Primary CNS lymphoma initially diagnosed as vasculitis

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Abstract

Purpose of review

A vasculitic pattern of injury seen on brain biopsy can be attributed to a multitude of primary or secondary disorders, leading to diagnostic challenges for clinicians.

Recent findings

This report describes the clinical presentation and histopathologic findings in 2 patients who initially received a diagnosis of primary CNS vasculitis, but did not show long-term response to treatment. In both cases, a second biopsy was performed, and the final diagnosis was primary CNS lymphoma (PCNSL).

Summary

Analyzing diagnostically challenging cases can increase recognition of PCNSL and improve outcomes in this rare condition.

Brain biopsies are typically performed when a patient presents with acute to subacute signs and symptoms and has corresponding abnormalities on brain MRI, and a definitive diagnosis cannot be made using less invasive diagnostic tests. Brain biopsies many times show a histologic pattern compatible with vasculitis defined by injury of tissue with transmural inflammation of blood vessels. This injury may be caused by primary rheumatologic/autoimmune disease or may be secondary to other etiologies, including infections, hematolymphoid malignancies, and other neoplasms. A vasculitic pattern of injury on brain biopsy specimens presents noteworthy challenges to clinicians.

This report describes the clinical presentation and histopathologic findings in 2 patients who underwent brain biopsy and initially received a diagnosis of primary CNS vasculitis (PCNSV), but did not show appropriate response to treatment. In both cases, a second biopsy was performed, and the final diagnosis was primary CNS lymphoma (PCNSL). Challenges of obtaining a definitive diagnosis in patients with PCNSL have been previously described.^{1,2} This report highlights the dilemma that the pathologic diagnosis of an initial biopsy can include nonspecific inflammation, vasculitis, or demyelination. Furthermore, the use of corticosteroid treatment and the location of the biopsy can limit interpretation of results.

The primary purpose of this report is to analyze diagnostically challenging cases to increase recognition of PCNSL. Our aim is to emphasize to clinicians in all relevant specialties the pitfalls of brain biopsies with vasculitic patterns.

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This case series was approved by the Cleveland Clinic Institutional Review Board. The 2 patients presented in this article had biopsies at outside hospitals and presented to Cleveland Clinic, Cleveland OH, for a second opinion where pathology review was requested.

Case 1

A 43-year-old man developed a bifrontal headache that was worsened by coughing and sneezing for 7 days. A noncontrast head CT revealed a right frontal mass lesion. Subsequent MRI of the brain revealed a right frontal enhancing lesion with several discrete small enhancing satellite lesions (data not shown). Brain MR angiography (MRA) was normal. CSF was notable for white blood cell (WBC) 6/ μ L, 85% lymphocytes. IgG index was normal and cytology was negative for malignant cells. A brain biopsy was performed on day 11 of symptomatic onset, following the treatment of dexamethasone (dose unknown) for 4 days. A satellite lesion was removed for pathologic evaluation, but the main mass was not sampled; postoperative MRI is displayed in figure 1, A and B. Frozen-section diagnosis was perivascular lymphocytic infiltrate with reactive astrocytosis. Sparse perivascular lymphocytes were present in the leptomeninges and parenchyma. High magnification (figure 1C) showed infiltration of the wall of a venule consistent with a vasculitic pattern of injury. Immunostains performed at the outside hospital demonstrated that both CD3-positive T cells and CD20-positive B cells were present within and around the

vessels, and all had a benign cytologic appearance. The initial biopsy material was not sent for flow cytometry. There was no evidence of malignancy in the tissue examined, and the final pathology diagnosis was lymphocytic vasculitis. The patient was treated with prednisone 60 mg daily and oral cyclophosphamide 200 mg daily. He improved initially, but there was recurrence of headache and cognitive impairment. MRI of the brain at week 10 showed enlargement of the right frontal mass (figure 1, D and E). Ophthalmologic examination at that time was normal. Repeat subtotal resection at our institution at 2 months showed a highly cellular infiltrate of malignant cells that was diagnostic of diffuse large B-cell lymphoma (figure 1F). Serum lactate dehydrogenase (LDH) measurement or bone marrow examination was not performed. He was treated with 12 monthly cycles of rituximab and intra-arterial methotrexate and carboplatin with blood-brain barrier disruption. There was complete radiographic and clinical response, and the patient remains well 7 years after the first biopsy.

