Molecular Diagnostics in Lymphoid Neoplasms of the Central Nervous System

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KEYWORDS

• CNS lymphoma • Molecular diagnostics • Genomic • DLBCL

Key points

- Diffuse large B cell lymphoma (DLBCL) is the most common and most aggressive of the primary lymphoid neoplasms arising within the central nervous system (CNS) and exhibits an activated B cell phenotype by both immunohistochemistry and mutational analysis. Frequent alterations in *MYD88*, *CD79B*, and *CD274/PDCD1LG2* serve as valuable diagnostic and therapeutic biomarkers in this disease.
- Primary low-grade B cell lymphomas are a group of relatively indolent tumors that include extranodal marginal zone lymphoma (EMZL), lymphoplasmacytic lymphoma, and small lymphocytic lymphoma. Although little is currently known about their genomic signatures, use of molecular diagnostics can greatly facilitate accurate diagnosis.
- EMZL preferentially involves dura and can mimic meningioma clinically, rendering it particular amenable to surgical resection and radiotherapy.
- CNS T cell lymphomas are especially challenging diagnostically given their rarity and frequently banal histologic appearance. They usually demonstrate a CD8-positive cytotoxic phenotype, creating additional overlap with inflammatory conditions. As with B cell lymphoproliferative disorders, T cell lymphomas of the CNS show recurrent mutations that confirm the diagnosis of neoplasia and may guide therapeutic strategy.

ABSTRACT

Primary lymphoid neoplasms of the central nervous system are rare tumors that span a wide range of histopathologic appearances and can overlap occasionally with non-neoplastic processes. Application of modern molecular techniques has not only begun to unravel their unique underlying biology but has also started to lay a valuable diagnostic and therapeutic framework for these frequently aggressive malignancies. This review summarizes the existing landscape of clinicopathologic and genomic features of lymphoid neoplasms that may arise primarily within the central nervous system.

OVERVIEW

Primary lymphoid malignancies of the central nervous system (CNS) are a rare and diverse group of entities. The most common of these by far is primary diffuse large B cell lymphoma (DLBCL); however, low-grade B cell neoplasms and T cell lymphomas may be infrequently encountered and, thus, pose a significant challenge to the diagnostician. Despite the rarity of these neoplasms, recent work has begun to elucidate their genomic landscapes, providing not only new diagnostic biomarkers but also potential targets of therapy. This review summarizes both the clinicopathologic features of CNS lymphoid malignancies and

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recent trends in molecular diagnostics and treatment strategies.

DIFFUSE LARGE B CELL LYMPHOMA

Clinical Features

DLBCL of the CNS accounts for roughly 3% of all brain tumors and less than 1% of all non-Hodgkin lymphomas.[1] Although this lymphoma can arise in patients of any age, most cases occur between the fifth and seventh decades.[2,3] The supratentorial compartment is the most frequent site of involvement (60% of cases); however, the posterior fossa, leptomeninges, eye, and spinal cord may all be affected.[4] Tumors most often present as solitary lesions (60%–70% of cases), but multifocal disease may be encountered.[4] Although it is not uncommon for DLBCL arising in other sites to secondarily involve the CNS, primary CNS DLBCL very rarely recurs in extraneural locations.[5–8]

Epstein-Barr virus (EBV)-positive DLBCL occurs most frequently in the elderly, with a peak incidence in the eighth decade; however, there is a second smaller peak occurring in the third decade.[9,10] Although associated with immunodeficiency, as many as 5% to 15% of patients may have no predisposing conditions.[11–21]

Intravascular large B cell lymphoma (IVLBCL) is a rare form DLBCL having no solid organ primary that grows exclusively within small vessels. Although any organ may be affected, the CNS shows involvement in greater than 75% of cases.[22] IVLBCL preferentially occurs in older adults, with a median age of 67 years.[23–27]

