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ORIGINAL ARTICLE

# Central nervous system lymphoma: a morphological MRI study

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## Abstract

**OBJECTIVES:** The aim of the present study was to evaluate morphological MRI findings in histologically-proven central nervous system lymphoma (CNSL) at time of their first appearance, and to describe dynamic changes on repeat MRI before the diagnosis was histologically proven.

**METHODS:** We retrospectively evaluated the MRI examinations of 74 patients with histologically-proven CNSL (10 secondary CNSL, 64 primary PCNSL; 10 immunocompromised, 54 immunocompetent). In 43 patients, we evaluated the evolution of CNSL on MRI before the diagnosis was proven.

**RESULTS:** Primary CNSL was typically localized supratentorially (63%), with multiple (59%) or infiltrative (36%) lesions showing diffusion restriction (98%), often (87%) reaching the brain surface. In approximately 50% of patients, meningeal, ependymal or cranial nerve involvement was found. We detected significant differences in enhancement patterns between immunocompromised and immunocompetent patients; non-homogenous enhancement present in 50% of immunocompromised patients. We did not find any significant differences in MRI appearance between primary and secondary CNSL. Regression was evident after corticosteroid treatment in 52% of patients; however, in 16% of cases overall progression was observed.

**CONCLUSION:** CNSL generally presents as an infiltrative lesion or multiple homogenously-enhancing lesions of the brain in contact with the brain surface. Involvement of the corpus callosum, cranial nerves, ependyma or meninges is common. No significant differences between primary and secondary CNSL were detected, however differences in enhancement type between immunocompromised and immunocompetent primary CNSL patients were found. We stress the variability of MRI findings in the course of the disease and also the variable response to corticotherapy.

**Abbreviations:**

| | |
|---|---|
| CNSL | - Central nervous system lymphoma |
| PCNSL | - Primary central nervous system lymphoma |
| DLBCL | - diffuse large B-cell lymphoma |
| AIDS | - acquired immune deficiency syndrome |
| MRI | - magnetic resonance imaging |
| MR | - magnetic resonance |
| CNS | - central nervous system |
| T | - tesla |
| TSE T2/PD | - turbo spin-echo T2/proton density weighted sequence |
| SE T1 | - Spin-echo T1 weighted sequence |
| DWI | - diffusion weighted images |
| CT | - computed tomography |

## INTRODUCTION

Central nervous system lymphoma (CNSL) is an aggressive and rare brain neoplasm. Involvement of the CNS can occur secondarily in the presence of systemic lymphoma or primarily without systemic involvement. Primary central nervous system lymphoma (PCNSL) is an extranodal lymphoma that arises within the brain, leptomeninges, spinal cord or eyes. The incidence of PCNSL has been increasing over the last several decades (Olson *et al.* 2002; Schabet 1999; Hoffman 2006). Both primary and secondary CNSL are typically characterized histologically as diffuse large B-cell lymphoma (DLBCL), and rarely as other types of lymphoma such as Burkitt lymphoma, T cell lymphoma or Hodgkin lymphoma (Bhagavathi & Wilson 2008; Da Silva *et al.* 2006). It is currently estimated that PCNSL accounts for roughly 2–5% of all malignant brain tumors and up to 1% of non-Hodgkin lymphomas (Haldorse *et al.* 2011; Haldorsen *et al.* 2007; van der Sanden *et al.* 2002; Villano *et al.* 2011; Sierra del Rio *et al.* 2009). In immunocompetent subjects, PCNSL usually affects older individuals with a slight male predilection (Partovi *et al.* 2014). Immunocompromised patients have an increased risk of developing PCNSL, which usually develops at a younger age (Schabet 1999). It has been suggested that, due to improved AIDS treatment, the incidence of PCNSL in younger immunosuppressed patients may decrease (Kaddan-Lottick *et al.* 2002). However, the incidence of PCNSL has been increasing in immunocompetent patients (Olson *et al.* 2002).

