

Imaging features of primary central nervous system lymphoma at presentation

Case series from a regional cancer centre

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ABSTRACT

Rationale: Imaging features in primary central nervous system lymphoma (PCNSL) vary considerably. It is often challenging to distinguish inflammatory or demyelinating white matter brain parenchymal disorders from neoplastic processes based on radiologic findings. This study's purpose was to evaluate the imaging features of PCNSL at presentation.

Methods and materials: We evaluated pretreatment magnetic resonance imaging (MRI) examinations of 43 patients diagnosed with PCNSL in our institution.

Results: Seventy lesions were found, with a mean diameter of 20 mm. The most frequent locations of PCNSL were the periventricular region in 18 patients (41.9%), followed by cerebral hemispheres in 10 (23.2%). Four patients (9.3%) had a lesion in the corpus callosum, 2 (4.6%) in basal ganglia bilaterally and 6 (13.9%) had diffuse white matter involvement. A dural-based metastatic lesion was evident in 1 patient (2.3%) and 2 (4.6%) had a lesion originating from the wall of the third ventricle. One patient presented with an epidural mass in the spinal canal at the level of the second lumbar vertebra. Edema was seen in 35 patients (81.4%), identified on T2-weighted images, and a mass effect was evident in 5 (14.2%). The lesions were hyperintense in 4 patients (9.3%) and hypointense in 9 (20.9%); the remainder (69.8%) had heterogeneous signal intensity.

Conclusions: PCNSL has a varied initial diagnostic imaging presentation with periventricular location being most common. Radiologically, PCNSL can mimic a variety of benign and malignant processes. New diagnostic tools are required for differentiation, such as single-photon emission computed tomography (SPECT), MR spectroscopy, perfusion MRI and iron nanoparticle studies. These tools can help in the differential diagnosis of neoplastic phenomena with inflammatory conditions and should be further investigated in clinical trials.

RATIONALE

Primary central nervous system lymphoma (PCNSL) is a rare form of extranodal high-grade non-Hodgkin B cell neoplasm, usually with large-cell or immunoblastic histologic features. It most frequently originates in the brain, less often in the eyes, and rarely in the leptomeninges and spinal cord. PCNSL typically remains confined to the central nervous system (CNS) and rarely metastasizes systemically.¹ Accounting for less than 2%

of cerebral neoplasms,² PCNSL is being diagnosed with increasing frequency in both immunocompetent and immunodeficient patients (i.e. people with AIDS and transplant recipients), and accounted for 2.7% of all primary brain tumours diagnosed in the United States from 1995 through 1999.³ Although the cells of origin are B lymphocytes, PCNSL is often considered a neurooncologic entity because its therapeutic challenges resemble those of primary brain tumours. Recognizing

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PCNSL by imaging criteria is essential to avoid unwarranted corticosteroid therapy prior to biopsy, as is standard in other brain tumours such as glioblastomas and astrocytomas. Corticosteroid therapy can cause rapid steroid-mediated apoptosis of lymphoma cells, inducing a false-negative diagnosis. Maximal debulking surgical resection, the standard initial treatment in other brain tumours, is of no value for PCNSL, which is treated primarily by systemic high-dose intravenous methotrexate-based chemotherapy and/or external beam radiation.

The purpose of this study was to retrospectively evaluate pretreatment imaging in 43 patients with PCNSL registered at CancerCare Manitoba from 1990 to 2005, to delineate the characteristic presenting imaging features.

METHODS AND MATERIALS

We evaluated the pretreatment radiologic records of 43 patients (22 men and 21 females), ranging from ages 27 to 83 years, with a mean age of 60, who had histologically proven PCNSL and were registered in the Cancer Registry of the province of Manitoba, Canada from 1990 to 2005. Magnetic resonance imaging (MRI) was evaluated for lesion location, number of lesions, associated edema, necrosis and proximity to the subarachnoid space (e.g. ependymal and leptomeningeal spread). To ensure uniformity, information was collected from the medical records on a standard form encompassing demographics and radiology.

RESULTS

Table 1 outlines the baseline characteristics seen in imaging. The most frequent locations of PCNSL were the periventricular region in 18 patients (41.9%) (**Figure 1A**, page 26), followed by the cerebral hemispheres in 10 patients (23.2%) (**Figure 1B**). Four patients (9.3%) had a lesion in the corpus callosum, 2 (4.6%) in the basal ganglia, bilaterally, and 6 (13.9%) had diffuse white matter involvement. Dural metastases were seen in 1 patient (2.3%) and 2 (4.6%) had a lesion originating from the wall of the third ventricle. One patient had an epidural mass in the spinal canal at the level of the second lumbar vertebra.

The number of lesions per patient was variable. A single lesion was found in 30 patients (69%). At least 1 cerebral hemisphere was involved in 20 patients (46.5%). The mean diameter was 20 mm (10 mm to 35 mm) (**Figure 1C**). Typical ring enhancing lesions > 20 mm were seen in 20 patients (46.5%). Leptomeningeal spread was evident in 1 patient at the time of presentation. Among those with diffuse white matter involvement, only 2 patients had deep infiltration in white matter.

