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## Brain biopsy in neurologic decline of unknown etiology

Shino Magaki, MD PhD<sup>a</sup>, Tracie Gardner, MD<sup>a</sup>, Negar Khanlou, MD<sup>a</sup>, William H. Yong, MD<sup>a</sup>, Noriko Salamon, MD, PhD<sup>b</sup>, and Harry V. Vinters, MD<sup>a,c,d</sup>

<sup>a</sup>Section of Neuropathology, Department of Pathology and Laboratory Medicine, University of California, Los Angeles (UCLA) Medical Center, Los Angeles, CA 90095-1732, USA

<sup>b</sup>Department of Radiological Sciences, University of California, Los Angeles (UCLA) Medical Center, Los Angeles, CA 90095-1732, USA

<sup>c</sup>Department of Neurology, University of California, Los Angeles (UCLA) Medical Center, Los Angeles, CA 90095-1732, USA

<sup>d</sup>Brain Research Institute; David Geffen School of Medicine at University of California, Los Angeles (UCLA) Medical Center, Los Angeles, CA 90095-1732, USA

### Abstract

Brain biopsies have an uncertain role in the diagnosis of patients with dementia or neurologic decline of unknown etiology. They are often performed only after an exhaustive panel of less invasive tests and procedures have failed to provide a definitive diagnosis. The objective of this study was to evaluate the sensitivity of brain biopsies in this patient group through the retrospective analysis of 53 brain biopsies performed for neurologic disease of unknown etiology at a single tertiary care institution between December 2001 and December 2011. Patients with known nonlymphomatous neoplasms thought to be associated with the neurologic symptoms or with immunodeficiency were excluded from the study. Furthermore, the clinical presentation, imaging and laboratory tests were compared between diagnostic groups to identify factors more likely to yield a diagnosis. Sixty percent of the biopsies were diagnostic (32 out of 53), with the most common histologic diagnosis of central nervous system lymphoma in 14 of 53 patients (26% of total) followed by infarct in four subjects (7.5%). A few patients were found to have rare and unsuspected diseases such as lymphomatosis cerebri, neurosarcoidosis and neuroaxonal leukodystrophy. Complications from biopsy were uncommon and included hemorrhage and infection with abscess formation at the biopsy site. These results suggest that brain biopsies may

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**Corresponding Author** Shino Magaki, MD, PhD, Department of Pathology & Laboratory Medicine, UCLA Medical Center, Center for Health Sciences, Rm. A7-215, Los Angeles, CA 90095-1732, Tel: 1 (310) 825-5719, Fax: 1 (310) 267-2058, smagaki@mednet.ucla.edu.

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### Conflict of interest

All authors have no conflicts of interest to disclose.

be useful in difficult cases in which less invasive measures have been unable to yield a definitive diagnosis.

## Keywords

Brain biopsy; dementia; vasculitis; central nervous system lymphoma; Alzheimer's disease

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## 1. Introduction

Brain biopsies are often the investigational procedure of last resort in patients with neurologic decline of unknown etiology, often after an exhaustive work up of less invasive tests including imaging, cerebrospinal fluid (CSF) analysis, and electroencephalography (EEG), have failed to lead to a definitive diagnosis. The sensitivity of brain biopsies for diagnosing tumors and lesions in immunodeficient patients have been reported to be above 90%, and the role of biopsy is well established as part of standard care [1,2]. However, their utility in diagnosing nonspecific neurologic deterioration and dementia are less well known, especially in light of recent advancements in imaging techniques and laboratory tests, including CSF analysis, in the diagnosis of Creutzfeldt-Jakob disease (CJD) and Alzheimer's disease, among others [3–6]. In patients presenting with a clinical suspicion of dementia, brain biopsies are often performed only in atypical presentations in which the differential diagnosis includes a treatable disease mimicking dementia [7]. Studies have shown a wide range, from 20% to 74%, in the diagnostic yield of these biopsies and their subsequent impact on patient care [7–11]. Some have shown that brain biopsies have little influence on changing clinical management and an even lower likelihood of leading to therapeutic benefit, such as in cases where no treatment is available [9,11]. Others have demonstrated these biopsies to have a significant impact on management and to be associated with relatively low morbidity [8,11]. The goal of our study was to evaluate the diagnostic yield of brain biopsies performed at a tertiary medical center, analyze presenting signs and symptoms associated with specific diagnoses, complication rates, and the effect of diagnosis on further management.