Magnetic resonance imaging (MRI) is the imaging modality of choice in CNSL (Haldorsen *et al.* 2011; Partovi *et al.* 2014). The MRI appearance of CNSL may be non-specific and in some cases can mimic other CNS pathologies, which may cause delays in diagnosis and treatment. Histologic verification is required for diagnosis and samples are often obtained by stereotactic biopsy (Elder & Chen 2006). Considering the risks involved in stereotactic sampling (Malikova *et al.* 2014), correct MRI assessment is crucial. In the present study, we describe morphological MRI findings in histologically proven CNSL at their first appearance as well as dynamic changes on repeat MRI, including reaction to corticosteroid therapy before the definitive diagnosis was histologically established.

## MATERIALS AND METHODS

We retrospectively evaluated all available MRI examinations of CNSL patients acquired at our institution from 2007–2015. The diagnosis of CNSL was confirmed by histological examination of specimens obtained by stereotactic biopsy or open surgery. Systemic lymphoma was excluded in all subjects with primary CNSL by bone marrow biopsy, whole-body computed tomography (CT), or whole-body positron emission tomography/CT.

MRI examinations were performed on 1.5 T whole body scanners and included T2-weighted images, as well as T1-weighted images acquired both natively and following intravenous gadolinium contrast administration. Diffusion weighted images (DWI) were not available in all patients. All MR images were independently evaluated by 2 experienced radiologists.

The following signs were assessed on the first MRI examination:

1. Lesion localization (supratentorial, infratentorial, or both supra- and infratentorial).
2. Lesion quantity (solitary or multiple) and quality (demarcated or infiltrative). Inclusion criteria for infiltrative lesions were as follows (at least one criterion): a) ill-defined borders, b) non-enhancing portions elsewhere, c) infiltration of ependyma, meninges or cranial nerves.
3. The type of enhancement (homogenous or non-homogenous).
4. The presence of diffusion restriction on DWI in enhancing or non-enhancing parts of the tumor (Figure 1).
5. Extension to the surface of the brain (meningeal, ependymal or both ependymal and meningeal).
6. Cranial nerve involvement (including optic chiasm and adjacent optic tracts), enhancing or non-enhancing (Figure 2).
7. Meningeal or ependymal involvement (not only lesions extending to the surface of the brain, but evident infiltration of the meninges or ependyma).

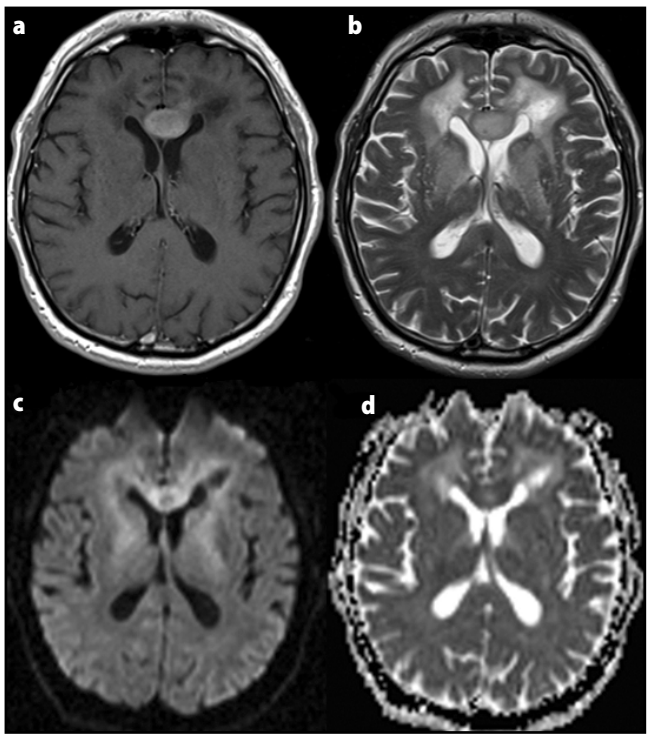


**Fig. 1.** PCNSL with butterfly-shaped infiltration. Enhancing lesion of the corpus callosum and large non-enhancing butterfly-shaped infiltration; contrast-enhanced SE T1 (a), TSE T2 (b), DWI (c), ADC (d).