Microscopy and Immunophenotype

Microscopically, DLBCL of the CNS is an infiltrative neoplasm that frequently exhibits sheeting and perivascular aggregates of tumor cells. Tumor cells show typical DLBCL morphology with high nuclear:cytoplasm ratio, coarse chromatin with one or more nucleoli, and frequent nuclear irregularity or clefting (**Fig. 1**A). Background brain tissue often shows marked reactive astrocytosis or frank necrosis, sometimes accompanied by a variably robust non-neoplastic lymphocytic infiltrate (**Fig. 2**) that may be mistaken for primary inflammatory disorders on small biopsy specimens. Importantly, tumors that have been treated with corticosteroids before biopsy may show little, if any, evidence of tumor involvement in an otherwise background of reactive brain tissue and lymphohistiocytic infiltrates.[28]

The tumor cells of IVLBCL closely resemble those in conventional CNS DLBCL, but are confined to vessel lumina with minimal extravasation into Virchow-Robin spaces and surrounding parenchyma. Importantly, the surrounding brain tissue often shows evidence of ischemic injury due to multifocal vascular occlusion, and careful examination must be conducted of the microvasculature for tumor cells, which can be present only focally.[28]

Immunohistochemistry in all forms of DLBCL demonstrates routine positivity for mature B cell markers, such as CD19, CD20, PAX5, and CD79a. Ki67 indices are exceptionally high, frequently exceeding 80% to 90%.[29] Over 80% of cases are double expressors of BCL2 (**Fig. 1**B) and MYC; unlike systemic DLBCL, however, this does not correspond well with translocation status, which is much rarer in the CNS.[29,30] Most cases exhibit an activated B cell phenotype and express BCL6 and MUM1 (**Fig. 1**C), whereas CD10 positivity is rare.[31] Overexpression of PD-L1 and PD-L2 may also be detected by immunohistochemistry; however, care must be taken to separate expression in background brain tissue and macrophages from infiltrating tumor cells (**Fig. 1**D).

EBV-driven tumors can be reliably classified by in situ hybridization for EBER.

Genetic Profile

CNS DLBCL shows a similar genetic profile to that of activated B cell (ABC) phenotype DLBCL elsewhere; however, the characteristic profile is much more stereotyped in the CNS. Activation of the Toll-like receptor, B cell receptor (BCR), and nuclear factor κB pathways are frequently observed, most often via activating mutations in *MYD88* and *CD79B* and inactivating mutations in *CARD11* and *TNFAIP3*.[32–41] Additional mutations in *PIM1*, *TBL1XR1*, *IRF4*, *ETV6*, and *PRDM1* are also frequently encountered.[32,38–41]

Most CNS DLBCL demonstrate evidence of genomic instability and numerous copy-number alterations.[41] This is likely the result of frequent deletion of *CDKN2A* and/or *FHIT*, which occur far more often in CNS DLBCL than in ABC-type DLBCL elsewhere.[32,38,41] Additional commonly observed events include amplification of *NFKBIZ* on 3q12.3, gain of 18q (leading to BCL2 overexpression), and amplification of 9p24, including *CD274* and *PDCD1LG2*.[41] Deletions of HLA class II genes on 6p21 are also seen in approximately 75% of CNS DLBCLs, further contributing to escape of immune surveillance.[32,37,41–43]

Structural variants involving *BCL6* are considerably less common than in DLBCL arising outside the CNS, and rearrangements of *MYC* and *BCL2* are essentially nonexistent.[29,41,44,45] Enhancer hijacking events leading to constitutive expression