## 2. Materials and methods

We retrospectively reviewed the medical records and pathology reports of 53 patients who underwent brain biopsy for dementia or neurologic decline of unknown etiology at UCLA Medical Center between December 2001 and December 2011. Patients with known nonlymphomatous neoplasms thought to be associated with the neurologic symptoms and those with immunodeficiency, such as HIV infection and transplant patients, were excluded from the study. Individuals under the age of 20 years or with a history of intractable epilepsy undergoing focal cortical excision for diagnostic or therapeutic purposes were also excluded. In three patients in whom a repeat biopsy was performed, only the last biopsy was included in the analysis. Imaging studies performed within our institution were interpreted by a neuroradiologist (usually NS) and pathologic slides by a neuropathologist (usually NK, WHY or HVV). Frozen sections were performed to guide biopsies and assess adequacy of sampling in approximately two thirds of our cases. Smears and touch preparations were

routinely performed when the submitted tissue was deemed sufficient. Furthermore, as brain biopsies often consist of small pieces of tissue, samples underwent minimal handling to prevent tissue loss. Even though immediate serial sectioning of unstained slides for possible further studies such as immunohistochemistry was not performed routinely and would have been helpful in saving tissue, enough tissue was usually submitted to allow for additional studies when needed for evaluation.

Microbiology studies are essential when the differential diagnostic consideration includes infection, and genetic or molecular analysis may be helpful when histologic findings are suggestive of a neoplasm. As samples are best procured in a sterile manner in the operating room, tissue was set aside by the surgeon for microbiology studies if there was any question of infection. Based on the discretion of the neuropathologists, no genetic, molecular or electron microscopy studies were done in the cases included in the study.

The presenting signs and symptoms were compared between diagnostic groups to identify clinical features that may be associated with certain disease entities. Furthermore, the odds ratio (OR) and 95% confidence interval (CI) were calculated to determine if any of the clinical variables, imaging and laboratory tests were associated with a greater likelihood of yielding a diagnostic biopsy. This study was carried out in accordance with the Institutional Review Board of UCLA Medical Center.

### 3. Results

At the time of the biopsy, patient ages ranged from 22 to 82 years with an average age of  $55.2 \pm$  standard deviation (SD) = 16.0. There were 28 males and 25 females (male to female ratio of 1.1). The final pathologic diagnoses of the biopsies are listed in Table 1. Sixty percent of the biopsies were diagnostic (32 out of 53), with the most common histologic diagnosis of central nervous system (CNS) lymphoma in 14 of 53 patients (26% of total) followed by infarct in four patients (7.5%). Of the non-diagnostic biopsies, three were normal (5.7%) and 18 (34.0%) showed abnormal findings with reactive changes in the majority (78%), such as nonspecific inflammation and gliosis. Approximately 40% of the biopsies led to an alteration in clinical management of the patient.

The presenting signs and symptoms for each of the diagnostic groups are shown in Table 2. The most common symptom was cognitive decline, which was seen in 37 out of 53 cases (70%) followed by focal neurologic signs in 26 (49%) and seizures or need for seizure prophylaxis (40%). Less than one third of patients had constitutional manifestations such as fever, weight change and fatigue. Symptom duration ranged from one week to 10 years, and 41 patients (77%) had symptoms for less than or equal to one year. Magnetic resonance imaging (MRI) was performed in all patients except one in whom pacemaker placement precluded MRI, and CT was done instead. Magnetic resonance angiography (MRA) was performed in 22 out of 53 patients (42%). Cerebrospinal fluid (CSF) analysis was done in 42 patients, and 31 underwent one or more electroencephalographic (EEG) studies. None of the symptoms and signs or preoperative testing results was associated with increased or decreased odds of a diagnostic biopsy (Table 3). As stereotactic biopsies have been shown to result in higher diagnostic yields when compared to open biopsies in patients with

neurological disorders of unknown etiology and abnormal imaging studies, stereotactic biopsies have been recommended when there are MRI lesions amenable to targeting [12]. In our subjects, approximately 58% (31 out of 53) patients underwent stereotactic biopsies and 42% (22 out of 53) had open biopsies. Sixty eight percent (10 out of 31) of the stereotactic biopsies were diagnostic while half (11 out of 22) of the open biopsies yielded a diagnosis. Autopsies were subsequently performed on four patients, a full autopsy in one case and three restricted to the brain.