Case 2

A 54-year-old White woman presented with behavioral changes 5 months before initial evaluation. She displayed pressured speech, grandiose mood, disinhibition (foul language, sent inappropriate emails to coworkers), and poor judgment (reckless driving, impulsive shopping). Neurologic examination at that time was nonfocal. Initial MRI of the brain revealed hyperintense T2/fluid attenuated inversion recovery (FLAIR) frontoparietal and bilateral frontal subcortical white matter lesions (figure 2A) without enhancement (figure 2B). CSF was notable for the presence of oligoclonal bands and increased IgG index 0.87. Other CSF studies were within normal limits including WBC 2/ μ L, protein 29 mg/dL, culture and stain, Epstein Barr virus, varicella zoster virus, cytomegalovirus, herpes simplex virus, John Cunningham virus, venereal disease

Figure 1 MRI and pathology, patient 1

After biopsy number 1, axial FLAIR MRI (A) demonstrated right frontal lesions, showing contrast enhancement on axial T1 with contrast sequence (B). Biopsy number 1 at 20 $\times$ magnification, hematoxylin and eosin stain showed infiltration of the wall of a venule consistent with a vasculitic pattern of injury (C). Axial FLAIR MRI (D) and T1 with contrast (E) at week 10 showed enlargement of the right frontal mass. Repeat subtotal resection showed a highly cellular infiltrate of malignant cells that was diagnostic of diffuse large B-cell lymphoma at 20 $\times$ (F). FLAIR = fluid attenuated inversion recovery.

research laboratory test, Lyme disease, and cryptococcus. Brain biopsy of the lesion was markedly hypercellular due to the presence of numerous perivascular and intramural infiltrates composed primarily of lymphocytes and macrophages. No corticosteroid treatment was administered before the biopsy. There was clinical concern for paraneoplastic/autoimmune encephalitis, so additional stains were performed. Figure 2C shows a low magnification of the specimen with the highest burden of neuropathology. High magnification (figure 2D) shows perivascular lymphocytes with benign-appearing CD3-positive T cells, consistent with a vasculitic pattern of injury. T-cell clonality studies revealed no evidence of a clonal population. Flow cytometry did not detect a lymphoproliferative disorder. The perivascular inflammation led to a final pathology diagnosis of lymphocytic vasculitis. No evidence of vasculitis was observed on MRA of brain or cerebral angiography. She was treated with cyclophosphamide 1,400 mg intravenously and intravenous methylprednisolone 1,000 mg for 3 days followed by prednisone taper with initial transient improvement. Subsequently, 5 weeks later, she deteriorated clinically with symptoms of pressured speech, tangential thinking, poor insight, and poor attention. Repeat MRI of the brain revealed considerable progression of prior lesions into the basal ganglia, posterior corpus callosum, and temporal lobes (figure 2E). Patchy contrast enhancement was also observed (data not shown). Despite treatment with intravenous immunoglobulin 2 g/kg for 5 days, rituximab 1,000 mg, and 2 sessions of plasmapheresis, she continued to progress clinically and radiographically. Right temporal pole resection 4 months after initial biopsy was diagnostic of extranodal natural killer/T-cell lymphoma of nasal type (figure 2, F–H). Ophthalmologic examination, serum LDH measurement, or bone marrow examination was not performed. She was started on high-dose intravenous methotrexate (8 Gm/m²). Course was notable for diffuse cerebral edema and she was transitioned to comfort care and died 10 months after initial presentation.

