Case Series

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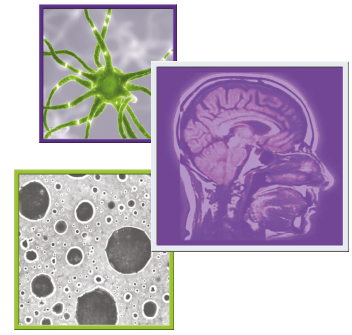
CNS Oncology



The clinical heterogeneity of entirely nonenhancing CNS lymphoma: a case series

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CNS lymphoma often presents with atypical imaging characteristics leading to delay in diagnosis and initiation of treatment. Among the most rarely reported of these is entirely nonenhancing CNS lymphoma, which is estimated at an incidence of about 1%. Here, we present three cases of nonenhancing CNS lymphoma in immune competent patients at both initial presentation and recurrence and in primary as well as secondary CNS lymphoma. Diffusion- and perfusion-weighted imaging was found helpful in diagnosis in some cases.

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The diagnosis of CNS lymphoma is a distinct challenge and often delayed due to a heterogeneity in clinical presentation, radiologic characteristics and prediagnosis management [1,2]. The typical MRI characteristics of primary CNS lymphoma (PCNSL) in both immunocompetent and immunocompromised patients are relatively well-established. Immune competent patients typically present with single or multiple homogeneously contrast-enhancing lesions in the periventricular white matter [3–9], whereas immunocompromised patients typically demonstrate ring-like enhancement [5,8,10]. However, as many as 25% of patients have 'atypical' radiologic presentations, encompassing a broad range of imaging findings [3]. Further, there are few reports on imaging patterns in recurrence or relapse [11].

Entirely nonenhancing CNS lymphoma remains among the most rarely reported of these atypical presentations, limited to case reports or larger case series estimating a prevalence of 1–3% (Table 1) [2–5,12–15]. Here, we present the cases of three immunocompetent patients with CNS lymphoma recently treated at our hospital who presented with nonenhancing lesions either initially, at the time of recurrence or both.

Case descriptions

Case #1

A woman in her 70s with Type 2 diabetes, hypertension, hypothyroidism and symptomatic bradycardia requiring a pacemaker presented to another hospital with several months of progressive truncal ataxia, lower extremity weakness, fatigue and unintentional weight loss. MRI, obtained 2 weeks later, demonstrated nonenhancing T2 hyperintensity in the corpus callosum and centrum semiovale without diffusion restriction (Figure 1A). Her symptoms continued to progress over the next 2 months while a broad work-up of possible rheumatologic, infectious, autoimmune and inflammatory causes was completed without diagnosis. A second MRI, approximately 3 months after initial presentation, demonstrated expansion of the FLAIR hyperintensity as well as development of scattered regions of restricted diffusion and contrast enhancement in a similar distribution (Figure 1B). Around this time, she became increasingly confused and was transferred to our inpatient neurology service for an expedited work-up that included leukemia/lymphoma panel, cerebrospinal fluid cytology, slit-lamp examination and skin punch biopsy – all of which were nondiagnostic.

Given the lack of a diagnosis and suspicion for malignancy, she underwent a right frontal needle biopsy. Pathology demonstrated diffuse large B-cell lymphoma. Staging imaging showed no systemic disease. She was initiated on

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Table 1. A summary of previously reported cases of entirely nonenhancing CNS lymphoma.

Author	Year	Age	Gender	Diffusion restriction?	IS?	Subtype	Time of diagnosis	Diagnosis	Ref.
DeAngelis	1993	60	M		No		Recurrence	Autopsy	[4]
		80	F		No		Recurrence	Autopsy	
		37	M		Yes		Initial	Autopsy	
		53	M		No		Recurrence	Prior	
Carlson	1996	76	F		No	Primary	Initial	Brain biopsy	[15]
Kuker *et al.*	2005					Primary	Initial	Brain biopsy	[13]
Lachenmayer *et al.*	2011	81	F		No	Primary	Initial	Brain biopsy	[14]
Fischer *et al.*	2011	52	M	Yes		Primary	Recurrence	Autopsy	[16]
Hu *et al.*	2019	61	M		No	Primary	Initial	Brain biopsy	[12]
Lin *et al.*	2020			Yes	No	Primary	Initial	Brain biopsy	[3]
Current article	2021	71	F	Yes	No	Primary	Initial	Brain biopsy	
		63	F	No	No	Primary	Recurrence	Prior	
		73	M	Yes	No	Secondary	Recurrence	CSF flow cytometry	

F: Female; IS: Immunosuppressed; M: Male.