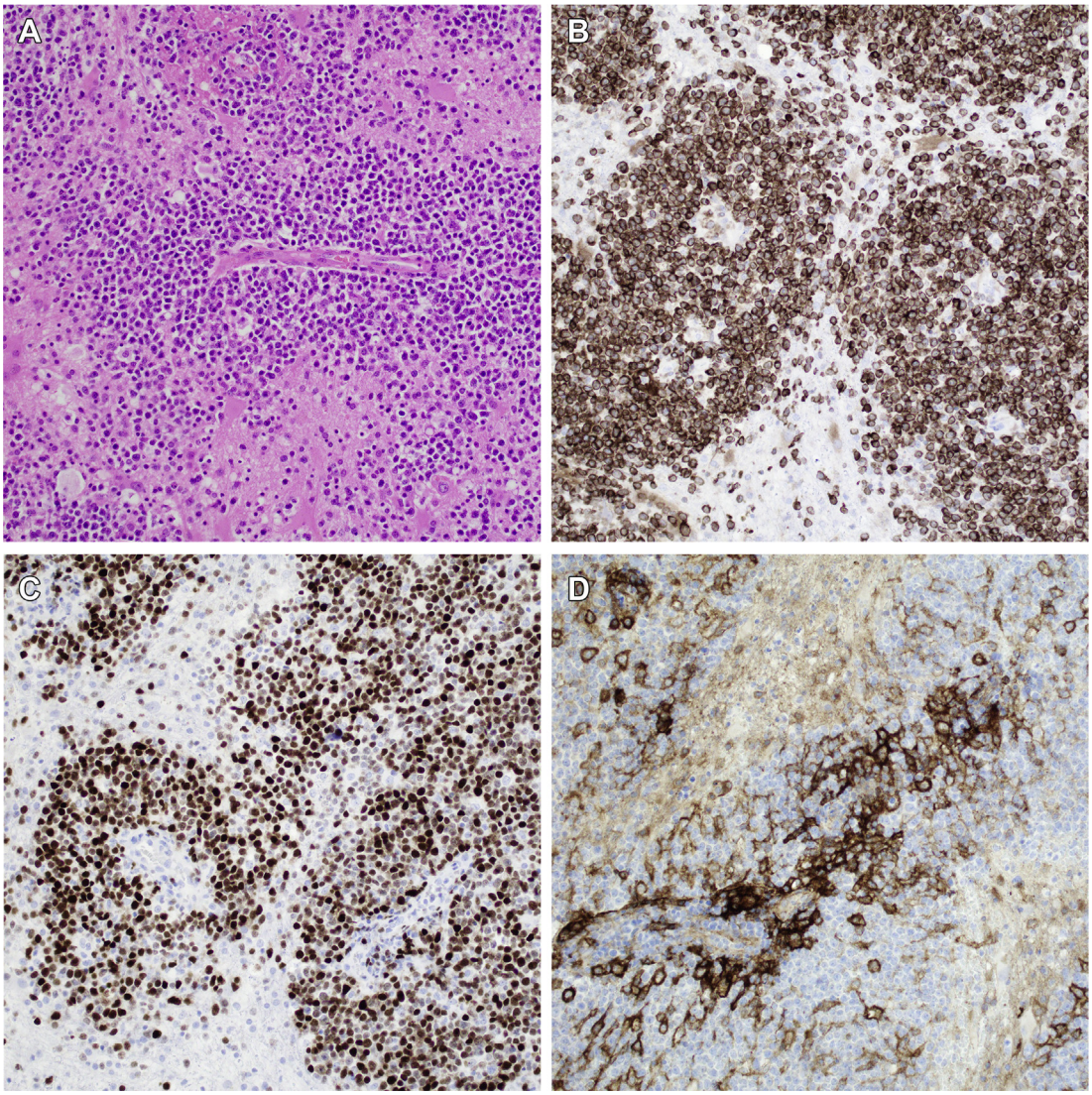

Fig. 1. Microscopic appearance of CNS DLBCL. (*A*) Tumor cells frequently aggregate around blood vessels and infiltrate into the surrounding brain parenchyma. Most CNS DLBCL exhibit increased expression of BCL2 (*B*) and MYC (not shown), along with the activated B cell markers MUM1 (*C*) and BCL6 (not shown). (*D*) PD-L1 immunopositivity can be patchy and correlates strongly with amplification or translocation of *CD274/PDCD1LG2*. Of note, infiltrating macrophages also show strong expression and must not be mistaken for tumor cells.