A few of the patients were found to have rare, unexpected conditions such as lymphomatosis cerebri, neurosarcoidosis, and neuroaxonal leukodystrophy. The two cases of lymphomatosis cerebri were diagnosed on biopsy in one patient and at autopsy in the second patient whose brain biopsy showed encephalitis. The first patient has been previously reported and briefly, is a 77 year old male who was transferred from an outside hospital for rapidly progressive memory deficits, confusion and behavioral changes with clinical suspicion for viral encephalitis. Other clinical considerations were vascular dementia and CJD, as MRI showed deep white matter disease, and the CSF was positive for 14-3-3 protein. Biopsy results were most consistent with a T/NK-cell lymphoproliferative disorder positive for CD2, CD7, and CD30 [13]. Detectable 14-3-3 protein has been reported in patients with CNS lymphoma, herpes simplex virus (HSV) encephalitis, stroke, multi-infarct dementia, and paraneoplastic syndromes [14,15]. In a study that evaluated neurologic disorders commonly mistaken for CJD, lymphomas were the most common neoplasm [16]. The second patient is a 51 year old male with progressive ataxia and fatigue whose biopsy showed changes consistent with chronic meningoencephalitis. Because of elevated *Coxiella burnetii* titers, he was presumptively diagnosed with *Coxiella burnetii* encephalitis and treated with doxycycline and ciprofloxacin. A brain only autopsy performed two months later demonstrated histologic changes of lymphomatosis cerebri with enlarged atypical cells expressing CD20 throughout the brain.

The remainder of CNS lymphomas included primary diffuse large B-cell lymphoma (DLBCL) in the majority, one low-grade B-cell lymphoma and one intravascular large B-cell lymphoma. A 58 year old male with biopsy showing primary CNS lymphoma was treated with corticosteroids, high dose chemotherapy and whole brain irradiation. On brain-only autopsy four months later, no residual lymphoma was detected, a phenomenon described as vanishing lymphoma due to the marked apoptotic effect of steroids on lymphoma cells [17]. Intravascular large B-cell lymphoma was diagnosed in a 61 year old female with acute confusion and altered mental status who was transferred from an outside hospital for further workup. A demyelinating process was initially suspected based on MRI, but she showed no clinical response to steroids. She also developed difficulties with eating and swallowing and was placed on rituximab for presumed acute disseminated encephalomyelitis (ADEM). CSF analysis was unremarkable. Brain biopsy showed large atypical lymphocytes within the lumens of cortical and meningeal vessels, with microinfarcts likely associated with thrombosis caused by tumor thromboemboli. The lymphoma cells were positive for CD20, Bcl-2, Bcl-6, and MUM1, with a Ki-67 proliferative index of greater than 95% (Fig. 1).

Despite the fact that 30% of patients (16 out of 53) had a clinical suspicion of CNS vasculitis, only two patients had positive biopsies, one with primary angiitis of the CNS (PACNS) (Fig. 2) and the second with A $\beta$ -related angiitis, sometimes described as ABRA. In both patients there was no evidence for systemic vasculitis, and CSF analysis showed 4 and 10 white cells/uL and mildly elevated protein of 81 and 85 mg/dL, respectively. One other patient with a clinical suspicion for vasculitis showed changes consistent with advanced Alzheimer's disease on biopsy, but no evidence of ABRA, confirmed by a brain-only autopsy performed five years later. Finally, brain biopsy performed on a 74 year old male with a history of mild cognitive decline for four years with a more rapid decline 2 to 4 weeks before the biopsy showed multiple subacute and chronic cortical microinfarcts with moderately severe hyaline arteriosclerosis but no evidence of vasculitis. He was nevertheless subsequently treated for vasculitis without improvement in his symptoms and was eventually transferred to a nursing care facility where he expired from pneumonia seven months after the biopsy. Full autopsy showed mixed dementia with features of Alzheimer's disease and concomitant ischemic lesions with unusually severe meningocortical cerebral amyloid angiopathy. There was no evidence of vasculitis either systemically or in the CNS.

Two patients were diagnosed with gliomatosis cerebri, the first patient with concern for CJD and the second with a clinical diagnosis of HSV encephalitis who was empirically treated with acyclovir even though polymerase chain reaction (PCR) for CSF HSV was negative. Approximately 17% of the patients (9 out of 53) had a clinical suspicion for Creutzfeldt-Jakob disease (CJD) but none showed morphologic features of the disease on biopsy. EEG was performed in all but one of these patients and was normal in one case, showed findings suggestive of encephalitis in another, and non-specific changes such as diffuse slowing in the remainder.

