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Necrotic Primary CNS Lymphoma in an Immunocompetent Patient: A Case Report and Literature Review

Peter Fiester*, Patrick Natter, Dinesh Rao, Jeet Patel and Dalys Castro

Department of Neuroradiology, University of Florida Health-Jacksonville, Jacksonville, FL, USA

***Corresponding author:** Peter Fiester

Peter.Fiester@jax.ufl.edu

Department of Neuroradiology, University of Florida Health-Jacksonville, 655 West 8th Street, Jacksonville, FL 32209, USA.

Tel: +813-842-3771

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Abstract

Primary lymphoma that arises *de novo* from the central nervous system (CNS) is most commonly a Non-Hodgkin's B cell lymphoma and by definition lacks the presence of disease outside the CNS. It demonstrates characteristic imaging aspects on computed tomography (CT) and magnetic resonance imaging (MRI) exams related to its inherent hyper cellularity. On CT, primary CNS lymphoma demonstrates hyperdense attenuation and on MRI it commonly demonstrates restricted water diffusion on diffusion weighted sequences and homogeneous enhancement on post-contrast sequences. We present a case of primary CNS lymphoma in an immunocompetent patient with progressive necrosis and loss of restricted diffusion on diffusion weighted imaging with an atypical enhancement pattern. We further provide a review of the literature regarding the CT and MRI characteristics of primary CNS lymphoma and discuss the role of immune status in determining the imaging characteristics of this disease process.

Keyword: MRI; Lymphoma; Necrosis

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Introduction

Lymphoma may occur as a *de novo* primary CNS lymphoma (PCNSL) with absence of disease outside the CNS or a secondary CNS lymphoma (SCNSL) related to systemic disease and CNS metastasis [1,2]. Both PCNSL and SCNSL are most commonly of B cell origin with 90-95% of PCNSL and 80% of SCNSL presenting as a B cell Non-Hodgkins lymphoma [1-3]. The precise origin of PCNSL is debated since the CNS lacks a lymphatic system and lymphocytes; however, PCNSL does demonstrate increased incidence in immunocompromised patients (e.g., HIV/AIDS patients), namely related to the activation of the Epstein Barr virus [1,3-5].

Whereas SCNSL typically involves the skull and dura, PCNSL much more commonly involves the brain parenchyma and has characteristic imaging aspects in the immuncompetent patient population related to the tumor's inherent hypercellularity, high nuclear/cytoplasmic ratio, and disruption of the blood brain barrier [6-9]. On non-contrast head CT, PCNSL is typically hyperdense on CT exam and demonstrates restricted water diffusion on diffusion weighted imaging (DWI) and avid enhancement on brain MRI. PCNSL has a predilection for the deep structures of the brain and typically demonstrates a periventricular or perivascular location. Two thirds of tumors present as a solitary mass. The presence of necrosis and hemorrhage with PCNSL is uncommon unless the patient is immunocompromised [1,10,11].

Case Presentation

A 50-year-old male with a past medical history of hypertension and heavy alcohol use in the past (reportedly sober for the past four months) presented to the Emergency Department for recurrent and progressive dizziness over the past month and worsening memory impairment. The patient also endorsed anomia, trouble with calculations and feeling confused. Neurologic exam demonstrated 3+ hyperactive lower extremity reflexes, a positive Babinski sign, decreased lower extremity vibratory sense, and conjugate nystagmus on lateral gaze with horizontal diplopia. Remaining neurologic exam was unremarkable.

Based on presenting signs and symptoms, the patient was tentatively diagnosed with Wernicke-Korsakoff Syndrome. A laboratory panel, including CMP, CBC, TSH, HIV and Thiamine level were ordered. Laboratory findings revealed an elevated white blood cell count of 12.6 and a normal thiamine level; remaining laboratory findings were within normal limits. A

lumbar puncture with CSF analysis was unremarkable. Non-contrast head CT followed by serial MRI examinations of the brain with and without IV gadolinium was performed for further assessment.

