). (F) Diffuse infiltration of cerebellar folia, including molecular and granular cell layer, highlighted by CD20 stain (inset). Original magnification: (C–F) 400×.
FIGURE 7. Primary CNS lymphoma presenting as lymphomatosis cerebri. **(A)** Preoperative MRI (T1, left; T2, middle; T1 postgadolinium, right) with extensive confluent T1 hypointense and T2 hyperintense lesions in the white matter of the parieto-occipital lobes and with minimal enhancement raised a wide differential diagnosis, including gliomatosis cerebri and, less likely, lymphoma. **(B, C)** Hematoxylin and eosin stain with mild hypercellularity and a number of cells with elongated nuclei suspicious at first for an infiltrating glioma. **(D, E)** Large atypical lymphoma cells were highlighted by CD20 immunostain **(D)**, whereas a low number of small reactive CD3-positive T lymphocytes were present in the underlying parenchyma **(E)**. Original magnification: **(B, D, E)** 200×; **(C)** 400×.
disorders), but there is a growing population of patients receiving immunosuppressive therapy for a variety of immune-related disorders (18). Although a significant proportion of these lymphoproliferative disorders may show at least partial regression in response to drug withdrawal, response seems to decrease as severity increases, and aggressive treatment is often needed in DLBCL cases. Occasionally, EBV-positive DLBCLs can develop in patients without any known primary and secondary immunodeficiency. When this occurs in patients older than 50 years, it is termed "EBV-positive DLBCL of the elderly," based on the WHO Classification of Tumours of Hematopoietic and Lymphoid Tissue (1). In rare instances, similar cases can occur in younger individuals. Although immunocompromised patients are generally younger than immunocompetent patients developing PCNSL, clinical presentation may be quite similar in both settings. On imaging, single or multiple brain lesions with a ring-enhancing appearance are relatively common in immunocompromised patients because of the presence of extensive necrosis, a feature that is very uncommon in PCNSL and may be difficult to distinguish from non-neoplastic infectious processes such as toxoplasmosis common in PCNSL and may be difficult to distinguish from the presence of extensive necrosis, a feature that is very uncommon in immunocompromised patients because of the presence of extensive necrosis, a feature that is very uncommon in PCNSL. Sometimes, EBV-associated DLBCL tends to be a more prominently angiocentric and angiodestructive process than the typical PCNSL and frequently shows extensive necrosis (Figs. 8a–c). Accompanying reactive T lymphocytes can vary markedly and, in some cases, may predominate in a morphologic pattern typical of lymphomatomatous granulomatosis (55), a large EBV-driven B-cell lymphoma associated with a florid T-cell reaction (56). Morphologic features, immunohistochemical markers, and EBV in situ hybridization are critical for reaching a definitive diagnosis. Because of the extensive necrosis often present in these biopsy samples, a definitive diagnosis may be quite difficult. In these cases, one can take advantage of the fact that some protein antigens may persist for some time even in necrotic cells. Ghosts of necrotic cells are often outlined by anti-CD20 antibodies (Figs. 8f, h) to such an extent that a confident diagnosis can often be made even in subtotally necrotic biopsies. At times, a similar phenomenon can be observed with EBV latent membrane protein 1 immunostain compared with EBV-encoded small RNA in situ hybridization, with RNA being more sensitive to degradation than proteins (Fig. 8i).

RARE LYMPHOMAS IN THE CNS

The CNS can be primarily affected by a variety of lymphoid tumors. Although we are only briefly describing the lymphoid tumors that affect the CNS with some frequency, we recognize that many histologic types, including follicular lymphoma (57, 58), Burkitt lymphoma (59, 60), precursor B-cell lymphoblastic lymphoma (61), and the recently described B-cell lymphoma with features intermediate between DLBCL and Burkitt lymphoma (62), have been reported in the CNS, often as single cases. Even when present in the CNS without systemic involvement, these lymphomas are not considered PCNSL.