of PD-L1 and PD-L2 have been demonstrated in a small subset of cases.[41] Currently, RNA-based or custom-designed hybrid capture DNA sequencing platforms are required to detect these alterations; however, immunohistochemistry may be a reliable surrogate assay where available.[38,41]

In contrast, EBV-driven DLBCL shows few of the above alterations, with the exception of occasional gain of 9p24.[46,47]

Treatment Considerations

Until recently, the only viable options for treating CNS DLBCL were limited to high-dose chemotherapy regimens, usually including methotrexate, whole-brain radiation, and autologous stem cell transplant.[48] Although these agents show excellent short-term efficacy, most tumors will recur within 2 years, and as many as one-third of patients do not respond at all.[48–51] The discovery of highly recurrent, targetable alterations in CNS DLBCL has led to several promising studies showing improved survival with novel agents. The presence of 9p24 amplifications in a subset of tumors has spurred several studies to investigate the use of checkpoint inhibitors, although long-term efficacy remains to be determined.[52,53]

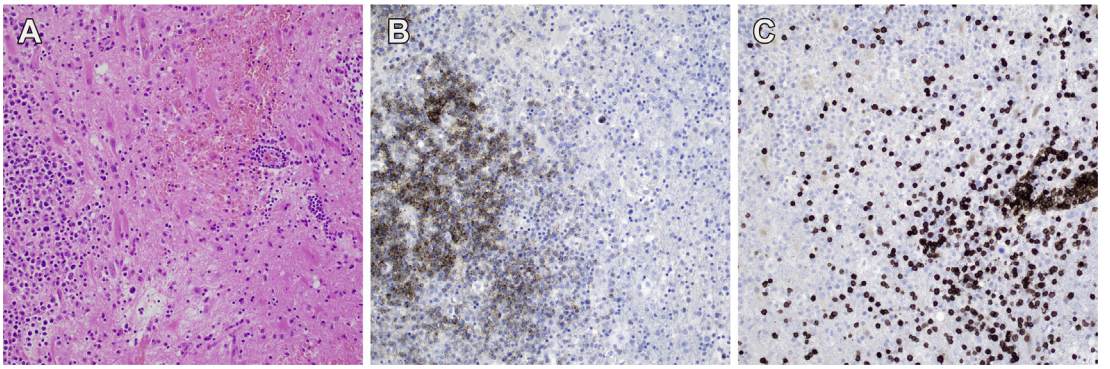

Fig. 2. Edge of DLBCL tumor. (*A*) Although most tumors show some degree of parenchymal infiltration, occasionally tumors show sharp boundaries with surrounding brain tissue with adjacent non-neoplastic inflammation and marked reactive changes. (*B*) CD20 highlights the tumor boundary, and CD3-positive T cells cluster in the adjacent reactive parenchyma (*C*).

Furthermore, early studies have begun to investigate the utility of BTK inhibition via ibrutinib, which has shown dramatic early results, even against tumors without evidence of *MYD88* or *CD79B* alterations.[54–56] Additional preclinical investigations have shown efficacy of targeted BCL2 and phosphoinositide 3-kinase (PI3K) inhibition in DLBCL models with evidence of BCR activation, which may soon be translated into clinical trials.[57]

Given the high rate of neurotoxicity associated with high-dose methotrexate and whole-brain radiation, targeted agents are likely to become first-line therapies in the near future, underscoring the importance of adequate tissue stewardship for molecular testing in this disease.

LOW-GRADE B CELL LYMPHOMAS

Clinical Features

Entities belonging to this broad category of lymphomas, including small lymphocytic lymphoma, extranodal marginal zone lymphoma (EMZL), follicular lymphoma, and lymphoplasmacytic lymphoma, arise primarily in the CNS with extreme rarity and account for less than 3% of all primary CNS lymphomas.[58,59] These lymphomas may occur throughout the CNS; however, the vast majority occur in the cerebral hemispheres.[60] EMZL by contrast shows a particular predilection for the dura, often forming mass lesions that can mimic meningioma.[61,62]

In addition, the histologic features of these tumors may be difficult to distinguish from inflammatory or infectious conditions, further leading to misdiagnosis. Ancillary molecular testing, therefore, can be of great utility in these cases.