Imaging findings and diagnosis

Initial non-contrast CT of the head demonstrated a well-demarcated area of slightly hyperdense attenuation with surrounding edema centered in the bilateral parietal lobes and splenium of the corpus callosum extending across midline (**Figure 1**). There was no hemorrhage or mass effect.

Based on the head CT findings and clinical presentation, a follow-up pre and post-contrast brain MRI was performed and demonstrated isotense T2/FLAIR mass in the subcortical white matter in the bilateral parietal lobes and splenium of the corpus callosum with extension across midline and surrounding vasogenic edema. B1000 Diffusion weighted imaging (DWI) and corresponding Apparent Diffusion Coefficient (ADC) map demonstrates mild restricted water diffusion. Following administration of intravenous gadolinium, the mass demonstrated areas of non-contiguous homogeneous enhancement. No associated mass effect, volume loss or hemorrhage was present (**Figure 2**).

PCNSL was suspected based on the imaging characteristics; however the patient declined biopsy and further treatment at that time. The patient slowly developed worsening neurologic symptoms, and subsequent follow-up pre- and post-contrast brain MRI exam was performed at three and five month intervals. T2 weighted imaging demonstrated progressive necrosis and cystic change within the corpus callosum and bilateral parietal white matter (**Figures 3 and 4**). Diffusion weighted imaging demonstrated T2 shine through in the areas of previously seen restricted water diffusion, and T1 weighted post contrast imaging demonstrated a peripheral incomplete ring of enhancement (**Figures 3 and 4**).

The question of whether this lesion may in fact represent tumefactive demyelination (TDL) was raised based on the follow-up imaging. The patient subsequently underwent a left occipital-approach stereotactic biopsy of the lesion. The specimen yielded sheets of large lymphocytes with open chromatin, nucleoli and high N:C ratio consistent with diffuse large B-cell lymphoma. Inpatient treatment with six cycles of chemotherapy (Methotrexate 8000/m^2 every 14 days) was initiated. Post treatment brain MRI demonstrated a positive response to therapy with decreased volume of the lesion and resolution of the peripheral enhancement (**Figure 5**).

Discussion

Our case is unique for several reasons. Serial follow-up brain MRI exams demonstrate intercurrent lack of hypercellularity associated with the tumor as no restricted water diffusion on DWI was present at the three and five month intervals. A study by Haldorsen et. al reviewed the CT and MRI findings of 76 patients with biopsy-proven PCNSL and found 100% of their patients demonstrated either isodense or hyperdense attenuation of the tumor relative to white matter on non-contrast head CT [12]. Furthermore, Mansour et al. reviewed the MRI characteristics of PCNSL in 21 immunocompetent patients and found either restricted water diffusion or isointense signal within the tumor on DWI [4]. However, this imaging finding on CT and MRI exams may be more common in low grade PCNSL (defined by the predominance of small, mature lymphocytes and a growth fraction <20%). In fact, Schob et al. demonstrated a significant correlation between low ADC levels and higher proliferative activity of PCNSL [7].

The serial follow-up MRI exams also demonstrated increasing necrosis of the tumor on T2 weighted imaging with internal areas of hyperintense signal intensity within the corpus callosum and biparietal deep white matter. This imaging characteristic on MRI has been observed in AIDS-related PCNSL with many of the lesions