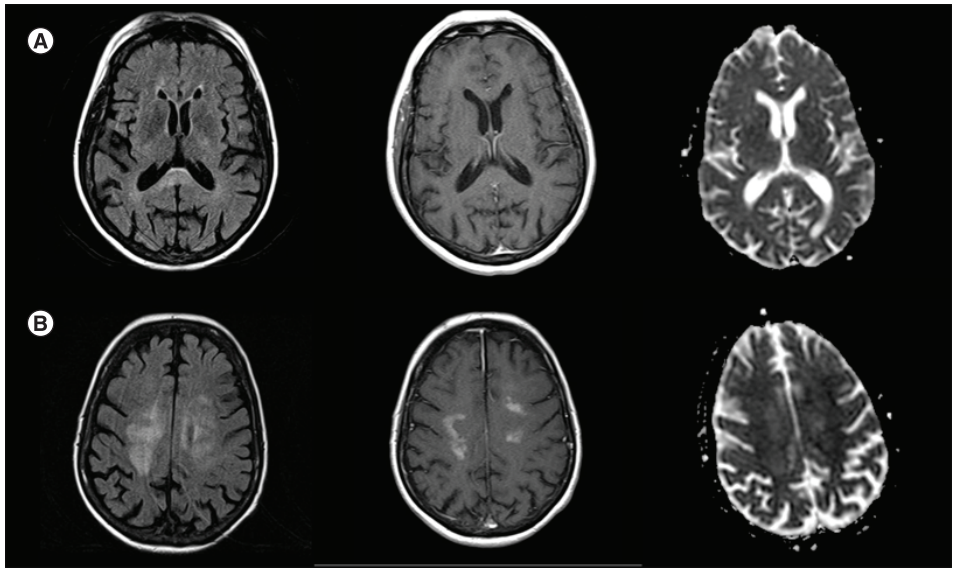

Figure 1. Axial slices from MRI with left: FLAIR, middle: postgadolinium T1; right: apparent diffusion coefficient. (A) MRI on initial presentation demonstrating a T2/FLAIR hyperintense lesion within the splenium that shows some diffusion restriction but does not enhance with contrast. **(B)** Repeat MRI after 3 months of continued neurologic decline showing the development of T2/FLAIR hyperintensity with patchy enhancement and some diffusion restriction in the bilateral centrum semiovale.

intravenous (iv.) high-dose rituximab and methotrexate infusions, but her hospital course was soon complicated by pneumonia causing severe encephalopathy and acute hypoxemic respiratory failure, requiring transfer to the intensive care unit. Her oxygenation quickly improved with antibiotics and pulmonary care; however, her family ultimately decided that further chemotherapy would not be in line with her goals of care. She was discharged to home hospice 1 month after admission.

Case #2

A woman in her 60s with a history of chronic hepatitis C and cirrhosis presented to an outside hospital with 3 years of progressive vision loss and 2 weeks of confusion and right hemiparesis. MRI revealed bilateral, asymmetrically distributed T2 signal abnormality within the subcortical white matter, deep structures and brainstem with evidence