LOW-GRADE B-CELL LYMPHOMA

Marginal zone B-cell lymphoma or low-grade mucosa-associated lymphoid tissue (MALT lymphoma) is likely the most common low-grade B-cell lymphoma involving the CNS. It most frequently presents as a dura-associated process mimicking meningioma; at times, the dural involvement is very diffuse, mimicking a diffuse pachymeningitis (63). Tumor cells are small to medium, with slightly irregular nuclei and inconspicuous nucleoli resembling centrocytes. They have relatively abundant clear pale cytoplasm and frequently show plasmacytoid differentiation. Extensive amyloid deposition may be present in MALT lymphoma of the dura. Immunophenotypically, tumor cells express B-cell markers, including CD19, CD20, and CD79a, occasionally express CD5, and do not express CD3, CD10, and CD23. Intrapparenchymal involvement of low-grade B-cell lymphoma is extremely rare. The largest series of "low-grade PCNSL" reported is the 2006 study by Jahneke et al (64). In this series of 32 patients retrospectively collected from 18 cancer centers over a wide period (1979–2004), most tumors (80%) were B-cell lymphomas, with the most common subtype being lymphoplasmacytic lymphoma. Although the diagnosis was originally made and/or confirmed by an experienced hematopathologist at each institution, no systematic central review of cases was possible because of logistic and regulatory issues. This, together with the paucity of material available and the application of older classification schemes, largely limited the ability to subclassify many of the cases. Despite the limitations that Jahneke et al (64) openly acknowledged, overall clinical and radiologic presentation in these patients seem to differ from that observed in PCNSL, and long-term outcome seems to be better.

T-CELL LYMPHOMAS

Primary peripheral T-cell lymphoma (PTCL) of the CNS is rare, accounting for 2% to 9% of all CNS lymphomas, depending on the patient population (4, 65). The largest series was published by the International Primary CNS Lymphoma Collaborative Group (66). In this series, the median age of presentation was 60 years, but with a wide age distribution. The most common site of involvement was the cerebral hemisphere, followed by the basal ganglia, corpus callosum, brainstem, and, rarely, the cerebellum. Although a pathologic diagnosis of PTCL was established in each case, detailed morphologic features, immunophenotype, or genetics were not available. A review of the literature and our experience suggest that the pathology of PTCL of the CNS is heterogeneous. Architecturally, neoplastic cells may have a pervillecular distribution but often spill into the surrounding parenchyma in a diffuse pattern (Fig. 9a). The diffuse parenchymal component may be difficult to observe in H&E sections due to marked reactive changes accompanying the neoplastic infiltrate. Most cases are composed of intermediate-size T-cells with cytologic atypia, including nuclear membrane abnormalities, which can be best appreciated by immunohistochemistry (Figs. 9b–d). A subset of the cases, in particular in young patients, may show small cell morphology with minimal cytologic atypia and may pose a major diagnostic challenge, particularly in the absence of
FIGURE 8. Epstein-Barr virus–associated lymphoma. Examples of DLBCLs associated with EBV. (A–C) A 62-year-old woman, who had received a kidney transplant 3 years earlier for IgA nephropathy, presented with recent-onset confusion and weakness. A left parietal rim-enhancing lesion was noted in the subcortical white matter. The lymphomatous infiltrate showed angiodestructive features, as demonstrated by the presence of fibrinoid necrosis in the vascular wall (A). Many of the large CD20-positive (B) lymphomatous cells were positive for EBV (C). (D–F) A 78-year-old woman with a history of Parkinson disease and extensively necrotic thalamic lymphoma (D, E). (F) CD20 stain corresponding to the same area illustrated in (E). CD20 immunoreactivity is maintained on the surface of “anucleated” necrotic cells. (G–I) A 59-year-old woman presenting with a right frontal lobe centrally necrotic mass and with no known history of immunosuppression. The biopsy showed a subtotally necrotic lymphoma. An area of complete necrosis is illustrated (G), with corresponding CD20 stain (H) and EBV latent membrane protein 1 (I) both showing partial preservation of surface stain despite the necrotic appearance of the tissue. Epstein-Barr virus in situ hybridization (inset) yielded negative results because RNA is more sensitive to degradation than proteins, which may persist for a somewhat longer period. Original magnification: (A–C, E, F) 400×; (D, G–I) 200×.
aberrant phenotype and/or clonality. Immunohistochemistry reflects the heterogenous nature of the biology. Neoplastic T-cells may show loss of some of the pan T-cell antigens, in particular CD5 and/or CD7. They may be of helper (CD4-positive) or cytotoxic (CD8-positive) T-cell origin and may express T-cell receptor α/β chains (most cases) or γ/δ chains (rare) (Fig. 9e). Demonstration of the clonal rearrangement of T-cell receptor genes, which are present in most T-cell lymphomas, is often critical for reaching a definitive diagnosis. T-cell receptor clonal rearrangement, however, should always be interpreted in conjunction with pathologic and clinical findings because many chronic immunostimulatory disorders may also be associated with the development of T-cell clones. The clinical course of PTCL in the CNS seems to be aggressive; however, a small number of cases with lower-grade cytology may have a more indolent behavior with a protracted disease course.