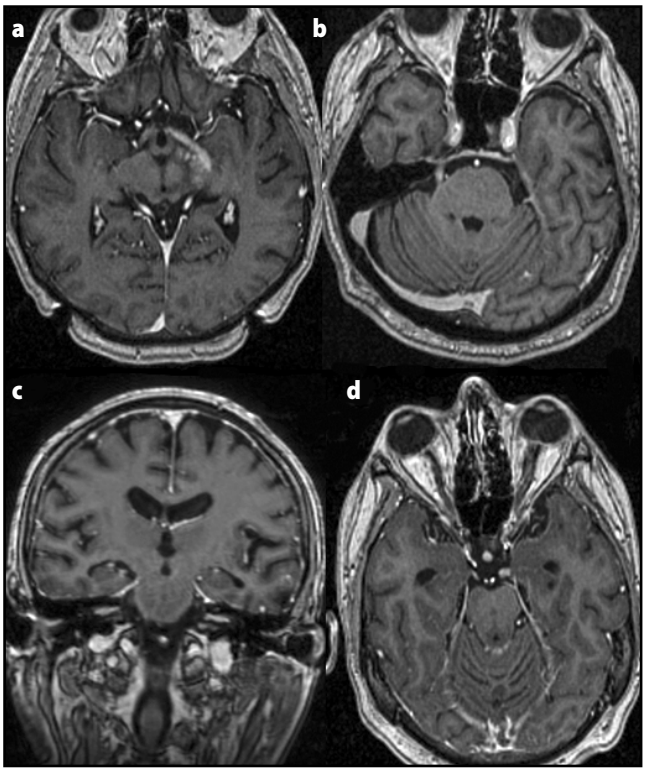


**Fig. 2.** PCNSL with cranial nerve infiltration. Infiltration is apparent in the optic tract (a), right trigeminal nerve (b), bilateral vestibulocochlear nerve (c), left occulomotor nerve (d).

8. Involvement of the corpus callosum and a butterfly pattern (infiltration spreading from one hemisphere to the contralateral hemisphere; Figure 1).
9. Signs of hemorrhage.

Dynamic morphological and enhancement changes were assessed on repeat MRI examinations before histologic verification, including changes after corticosteroid therapy as follows:

1. Progression in size, number (or both) of lesions
2. Regression of some lesions and progression of others.
3. Migrating lesions (Figure 3), i.e., complete regression of the original lesion or lesions and the appearance of a new lesion or lesions.
4. Regression
5. Changes in lesion enhancement patterns.

Statistical analyses were performed to assess differences in the stated parameters between primary and secondary CNS lymphomas, as well as between immunocompetent and immunocompromised patients with PCNSL. We also compared dynamic changes on follow-up MRI between patients treated with corticosteroids and patients without corticosteroid therapy. We applied the chi-square test and Z-test; with the level of significance set at $p<0.05$.

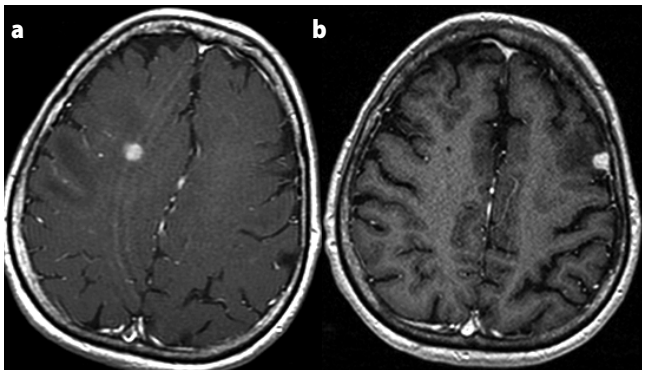


**Fig. 3.** Effect of corticotherapy: migrating lesions. Original small homogenously enhancing lesion in right frontal region (a) completely regressed after corticotherapy and a new lesion appeared on the left (b).