Among the rare diagnoses, isolated neurosarcoidosis was seen in a 34 year old male clinically diagnosed with multiple sclerosis but without response to treatment. He underwent a brain biopsy that was non-diagnostic, showing only reactive changes. A second biopsy one month later revealed multiple nodular foci of non-necrotizing granulomatous inflammation consistent with neurosarcoidosis. A 34 year old female with development of personality changes, mild gait difficulties and rapidly progressive dementia over approximately one year was diagnosed with neuroaxonal leukodystrophy on biopsy.

Post biopsy complications were observed in four patients (8%) and included intracranial hemorrhage in two patients and abscess formation at the biopsy site in two patients, which required additional operations to resect.

#### 4. Discussion

Brain biopsies have established utility in patients with malignancies and suspected infections associated with immunodeficiencies but are controversial in patients outside of these categories, such as individuals presenting with dementia or nonspecific neurologic decline, especially with the recent advances in imaging diagnostics and laboratory testing. Diagnostic yields in these patients have varied widely, and the usefulness of even diagnostic biopsies has been questioned due to their lack of impact in changing management [11]. The

proportion of biopsies that have led to an alteration in management has ranged from 8% to 44%, with higher rates in studies in which lymphomas constitute a major diagnostic category [7,9,11,18]. In our convenience sample, CNS lymphoma was the second most common diagnosis after “abnormal but no definite diagnosis.” Similar to other studies with a high proportion of CNS lymphomas, approximately 40% of the biopsies led to an alteration in management.

The CNS lymphoma subtypes included primary DLBCL of the CNS in the majority, lymphomatosis cerebri, low-grade B-cell lymphoma, and intravascular large B-cell lymphoma. Intravascular lymphoma is a rare and aggressive subtype of B-cell lymphoma characterized by the growth of neoplastic cells within blood vessel lumens, especially capillaries and arterioles, often causing disseminated microinfarcts. Symptoms are most commonly due to ischemia and can have a wide range of presentations. It was frequently diagnosed only postmortem in the past but is increasingly being detected by brain biopsy due to heightened awareness and immunohistochemical tools such as lymphoid markers and Ki-67 [17]. Although these lymphomas have been associated with a poor prognosis due to lack of response to chemotherapy, successfully treated cases have been reported with high dose methotrexate chemotherapy, highlighting the importance of brain biopsy early in the disease course [19]. Lymphomatosis cerebri is a rare type of CNS lymphoma characterized by lymphoma cells diffusely infiltrating the brain parenchyma without forming a mass or distorting the cerebral architecture. MRI typically shows diffuse white matter disease, raising the possibility of infection, inflammatory or neurodegenerative disorders. Clinically it often presents as a rapidly progressive dementia and can be confused with CJD, as in our previously reported case [20].

Approximately a third of our patients had vasculitis as the primary clinical suspicion or as part of the differential diagnosis, but only two patients actually showed vasculitis on biopsy. Of the patients with clinical suspicion for vasculitis, ten underwent MRA but only one case showed imaging findings suggestive of vasculitis; however, biopsy demonstrated infarction and was not diagnostic of vasculitis. The two patients with CNS vasculitis, one with PACNS and the other with A $\beta$ -related angiitis, had negative MRA studies. PACNS is a rare form of vasculitis restricted to the CNS that is most commonly characterized by granulomatous inflammation of the intracerebral vessels, particularly the small arteries, but a lymphocytic and necrotizing pattern can also be seen [21,22]. Common symptoms include headache, which is seen in up to 60% of patients, a myriad of symptoms arising from transient ischemic attacks or strokes, encephalopathy, and cognitive impairment [23,24]. Seizures are seen in approximately 5% and behavioral manifestations are being increasingly recognized [25]. As symptoms tend to be nonspecific and insidious, diagnosis may be delayed for months after symptom onset [24]. Brain biopsy is the gold standard in diagnosis, but it is plagued with low diagnostic yields with a sensitivity of less than 50% [22,26]. The high false negative rate in autopsy documented cases is attributed to the patchy nature of the inflammation leading to sampling error. Angiography has been preferred as a less invasive means of diagnosis, but its sensitivity and specificity can be as low as 30% [23]. Because PACNS often requires prolonged immunosuppression, tissue diagnosis is important in excluding other diseases, especially those that are managed differently such as infectious encephalitis, which is often also a diagnostic consideration [24]. In an autopsy study of 71