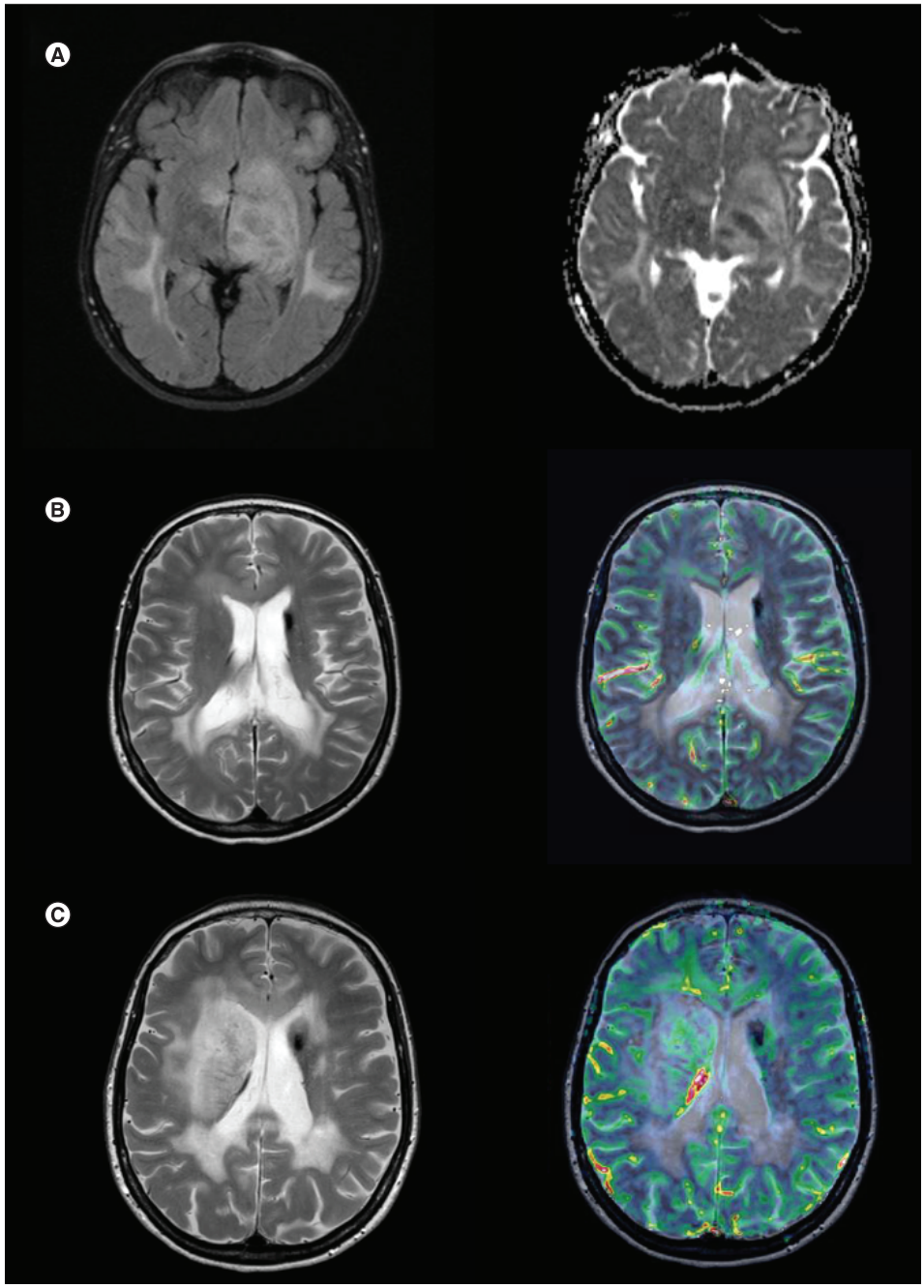

Figure 2. Axial slices from Case #2 MRI. (A) Axial slices from MRI with left: FLAIR, right: apparent diffusion coefficient. MRI after 2 weeks of confusion and right hemiparesis demonstrating diffuse T2/FLAIR hyperintense, nonenhancing lesion with mixed diffusion restriction in the left basal ganglia and subcortical white matter. **(B)** Axial slices from MRI with left: T2, right: cerebral blood volume. Surveillance imaging off treatment demonstrated bulky T2 hyperintensity in the splenium of the corpus callosum without enhancement or elevated cerebral volume. **(C)** Imaging of frank recurrence with large, bulky T2/FLAIR hyperintensity in the right basal ganglia and subcortical white matter without definitive enhancement but with markedly elevated cerebral blood volume.

