

Inflammatory Demyelinating Brain Lesions Herald Primary CNS Lymphoma

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ABSTRACT: Brain biopsy plays a crucial role in the exploration of suspect white matter lesions in the differential diagnosis of primary central nervous system lymphoma (PCNSL) and inflammatory demyelination. We present the case of a previously healthy, immunocompetent woman, aged fifty-nine, who developed a histologically confirmed demyelinating white matter lesion months prior to the manifestation of a PCNSL. Similar cases of “sentinel lesions” preceding a PCNSL have been reported. In a literature review, we compared the diagnostic features that may be useful to differentiate a PCNSL from inflammatory demyelinating disease in older age. We conclude that the occurrence of large, contrast-enhancing cerebral lesions in older patients with a relapsing-remitting disease course and steroid-resistant vision disorders should lead to the consideration of a PCNSL.

RÉSUMÉ: Lésions cérébrales démyélinisantes inflammatoires annonciatrices d'un lymphome du SNC. La biopsie de lésions suspectes de la substance blanche joue un rôle crucial dans le diagnostic différentiel du lymphome primitif du système nerveux central (LPSNC) et de la démyélinisation inflammatoire. Nous présentons le cas d'une femme immunocompétente, âgée de 59 ans et en bonne santé antérieurement, qui a présenté une lésion démyélinisante de la substance blanche confirmée en anatomopathologie, quelques mois avant qu'elle ne présente des manifestations d'un LPSNC. Des cas semblables de “lésions sentinelles” précédant un LPSNC ont été rapportés antérieurement. En nous basant sur une revue de la littérature sur le sujet, nous avons comparé les caractéristiques diagnostiques qui peuvent être utiles pour différencier un LPSNC d'une maladie démyélinisante inflammatoire chez les patients plus âgés. Nous concluons qu'en présence de grosses lésions cérébrales rehaussées par les agents de contraste chez des patients plus âgés à évolution rémittente et de troubles visuels résistants au traitement par les stéroïdes on devrait envisager la possibilité qu'il s'agisse d'un LPSNC.

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Among intracranial tumors, primary central nervous system (CNS) lymphoma (PCNSL) in immunocompetent patients represents a rare neoplasm of the older age. Most primary CNS lymphomas belong to the group of diffuse large B-cell non-Hodgkin's lymphomas. Primary CNS lymphoma has a poor prognosis with a median survival of two to three months when untreated¹. As multifocal or periventricular manifestations and spontaneous or corticoid-induced remissions are not uncommon, PCNSL may mimic the clinical course and imaging features of an inflammatory demyelinating CNS disease. Therefore, brain biopsy plays a crucial role in the exploration of suspect white matter lesions especially in older patients. Nevertheless, several cases of patients who developed histologically confirmed inflammatory demyelinating brain lesions only months prior to the diagnosis of PCNSL have been reported in literature²⁻⁴. Alderson et al² created the term of “sentinel lesions” for those inflammatory demyelinating brain lesions preceding PCNSL that are characterized by contrast enhancement on cranial magnetic resonance imaging (MRI). In most cases,

histopathological analysis of the “sentinel lesions” showed a cellular infiltrate predominantly consisting of T lymphocytes with only rare B lymphocytes^{2,4}. Based on an exemplary case history of an inflammatory demyelinating CNS lesion heralding the manifestation of a PCNSL in an immunocompetent patient, we will discuss the phenomenon of “sentinel lesions” in the context of the sometimes difficult differential diagnosis of inflammatory demyelinating CNS disease and PCNSL.

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Inflammatory demyelinating disease or primary CNS lymphoma?

In the majority of the published cases of “sentinel lesions”, patients aged over 50 years are affected, representing the typical age group for PCNSL in immunocompetent individuals as well as for late-onset multiple sclerosis (LOMS)^{5,6} (Table). Thus, the comparison of clinical symptoms and radiologic features of LOMS and PCNSL may be helpful in the assessment of inflammatory demyelinating brain lesions appearing in older age.

