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Oncological Mimics in Inflammatory CNS Disease

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Key Points

1. Oncological conditions involving the central nervous system (CNS) are serious, often difficult to diagnosis, and are associated with unique treatment strategies.
2. Histiocytic disorders are a rare, heterogeneous class of diseases that have the propensity for both CNS and systemic involvement.
3. Activating mutations in the mitogen-activated protein kinase (MAPK) pathway are found in a significant number of histiocytic disorders indicating a clonal, neoplastic origin with potential for targeted treatments.
4. Primary central nervous system lymphoma is a rare extranodal form of non-Hodgkin lymphoma involving the CNS without systemic involvement. Though highly aggressive, it is a potentially curable malignancy.
5. Though lacking formal diagnostic criteria, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is typically associated with characteristic clinical, imaging, and pathologic findings typically involving the brain stem. Central to the diagnosis is the exquisite sensitivity to steroids, but CLIPPERS has been associated with the subsequent development of malignancy.

Introduction

Evaluation of inflammatory disease within the central nervous system (CNS) can be a diagnostic challenge given diverse presentations of patients. Extensive diagnostic evaluation is often unrevealing and can lead to further uncertainty. Malignancy or "premalignant" conditions within the CNS can mimic inflammatory disease, thus making these entities important for consideration when evaluating for inflammatory conditions. While rare, disease such as histiocytic disorders and primary central nervous system lymphoma (PCNSL) occurs with enough frequency to be considered when presented with a potential CNS

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inflammatory process. Entities such as chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) exhibit common characteristics suggestive of the diagnosis and may represent early manifestations of malignancy. Metastatic disease to the brain or CNS effects from systemic malignancy are important conditions to consider but are outside the scope of this chapter. Similarly, neurologic paraneoplastic conditions are discussed in Chap. 16 in this book. Herein, we review common oncological mimics of CNS inflammatory disease including histiocytic disorders, PCNSL, and CLIPPERS.

Histiocytic Disorders

Histiocytic disorders are a rare heterogeneous class of diseases of varied clinical course and prognoses. The World Health Organization Classification of Tumors of the Nervous System subclassifies histiocytic disorders into several different entities including Langerhans cell histiocytosis (LCH), Erdheim-Chester disease (ECD), Rosai-Dorfman-Destombes disease (RDD), juvenile xanthogranuloma (JXA), histiocytic sarcoma (HS), and indeterminate cell histiocytosis (ICH) [1]. These conditions are essentially malignancies of histiocytes or tissue macrophages that can present with isolated or multifocal tissue infiltration both intracranially and systemically. Since histiocytes are part of the mononuclear phagocyte system, they can present like and often be mistaken for immunologic conditions. Indeed, while the pathophysiology of these disorders has long been debated to be autoimmune, recent discovery of activating mutations in the MAPK and phosphatidylinositol 3-kinase/protein kinase B (PI3K-AKT) pathways involving a large proportion of patients has cemented that these are likely clonal and neoplastic in origin [2].

Langerhans Cell Histiocytosis

LCH is characterized by the proliferation of CD1a-positive and CD207-positive histiocytes [3]. Initially thought to be related to epidermal Langerhans cells, transcriptional profiling of Langerhans histiocytosis suggests greater similarity to bone marrow-derived monocyte and dendritic cell precursors [4]. The pathogenesis is not entirely clear, and there is some suggestion that it may result from an abnormal inflammatory response as well as secondary malignant transformation [5]. Biopsy for pathologic confirmation is recommended in all cases, particularly for patients requiring systemic therapy.

LCH typically occurs in childhood with an incidence of 0.5 cases per 100,000 individuals under age 15 and 0.1 cases per 100,000 in patients older than 15 years [6, 7]. This disorder can affect any organ but most frequently affects the bone, skin, and pituitary gland. Central nervous system involvement occurs in about 20–50% of cases [8] and most commonly occurs via direct extension through the calvarium but can involve the meninges or less commonly present as intraparenchymal masses [9]. A wide variety of neurologic symptoms can occur depending on the location of the lesion; diabetes insipidus is the most common neurologic manifestation and occurs in 15–50% of patients with CNS involvement [10].

Two major types of CNS lesions have been described: tumor lesions and degenerative lesions. Tumor lesions are space-occupying lesions that avidly enhance on magnetic resonance imaging (MRI) (Fig. 26.1) and are associated with clinical signs and symptoms related to tumor infiltration including acute to subacute focal neurologic deficits, cranial nerve palsies, increased intracranial pressure, seizures, or behavior change. In contrast, neurodegenerative lesions are accompanied by slowly progressive cerebellar dysfunction, cognitive impairment, or a pyramidal syndrome. Degenerative lesions are atrophic on MRI scan, do not typically enhance, and are associated with high T2 signal in the white matter [11, 12].