Microscopy and Immunophenotype

The microscopic appearance of these lymphomas can vary somewhat, depending on the precise classification, but most cases generally contain dense or diffuse collections of small to medium lymphocytes with monomorphic to irregular nuclei and variable proportion of plasmacytoid forms (**Fig. 3**A). EMZL often forms a well-circumscribed mass lesion in the dura and may exhibit characteristic monocytoid forms, with clear cytoplasm and distinct cell borders (**Fig. 4**).[61] Perivascular collections may also be encountered. Cells are positive for CD20 and other mature B cell markers, and the plasma cell component shows monotypic light chain expression (**Fig. 3**B–E). CD5 and CD23 are generally negative outside of instances of small lymphocytic lymphoma. Ki67 proliferation rates are generally low (**Fig. 3**F).

Genetic Profile

Extensive analysis by fluorescence in situ hybridization of CNS marginal zone lymphomas showed no evidence of the characteristic translocations in *BCL6*, *MALT1*, or *IgH*.[61] Trisomy of chromosome 3 was the most common finding, followed by occasional polysomy of 7, 12, and 18.[61]

Although no published series exist to date describing the comprehensive mutational genomic signatures of low-grade CNS lymphomas, in this author's experience they tend to overlap with the expected signatures of similar extraneural examples. For example, mutations in *MYD88* would be most consistent with lymphoplasmacytic lymphoma, whereas evidence of NF-kB pathway activation via deletion of 6q23 (*TNFAIP3*) or another mechanism would suggest marginal zone origin.

Regardless, targeted sequencing panels can be of great utility in accurately subclassifying or confirming the diagnosis of neoplasia in these difficult cases, because immunoglobulin H (IgH) rearrangement studies do not always reveal clear