ANAPLASTIC LARGE CELL LYMPHOMA

Anaplastic large cell lymphoma occurs very rarely in the CNS. It is an uncommon, generally T-cell lymphoma composed of large pleomorphic CD30-positive cells. It most frequently occurs at nodal sites, primary involvement or secondary spread to extranodal sites may occur. Most cases arising in the CNS have been reported as single case reports, with the largest series describing 9 cases, 5 of which had been previously reported (67). Six (of 9) cases occurred in women across a wide age range (4–66 years), and the majority (7 of 9) of cases involved the dura or leptomeninges rather than the CNS parenchyma. Most tumors were T-cell–positive (n = 7), 2 were null cell positive and 5 were ALK1-positive. Although mortality was high (n = 6), 3 patients were alive at 4.8- to 6.1-year follow-up. These 3 patients were young (4–18 years), and their anaplastic large cell lymphoma was ALK1-positive, supporting the view that young

**FIGURE 9.** Primary peripheral T-cell lymphoma. A 79-year-old man presented with a left frontal lobe mass. (A-E) On biopsy, a dense lymphoid infiltrate was present, accumulating around vessels (A, left) and diffusely infiltrating the adjacent parenchyma (A, middle), which shows marked reactive gliosis (A, right). Intermediate-size tumor cells with cytologic atypia (B) show phenotypic features of T-cell, expressing CD3 (C, D), CD2, CD4, CD5 (not shown), and T-cell receptor γ/δ (E), a very uncommon finding in CNS PTCL. CD10, CD20, CD30, CD7, CD8, TCR βF1, TdT, TIA-1, and granzyme B were not expressed in tumor cells (not shown). Original magnification: (A, C) 100×; (B, D, E) 400×.

© 2014 American Association of Neuropathologists, Inc.
A 69-year-old woman presented with a left temporal lesion with substantial hemosiderin deposition following the distribution of a left middle cerebral artery branch. Extensive changes of subacute hemorrhagic infarct were present in the biopsy, with no evidence of amyloid angiopathy. Very focally, a small leptomeningeal vessel appeared to be filled by large lymphoma cells (A), which were CD20-positive (B), MUM1-positive (C), and PAX5-positive (D), consistent with a B-cell phenotype. The cells also expressed BCL6 but did not express CD10 (not shown). (E, F) A 62-year-old woman presented with a right temporal hemorrhagic lesion, submitted in consultation with a suspicion of cerebral amyloid angiopathy. Intravascular large B-cell lymphoma was instead present in 2 of the biopsy fragments. Intravascular large B-cell lymphoma cells with large prominent nucleoli and a central mitotic figure (E); the large lymphoma cells were CD20-positive, consistent with a B-cell phenotype (F). Original magnification: (A–F) 400×.

FIGURE 10. Intravascular large B-cell lymphoma. (A–D) A 69-year-old woman presented with a left temporal lesion with substantial hemosiderin deposition following the distribution of a left middle cerebral artery branch. Extensive changes of subacute hemorrhagic infarct were present in the biopsy, with no evidence of amyloid angiopathy. Very focally, a small leptomeningeal vessel appeared to be filled by large lymphoma cells (A), which were CD20-positive (B), MUM1-positive (C), and PAX5-positive (D), consistent with a B-cell phenotype. The cells also expressed BCL6 but did not express CD10 (not shown). (E, F) A 62-year-old woman presented with a right temporal hemorrhagic lesion, submitted in consultation with a suspicion of cerebral amyloid angiopathy. Intravascular large B-cell lymphoma was instead present in 2 of the biopsy fragments. Intravascular large B-cell lymphoma cells with large prominent nucleoli and a central mitotic figure (E); the large lymphoma cells were CD20-positive, consistent with a B-cell phenotype (F). Original magnification: (A–F) 400×.
age and ALK1 positivity are associated with a better outcome, similar to systemic anaplastic large cell lymphoma.

**INTRAVASCULAR LARGE B-CELL LYMPHOMA**

Intravascular large B-cell lymphoma, also called angiotropic large cell lymphoma, is a rare type of large B-cell lymphoma in which atypical lymphocytes selectively grow within blood vessel lumens, particularly in small vessels and capillaries. This is likely caused by a defect in homing receptors in neoplastic cells (68, 69). Extravascular extension of neoplastic cells, if present, is minimal. This lymphoma occurs predominantly in adults (median age, 67 years), with nearly equal frequency in men and women (70). It is usually a widely disseminated lymphoma in extranodal sites and may be virtually present in any organ. Two main patterns of presentation occur: one pattern is characterized by symptoms related to the organs involved, primarily cutaneous or neurologic (so-called Western form); the other in which multorgan failure, hepatosplenomegaly, pancytopenia, and hemophagocytic syndrome predominate (so-called Asian form), in reference to the patient population in which they are more frequently, but not exclusively, seen. Involvement of the CNS is common, with intraluminal lymphoma cell accumulation causing small vessel occlusion and disseminated infarcts that are, at times, associated with fibrin microthrombi and hemorrhage. Clinical presentation seems to result from ischemia, which can be widespread with involvement of the entire neuraxis, resulting in a wide range of symptoms from acute or chronic encephalopathy to progressive dementia, spinal cord symptoms, cranial neuropathy, or cauda equina syndrome. Rarely, IVLBCL can present with a mass-like lesion (71). Although the diagnosis of IVLBCL used to be predominantly postmortem, awareness of this rare lymphoma type and of its variable presentation has made diagnosis by surgical biopsies more common. Signs of acute or subacute ischemia can be seen in the cerebral parenchyma, raising a wide differential diagnosis, including primary CNS vasculitis, thromboembolic conditions, and amyloid angiopathy. Vascular changes in IVLBCL can be very focal and subtle. It is important for the neuropathologist to systematically examine the lumens of the small and medium leptomeningeal and parenchymal vessels to identify the diagnostic cells. Two cases are illustrated in Figure 10.