treatable neurologic cases misdiagnosed as CJD, seven were ultimately diagnosed with CNS vasculitis [16]. A $\beta$ -related angiitis (ABRA) is a form of PACNS associated with cerebral amyloid angiopathy (CAA) [27]. In CAA, amyloid  $\beta$  peptide (A $\beta$ ) replaces the arteriolar media of blood vessels in the cerebrum and leptomeninges to cause weakening of the walls, commonly leading to lobar cerebral hemorrhage and less frequently ischemic lesions. CAA is most common and severe in patients with Alzheimer's disease but can also be seen in non-demented elderly adults [27–30]. ABRA is thought to be one manifestation of the CNS immune response to A $\beta$  and has a similar presentation to PACNS both clinically and radiographically although hallucinations have been reported more often in ABRA [27].

The limitations of this study include the generalizability of the results due to the referral bias inherent in a study conducted at a tertiary referral center, using a convenience sample. Additionally, some of the patients, especially those referred from outside institutions, had limited medical records and follow up available. On the other hand, rare diseases were successfully detected on brain biopsy in a few patients after exhaustive evaluation at the referring institution and our medical center failed to reach a diagnosis clinically. Another limitation is the few follow-up autopsies available in our subject population. Although autopsy confirmation of brain biopsies is challenging, especially with the continuing trend of declining autopsy rates, they are important not only because a complete neuropathologic examination is the gold standard for diagnosing neurodegenerative disorders but in the clarification of contributing factors to non-diagnostic biopsies including limited tissue availability for adequate evaluation, sampling error or pathological interpretation [31].

Sampling error was likely a major factor underlying non-diagnostic biopsies in a significant proportion of our subjects, although more autopsy follow up studies would be needed for an accurate assessment. In one of the three patients in whom a repeat biopsy was performed, the first biopsy revealed only nonspecific reactive changes while the second biopsy demonstrated neurosarcoidosis. One patient with Alzheimer's disease demonstrated on autopsy had a non-diagnostic brain biopsy and in another patient with lymphomatosis cerebri on autopsy, brain biopsy showed only chronic meningoencephalitis despite ancillary immunohistochemical studies performed on the biopsy tissue. The impact of sampling was shown in a study by Venneti et al. in which autopsy-confirmed cases of neurodegeneration were used to simulate brain biopsies. Sensitivity and specificity of diagnoses based on sampling four brain regions were higher than that based on frontal cortex only, the common site of biopsies performed for cognitive decline of unclear etiology, and also varied with the type of dementia, being higher in those with a more cortical distribution [31]. Thus, the importance of autopsies cannot be overemphasized even with the current advancements in imaging and other diagnostic modalities, especially in diagnostic dilemmas such as those included in this study. Despite many of our cases having undergone extensive investigational workup including what may be the most invasive testing of all, brain biopsy, a definite diagnosis could not be reached in a significant proportion of patients. Autopsy examinations were available in only four of our patients, but in most cases they either led to a definitive diagnosis after non-diagnostic biopsies or confirmed the diagnosis made on biopsy. Finally, although diagnostic systems were standardized and internal consultations extensively utilized, as microscopic diagnoses were rendered mainly by three neuropathologists, interobserver variability is a potential source of bias [32]. However,

controversial or challenging cases are often reviewed at a periodic quality assurance conference usually attended by all three neuropathologists.

The consensus is that biopsies should be undertaken only after all other diagnostic modalities have been exhausted, but not too late in the course of the disease as to delay therapeutic intervention [7]. However, determining the appropriate timing of biopsy is difficult when the disease process and tempo are unknown. Furthermore, brain biopsies in non-treatable neurodegenerative conditions are controversial. They are generally recommended only to exclude a treatable cause and discouraged when the positive predictive value of a clinical diagnosis is high and sufficient to guide management [33]. Autopsy is the diagnostic gold standard in the definitive classification of dementia as brain biopsies are limited by sampling error. However, emergence of new therapies as well as diagnostic modalities for dementia may result in brain biopsies coming to play a more prominent role in diagnosing neurodegenerative diseases both for guiding treatment and validating the new methods [31]. Moreover, even if not directly changing management or outcome, a definitive diagnosis may be valuable in assessing prognosis for clinicians as well as for the patients and their families [7].