of mass effect as well as vague areas of contrast enhancement in the left thalamus/midbrain and posterior corpus callosum (Figure 2A). Flow cytometry from a vitreous biopsy was unremarkable. She underwent a needle biopsy of the left caudate head and slit-lamp examination and was diagnosed with PCNSL with ocular involvement. She was treated with induction iv. chemotherapy and intra-arterial methotrexate. Thereafter, she was transferred to our hospital, where she completed four cycles of iv., intra-arterial and intra-ocular chemotherapy with resolution of

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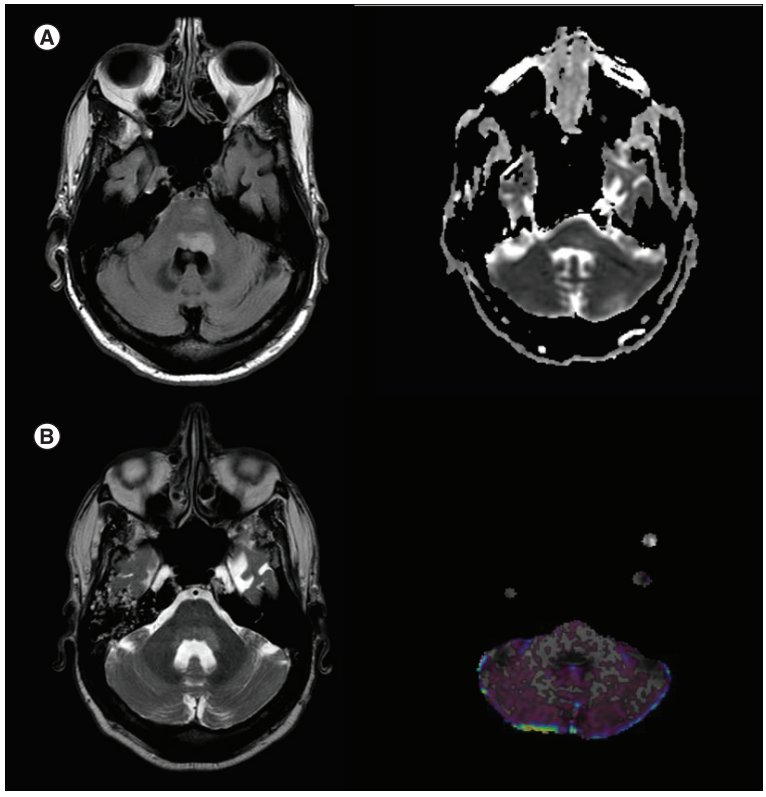

Figure 3. Axial images from MRI with top left: FLAIR, top right: apparent diffusion coefficient (ADC); bottom left: T2; bottom right: cerebral blood volume. (A) MRI 7 months after diagnosis of systemic lymphoma demonstrating a FLAIR hyperintense lesion in the dorsal pons without enhancement or reduced diffusion. **(B)** Imaging of local relapse several months later demonstrating a T2 hyperintense, nonenhancing dorsal pontine lesion with normal cerebral blood volume.

pathologic enhancement on imaging. After 2 subsequent years off treatment, surveillance imaging demonstrated focal enlargement of a T2 hyperintensity within the corpus callosum and corresponding elevated cerebral blood volume (Figure 2B). This finding was felt to be concerning for, but not definitive of, nonenhancing disease recurrence. She resumed iv. rituximab until follow-up imaging 7 months later was definitive for disease progression on T2, postcontrast and perfusion sequences (Figure 2C). She then received 14 cycles of iv. high dose methotrexate and rituximab with good response. She continues to receive maintenance rituximab every 3 months and has had stable imaging for 2 subsequent years.