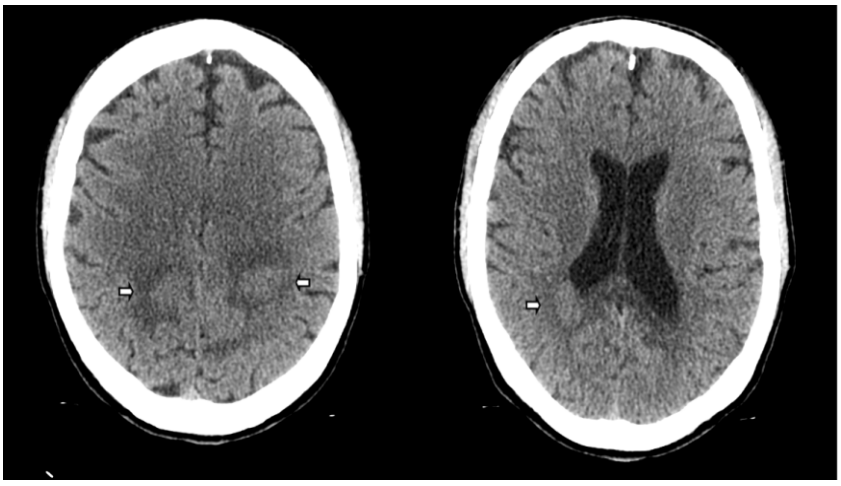

Figure 1 Two CT axial images demonstrate a slightly hyperdense mass with adjacent edema involving the parietal white matter (first image arrows) and the splenium of the corpus callosum (second image arrows).

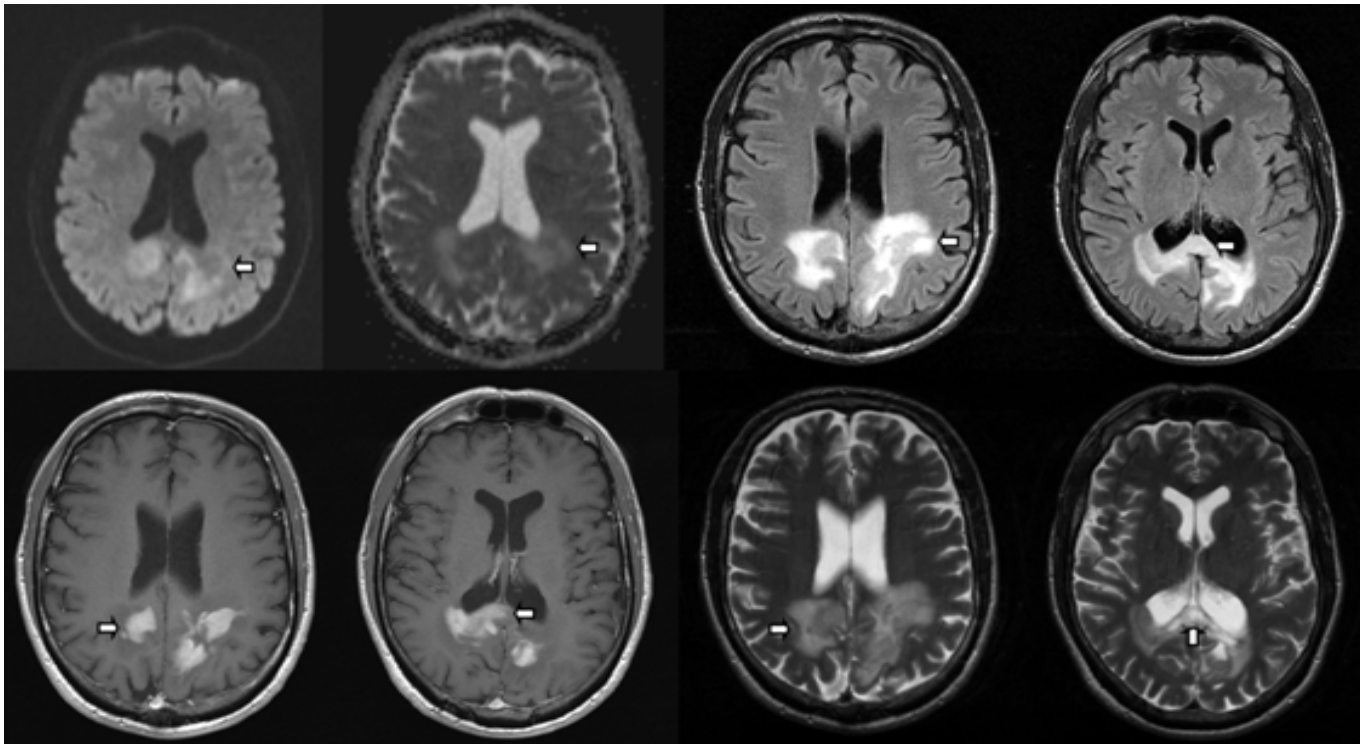

Figure 2 Brain MRI with provided DWI/ADC sequences (top left) demonstrate mild restricted water diffusion associated with a mass in the bilateral parietal lobes and splenium (arrows). FLAIR sequence (top right) demonstrate perilesional vasogenic edema within the splenium of the corpus callosum and in the adjacent parietal lobes (arrows). T1 weighted post contrast sequence following administration of IV gadolinium (bottom left) demonstrate discontinuous, homogeneous enhancement (arrows). T2 sequence (bottom right) demonstrates an isointense mass in the splenium of the corpus callosum and in the adjacent parietal lobes with surrounding vasogenic edema (arrows).