In conclusion, these results suggest the utility of brain biopsy in the diagnosis of atypical presentations of more common diseases as well as in difficult cases of rare and unsuspected disorders in which less invasive measures are unable to reach a diagnosis. In such cases brain biopsy may be a worthwhile option to assess for treatable disease as long as there are no contraindications, which include coagulopathy and thrombocytopenia as well as the inability to tolerate local or general anesthesia. However, as the pathology of many neurologic diseases such as PACNS and demyelinating disorders including multiple sclerosis is heterogeneous and multifocal, a patient may need to undergo more than one biopsy for a definitive diagnosis. A major caveat is the risks involved in a highly invasive diagnostic procedure. The complication rate for brain biopsies for neurologic decline of unknown etiology or dementia have ranged from 4 to 7% with an overall mortality of approximately 1% [10,11,18]. Although the incidence of complications is rare, the adverse effects that do occur are not insignificant, and the potential benefits must be carefully weighed against the risks.

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## Abbreviations

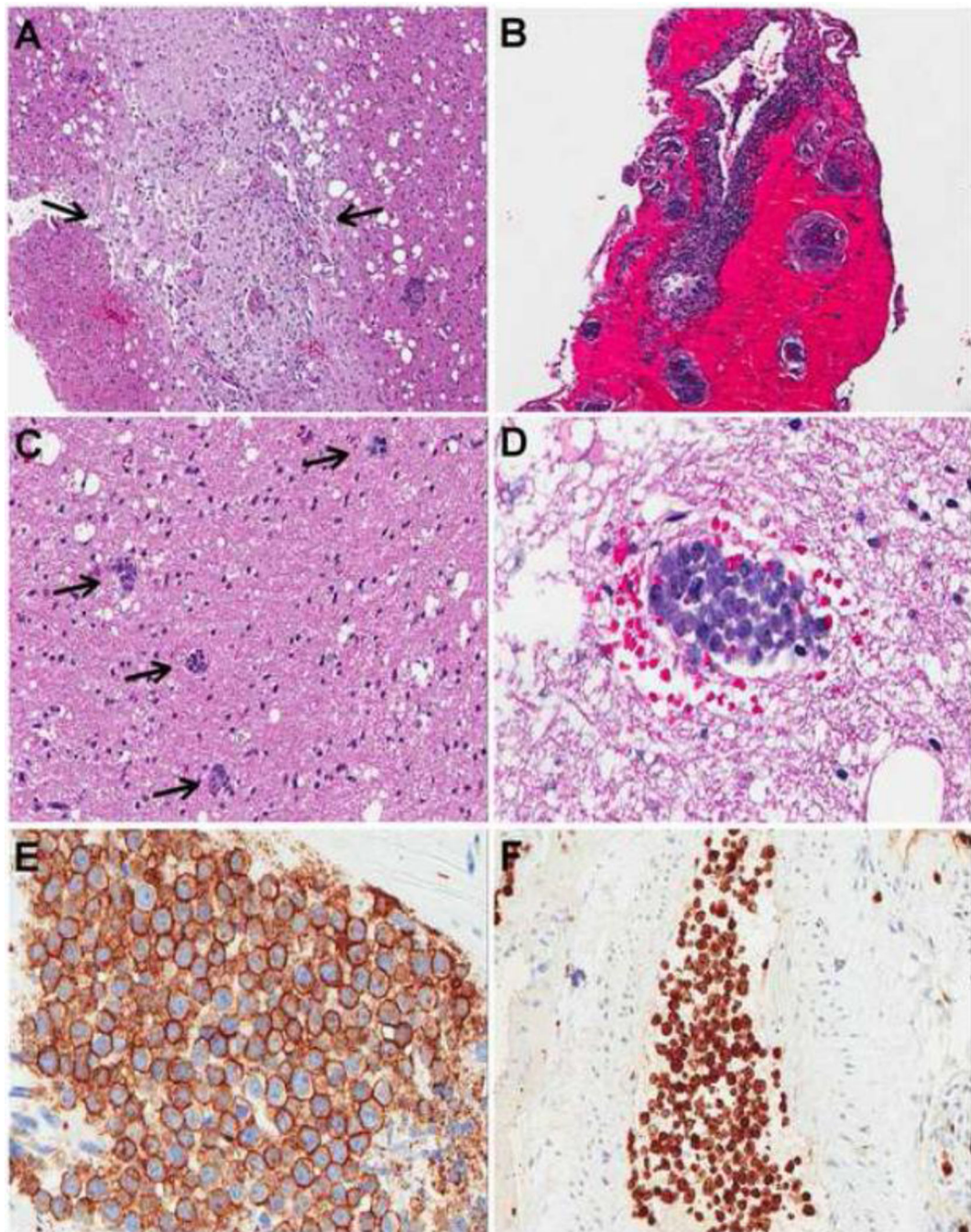
<b>CNS</b>	Central nervous system
<b>DLBCL</b>	diffuse large B-cell lymphoma
<b>PACNS</b>	primary angiitis of the central nervous system
<b>ABRA</b>	A $\beta$ -related angiitis