Consensus guidelines exist for the diagnosis, workup, and treatment of LCH [13]. However, the evidence to support any one treatment over another is scant. The discovery that slightly over half of all cases harbor oncogenic *BRAF* mutations [14] has opened the door to targeted treatments.

Erdheim-Chester Disease

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis. Fewer than 800 cases have been reported, but recognition of this disease is improving [15, 16]. The mean age at diagnosis is approximately 55 years with a male predominance (3:1) [15]. Diagnosis is based on histopathologic demonstration of foamy or eosinophilic histiocytes positive for CD68 and CD163 and negative for CD1a, CD207, and S100 (Fig. 26.2a, b) [15].

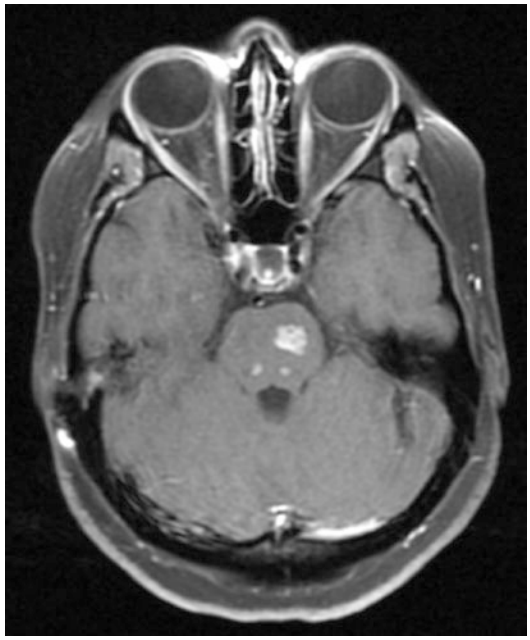

Fig. 26.1 Magnetic resonance imaging of a 28-year-old presenting with dysarthria and hemiparesis. Biopsy showed Langerhans cell histiocytosis

ECD is a heterogenous multisystem disease that can affect any organ including the CNS. Commonly, the presenting symptom is bone pain due to sclerotic lesions of the long bones, which occur in 96% of reported cases [17]. Cardiac involvement is also quite common and is a source of increased mortality [18]. Close to half of patients with ECD have neurologic manifestations. When the CNS is involved, presenting symptoms typically involve cerebellar (41%) or pyramidal symptoms (45%) [19]. However, a wide variety of neurologic manifestations can occur depending on the location of CNS involvement. Signs and symptoms can include seizures, headaches, neurocognitive deficits, weakness, and numbness [19]. Much like LCH, diabetes insipidus occurs in about 25% of patients, although other endocrinopathies have been reported as well [16]. CNS involvement has also been identified as a poor prognostic factor [20].

Radiographic manifestations of ECD typically include an intraparenchymal predominance, a meningeal predominance, or a combination of both. Intraparenchymal lesions tend to be enhancing T2 hyperintense abnormalities on MRI (Fig. 26.3). Intraparenchymal lesions may be mistaken for demyelinating disease in many cases as lesions often may not appear to be space occupying. Lesions that involve the meninges can appear as dural thickening and may resemble other intracranial meningeal-based tumors like meningiomas [21].

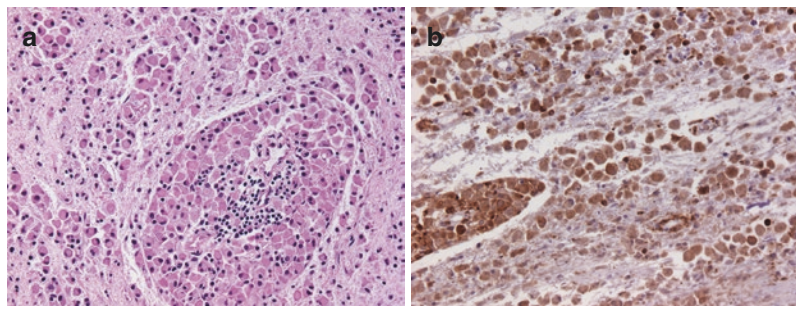

Fig. 26.2 Photomicrograph of brain tissue from a patient with Erdheim-Chester disease. (**a**) Seen are variably foamy histiocytes with cytologically normal nuclei. (**b**) Histiocytes strongly staining for CD68. Notably, normal macrophages seen in conditions such as infarcts of demyelinating disorders are also CD68 positive