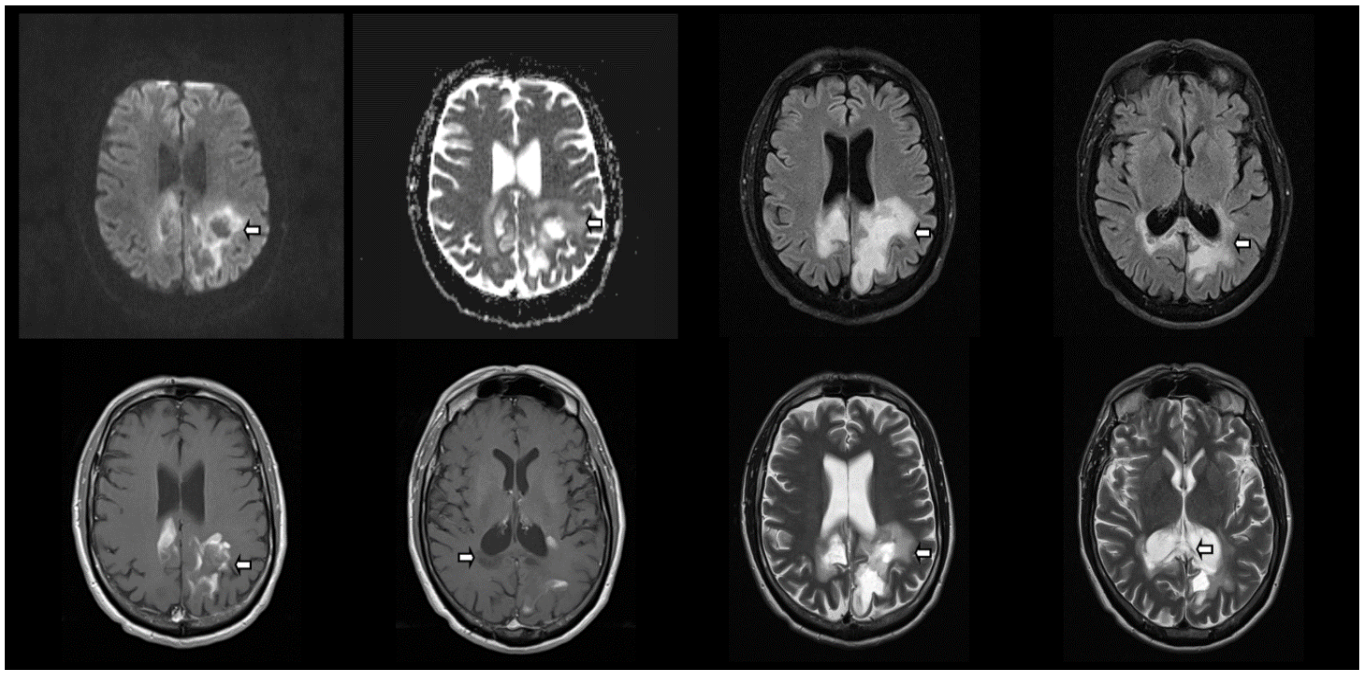

Figure 3 Three month follow-up brain MRI with provided DWI/ADC sequences (top left) demonstrate T2 shine through without restricted water diffusion (arrows) in the region of previously seen restricted water diffusion. FLAIR and T2 weighted sequences (top and bottom right) demonstrate necrosis and cystic change within the corpus callosum and subcortical white matter of the bilateral parietal lobes (arrows). T1 weighted post contrast sequence (bottom left) demonstrate resolution of the homogeneous enhancement with an incomplete, peripheral enhancement pattern.