Patients with PCNSL may present with nonspecific neurologic symptoms such as headache, change in mood or personality, or focal deficits.

Discussion

CNS vasculitis encompasses a heterogeneous group of primary or secondary disorders characterized by inflammatory injuries occurring in the cerebral vessel walls. Therefore, a diagnosis of PCNSV should not be automatically assigned following a histologic diagnosis of cerebral vasculitis. Multiple other possibilities still need to be considered including PCNSL. CNS vasculitis may occur in many systemic vasculitides (e.g., Wegener's granulomatosis, polyarteritis nodosa, eosinophilic granulomatosis with polyangiitis) or be secondary to connective tissue disorders (e.g., systemic lupus erythematosus). Systemic inflammatory markers of erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, and antinuclear cytoplasmic antibodies at high levels should prompt further systematic evaluation to exclude these conditions. Infections such as tuberculosis, varicella-zoster virus, or aspergillus can cause a CNS vasculitis. Intravascular lymphoma can be present in the lumen or infiltrate the walls of blood vessels. Sarcoidosis can rarely cause a true CNS vasculitis. Vasculitis can also occur in cerebral amyloid angiopathy in vessels with heavy beta amyloid deposition. Cerebral vasculitis has been associated with substance (such as cocaine or amphetamine) abuse. A systematic approach should be taken to rule out these disorders that may result in CNS vasculitis.^{3,4}

This report summarizes 2 patients originally diagnosed with PCNSV based on an initial biopsy who were subsequently found

Figure 2 MRI and pathology, patient 2

Before biopsy number 1, axial FLAIR MRI (A) demonstrated site of bilateral frontal lesions, without enhancement on contrast enhance sequence (B). Biopsy number 1 at 4× magnification, hematoxylin and eosin stain, demonstrating perivascular inflammation (C). Biopsy number 1 at 20× magnification, CD3 stain, shows perivascular lymphocytes with benign-appearing CD3-positive T cells (D). At week 16, axial FLAIR MRI revealed hyperintense lesions in the frontal, bilateral basal ganglia and corpus callosum (E). Temporal pole resection at 20× hematoxylin and eosin (F), 10× CD3 stain (G), and 10× Epstein-Barr encoding region in situ hybridization stain (H) was diagnostic of extranodal NK/T-cell lymphoma of nasal type. FLAIR = fluid attenuated inversion recovery; NK = natural killer.

to have PCNSL on repeat biopsy. Patients with PCNSL may present with nonspecific neurologic symptoms such as headache, change in mood or personality, or focal deficits. MRI may demonstrate solitary or multiple homogeneously enhancing intraparenchymal masses or less commonly, diffuse infiltrating hyperintense T2 and FLAIR lesions.⁵ Contrast enhancement is variable. A homogeneously enhancing pattern is seen in majority of non-AIDS PCNSL, but there may also be ring-like enhancement and linear enhancement along perivascular spaces.⁶ The differential diagnosis for these presentations is broad and includes primary malignancy, metastasis, demyelination, vasculitic, infectious, and autoimmune etiologies. Initial evaluation often begins with blood tests, CT chest, abdomen, and pelvis for malignancy screening, and CSF analysis to evaluate for infectious and inflammatory markers. In our patients, body CT scans were unremarkable. While spinal fluid revealed lymphocytic pleocytosis (range 85%–100%), cytology was negative for malignant cells, and flow cytometry did not detect a lymphoproliferative disorder.