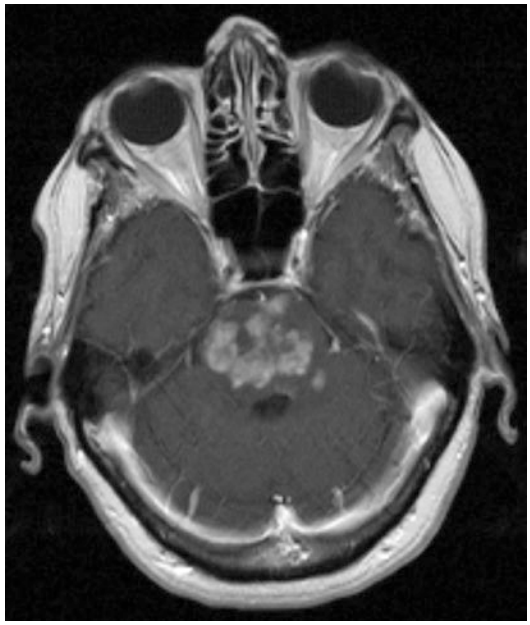

Fig. 26.3 Magnetic resonance imaging of a 70-year-old woman with progressive brain stem symptoms. Biopsy showed Erdheim-Chester disease with a *BRAF V600E* mutation

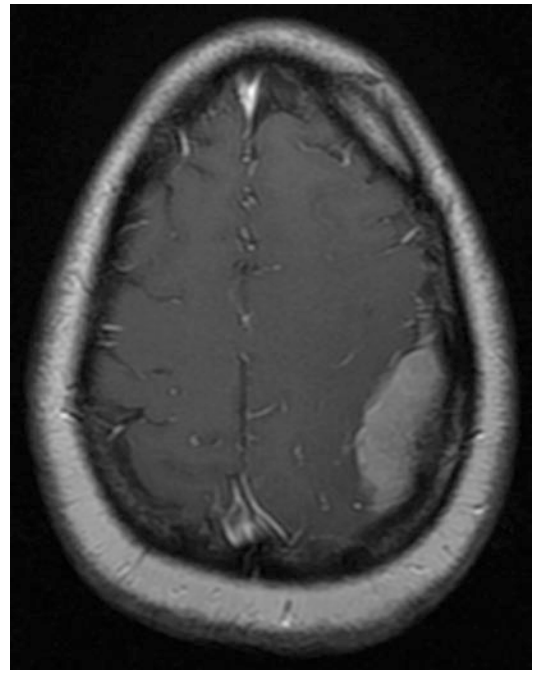

Fig. 26.4 Magnetic resonance imaging of a 42-year-old African-American patient with biopsy-proven Rosai-Dorfman-Destombes disease

Many reported regimens have been used with varied success for the treatment of ECD [15]. However, much like LCH, many cases of ECD exhibit *BRAF* mutations and can respond successfully to medications targeting this mutational pathway [22].

Rosai-Dorfman-Destombes Disease

Rosai-Dorfman-Destombes disease (RDD) is considered a non-Langerhans cell histiocytosis much like ECD. As compared to ECD, it has a lower mean age of 21 years and is more common in males and patients of African descent [23, 24]. Histopathologic features include accumulation of CD68-positive and CD1a-negative histiocytes; however, unlike ECD, RDD histiocytes are S100 positive [23]. Unlike both LCH and ECD, RDD is not typically associated with *BRAF* mutations [25].

Classically, patients present with systemic findings of bilateral massive lymphadenopathy, but extranodal disease may occur in up to 43% of cases [26]. Extranodal sites may include the nasal sinuses, skin, bone, liver, mediastinum, and CNS. In the CNS, RDD typically presents with dural-based disease that may occur in almost any location, including the spinal cord, with a predilection for the cerebral convexities (Fig. 26.4). It may also be associated with intraparenchymal lesions which involve the brain stem and cerebellum, although this is less common [23].

Outcomes for RDD are typically favorable in patients with nodal or cutaneous disease. Patients with kidney, liver, or lower respiratory tract disease seem to have a worse prognosis and may warrant more aggressive therapies [23]. CNS disease can be fatal and can have significant associated morbidity. In these cases, aggressive therapies may also be warranted. While multiple treatment approaches have been attempted, typically in case reports, no standard treatment recommendations exist.

Juvenile Xanthogranuloma

Juvenile xanthogranuloma (JXG) typically presents in very young patients with a mean age of

approximately 2 years and is typically a self-limited disease [27]. Cutaneous papules or nodules present typically on the face or head and neck but can involve any skin surface. Lesion number ranges from a few to hundreds. The condition is typically self-limiting with gradual resolution over months to years. Systemic JXG can occur in 5–10% of patients; CNS involvement can also occur [28]. In most cases when the CNS is involved, it presents in the brain with a much smaller percentage of spinal cord involvement. As is the case in most of the histiocytic disorders, neurologic symptoms at presentation are typically based on lesion location. Although CNS involvement in this condition is rare, it is associated with a high degree of morbidity and mortality in this otherwise benign condition [28].