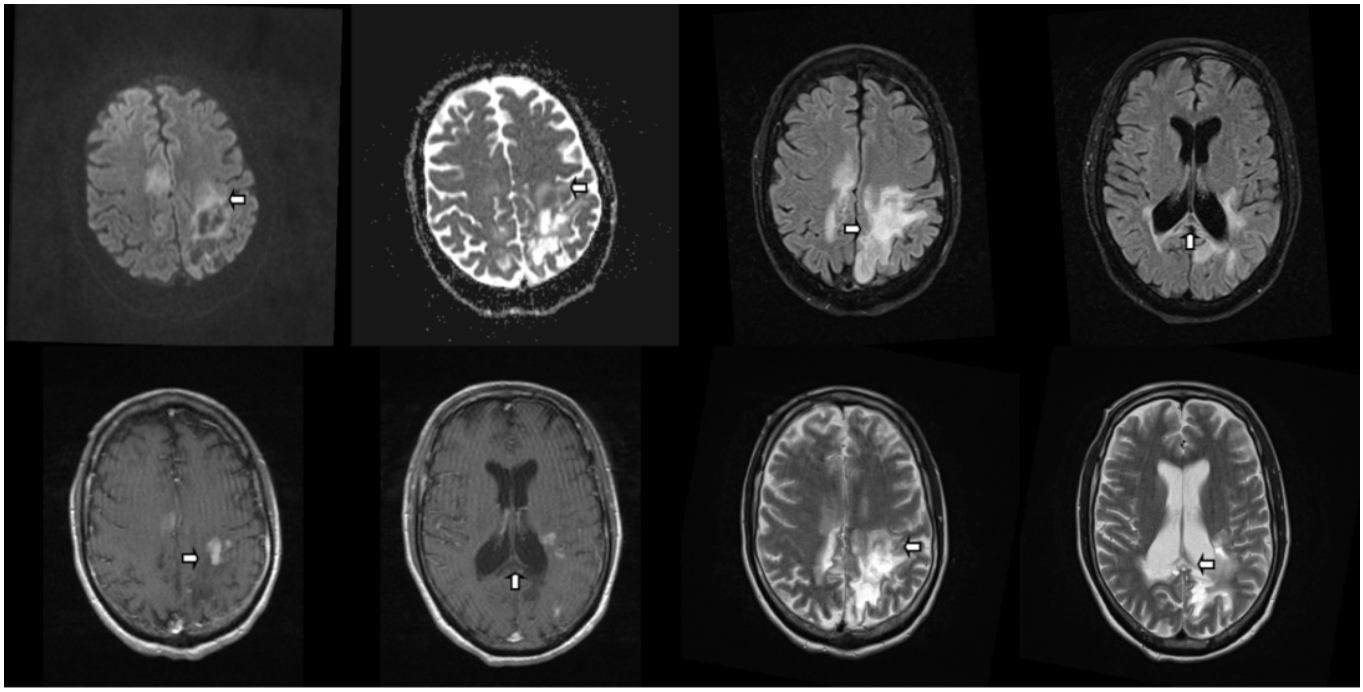

Figure 4 Five month follow-up brain MRI demonstrates lack of restricted diffusion on DWI (top left), increase necrosis and cystic change on T2/FLAIR sequences (top and bottom right), and scattered, leading edge enhancement pattern (bottom left).