The relapsing-remitting disease course seen in the patients with “sentinel lesions” is rather uncharacteristic in LOMS patients who predominantly display a primary progressive course (primary progressive course in 83% of the LOMS patients versus relapsing remitting course in 8% of the LOMS patients⁶). Vision disorders caused by optic neuritis, which frequently occurs in younger multiple sclerosis patients, are less common in LOMS patients (10% of the LOMS patients⁶). In PCNSL patients, vision disorders are more frequent. According to Hochberg et al⁷, 15% of PCNSL patients suffer from concurrent or subsequent ocular involvement, others report a frequency of up to 25%^{8,9}. In 10-20% of the cases, PCNSL is preceded by an isolated primary intraocular lymphoma¹⁰, which often presents as chronic uveitis masquerade syndrome in older patients¹¹ and may occur many months prior to the manifestation of PCNSL¹². A lack of corticosteroid sensitivity is characteristic of intraocular lymphomas, but certainly not specific. In the diagnosis of intraocular lymphoma, MRI imaging of the orbits seems to be less sensitive than clinical ocular examination. Furthermore, a secure distinction from inflammatory processes such as uveitis cannot be achieved by MRI examination¹¹. Only in 25% of PCNSL patients with known MRI lesions lymphoma cells can be detected in the cerebrospinal fluid¹³. As lymphocytic pleocytosis in the cerebrospinal fluid occurs in about 50% of PCNSL patients and CSF oligoclonal banding is found in 27%¹⁴, conventional examination of the cerebrospinal fluid yields no further evidence that would aid in the distinction of PCNSL from inflammatory demyelinating diseases if malignant cells cannot be isolated. In a clinical study examining MRI features of PCNSL in 100 immunocompetent patients before treatment, multifocal cerebral involvement contributing to the danger of confusing PCNSL with an inflammatory demyelinating disease was noted in 35% of the patients at the time of first presentation¹⁵. Lesions of PCNSL were most frequently located in the cerebral hemispheres, followed by the basal ganglia, thalamus and corpus callosum and had a diameter of at least 15 mm. Contrary to LOMS patients, who have spinal lesions in over 80%⁶, spinal involvement was detected only in 1.2% of the PCNSL patients. Marked contrast enhancement was found in the vast majority of PCNSL lesions, whereas contrast-enhancing cerebral lesions are less likely to be detected in LOMS patients (contrast enhancement in 15% of the cerebral and 7% of the spinal lesions⁶). Nevertheless, also moderate or even absent contrast enhancement occurred in some PCNSL patients (strong versus moderate contrast enhancement: 85 versus 10 patients, no contrast enhancement in one patient). Proton magnetic resonance spectroscopy of PCNSL lesions shows markedly decreased NAA levels and increased choline levels with relatively high incidence of lactate or lipid¹ and very pronounced lipid peaks when

present⁴. In chronic multiple sclerosis lesions, decreased NAA levels are considered a marker for neuro-axonal loss. A decrease of NAA levels does occur in acute, enhancing multiple sclerosis lesions as well and is often reversible, as it may be due to the inflammatory edema. Increased choline and lactate levels are also seen in active multiple sclerosis lesions. Levels of lipids as a marker of tissue necrosis seem to be more elevated in PCNSL than in multiple sclerosis lesions^{16,17}.