Histiocytic Sarcoma

This condition is a rare aggressive neoplasm involving malignant histiocytes. Primarily, this condition is reported in case reports, which have described cases involving the parenchyma, meninges, and cavernous sinus. Radiologically, CNS involvement often mimics demyelinating disease, lymphoma, or even glioma. Due to the extreme rarity of this condition, it is often mistaken for these other entities [29].

Primary Central Nervous System Lymphoma

Primary central nervous system lymphoma (PCNSL) is an uncommon extranodal non-Hodgkin lymphoma involving the brain, spinal cord, leptomeninges, or eyes without evidence of systemic involvement. Though highly aggressive, it is a potentially curable malignancy. Up to 90% of patients will respond to appropriate treatment, but half of patients will relapse within 2 years, and prognosis after recurrence is poor [30]. PCNSL is rare and accounts for only 4% of all tumors involving the CNS and 4–6% of all extranodal lymphomas [31, 32]. The median age of diagnosis is 65 years, and the incidence in the elderly population is rising [33, 34]. PCNSL also occurs in the setting of immunosuppression such as human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), post-transplant immunosuppression, or congenital immunodeficiency.

Two widely recognized prognostic models were developed to predict outcomes in patients with PCNSL. The International Extranodal Lymphoma Study Group identified age, Eastern Cooperative Oncology Group (ECOG) status, serum lactic dehydrogenase (LDH), cerebrospinal fluid (CSF) protein concentration, and presence of deep brain structures as independent predictors of survival [35]. The Memorial Sloan Kettering Cancer Center model is a simplified model using only Karnofsky performance status (KPS) and age as predictors of outcome [36]. It is also worth noting that delays in treatment have been associated with poorer outcomes [37]. Thus, prompt diagnosis and initiation of treatment is of utmost importance.

PCNSL can present in any compartment of the CNS. As such, a wide variety of symptoms can occur in these patients including focal neurologic deficits, seizures, increased intracranial pressure, and cognitive difficulties, which can progress rapidly over weeks. Most cases of PCNSL present with lesions involving the brain parenchyma, primarily in the supratentorial compartment. Lesions are often periventricular and involve the deep white matter or corpus callosum. PCNSL can appear as a solitary lesion or multifocal disease. The frontal lobe white matter is thought to be the most common location. A hemispheric location, as opposed to deep structures, is seen in up to 38% of patients [38]. Rarely, lesions develop in the cerebellum or spinal cord. Leptomeningeal disease is seen in approximately 20% of cases of PCNSL but can be present in close to two-thirds of secondary CNS lymphoma [39, 40]. Isolated leptomeningeal involvement is unusual.

Computed tomography (CT) imaging typically reveals iso- or hypo-dense lesions. Contrast enhancement is quite common and is present in nearly all cases of CNS lymphoma [40]. On MRI, PCNSL typically presents as sharply demarcated

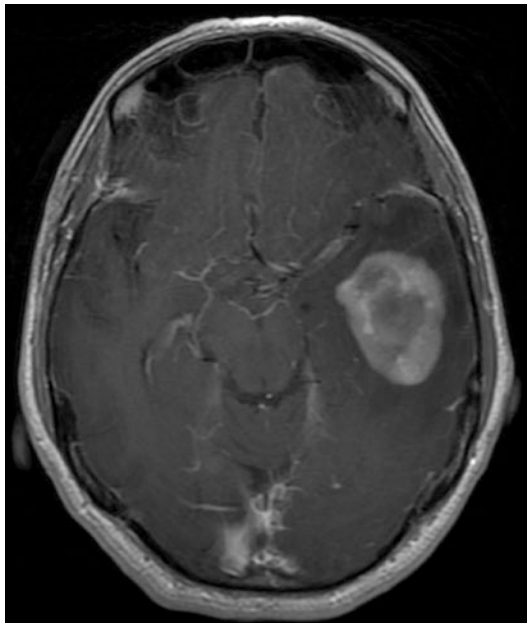

Fig. 26.5 Magnetic resonance imaging of a 72-year-old man who presented with confusion and word-finding difficulties. Biopsy showed diffuse large B-cell lymphoma. Negative systemic imaging confirmed primary central nervous system lymphoma

homogeneous enhancement that is iso- to hypointense on pre-contrast T1-weighted sequences (Fig. 26.5). Due to the dense cellularity, there is often diffusion restriction on diffusion-weighted imaging (Fig. 26.6a–d) [41]. It is very uncommon for CNS lymphoma patients to present without enhancement. However, in the setting of immunosuppression such as HIV/AIDS, enhancement may be more heterogeneous, exhibit central necrosis, or be absent [42, 43]. Symptoms concerning for PCNSL should prompt urgent imaging, preferably with MRI.