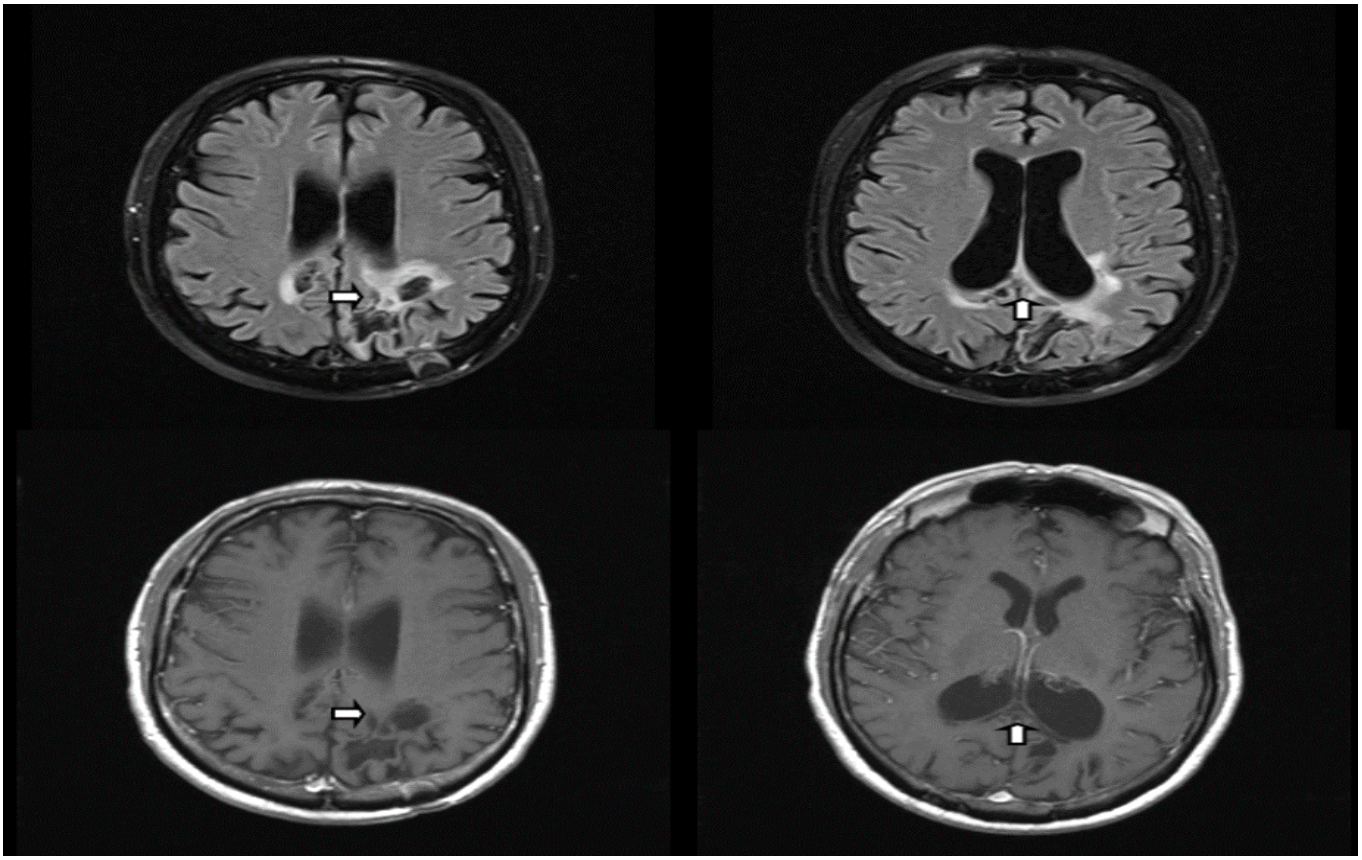

Figure 5 Pre and post contrast brain MRI following chemotherapy. FLAIR-weighted sequence (top images) demonstrates decreased volume of the lesion (arrow). T1-weighted pre and post-contrast sequence (bottom images) demonstrate resolution of the previously seen enhancement (bottom images arrows).

exhibiting necrotic regions and more commonly a multifocal or disseminated distribution [1,5,11]. Subsequent MRI exams also demonstrated a peripheral "leading edge" of enhancement. Intrinsic enhancement within PCNSL results from disruption of the blood brain barrier and accumulation of contrast material within the tumor. PCNSL in immunocompetent patients has a characteristic avid and homogeneous enhancement pattern. In all 21 patients with PCNSL, Mansour et al. describe positive enhancement pattern and most commonly avid enhancement [4]. Haldorsen et al. describe homogeneous contrast enhancement on MRI in 90% of patients in the non-AIDS population [11].