## RESULTS

*Patient selection data*

Seventy-four consecutive patients with histologically-proven DLBCL were included (patient demographic data are summarized in Table 1). Histological samples were obtained by stereotactic biopsy in 57 patients and by open surgery in 17 patients. Biopsy was repeated in 8 patients (in 7 patients once, in 1 patient twice) due to non-conclusive histology. The patients were divided into 2 groups: PCNSL (n=64) and secondary CNSL (n=10). Fifty-four patients with PCNSL were immunocompetent and 10 immunocompromised. Concomitant factors in immunocompromised subjects included acquired immune deficiency syndrome (AIDS; n=1), multiple sclerosis (n=2), history of oncological treatment (n=4), chronic corticosteroid therapy for systemic autoimmune disease (n=2) and chronic parenteral nutrition for malabsorption syndrome (n=1).

The median interval from neurological onset to initial brain MRI was 3 weeks (range 0–25 weeks). The patients presented with various symptoms (in some patients a combination of multiple symptoms were present): organic brain syndrome (n=27), signs of intracranial hypertension (n=24), paresis (n=23), vertigo (n=18), phatic disorder (n=14), visual disturbances (n=8), cranial nerve dysfunction other than visual disturbance(n=6), fatigue (n=5), dysesthesia or hypesthesia (n=4), seizure (n=4), disturbance of consciousness (n=2), mineral imbalance (n=1) and psychiatric symptoms (n=1). Two patients did not suffer from any neurological manifestations and were examined for different reasons. The median interval from the initial MRI to histological diagnosis was 17 days (range 1–547 days).

*MRI findings at the time of clinical presentation*

Results of the first diagnostic MRI examinations for all patients are summarized in Table 2. The optic nerves

**Tab. 1.** Demographic data of included patients.

| | PCNSL immunocompetent | PCNSL immunocompromised | PCNSL | Secondary CNSL |
|---|---|---|---|---|
| NO of patients | 54 | 10 | 64 | 10 |
| Sex | 26 female, 28 male | 3 female, 7male | 29 female, 35 male | 5 female, 5 male |
| Age | 33–82 y (median 65 y, mean 62.6±11.5 y) | 31–83 y (median 63.5 y, mean 55.4±17.2 y) | 31–81 y (median 64.5 y, mean±12.7 y) | 22–82 y (median 64 y, mean 60.5±17.7 y) |
| NO of patients with corticotherapy before the first MRI | 13 | 7 | 20 | 4 |

PCNSL, primary central nervous system lymphoma; CNSL, central nervous system lymphoma; NO, number; y, years; MRI, magnetic resonance imaging