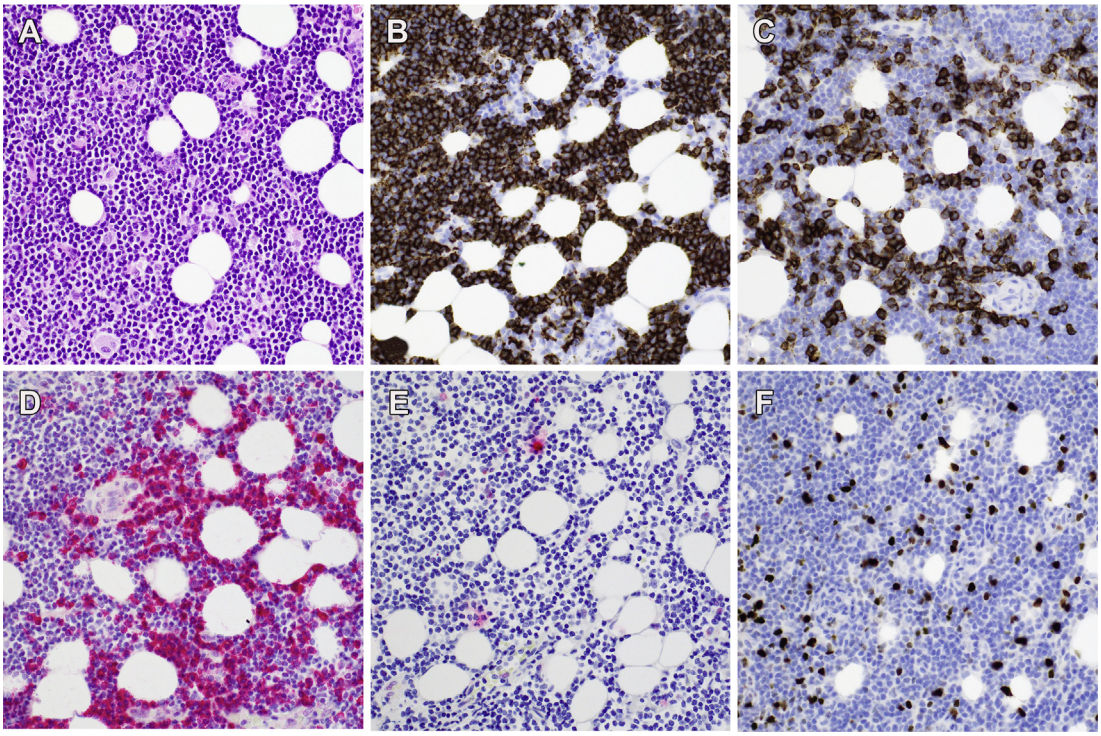

Fig. 3. Example of a low-grade B cell lymphoma involving a sacral nerve root with soft tissue extension. (*A*) The tumor is composed of small lymphocytes with minimal atypia and occasional plasmacytoid forms. (*B*) CD20 is diffusely positive in the lesion, and CD138 marks a subset of plasma cells (*C*). (*D*) The plasma cell component shows monotypic expression of kappa light chain by in situ hybridization compared with lambda light chain (*E*). (*F*) Ki67 staining demonstrates a low proliferative rate.

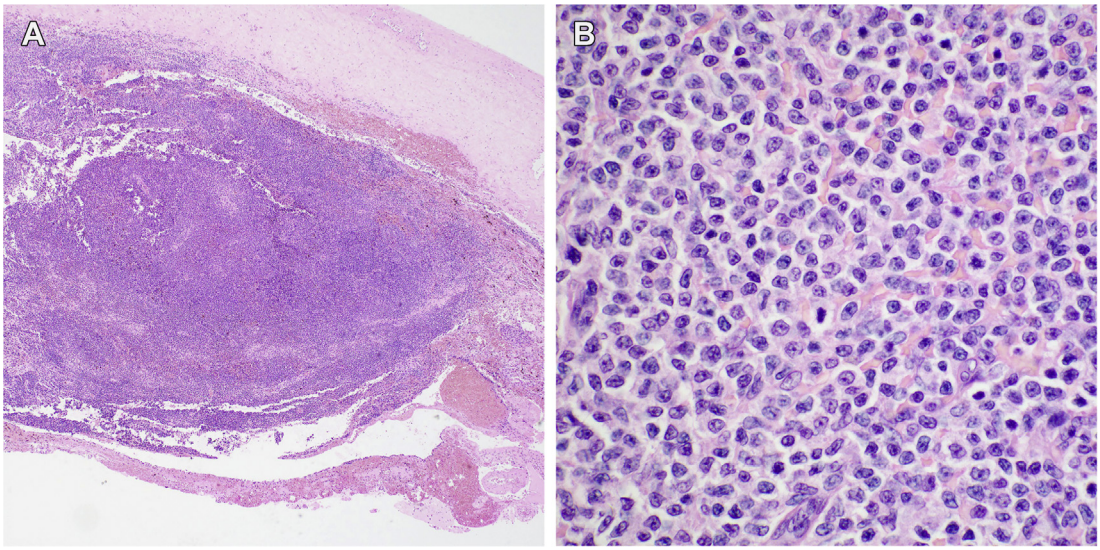

Fig. 4. Example of extranodal marginal zone lymphoma involving dura. (*A*) Dural-based EMZL frequently shows a circumscribed nodular pattern, which can mimic meningioma clinically. (*B*) High-power magnification of the tumor shows characteristic morphology with abundant clear cytoplasm ("monocytoid" appearance), distinct cell borders, irregular nuclei, and small nucleoli.

evidence of clonality, especially in the presence of dense background inflammation.