Atypical MRI aspects of PCNSL (e.g., necrosis, irregular or peripheral enhancement) in an immunocompetent patients is rare in the USA. This presentation is more common among patient with tumors who are positive for Epstein-Barr virus (EBV) [5,13]. EBV-positive PCNSL is more common in males and patients >60 years old with immunocompromised conditions such as HIV, chronic alcoholism, and several collagen vascular diseases. However recent studies have shown that this process may be also be related to immunologic deterioration associated with the normal aging process [5]. Several studies have postulated a relationship between EBV-positive PCNSL and disease survival. One study concluded that patient with EBV-positive PCNSL had shorter lifespans than EBV-negative PCNSL [6].

Given the imaging appearance on follow-up brain MRI exams, the question of whether this lesion could represent tumefactive demyelination (TDL) was also raised. Differentiating PCNSL from TDL may be extremely difficult in some patients due to the variability of clinical presentation and imaging findings. The lymphodepletive effect of corticosteroid drugs, which is routinely given to patients with suspected TDLs before biopsy, can obscure the histologic features of both PCNSLs and TDLs [14,15]. Corticosteroids can also further confound the diagnostic dilemma by obscuring radiologic findings of both TDLs and PCNSLs [14-16]. Demyelination may also be associated with paraneoplastic phenomena, since anti MOG antibodies have been found in the serum of patients with sentinel demyelination lesions preceding the presentation of PCNS lymphoma [17].

Histologically, differentiating demyelination from PCNSL may also be challenging due to the fact the PCNSL may present in association with steroid-responsive multifocal demyelinating sentinel lesions, which histologically are indistinguishable from MS, containing predominantly T cells infiltrates and a few B cells [18,19]. Additionally, abnormal mitotic figures in reactive astrocytes within TDLs can potentially mimic high-grade gliomas on histology [20]. One author postulate the hypothesis that T cell infiltrates represent a cell mediated anti- tumor response to B cell lymphoma [19,21,22]. This observation is derived from reports of spontaneous regression of lymphomas in immunocompetent individuals as well as improved survival in follicular lymphoma [23].

A few studies have tried to differentiate TDLs from PCNSLs using advanced MR imaging techniques. Two studies demonstrated a significantly higher ADC minimum in TDL than in PCNSL with 1 study demonstrating that ADC minimum with a threshold of 556 × 10-6 mm^2/s was the best indicator for differentiating TDL from atypical PCNSL (a sensitivity of 81% and specificity of 89%) [14,15].

Another study showed a lower choline/NAA ratio in TDLs than in PCNSLs, with a threshold for differentiation of 1.73 (a sensitivity of 89% and specificity of 76%) [16]. In addition, noncontrast CT hypoattenuation of MR imaging–enhanced regions was observed in 93% of TDL cases, but only 4% of primary brain tumors [20]. One study revealed that the combination of conventional MR imaging and advanced MR imaging improved the diagnostic performance for differentiating TDL from PCNSLs or high-grade gliomas. ADC values, MR spectroscopy, and noncontrast CT may help in diagnosing TDLs; however, further study is required to determine the added value of advanced MR imaging techniques in the differentiation of TDLs from PCNSLs. SWI may provide additional information when evaluating patients with atypical PCNSL. Lee et al. showed a considerable frequency of hemorrhage (18%) in immunocompetent patients with PCNSL, with significant predominance among patients with EBV-positive PCNSL vs EBV-negative PCNSL (70% vs 7%) [5].

Conclusion

We present an unusual case of PCNSL in an immunocompetent patient demonstrating progressive, atypical imaging characteristics on MRI. Findings help reinforce the protean appearance of PCNSL, which may occasionally lack the characteristic hypercellular imaging findings on CT and MRI exams especially if left untreated. Review of the literature suggests the presence of necrosis and peripheral enhancement on MRI to be uncommon in the immunocompetent population and more commonly associated with EBV-positive tumors or in HIV positive patients. The lack of the typical imaging characteristics of PCNSL should not dissuade one from the diagnosis, especially for a lesion located in the deep white matter or corpus callosum.

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