**Tab. 2.** MRI findings in PCNSL and its subgroups and secondary CNSL at presentation.

| | | PCNSL immunocompetent NO=54 | PCNSL immunocompromised NO=10 | PCNSL all NO=64 | Secondary CNSL NO=10 |
|---|---|---|---|---|---|
| Localization | only supratentorial | 66.7% | 40% | 62.5% | 80% |
| | only infratentorial | 5.5% | 0% | 4.7% | 0% |
| | supra- and infratentorial | 27.7% | 60% | 32.8% | 20% |
| Type of lesions | solitary round shape lesion | 3.7% | 10% | 4.7% | 0% |
| | solitary infiltrative type | 37% | 30% | 35.9% | 20% |
| | multiple lesions | 59.2% | 60% | 59.4% | 80% |
| Type of enhancement | homogenous enhancement | 83.3% | 50% | 78.1% | 90% |
| | non-homogenous | 16.6% | *50% | 21.9% | 10% |
| **DWI | free diffusion | 1.9% | 0% | 1.6% | 0% |
| | restricted diffusion only in enhancing lesions | 48.6% | 16.7% | 43.9% | 42.9% |
| | restricted diffusion in enhancing and non-enhancing lesions | 48.6% | 83.3% | 53.7% | 57.1% |
| | restricted diffusion in any part of the lesion | 97% | 100% | 97.6% | 100% |
| Involvement of the brain surface | without reaching brain surface | 12.9% | 10% | 12.5% | 0% |
| | reaching brain surface | 87% | 90% | 87.5% | 100% |
| | meningeal surface only | 22.2% | 40% | 25% | 40% |
| | ependymal surface only | 22.2% | 10% | 20.3% | 0% |
| | meningeal and ependymal surface | 42.9% | 40% | 42.2% | 60% |
| Cranial nerve infiltration | solitary | 1.9% | 0% | 1.6% | 0% |
| | including other lesions | 48.1% | 40% | 46.9% | 40% |
| Meningeal infiltration | | 35.2% | 60% | 39.1% | 50% |
| Ependymal infiltration | | 53.7% | 70% | 56.3% | 60% |
| Corpus callosum infiltration | | 42.6% | 30% | 40.1% | 40% |
| Butterfly pattern | | 24.1% | 30% | 25% | 40% |
| Signs of bleeding | | 5.6% | 0% | 4.7% | 0% |

*All immunocompromised patients with non-homogenous enhancement were treated with corticosteroids before the first MRI. **DWI was available in 41 patients (55.4%).
PCNSL, primary central nervous system lymphoma; CNSL, central nervous system lymphoma; DWI, diffusion weighted images; MRI, magnetic resonance imaging; NO, number

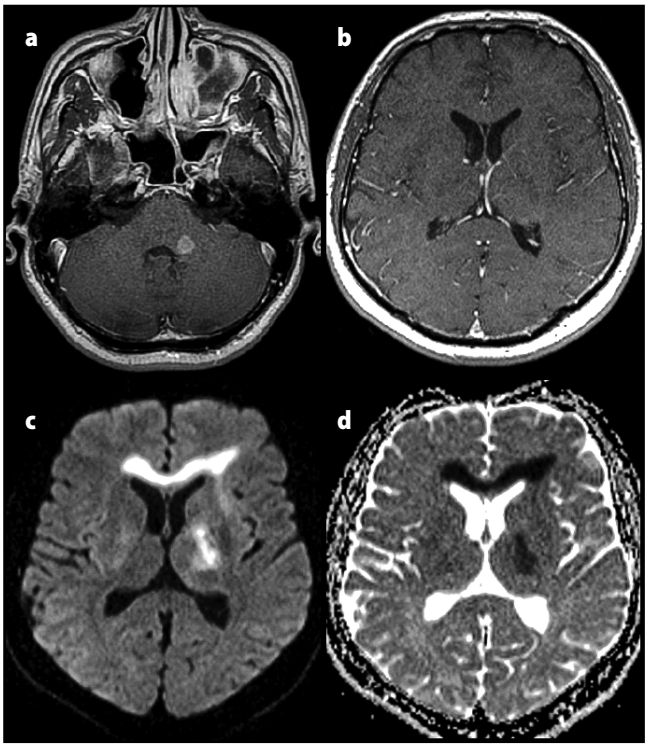


**Fig. 4.** Original enhancing lesion in left middle cerebellar peduncle (a), on long-term corticotherapy the original lesion vanished and multiple new non-enhancing lesions appeared supratentorially (c–d)

were the most commonly affected cranial nerves (34 patients), the vestibulocochlear nerve was affected in 4 patients, and the facial nerve, trigeminal nerve and oculomotor nerve were all affected in 1 patient (Figure 2).

We found significant differences in the type of enhancement between immunocompetent and immunocompromised PCNSL patients ($p$=0.019). A non-homogenous pattern of enhancement was observed in 50% of immunocompromised patients but only in 16.6% of immunocompetent patients. All immunocompromised patients with non-homogenously enhancing lesions were treated by corticosteroids before the first MRI. We did not detect any differences in assessed parameters in MRI findings between PCNSL and secondary CNSL.