The diagnosis of primary CNS lymphoma is dependent on pathologic examination and thus requires the tumor sampling in most cases. Stereotactic biopsy is the procedure of choice. Corticosteroids should be avoided prior to biopsy as they are lymphotoxic and can obscure pathology results [44, 45]. Greater than 90% of cases are diffuse large B-cell lymphoma (DLBCL), with the remainder consisting of T-cell, Burkitt, or low-grade lymphomas [46]. Microscopically, these lesions tend to be densely populated with numerous small cells with large central, pleomorphic nuclei. Perivascular aggregates with invasion into surrounding parenchyma are common. Malignant lymphoma cells exhibit expression of pan-B-cell markers including CD19, CD20, and CD79a. MUM1 is nearly always positive, BCL6 positivity is seen in half of cases, and BCL-2 is variably expressed [46]. These characteristics suggest that the majority of PCNSL most closely resembles a postgerminal center or activated B-cell (ABC) immunophenotype [47]. While subtyping may have prognostic implications, it does not affect treatment.

Although most patients presenting with lymphoma of the CNS are thought to have primary disease, systemic spread to the CNS does occur. Differentiating between primary and secondary CNS lymphoma is important as the treatment approach differs. Workup to determine the extent of spread throughout the CNS is imperative as well. Standard serum evaluation for patients with PCNSL should include a complete blood count, metabolic panel with liver function tests, hepatitis serologies, LDH, and HIV testing. Baseline evaluation with a CT scan of the chest, abdomen, and pelvis or preferably a positron emission tomography (PET) scan is required to identify potential systemic disease. A bone marrow biopsy is also warranted [48]. In men, testicular ultrasound to rule out concomitant testicular lymphoma is warranted as up to 15% of patients with testicular lymphomas metastasize to the brain [49]. Further, a thorough ophthalmologic evaluation including slit lamp examination is always necessary as the eye can serve as a reservoir of disease and potentially reseed the CNS following treatment. To assess for leptomeningeal involvement, a lumbar puncture should also be done if there is no risk for herniation. CSF should be sent for flow cytometry, cytology, and IgH rearrangement in addition to basic CSF studies [50]. Documented involvement of any of these compartments should prompt end of treatment reassessment to ensure disease is eradicated.

Treatment of PCNSL consists of induction therapy with the goal of achieving a complete response (CR) or elimination of gross disease. This is followed by consolidation to eliminate

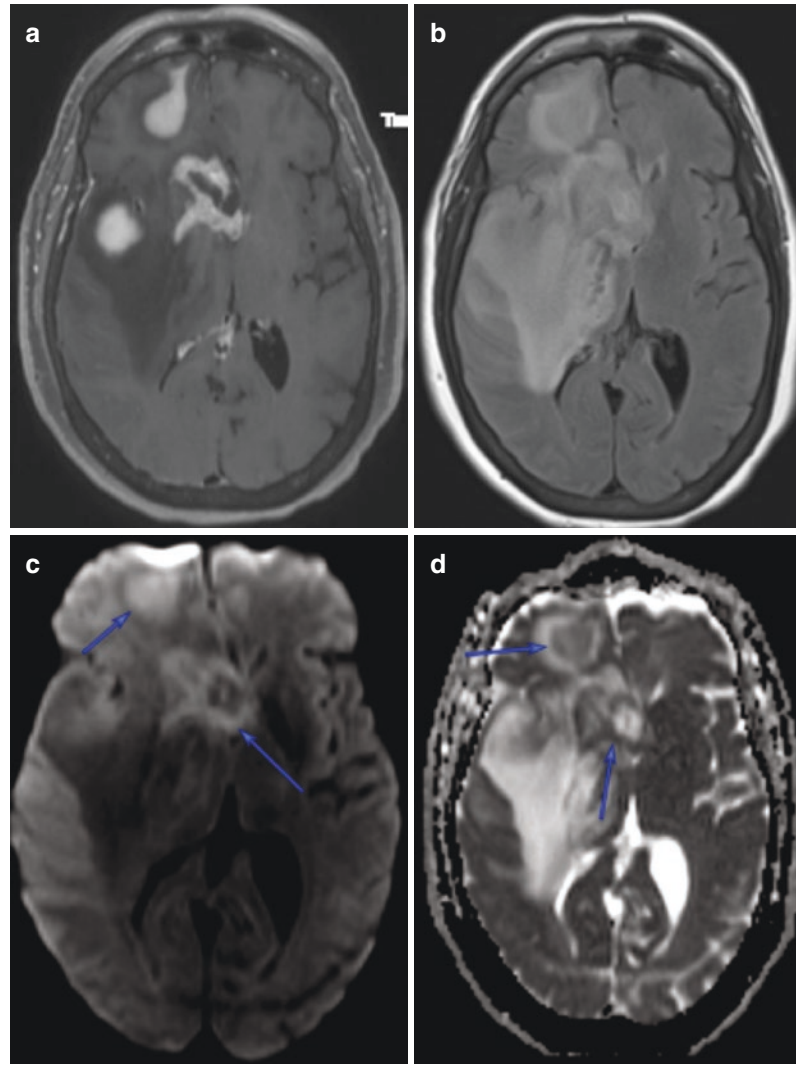

Fig. 26.6 Magnetic resonance imaging of a 66-year-old woman presenting with 2 weeks of confusion and found to have multifocal enhancing lesions (**a**). T2 fluid-attenuated inversion recovery (FLAIR)-weighted imaging (**b**) showed significant edema associated with the enhancing lesions. Diffusion-weighted imaging (**c**) and apparent diffusion coefficient imaging (**d**) showed mild diffusion restriction. Biopsy proved diffuse large B-cell lymphoma