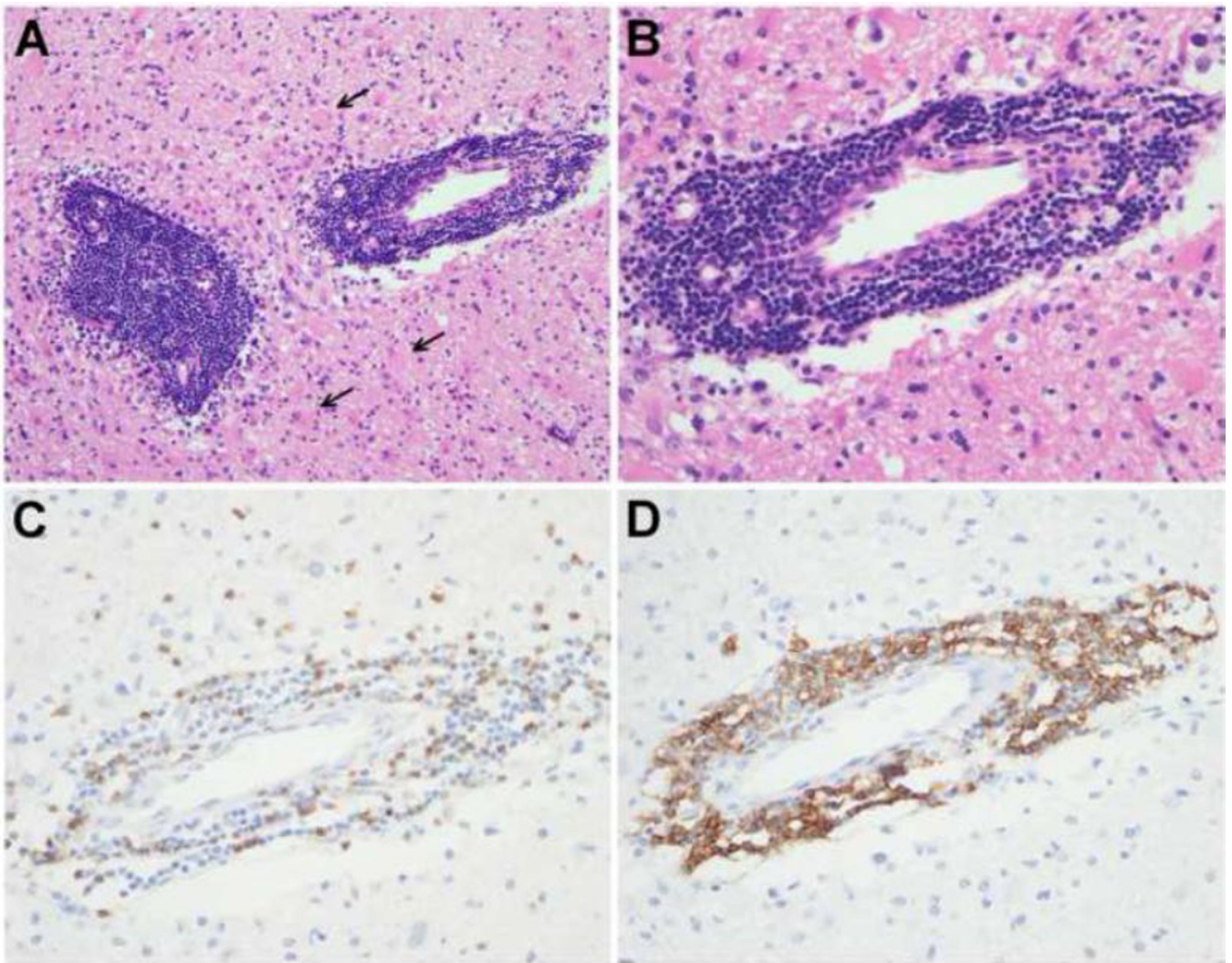
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**Fig. 1.** Intravascular B-cell lymphoma. Area of microinfarction (arrows, A) likely due to tumor thrombosis,  $\times 100$  (A) with intravascular tumor within leptomeningeal,  $\times 100$  (B) and cerebral vessels,  $100\times$  (arrows, C). The intravascular lymphoma cells show rare mitoses,  $400\times$  (D) and express CD20,  $400\times$  (E) with a Ki67 proliferative index of greater than 95%,  $200\times$  (F).