Rare examples of intravascular T-cell or natural killer cell lymphoma have been reported (72), which, according to World Health Organization classification, should be considered a different entity (70). Intravascular large B-cell lymphoma is an aggressive lymphoma and is generally poorly responsive to chemotherapy (70). However, poor prognosis may, in part, be a reflection of the fact that many of these cases are diagnosed late in the course of the disease, with early diagnosis potentially leading to successful treatment (73).

**HODGKIN LYMPHOMA AND THE CNS**

Although neurologic manifestations in Hodgkin lymphoma (HL) are rare, several unique disorders may occur in HL, with which the pathologist should be familiar. Complications of HL can be categorized as direct and indirect, resulting either immediately from the lymphoma, including direct/metastatic involvement of the CNS (intraparenchymal, dural, leptomeningeal, and ‘‘epidural at the spinal cord level’’) or from its treatment (secondary to radiotherapy and chemotherapy) and/or infection (74). Direct/metastatic involvement of the CNS by HL is rare and typically occurs in advanced-stage disease. Central nervous system involvement has been reported in rates varying from 0.5% to 3% (75, 76). As in secondary CNS involvement by systemic lymphoma, dura-based lesions are more common than parenchymal involvement. Primary CNS presentation of HL is exceedingly rare (77–85), with less than 10 cases reported. Interestingly, most cases primarily involving the CNS had parenchymal (77–85) rather than dural localization (86–88). Diagnosis of HL requires identification of Hodgkin and Reed-Stenberg cells, with the appropriate immunophenotype occurring in a typical non-neoplastic background with lymphocytes, plasma cells, macrophages, and eosinophils.

In addition, HL may occur in association with several paraneoplastic syndromes, including cerebellar degeneration and limbic encephalitis, which are typically associated with onconural autoantibodies, including anti-Tr antibodies (89, 90) directed against cerebellar Purkinje cells, and anti-Hu (91) and anti-NMDA (92) antibodies in cases of limbic encephalitis. Of particular interest to the neuropathologist is the association with CNS granulomatous angiitis (93–96), a unique, often necrotizing granulomatous vasculitis. The pathogenesis of this ‘‘secondary’’ CNS granulomatous angiitis remains unclear, although varicella zoster virus reactivation has been implicated by some (97). In most cases, the diagnoses of granulomatous angiitis and HL are made simultaneously or closely correlated in time, with either the diagnosis of HL or the diagnosis of granulomatous angiitis preceding the other (96, 98–100). Morphologically, this CNS granulomatous vasculitis is similar to the granulomatous pattern of primary CNS vasculitis, which is, however, frequently associated with amyloid angiopathy (101). Accurate clinical history and examination may be the only key to the correct diagnosis. Although full recovery is uncommon, early diagnosis is critical since the disease is responsive to steroids and/or immunosuppression in association with specific HL chemotherapy (93, 95).

In summary, PCNSL, morphologically a DLBCL confined to the CNS (and/or to the eye) that occurs in immunocompetent patients, is the most common lymphoma occurring in the CNS. In addition, many other lymphoma subtypes, some primary or exclusive to the CNS, such as immunodeficiency-associated lymphomas, intravascular large cell lymphoma, and lymphomas of the dura, can occur in the CNS. Although, in many cases, the biopsy diagnosis of CNS lymphoma is straightforward, a variety of reasons may make it quite challenging at times. Maintaining a high index of suspicion (clinically and diagnostically) and optimizing use of the tissue at hand will generally allow the pathologist to achieve a definitive diagnosis of CNS lymphoma in most cases.

**ACKNOWLEDGMENT**

The authors would like to thank Dr Fausto J. Rodriguez for his critical review of the manuscript and his invaluable advice.

© 2014 American Association of Neuropathologists, Inc.