*MRI follow-up*

Forty-three patients underwent follow-up MRI before the diagnosis was established; thirty-one of these patients were treated with corticosteroids. The number of MRI examinations ranged from 2–10 (mean 2.9) and the interval from the first to the last MRI examination ranged from 1–80 weeks (mean 10 weeks).

MRI follow-up data in patients with and without corticosteroid therapy are summarized in Table 3. We found significant differences between patients treated with corticosteroids and patients without corticosteroid therapy in the following parameters: overall regression ($p$=0.0093), change of enhancement pattern ($p$=0.024) and overall progression ($p$=0.0012). Overall regression was in 52% in patients treated with corticosteroids and only in 8% in patients without corticotherapy. Change of enhancement pattern was present in 32% of patients with corticotherapy but in none without corticotherapy. Overall progression was found in 67% of patients without corticotherapy but only in 16% of patients treated with corticosteroids.

## DISCUSSION

In the present study, we have clarified some of the typical features of CNSL. In PCNSL, lesions were mostly localized supratentorially, with multiple lesions more common than solitary lesions (6:4). In nearly 90% of patients, some of the lesions reached the meningeal or ependymal surface of the brain. Diffusion restriction was detected in nearly all examinations in some part of brain lesion. Approximately 50% of patients had meningeal (40%), ependymal (57%) or cranial nerve (47%) involvement. In contrast to our findings, Haldorsen *et al.* (2007) reported that PCNSL are mostly solitary, homogenously-enhancing parenchymal masses. Our findings are consistent with those of Senocak *et al.* (2011), who reported multiple lesions (58%) enhancing after IV gadolinium contrast administration with diffusion restriction (83%). Lesions contacting meningeal or ependymal surfaces have been described previously (Eichler & Batchealor 2006; Go *et al.* 2006; Bühring *et al.* 2001; Küker *et al.* 2005) and this pattern is considered characteristic for CNSL. Diffusion restriction in CNSL lesions is also typical due to their high cellularity (Haldorsen *et al.* 2011).

We found significant differences in the type of enhancement between immunocompetent and immunocompromised PCNSL patients. In the immunocompromised subgroup, non-homogenous enhancement was much more frequent. Non-homogenous and ring-like enhancement has been described in AIDS-related PCNSL (Haldorsen *et al.* 2011); however, in the present study, only one patient with AIDS was included while the remainder of the immunocompromised patients suffered from another type of immunodeficiency. All immunocompromised patients with non-homogenous lesions were treated with corticosteroids at the time of the first MRI examination. Thus, differences in enhancement between immunocompromised and immunocompetent patients in the present study may be related corticosteroid therapy.

We did not detect any differences in MRI appearance between PCNSL and secondary CNSL. This finding is in contrast to the results of previous studies. The findings of 14 previous studies from the years 1985 to 2004 were summarized in a review by Hill and Owen (2006), where they reported meningeal involvement in 66% of patients with secondary CNSL but brain involvement in only 33% of patients with secondary CNSL. However, in most of the studies reviewed, the findings were

not based on a combination of MRI examinations and histological verification and thus the diagnosis was not unequivocally proven. In some studies, the diagnosis was made on cerebrospinal fluid preparations, by CT examination, or only from clinical data without histological or radiological validation (Keldsen *et al.* 1996; van Besien *et al.* 1998; Zinzani *et al.* 1999; Hollender *et al.* 2002). All of our patients underwent MRI and the diagnosis was proven by stereotactic biopsy or open surgery, thus we consider our data valid.

The results of the present study are consistent with the findings of Senocak *et al.* (2011), who compared MRI findings in subjects with PCNSL and secondary CNSL. They concluded that MRI findings do not differ between PCNSL and secondary CNSL and that it is not possible to differentiate between the two on MRI. However, they included only 12 subjects with PCNLS and 6 subjects with secondary CNLS.