Contrast enhancement with gadolinium was significant in 35 patients (81.4%) and moderate in 7 (16.2%). Edema was seen in 35 patients (81.4%), as identified on T2-weighted images, and local mass effect (i.e. shifting of brain contents) was evident in 5 patients (14.2%) (**Figure 1D**). The mass effect was attributed mainly to edema and not to the lesion itself. The extent of edema did not depend on the location of the lesion(s). Necrosis was seen in 5 patients (11.6%). The signal intensity on T2-weighted images was variable. The lesions were hyperintense in 4 patients (9.3%) (**Figure 1A**)

and hypointense in 9 (20.9%); the remainder (69.8%) had heterogeneous signal intensity. No relationship between location of lesions, number of lesions or edema was established. Computerized tomography (CT) scan or MRI of the spine was done in all patients who were registered in or after 1998, reflecting a shift in practice. Cerebrospinal fluid (CSF) analysis was done in 20 patients (46.5%). Only 1 patient (2.3%) had positive cytology.

Clinically, 21 patients (48.8%) presented with weakness in 1 or more extremities, 12 (27.9%) had headache, 6 (14.0%) had blurring of vision with or without diplopia, 3 (6.9%) had difficulty with speech and 1 (2.3%) presented to the emergency room with a decreased level of consciousness. Only 2 patients (4.6%) were immunocompromised due to underlying HIV infection; in these patients lesions were multifocal with a diffuse enhancement pattern on MRI. Immunocompetent patients had single or multiple enhancing lesions, usually located in periventricular frontal, parietal and temporal white matter or in the splenium of the corpus callosum (**Figure 1E**).

DISCUSSION

Ninety percent of PCNSL cases are diffuse large B cell lymphomas; the remaining 10% are poorly characterized low-grade lymphomas, Burkitt lymphomas and T cell

TABLE 1. Baseline imaging characteristics

Tumour feature	
Location	number of patients (%)
periventricular	18 (41.9%)
cerebral hemisphere	10 (23.2%)
corpus callosum	4 (9.3%)
basal ganglia	2 (4.6%)
diffused in white matter	6 (13.9%)
dural metastases	1 (2.3%)
third ventricle	2 (4.6%)
epidural	1 (2.3%)
Appearance of lesion	
single	30 (69%)
ipsilateral cerebrum	20 (46.5%)
ring enhancing appearance	20 (46.5%)
leptomeningeal spread	1 (2.3%)
necrotic appearance	5 (11.6%)
Contrast enhancement on T2 imaging	
significant	35 (81.4%)
moderate	7 (16.2%)
hyperintense	4 (9.3%)
hypointense	9 (20.9%)
heterogeneous intensity	30 (69.8%)

lymphomas.⁴ In our series all patients had B cell non-Hodgkin histology. PCNSL contains perivascular B cells expressing pan-B cell markers such as CD19, CD20 or CD79a. A “reactive” T cell infiltrate, recognized by anti-CD3 antibodies, is usually present.

Several variant presentations of PCNSL have been discussed in the literature. Patients with AIDS are more likely than other PCNSL patients to present with an encephalopathy. This correlates with the more often multifocal, diffuse enhancement pattern seen on MRI,⁵ also evident in our series. Diagnosis of PCNSL in both immunocompetent and immunocompromised patients is particularly difficult if they present with isolated lesions. In PCNSL, T2-weighted MRI images usually show a hypointense lesion or lesions, which enhance densely and homogeneously after contrast administration on T1-weighted imaging. Lesions are multifocal in 50% of patients with AIDS, whereas only 25% of immunocompetent patients have multifocal disease at presentation, usually with 1–3 lesions measuring 3–5 cm.

Ring enhancing lesions in almost any location, but usually deep in white matter, have been reported. Twenty patients (46.5%) in our series had ring enhancing lesions of considerable size at presentation (mean diameter 20 mm) so it may be that lymphoma causes few clinical symptoms unless the lesions are in eloquent regions or deep in white matter. MRI also provides useful information about leptomeningeal enhancement and mass effect, but it may remain difficult to discern alternative diagnoses (such as infections in patients with AIDS) as sometimes both entities look alike.⁶

MRI of the spine with contrast should be performed in patients with focal, spinal or root symptoms, as they may require radiation to localized deposits of lymphoma. The sensitivity of MRI for detection of leptomeningeal spread is lower compared to solid tumours, estimated at around 20%,⁷ so lumbar CSF analysis remains an indispensable investigation in this subset of patients.