Treatment Considerations

As a group, these lymphomas are far more indolent than CNS DLBCL, with a 5-year survival of roughly 60%, and are generally responsive to conventional chemotherapeutic regimens.[59,63–68] Marginal zone lymphoma is particularly radiosensitive and amenable to surgical resection given its predilection for localized involvement of the dura, leading to complete remission in nearly 80% of patients.[62] Given the extreme rarity and hitherto lack of information regarding genomic profiles of these lesions, targeted therapy trials have not yet been attempted.

T CELL LYMPHOMAS

Clinical Features

Like low-grade B cell lymphomas, primary T cell lymphomas of the CNS are exquisitely rare, comprising fewer than 2% of all primary CNS lymphomas.[69,70] Incidence is higher is Asia than other parts of the world, and younger or middle-aged adults are preferentially affected.[59,71] All regions of the neuroaxis may be involved, with most examples arising in the cerebral hemispheres.[70,72] Most tumors are subclassified as peripheral T cell lymphoma when reported.[72]

Anaplastic large T cell lymphoma (ALCL) is even less common and tends to occur in children and young adults.[73–77] Involvement seems to be more prevalent in the dura and leptomeninges than in the CNS parenchyma, and ALK positivity confers a better prognosis.[74]

Microscopy and Immunophenotype

T cell lymphomas may exhibit a wide spectrum of morphologies, and definitive diagnosis usually requires demonstrating aberrant T cell immunophenotype or evidence of clonality. Tumor cells are generally small to medium sized with irregular nuclei, finely dispersed chromatin, and variably prominent nucleoli.[28,72] Similar to CNS DLBCL, CNS T cell lymphomas often show dense clustering around blood vessels and background necrosis (**Fig. 5**A). Diffuse parenchymal infiltration is also commonly observed, which can prove especially challenging diagnostically on small biopsies