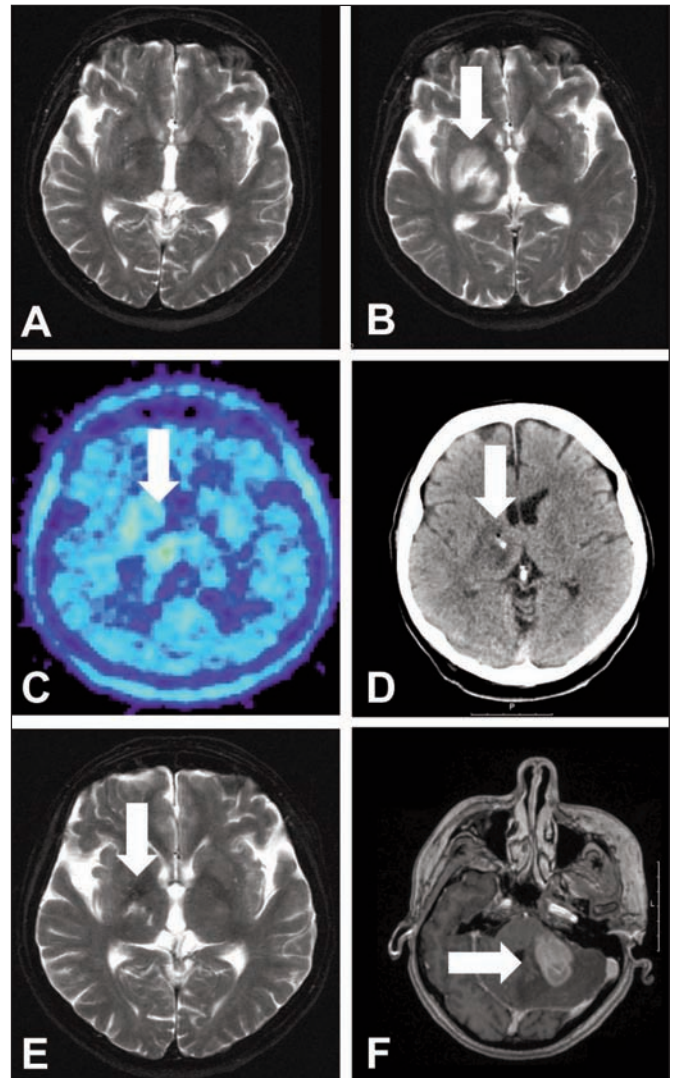


Figure 1: Imaging studies: When the patient reported first clinical symptoms the cerebral MR scan was normal (A); few months later, a hyperintense lesion on T2 was detectable (B, arrow), which revealed increased metabolism on PET scan (C); stereotactic surgery was performed (D); post biopsy CCT, titan marker visible; follow-up MRIs were stable for years (E); two years after the first biopsy new lesions on MRI were seen (F).

Table: Comparison of primary CNS lymphoma (PCNSL) and late onset multiple sclerosis (LOMS)

	Primary CNS lymphoma in immuno-competents	Late onset multiple sclerosis
Age at diagnosis	median age 60 years ⁵	mean age (+/- SD) 57 (+/- 7) years ⁶
Vision disorders	15 to 25% of the patients ^{7,8}	10% of the patients ⁶
Spinal involvement	1,2% of the patients ¹⁸	80% of the patients ⁶
Cerebrospinal fluid	positive oligoclonal banding in 27% of the patients ¹⁴	positive oligoclonal banding in 98% of the patients ⁶
Contrast enhancement of the cerebral lesions	strong in 88,5%, moderate in 10,4%, no contrast enhancement in 1% ¹⁸	in 15% ⁶

An exemplary case report of a “sentinel lesion” preceding PCNSL

To illustrate the phenomenon of “sentinel lesions” and the resulting diagnostic pitfalls, we present an exemplary case report. An immunocompetent 59-year-old woman initially presented in December 2005 with acute left central paralysis and left hemihypesthesia. Since the patient fully recovered eight hours after the onset of the symptoms and a cranial MRI disclosed no pathological findings, the incident was interpreted as transient ischemic attack. Starting in January 2006, the patient noticed slowly progressive, sensorimotor left hemispheric symptoms. Cranial MRI now revealed a T2 hyperintense lesion with only mild contrast enhancement on T1 involving the right basal ganglia and thalamus (Figure 1A-B). Examination of the cerebrospinal fluid showed mild lymphomonocytic pleocytosis and no oligoclonal bands. Since MR-spectroscopy with a pronounced decrease of NAA levels and elevated choline and lactate levels was suggestive of a possible neoplastic nature of the lesion, a stereotactic thalamic biopsy was performed. Histopathological analysis showed chronic inflammatory and resorptive changes of the brain tissue, accompanied by partial demyelination. The inflammatory infiltrate mainly consisted of CD3-positive T lymphocytes and CD68-positive macrophages with only few CD20-positive small B lymphocytes present (Figure 2). On the assumption of an inflammatory demyelinating disease, high-dose intravenous corticosteroid pulse therapy (1000 mg methylprednisolone daily for five days), followed by an oral methylprednisolone therapy tapered over the next two weeks, was administered. This produced a partial remission of the clinical symptoms and the basal ganglia lesion in the subsequent MRI follow-up examination in June 2006.

In July 2006, for the first time, the patient complained about seeing flashes and developed blurred vision in both eyes. Bilaterally delayed P100 latencies of visual evoked potentials were consistent with acute demyelination of the optic nerves.