CNSL variably changes over time and the clinical and MRI appearance may be dramatically affected by the administration of corticosteroids. We observed statistically significant differences in MRI morphological changes between patients treated with corticosteroids and patients without corticotherapy. In patients treated with corticosteroids, overall regression and change in enhancement pattern was significantly more common than in patients without corticotherapy; however, we also observed overall progression in some patients. Progression was much more common in patients without corticotherapy. Regression of CNS lymphoma after the administration of corticosteroids is well established; however, spontaneous regression has also been described (Alderson *et al.* 1996; Hernández *et al.* 2013; Partap & Spence 2006). In the present study, we observed spontaneous regression in one patient. In one patient, spontaneous lesion migration was evident. Spontaneous regression or migration in CNSL has also been reported previously (Okita *et al.* 2012).

Typically CNSL markedly enhances (Haldorsen *et al.* 2011); however non-enhancing lymphomatous infiltrations have been described in patients with or without corticosteroid therapy (Partovi *et al.* 2014; Küker *et al.* 2005; Kanai *et al.* 2008; Renard & Milhaud 2006; De Angelis 1993). In the present study, enhancing lesions were detected on the initial MRI examination in all CNSL patients. However, additional non-enhancing lesions (on T2- and diffusion-weighted images) were detected in more than 50% of patients. In 6 patients, we observed the progression of enhancement into previously non-enhancing lesions on follow-up MRI. CNSL enhancement is due to increased permeability of the hematoencephalic barrier (Molnár *et al.* 1999), and the administration of corticosteroids can lead to apoptosis of tumorous cells as well as to improvement of the affected hematoencephalic barrier (Molnár *et al.* 1999; Dietrich *et al.* 2011). This may explain changes in enhancement patterns detected in more than 30% of our patients treated with corticosteroids (Figure 4). The effect of corticosteroids on enhancement in PCNSL may also explain the significant difference in enhancement between immunocompetent and immunocompromised patients, as all immunocompromised patients with non-homogenously enhancing lesions were treated with corticosteroids.

We detected signs of hemorrhage in 4.7% of PCNSL subjects. Hemorrhage is not a common feature of CNS lymphoma but may be observed in some patients (Partovi *et al.* 2014). Presentation with massive CNS hemorrhage is rare (Kim *et al.* 2008).

Although we have described several important MRI findings that are helpful in the evaluation CNSL, we must stress that MRI findings in CNSL are extremely variable and are dependent on corticosteroid therapy. It is also important to consider that CNSL is not a focal disease; microscopic lymphomatous infiltration can be found far beyond the macroscopic or MRI-detectable borders of the tumor (Lai *et al.* 2002). Lymphoma typically spreads along the ependyma, meninges and cerebral white matter tracts (Hochberg *et al.* 2007), which we macroscopically observed in some of our patients.

The present study has several limitations. Due to its retrospective nature, some MRI examinations were of lower quality and acquired on different whole-body systems. We did not have sufficient data for reviewing advanced MRI techniques, such as MR spectroscopy or perfusion. Finally, the number of subjects included in the PCNSL and secondary CNSL groups were asymmetrical, with more patients diagnosed as PCNSL.

## CONCLUSION

CNSL typically presents as an infiltrative lesion or multiple lesions of the brain with homogenous enhancement, and in contact with the surface of the brain. Involvement of the corpus callosum, cranial nerves, ependyma or meninges is common. We did not detect any significant differences in MRI appearance between PCNSL and secondary CNSL. We did however detect significant differences in the type of enhancement in immunocompromised and immunocompetent patients with PCNSL; with non-homogenous enhancement present in 50% of immunocompromised patients. We hypothesize that this difference may be related to corticosteroid therapy. We further stress the variability of MRI findings over time. Corticosteroids typically cause regression or migration of lesions; however, progression may occur. Corticosteroids may additionally modify the enhancement of CNSL, and regression or migration in CNSL may occur spontaneously.

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