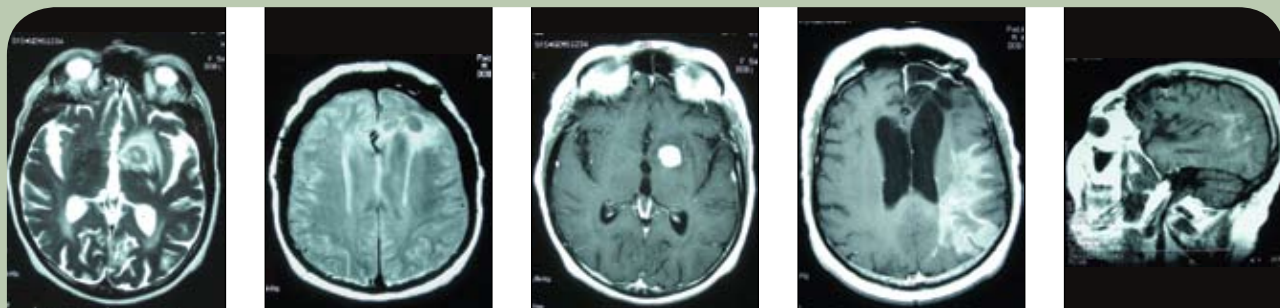
Patients with AIDS may have a cystic, ring enhancing lesion with PCNSL instead of the homogeneously enhancing abnormalities seen in immunocompetent patients. The presence of single or multiple ring enhancing lesions in patients with AIDS raises the suspicion of toxoplasmosis, *Nocardia asteroides* infection or neurosyphilis.⁸ In the literature the most important differential diagnosis has been toxoplasmosis, a relatively common opportunistic infection in patients with AIDS. It is frequently quite difficult to differentiate the 2 entities so patients may have to undergo biopsy for definite diagnosis.⁹ Experience with T1 thallium single-photon emission computed tomography (SPECT) imaging in HIV patients with mass lesions, to distinguish between lymphoma and toxoplasmosis, is encouraging. MRI and T1 SPECT appear to be complementary for the distinction between brain lymphoma and toxoplasmosis.¹⁰

In the literature there is mention of a close relationship between hypercellularity of brain tumours and high signal on diffusion-weighted MRI.¹¹ Systemic administration of radiolabelled monoclonal antibodies (MAbs) has also been tried, but due to lower accumulation in the tumour compared to blood vessels and bone marrow it has not been found useful.¹² So far no feature seen on imaging has been found to have prognostic importance. Patients with infiltration of ependymal and leptomeningeal spaces have a high risk of seeding into CSF. Identification of lesions deep in white matter often predicts a poor outcome.¹³

MRI shows diffuse and dense gadolinium enhancement with varying degrees of perilesional edema in 90% of PCNSL cases. Sixty percent of the patients may present with a single, typically periventricular lesion.¹⁴ This was the most frequent finding in our study, consistent with most published series. However, the occasional patient with PCNSL may present with normal MRI.¹⁵

SPECT performed with thallium-201 has also been shown to have high sensitivity and specificity in differentiat-

FIGURE 1. MRI of PCNSL



A. PCNSL in the periventricular region, with hyperintense signal intensity on T2-weighted images.

B. A single lesion in the frontal cortex.

C. A solitary lesion in the periventricular area.

D. Vasogenic edema and mass effect seen on T2-weighted MRI.


E. Multiple enhancing lesions located in periventricular, parietal and temporal white matter, and the splenium of the corpus callosum.

ing malignant tumours such as PCNSL (which is hypermetabolic) from other non-neoplastic entities (which are iso- to hypometabolic). The utility of Tl-201 SPECT appears to be directly related to regional blood flow, blood-brain barrier permeability and cellular uptake, possibly through an adenosine triphosphate pump transport mechanism.¹⁶

Di Chiro et al¹⁷ demonstrated the usefulness of positron emission tomography (PET) in the detection of CNS tumours. The increased metabolism of the tumour causes rapid uptake of the radiotracer carbon-11 methionine (C-11), which is seen on PET images in areas that extend beyond the areas of enhancement seen on CT or MR images; these areas of uptake have been histologically proven to represent the tumour margins. C-11 methionine PET has also been useful in monitoring the effects of therapy such as steroids or radiation.¹⁸

A few years ago, a new nanoparticle called ferumoxtran-10 was found to be useful in detecting CNS-related pathologies. Ferumoxtran-10 is a high molecular weight, cell-specific intracellular contrast agent that attaches to the cell membrane of phagocytes. It has a very long plasma half-life and shows prolonged accumulation in brain tumours. Ferumoxtran-10 can increase or decrease the magnetic resonance signal intensity, depending on both the concentration of drug in tissue and the specific pulse sequences used. MRI with ferumoxtran-10 shows different size and locations of lesions in PCNSL and other CNS inflammatory lesions compared to imaging with gadolinium, differences thought to be related to molecular size and specificity for phagocytes. Ferumoxtran-10 has not been found to enhance in multiple sclerosis as it does in tumours and strokes, which may be indicative of different blood brain barrier defects in multiple sclerosis, PCNSL and stroke.¹⁹ This physiological difference can be utilized in future to develop different tracers more sensitive for neoplastic processes.

CONCLUSION

The new imaging techniques like SPECT, MR spectroscopy, perfusion MRI and iron nanoparticle studies have been found to be useful in the differential diagnosis of neoplastic phenomena with inflammatory conditions, and should be further investigated in prospective randomized clinical trials. 

Disclosure

The authors declare no conflict of interest pertaining to this report of this study.

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