microscopic disease and maintain remission. Due to the rarity of primary CNS lymphoma and lack of phase three randomized trials, a standardized treatment regimen does not exist. Untreated, this disease is almost universally fatal within the first few months of symptom onset. However, with aggressive treatment, improved response rates and prolonged disease control are achievable.

Traditionally, whole-brain radiation therapy (WBRT) was used with overall response rates of 90% and extension of survival beyond a year [51, 52]. Treatment with radiotherapy is not curative, however, and overall survival with WBRT alone is only 12–18 months [51, 53]. Ultimately, the role of WBRT is debated. When combined with chemotherapy, neurotoxicity rates are high and does not likely prolong overall survival [54, 55].

Chemotherapy regimens used to treat systemic lymphoma have limited effectiveness in treating CNS disease [39]. This is likely due to limited blood-brain barrier penetration of most chemotherapies used to treat systemic lymphoma. In general, the chemotherapeutic approach to PCNSL has trended toward multi-agent chemotherapeutic regimens; however, there is no standard first-line regimen. High-dose methotrexate (MTX) is considered the backbone of therapy for PCNSL. MTX, when

given at relatively high doses (>1.5 gm/m^2) and as a rapid infusion, results in tumoricidal concentrations with the brain and CSF [56, 57]. Single-agent MTX has been given at doses as high as 8 gm/m^2 [58]. The addition of high-dose cytarabine to MTX has resulted in improved response rates and progression-free survival but with increased rates of hematological toxicity [59]. Rituximab, an anti-CD20 monoclonal antibody, has been incorporated into many varied chemotherapy regimens with noted improvement in response rates and overall survival [60–64]. It has become common practice to incorporate rituximab into MTX-containing regimens. Common combination regimens include MTX typically with an alkylating agent with or without rituximab.

High-dose MTX is relatively well tolerated and specific toxicities vary based on regimen. Aside from the potential delayed neurotoxicity (particularly when combined with WBRT), an additional limitation is the need for hospitalization during administration. Common systemic side effects include renal toxicity, hepatitis, myelosuppression, and mucositis. Treatment is administered with aggressive hydration, urine alkalinization, and leucovorin to prevent systemic organ damage. With appropriate supportive care, MTX-based regimens are safe to administer, even in older patients with medical comorbidities. However, impaired renal function (creatinine clearance <30 mL/min) is a contraindication for MTX.

Consolidative therapies following complete response to induction vary depending on physician preference, and no standard exists. Reduced-dose WBRT has been used as a consolidative approach with encouraging results and low rates of neurotoxicity, but the small numbers of patients and limited follow-up limit the applicability [65, 66]. There has been increasing interest in pursuing high-dose chemotherapy with autologous stem cell transplantation with curative intent as a consolidative option. In younger otherwise healthy patients, this may be a good option, and early studies suggest an improvement in survival with the use of stem cell transplantation for consolidation [67, 68]. Certain patients may not be able to tolerate the rigors of high-dose chemotherapy given in preparation for transplantation. These patients may rely on other chemotherapeutic approaches for consolidation [37]. Maintenance rituximab has been used as a strategy to maintain remission, and trials using maintenance strategies are ongoing [69].

Primary CNS Lymphoma in the Elderly

More than half of patients with PCNSL are 60 years of age or greater, and age is an independent predictor of survival [35, 36]. Moreover, the risk of neurotoxicity is highest in the elderly, and treatment may be complicated by multiple comorbidities. Thus, the optimal treatment for this group has yet to be defined. However, a large meta-analysis of elderly patients with newly diagnosed PCNSL showed that 73% of patients received a MTX (median dose of 3 g/m^2)-containing regimen, and this was associated with improved survival, particularly when combined with an oral alkylating agent. Interestingly, more aggressive chemotherapy regimens were not associated with superior outcomes [70]. It is generally agreed that WBRT should be avoided and multi-agent MTX-based regimens be considered for first-line treatment.