Repeated cranial MRI examinations with imaging of the orbit were, besides the residual basal ganglia lesion, normal (Figure 1E). During the following weeks, high-dose methylprednisolone pulse therapy and plasma separation could not prevent development of progressive visual loss in both eyes. In October 2006, a “leopard skin pattern” of the left ocular fundus raised the suspicion of an intraocular non-Hodgkin’s lymphoma. However, a vitreous biopsy of the left eye in October 2006 revealing an

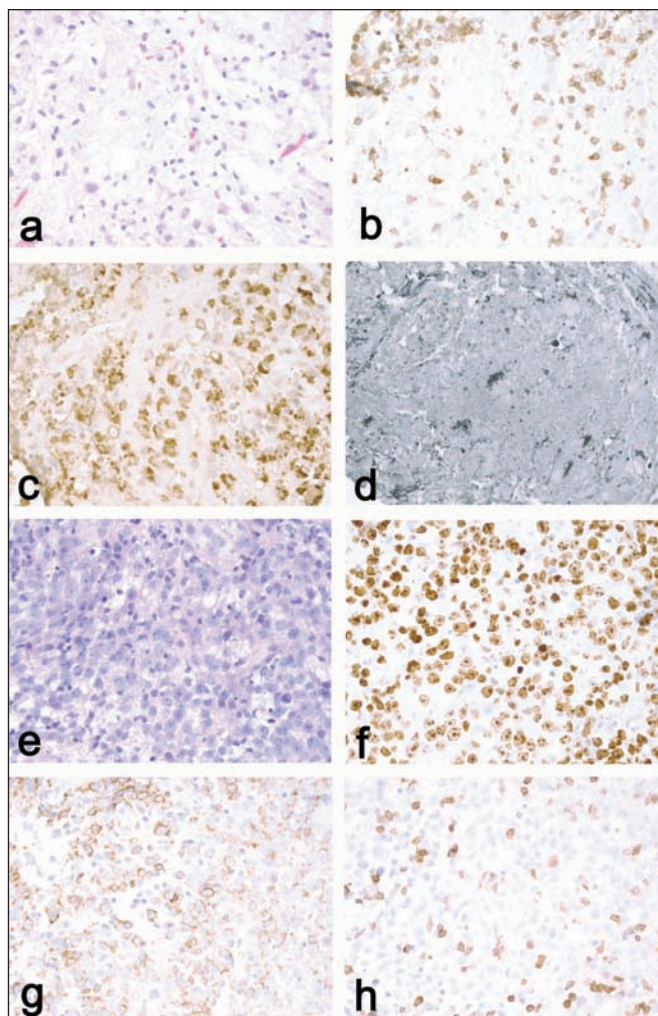


Figure 2: Histopathological and immunohistochemical findings in the first biopsy. (A) Conventional histology (hematoxylin-eosin) shows a moderately cellular CNS lesion with edema, reactive gliosis and infiltration by macrophages and lymphocytes. (B) Immunostaining for CD3 demonstrates perivascular and intraparenchymal T cells. (C) Numerous macrophages are stained for CD68. (D) Nearly complete loss of myelin demonstrated by absent Sudan black staining. (E-H) Histopathological and immunohistochemical findings in the follow-up biopsy demonstrating a primary CNS lymphoma. (E) Hematoxylin-eosin staining shows a densely cellular lesion composed of lymphoma cells with enlarged nuclei. (F) High proliferative activity of the lymphoma as revealed by expression of Ki-67 (MIB-1). The lymphoma cells express CD20 (G) while CD3 positivity is restricted to intermingled T cells (H). The immunohistochemical sections (B-C, F-H) are counterstained with hemalaun; original magnification 400 x.

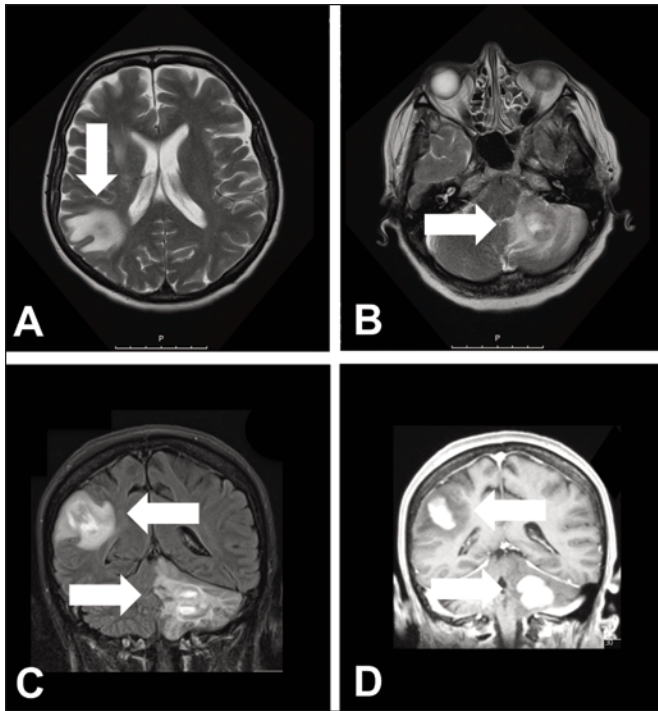


Figure 3: Multifocal manifestation of the primary CNS lymphoma with supra- (A) and infratentorial (B) hyperintense lesions on T2-weighted images as well as on FLAIR (C). After application of gadolinium strong contrast enhancement was visible (D).