**Fig. 2.** Primary angiitis of the central nervous system. Diffuse and marked perivascular and transmural infiltration of cerebral blood vessels by small lymphocytes. There is a surrounding prominent reactive astrocytosis, 200 $\times$  (arrows, A). Vessels show patent lumens, although compromised by expansion of the vessel walls associated with the inflammation, 400 $\times$  (B). The infiltrate of T-lymphocytes is highlighted by CD3 immunostain, 400 $\times$  (C) and B-lymphocytes by CD20, 400 $\times$  (D).

**Table 1**

## Final pathologic diagnoses

<b>Pathologic diagnoses</b>	<b>Number of patients (% of total)</b>
Abnormal, no definitive diagnosis	18 (34)
CNS lymphoma	14 (26)
Infarct	4 (8)
Normal	3 (6)
Demyelinating disease	3 (6)
Gliomatosis cerebri	2 (4)
Vasculitis	2 (4)
Neurosarcoidosis	1 (2)
Histiocytosis	1 (2)
Neuroaxonal leukodystrophy	1 (2)
Alzheimer disease	1 (2)
Encephalitis	1 (2)
Necrotizing granulomatous Inflammation	1 (2)
Tuberculosis	1 (2)

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Table 2

Frequency of symptom and signs in major diagnostic categories

	Cognitive decline	Behavioral changes, psychiatric symptoms	Focal neurologic signs	Gait problems, ataxia	Seizures, seizure prophylaxis	Headache	Constitutional
Abnormal, no definitive diagnosis	13	5	9	5	8	7	3
CNS lymphoma	9	4	7	5	3	3	5
Infarct	4	3	2	2	2	...	1
Normal	2	2	1	...	2	2	1
Demyelinating disease	1	1	1	...	2	2	...
Gliomatosis cerebri	2	...	1	1	1	1	...
Vasculitis	2	1	...	...	1	...	2
Neurosarcoidosis	1	1	1	...	...	...	1
Histiocytosis	...	...	1	1	...	...	1
Neuroaxonal leukodystrophy	1	1	...	1	...	...	...
Alzheimer disease	1	...	...	...	...	1	...
Encephalitis		1	1	1	...	...	1
Necrotizing granulomatous inflammation	1	1	1	...	1	1	1
Tuberculosis	...	...	1	...	1	...	...
<b>Total</b>	<b>37</b>	<b>20</b>	<b>26</b>	<b>16</b>	<b>21</b>	<b>17</b>	<b>16</b>

**Table 3**

Likelihood of diagnostic biopsy based on symptoms/signs and preoperative test results

	<b>Diagnostic biopsy (%)</b>	<b>Odds ratio</b>	<b>95% Confidence interval</b>	<b>P-value</b>
<b>Symptoms/signs</b>				
Cognitive decline	24/37 (65)	1.60	0.50–5.17	0.432
Behavioral changes, psychiatric symptoms	13/20 (65)	1.37	0.43–4.32	0.593
Focal neurologic signs	16/26 (62)	1.10	0.37–3.31	0.865
Gait problems, ataxia	11/16 (69)	1.68	0.48–5.80	0.415
Seizures, seizure prophylaxis	11/21 (52)	0.58	0.19–1.77	0.337
Headache	8/17 (47)	0.44	0.14–1.44	0.177
Constitutional	12/16 (75)	2.55	0.69–9.39	0.159
<b>Preoperative test results</b>				
MRI diffuse changes	12/22 (55)	0.66	0.22–2.01	0.466
MRI focal, multifocal	20/29 (69)	2.22	0.72–6.83	0.163
MRA abnormal	1/4 (25)	0.19	0.02–2.00	0.168
EEG abnormal	13/24 (54)	0.62	0.21–1.89	0.402
CSF pleocytosis	19/27 (70)	2.38	0.77–7.34	0.133

Abbreviations: MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; EEG, electroencephalography; CSF, cerebrospinal fluid