Primary CNS Lymphoma in the Immunocompromised

The epidemic of HIV in the 1980s and 1990s led to an increase in CNS lymphoproliferative disorders including CNS lymphomas. Prognosis in these patients was initially quite poor [71]. PCNSL in these patients is thought to be driven by Epstein-Barr virus (EBV) infection. The advent of antiretroviral therapies has significantly reduced the incidence of this subtype of CNS lymphoma in patients with HIV-related lymphoproliferative disorders [72]. WBRT is an option

for treating patients with this condition and is especially useful in patients with significant comorbidities. In general, treatment of the cause of the immunosuppression has improved survival in these patients, thought to be due to immune recovery [73]. Aside from WBRT, other approaches include the use of MTX alone or in combination with additional chemotherapies concurrently with antiretroviral management. A recent study suggested that a combination of zidovudine, ganciclovir, and rituximab without MTX produced complete and durable responses in these patients [74].

Subtypes of CNS Lymphoma

There are many subtypes of PCNSL, which are differentiated by unusual areas of disease involvement or uncommon cellular type. Primary ocular lymphoma is uncommon and is felt to be a subtype of PCNSL as opposed to systemic disease. Due to the blood-ocular barrier, this condition is treated in similar fashion to CNS lymphoma with methotrexate- or cytarabine-based regimens. Primary leptomeningeal lymphoma is also an uncommon presentation of CNS disease but treated in a similar fashion.

Hodgkin lymphoma can rarely involve the brain as well as lymphomas of the T-cell type [75, 76]. Low-grade lymphomas such as marginal zone lymphoma or mucosa-associated lymphoid tissue (MALT) lymphoma can involve the CNS; however, dural or extra-axial involvement is much more typical of these lower-grade lesions [77]. Intravascular lymphoma is a subtype of lymphoma that has typical CNS involvement but is considered disease with systemic involvement. This condition involves invasion of malignant B cells into the lumens and vessel walls of smaller blood vessels. It is often rapidly fatal, can affect multiple organs, and causes ischemic injury. Intracranially, MR imaging may be variable but often shows infarct-like white matter lesions in vascular territories with variable patterns of parenchymal and meningeal enhancement (Fig. 26.7a, b) [78].

Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis is an uncommon lymphoproliferative disorder that primarily involves the lungs but in rare occasions can involve other sites including the CNS. In even rarer instances, it can involve the CNS in isola-

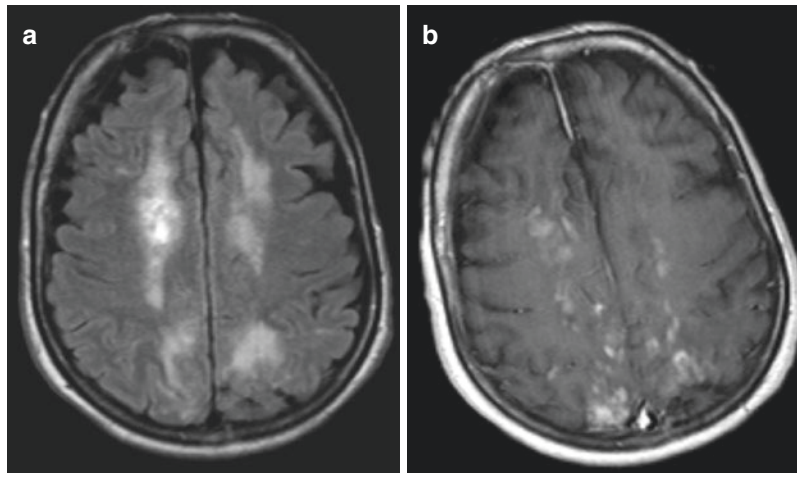

Fig. 26.7 Magnetic resonance imaging of a 48-year-old woman presenting with diffuse white matter disease. T2 fluid-attenuated inversion recovery (FLAIR)-weighted imaging (**a**) showed diffuse areas of high signal within the white matter. T1-weighted post-contrast images (**b**) showed variable patchy enhancement. Biopsy demonstrated malignant lymphoid cells aggregated within the vasculature consistent with intravascular lymphoma