Case #3

A man in his 70s with a history of gout, mild cognitive impairment and systemic B-cell lymphoma underwent systemic chemotherapy and CNS prophylaxis with complete systemic response. Seven months later, he presented with headaches, left facial numbness and left nasolabial flattening. He was found to have a nonenhancing, expansile T2/FLAIR hyperintense lesion in the rostral medulla/pons without clearly reduced diffusion (Figure 3A), felt to represent CNS lymphoma despite negative cerebrospinal fluid cytology. He received induction and maintenance chemotherapy, the latter of which was complicated by a large subacute subdural hematoma requiring surgical evacuation. Thereafter, he transferred his care to our institution and remained clinically stable off therapy. After 8 months of surveillance, he was hospitalized with generalized weakness, abdominal pain, nausea and shortness of breath after finding a new nonenhancing medullary, T2/FLAIR hyperintense lesion with normal cerebral blood volume (Figure 3B). A lumbar puncture after admission to the hospital was positive for B-cell lymphoma on flow cytometry. He elected to pursue further treatment with methotrexate and rituximab, but developed acute respiratory distress and expired prior to initiating chemotherapy.

Discussion

Gadolinium-enhanced MRI remains the imaging modality of choice for initial work-up and response assessment. CNS lymphoma in immune competent patients typically presents with homogeneously enhancing lesions. The volume of enhancement is frequently used as a surrogate for tumor burden in the CNS and changes in the enhancing abnormalities on gadolinium enhanced MRI remain the most important radiologic criteria for response assessment [17]. Autopsy studies have suggested that CNS lymphoma is in fact a whole brain disease and, in reality,

pathologic enhancement represents only regions of blood–brain barrier disruption, which does not correlate with the true extent of disease [18]. The significance of the nonenhancing T2 signal abnormalities in CNS lymphoma remains unclear.

Here, we present three distinctive cases of entirely nonenhancing CNS lymphoma to underline the radiologic heterogeneity of clinical scenarios in which it may arise. This series includes entirely nonenhancing lesions at incident discovery in both primary and secondary CNS lymphoma and at recurrence of both previously nonenhancing and previously enhancing lesions. In doing so, we add to previous reports of nonenhancing CNS lymphoma by reporting the first cases of a nonenhancing secondary CNS lymphoma and a nonenhancing recurrence of previously nonenhancing PCNSL to our knowledge.

All three patients were immunocompetent and defied the most common radiologic characteristics – homogeneous enhancing lesion(s) in the periventricular white matter [3–9] – of this population in several ways. Case 1 presented with initially nonenhancing disease, for which lymphoma remained low on the differential until a thorough work-up had been completed. Ultimately, a clinical decline 2 months later led to the discovery of pathologic contrast enhancement on follow-up imaging that was evaluated with a brain biopsy. Case 2's extensive T2/FLAIR abnormality with a relative paucity of enhancement also conflicts with expected findings for CNS lymphoma. Likely due to the concerning volume of disease and the wisp of enhancement, a brain biopsy was performed early in her diagnostic work-up. Her recurrence was initially interpreted cautiously, due to its disparate radiologic characteristics, until she ultimately developed frank recurrence with enhancement despite treatment. Case 3 is atypical for its lack of enhancement, location, isolated brainstem disease and parenchymal rather than leptomeningeal involvement in a secondary CNS lymphoma. Fortunately, treatment was initiated quickly as his history of recently treated systemic lymphoma rendered a narrow differential diagnosis. The former two cases, together with a similar previous report of initially nonenhancing CNS lymphoma [12], may suggest that all such nonenhancing disease will eventually enhance, the mechanisms of which are beyond the scope of this report.

As in our first case, diagnostic delay is a common problem in PCNSL, yet remains poorly studied [1]. Only certain neurologic symptoms are associated with a longer time to imaging from initial presentation, while the withdrawal or corticosteroids prior to brain biopsy and a need for second brain biopsy are associated with a delay in achieving diagnosis [2]. While there is no known association between atypical imaging characteristics and diagnostic delay, it is certainly a potential consequence of such an unusual presentation as entirely nonenhancing disease [14]. To this end, our first patient in this series corroborates previous reports of protracted disease courses prior to diagnosis and initiation of therapy [4,12]. The clinical implications of such delays remain unclear; however, this series supplements mounting evidence that thorough evaluation for lymphoma should be considered early even in instances of atypical imaging.