Due to similarities in clinical, radiographic, and pathologic findings differentiating between PCNSL and PCNSV may initially be difficult. Several cases highlight the overlapping features of these 2 conditions^{7–9} and the 2 cases presented here illustrate common problems clinicians encounter with these types of cases. Several reports describe cases of PCNSL initially diagnosed as PCNSV. One case series describes 5 patients with presumed CNS vasculitis based on clinical history and MRI findings. All of the patients were later found to have an alternative diagnosis, including 1 patient with diffuse lymphoma.⁷ In another study of 61 patients with suspected PCNSV, brain biopsy revealed an alternative diagnosis in 39% of cases, and 6/24 had PCNSL.⁸ A previously published case described a patient who presented with seizure, dysarthria, and right-sided weakness and was found to have multiple infarcts. The patient was presumptively diagnosed with PCNSV, but autopsy revealed intravascular lymphoma.⁹

When the diagnostic evaluation remains inconclusive based on noninvasive data, biopsy can be performed for further diagnostic and prognostic information. In both of the cases presented here, the initial biopsy yielded tissue that showed a vasculitic pathology, demonstrating vasculitic injury, rather than the final diagnosis of PCNSL. On pathology, PCNSL is highly cellular with large atypical lymphocytes and high mitotic activity.¹⁰ In contrast, PCNSV displays a lymphocytic inflammatory reaction without atypia.⁴ Multiple reasons might account for the misdiagnosis in these 2 patients on pathology. Patient 1 received a short course of dexamethasone before biopsy. Variable response of lymphoma cells to glucocorticoids has been shown to prevent a lymphoma diagnosis in up to 50% of the patients due to the profound apoptotic effect of glucocorticoids on malignant cells.¹⁰ Disruption of the cellular morphology leaves behind the nonspecific inflammatory infiltrate. This has been coined the “vanishing” tumor phenomenon and can lead to rapid improvement in clinical and radiographic findings. In addition, review of imaging in our patients demonstrated that the tissue sample obtained from the first biopsies in both patients was at the periphery of the radiographic abnormality, rather than from

a central location. Peripheral sampling may show gliosis or reflect a secondary response to the primary pathology of lymphoma. While central biopsies may at times reveal only central necrosis. Without evidence of malignant cells in the sampled tissue, advanced biomarker analysis by PCR did not yield additional information. Therefore, a sampling error to include reactive cells from the periphery of the lesion rather than the substance of the central mass might have accounted for the misdiagnosis. Taking biopsy samples from multiple locations may decrease this risk.

It is important to note the progressive presentation of both our cases is more consistent with a neoplastic etiology, rather than an acute or stepwise deterioration that may be more suggestive of vasculitic etiology. Brain MRI did not show restricted diffusion to implicate ischemia, which could be a sign pointing against PCNSV. Another unifying theme in our 2 cases was a failure to respond to therapy for vasculitis. PCNSV is dependent not only upon clinical and pathologic criteria, but also appropriate response to treatment. Close clinical/radiologic follow-up and judgment of the treatment response is required to determine whether a correct diagnosis has been made. In our cases, a high clinical suspicion prompted the search for an alternative diagnosis and repeat biopsy. Multidisciplinary consultation with neurology, neurosurgery, pathology, and radiology should be utilized early to evaluate the radiographic and histologic correlation, to assess the adequacy of the sample, and to discuss timing and location of repeat biopsy. Repeat biopsy should be considered promptly in the setting of clinical or radiographic progression. Analyzing these diagnostically challenging cases can increase recognition and improve outcomes for this rare, but morbid condition.

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TAKE-HOME POINTS

- A vasculitic pattern of injury on brain biopsy specimens presents challenges to clinicians.
- The use of corticosteroid treatment and the location of brain biopsy can limit interpretation of results.
- Repeat biopsy should be considered when despite treatment, the patient demonstrates clinical or radiographic progression

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Appendix Authors

Name	Location	Contribution
Lauren Feldman, DO	Cleveland Clinic, Cleveland, OH	Study concept, collection of data, and drafting of the manuscript
Yuebing Li, MD, PhD	Cleveland Clinic, Cleveland, OH	Study concept and revision of the manuscript
Daniel Ontaneda, MD	Cleveland Clinic, Cleveland, OH	Study concept and revision of the manuscript

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