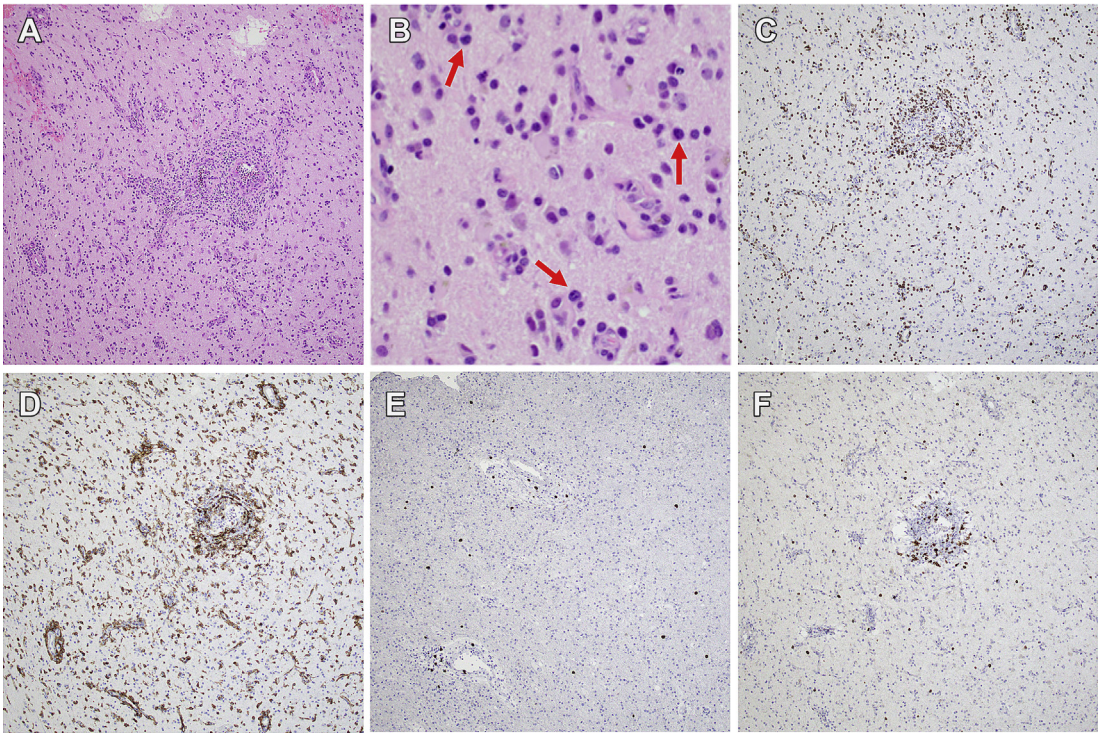

Fig. 5. Example of CNS T cell lymphoma. (*A*) Similar to DLBCL, T cell lymphomas of the CNS typically show perivascular aggregates of tumor cells that diffusely infiltrate surrounding brain tissue. (*B*) Higher magnification of the infiltrating component illustrates the subtlety that these lesions may exhibit, with intermediate-sized cells showing minimal atypia and nuclear hyperchromasia (*arrows*). This tumor expressed CD3 (*C*) and showed subset loss of CD2 (*F*). Uncharacteristically, this example showed CD4 positivity (*D*) and was negative for CD8 (*E*).

(**Fig. 5**B). Large-cell variants may mimic DLBCL morphologically and contain characteristic "hallmark" cells.[72]

Most tumors show loss of one or more of the T cell markers CD2, CD3, CD5, and CD7 (**Fig. 5**C and F).[28,72] A cytotoxic CD8-positive phenotype is common irrespective of morphology, and positivity for TIA1, granzyme-B, and perforin can lead to confusion with inflammatory conditions.[28,72] Less often, CD4-positive or aberrant double-negative (CD4–/CD8–) phenotypes may be observed (**Fig. 5**D and E).[72] ALCL also shows typical expression of CD30 and ALK.[72]

Genetic Profile

Irrespective of microscopic appearance, evidence of T cell receptor clonality is almost universal.[72] Genomic evaluation of CNS T cell lymphomas has been quite limited to date, with targeted sequencing data available for only a handful of cases. Nonetheless, mutations in commonly implicated genes in other T cell lymphomas, such as *DNMT3A*, *GNB1*, *KRAS*, *TET2*, *JAK3*, *STAT3*, and *STAT5B* have been reported.[72]

Treatment Consideration

Prognosis for primary CNS T cell lymphoma is generally poor with few long-term survivors. Median survival for patients has been reported at 25 months, and 1 study of 7 patients showed similar outcomes relative to patients with CNS DLBCL.[59,70] Although there is no consensus as to optimal treatment regimen, most include high-dose methotrexate followed by autologous stem cell transplantation.[70,78]

Nonetheless, several targeted approaches are being explored in systemic T cell malignancies that may show benefit in CNS tumors. Federal Drug Administration approval already exists for use of the anti-CD30 antibody-drug conjugate brentuximab vedotin in CD30-positive lymphomas and the ALK inhibitor crizotinib in *ALK*-positive ALCL.[79,80] Furthermore, several clinical trials have already opened exploring the efficacy of other targeted regimens against commonly activated pathways in T cell lymphoma, including inhibitors against PI3K, Jak/STAT signaling, and DNA methylation.[80]

SUMMARY

DLBCL is by far the most common primary lymphoid malignancy of the CNS and, given adequate tissue sampling, is rarely a diagnostic conundrum. Nonetheless, molecular studies have identified a stereotyped genomic signature in CNS DLBCL that implicates a distinct biology from extraneural examples and provides a rich array of druggable targets. Less common neoplasms, including T cell lymphomas and low-grade B cell lymphomas, may pose a much greater diagnostic challenge and overlap considerably with inflammatory or infectious processes. Here again, ancillary molecular testing can solidify the diagnosis of neoplasia, assist with subclassification, and help direct treatment. As neuropathology continues to move toward routine molecular testing for classifying and identifying clinically relevant biomarkers in brain tumors, lymphoid neoplasms are also likely to benefit from this approach, and proper conservation and triage of tissue should be considered in the handling of these cases.

DISCLOSURE

The authors have nothing to disclose.

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