inflammatory T cell infiltrate could not secure the diagnosis of a neoplasm. The patient underwent regular follow-up examinations. With some delay, vision improved and the fundus changes partly receded, now exhibiting the image of a chronic uveitis. Consecutive vitreous and chorioretinal biopsies as well as a lumbar puncture and a cranial MRI in January 2008 yielded no evidence of a neoplasm. In May 2008, the patient presented with severe nausea, vomiting and rotatory vertigo. A left-sided gaze-evoked nystagmus, left arm dysmetria and mild gait ataxia indicated a cerebellar syndrome. The cranial MRI revealed three large lesions in the right frontal and parietal lobe and the left cerebellar hemisphere with strong and homogeneous contrast enhancement and intracranial mass effect (Figure 3). The residual non-enhancing right basal ganglia lesion remained unchanged. A stereotactic biopsy of the cerebellar lesion finally secured the diagnosis of a diffuse large B-cell lymphoma (Figure 2). A subsequent bone marrow biopsy, ^{18}F -FDG-PET and truncal computed tomogram scan provided no evidence of a systemic lymphoma. Thus, 30 months after the onset of the neurological symptoms, the patient was diagnosed with a PCNSL and was admitted to a systemic high-dose methotrexate-based chemotherapy. After a relapse in October 2008, chemotherapy with rituximab, cytarabine and thiotepa followed by stem cell apheresis could not stop disease progression. In February 2009, ten months after diagnosis and after the initiation of a palliative whole brain radiation, the patient died from a septic shock.

DISCUSSION

Diagnostic error?

We have reported the case of a patient who developed an inflammatory demyelinating brain lesion two-and-a-half years prior to the final diagnosis of a PCNSL. The relatively close time interval between the appearance of the inflammatory demyelinating lesion in the right basal ganglia and the manifestation of the PCNSL is characteristic for “sentinel lesions” and raises the question of a false-negative diagnosis of the initial lesion. Corticosteroid treatment which may lead to remission of an intracerebral lymphoma was not performed before the initial biopsy. The thalamic defect caused by the biopsy and a titan marker, which was deposited next to the site of the biopsy, confirmed that the specimen originated from the right basal ganglia lesion (Figure 1D). Therefore, in this case, no diagnostic error occurred that could account for the histological discrepancy of the thalamic and cerebellar biopsy results. However, in several published cases of “sentinel lesions”, corticosteroid treatment had taken place before biopsy².

Hypotheses on the pathogenesis of “sentinel lesions”

The clinical course and imaging features of PCNSL may be difficult to distinguish from an inflammatory demyelinating disease. Yet, in our patient, the histopathological analysis of the initial basal ganglia lesion classified as inflammatory demyelinating disease and of the cerebellar lesion appearing months later which was identified as PCNSL indicate that they truly represent two different pathological entities. It is tempting to speculate on a causal relation between the inflammatory demyelinating process and the subsequent PCNSL. While a link between Epstein-Barr-virus infection and PCNSL was revealed in immunodeficient patients, the pathogenesis of PCNSL in immunocompetent individuals still remains unclear. Lymphoma cells may develop accidentally due to an intrathecal clonal proliferation among normal B lymphocytes within the context of an inflammatory CNS disease becoming manifest in “sentinel lesions”². On the other hand, “sentinel lesions” may be the first immunological response mounted against a developing CNS lymphoma, which may escape diagnosis in an inflammatory environment.

CONCLUSION

Since the introduction of high-dose methotrexate-based chemotherapy in the treatment of PCNSL, an improvement of median survival could be achieved¹⁹. Nevertheless, it remains unclear whether early diagnosis of PCNSL results in a longer overall survival and better outcome of the patient. The occurrence of large, contrast-enhancing cerebral lesions in older patients with a relapsing-remitting disease course and steroid-resistant vision disorders should lead to the consideration of a PCNSL and close follow-up examinations. Proton magnetic resonance spectroscopy may be a useful tool for the differentiation of inflammatory demyelinating lesions from PCNSL.

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