As part of the effort in hastening diagnosis, advanced imaging such as diffusion- and perfusion-weighted sequence MRI have been explored in search of a noninvasive biomarker for CNS lymphoma with mixed success. Diffusion-weighted imaging can adequately distinguish between CNS lymphoma and high-grade gliomas [19–21], metastases [21] and tumefactive demyelinating disease [6]. Beyond this, it may even predict clinical outcomes [22]. Our first case demonstrated reduced diffusion at initial imaging, but unfortunately was not referred to our institution until 2 months later, by which time her lesions began to enhance. In contrast, there was no abnormally reduced diffusion at the time of presentation in the second and third cases. Perfusion-weighted imaging can also differentiate between lymphoma and high-grade tumors, such as glioblastoma and metastasis [21,23]. Cerebral blood volume aided in confirming a suspected recurrence in our second case; however, it remained normal in our first case's recurrence.

There is more limited and less compelling evidence for evaluating atypical CNS lymphoma with such advanced imaging; however, Reiche *et al.* [24] found diffusion-weighted imaging useful in four patients with atypical features, but notably only one of the patients described had entirely nonenhancing disease. Brain biopsy was delayed in that patient until a neurologic decline 2 weeks later, at which time repeat imaging demonstrated abnormal enhancement. Such a delay is again similar to our third case description. Some success was reported in a single case by Kawai *et al.* [25] where decreased 18F-fluorodeoxyglucose transport and increased hexokinase activity on 18F-fluorodeoxyglucose-PET raised suspicion for a neoplastic process in an otherwise benign-appearing, nonenhancing lesion. These findings led to a brain biopsy and diagnosis of lymphoma without delay. Unfortunately, this has not been duplicated to our knowledge and a follow-up study of 17 patients demonstrated little utility for PET in atypical PCNSL [26].

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Recognizing relapse is a separate and distinct problem from that of primary recognition. The spatial characteristics of relapse are relatively well described, with a preponderance of distant rather than local relapse [11,27,28]. However, there are no reports of other features of imaging recurrence in CNS lymphoma to our knowledge and, importantly, the aforementioned studies were limited to patients with distinct contrast-enhancing lesions. The spatiotemporal and radiologic characteristics of relapsed CNS lymphoma with atypical imaging features merits further study. In this context, treatment-related T2 signal abnormalities after high-dose methotrexate based regimens may further complicate response assessment [29]. The second and third cases in this series highlight the variability that may be seen in such relapses of atypical disease, with both local and distant recurrence, as well as disparate imaging features. These cases underscore the need for a low threshold to pursue diagnosis and initiate therapy in order to optimize patient outcomes.

Conclusion

There is great radiologic heterogeneity in nonenhancing CNS lymphoma at both initial presentation and recurrence. Advanced imaging modalities, including diffusion- and perfusion-weighted sequences, may inform the differential diagnosis and prevent diagnostic delay.

Executive summary

- Both primary and secondary CNS lymphoma can be entirely nonenhancing at presentation.
- Relapse or recurrence should be considered with T2 hyperintense abnormalities in patients with a history of CNS lymphoma, even if it was previously nonenhancing.
- CNS lymphoma should be considered early in diagnostic work-up of entirely nonenhancing, T2 hyperintense abnormalities in immune competent patients.
- Diffusion- and perfusion-weighted as well as PET imaging can supplement common MRI sequences in informing diagnosis.
- Delay in diagnosis and treatment initiation may contribute to worse outcomes in CNS lymphoma.

Author contributions

SG Bowden: conception and design of idea; acquisition, analysis and interpretation of data; drafting the work and critically revising it; final approval of the version to be published; accountable for all aspects of the work. DN Munger, J Thiessen, SCS Woll: acquisition, analysis and interpretation of data; drafting the work; final approval of the version to be published; accountable for all aspects of the work. SJ Han, EA Neuwelt, RF Barajas, P Ambady: conception and design of idea; drafting the work and critically revising it; final approval of the version to be published; accountable for all aspects of the work.

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No writing assistance was utilized in the production of this manuscript.

Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patients for the inclusion of their medical and treatment history within this case series.

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