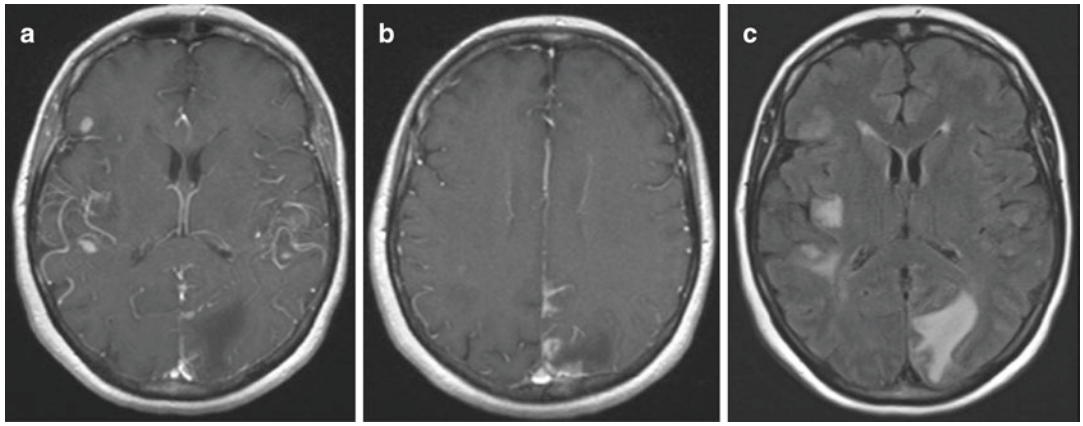

Fig. 26.8 Patient with biopsy-proven lymphomatoid granulomatosis. T1 post-contrast imaging (**a**, **b**) shows multifocal enhancement throughout both cerebral hemispheres. T2 fluid-attenuated inversion recovery (FLAIR) imaging (**c**) with areas of surrounding edema

tion. In cases of primary CNS lymphomatoid granulomatosis, this disease can present with both mass-like lesions and more diffuse-infiltrating lesions, the former being more common [79]. There is no classic presentation seen on MRI or CT imaging of the brain, necessitating evaluation for more common conditions. Linear or punctate enhancement is slightly more specific for this condition and is thought to represent the angiocentric nature of this condition (Fig. 26.8a–c) [79, 80].

Histopathologically, this condition is characterized by angiocentric lymphoid aggregates that can invade and destroy blood vessels. This can lead to infarcted tissue, both brain and tumor alike. The infiltrate is generally a mixture of CD20-positive large, monoclonal, neoplastic B cells with a significant T-cell population without clonality. The B-cell population is of uncertain malignant potential and may not make up a large percentage of cells within the infiltrate. Pathogenesis is unclear; however, it is generally thought to be an EBV-driven process, particularly in cases with systemic presentations [81, 82]. The World Health Organization separates this condition into three grades: grade 1 is the least aggressive; grade 3 is the most aggressive with large atypical CD20+ B cells and extensive necrosis [82].

There is no standard therapy for this condition, and treatment depends on extent of involvement and grade of disease. For more benign-appearing presentations, steroids alone may be enough to treat this condition. More aggressive disease may warrant treatment similar to PCNSL with systemic chemotherapy. In a review of 22 cases of isolated CNS lymphomatoid granulomatosis, treatment included steroids alone, radiotherapy alone, chemotherapies including cyclophosphamide, cisplatin, cytarabine, methotrexate, or a combination of these treatments [79].

Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS)

CLIPPERS is a CNS inflammatory disorder of unknown etiology predominantly affecting the brain stem. It is characterized by punctate, curvilinear gadolinium-enhancing lesions "peppering" the pons and cerebellum and is noted to have exquisite sensitivity to steroids [83]. While associated with characteristic clinical, imaging, and pathologic findings, the lack of formal diagnostic criteria and biomarkers often leads to uncertainty regarding the diagnosis.

Given the predilection for involvement of the brain stem, common presenting symptoms include dysarthria, diplopia, gait ataxia, vertigo, sensory changes of the face, and cognitive impairment [84]. Symptoms typically progress over weeks to months and rapid progression is unusual. Typical age of onset is in midlife, but a wide range has been reported [83, 84]. While clinical symptoms may be suggestive, none make the diagnosis. Further, no specific laboratory abnormalities are characteristic of CLIPPERS, and laboratory testing should be used to exclude alternative diagnoses. No pathologic hallmark has been identified in CLIPPERS, and the primary reason for biopsy is to exclude other diagnoses. Typical histologic findings include perivascular inflammation with CD3-reactive T-lymphocytes (predominantly CD4 positive), activated microglia, CD68-positive histiocytes, and occasionally CD20-positive lymphocytes [83, 84]. Diagnostic criteria using clinical, radiological, and pathologic criteria have been proposed [84].

Central to the diagnosis of CLIPPERS is the overall radiographic and clinical responsiveness to steroids. The natural history seems to be that of a relapsing-remitting disorder, and some patients require long-term immunosuppression [84]. The occurrence of suspected CLIPPERS has been associated with malignancy, and it has been postulated that CLIPPERS represents a premalignant state [85–89]. While likely that CLIPPERS represents a spectrum of entities, it is clear that long-term follow-up is necessary to determine the course of the disease as well as potential development of other diseases.

Conclusion

While rare, oncological disorders occur within the CNS with enough frequency to warrant consideration when evaluating patients for potential inflammatory disease. Varied presentations and diagnostic uncertainty can complicate evaluation and treatment. However, conditions such as histiocytic disorders, PCNSL, or CLIPPERS represent specific diseases with unique therapeutic strategies. As our understanding of these diseases evolves, outcomes are improving making early and accurate diagnosis imperative.

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