Imaging in cranio-cerebral lymphomatous disease - a pictorial review

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Learning objectives

1. To present typical and particular aspects in conventional CT and MRI of cranio-cerebral lymphomatous disease, based on a series of 88 patients.

2. To emphasise the role of advanced MRI techniques (DWI, with ADC map and MRS) in pretherapeutic diagnosis and posttherapeutic follow-up.

Background

Introduction. While lymphoma is a neoplasm of lymphoid tissue, a significant number of patients will present or develop disease outside the traditional lymphoid tissue of lymph nodes, this means lymphomatous disease involving a particular organ or structure as part of disseminated disease, or 'primary' extranodal disease. [5,7,8,10].

PCNSL (Primary Central Nervous System Lymphoma), a rare form of non-Hodgkin's lymphoma (NHL), accounts for 1%-5% of all brain tumors and approximately 1% of all NHL [8]. Immunocompromised patients (eg, individuals infected with HIV) have an increased risk of developing PCNSL.[8]. But, unlike many primary brain tumors, PCNSL is very responsive to treatment, and aggressive management may lead to prolonged remission or cure.[2]

Incidence. The incidence of cranio-cerebral involvement with malignant lymphoma whether primary or secondary (highly dependent on histologic subtype) has increased significantly in last years. As a result, there is increasing interest in the pretreatment diagnosis and post-treatment surveillance for residual disease using imaging technics. [2,8,9]

Male predominance was reported, with great variability of man/ female ratio: from 1,2/1 to 1.7/1.

Clinical features. The clinical presentation of CNS involvements varies widely from severe headache (especially in leptomeningeal involvements), muscle weakness, change in mental status, nausea, headache, cranial nerve palsies, and visual disturbances to other neurological signs (determined by tumor location (including nonspecific focal neurologic deficits).[1,9]
**Imaging.** In contemporary diagnostic imaging protocols for malignant lymphoma, and in particular for pediatric malignant lymphoma, emphasis is placed on limiting radiation exposure. Magnetic resonance imaging (MRI) is a radiation-free imaging method and may be an attractive alternative diagnostic modality to CT and/or FDG-PET.[20]

At present, MRI is mostly considered to be a complementary technique to contrast-enhanced CT and bone marrow biopsy, allowing, in some anatomical regions, for further and more specific anatomical information.[21] Owing to its high spatial resolution and excellent soft-tissue contrast, MRI is an ideal tool for the detection of parenchymal and bone marrow abnormalities and even MRI may be superior to CT in the detection of CNS and bone marrow lesions.[22] Advanced MRI techniques could provide added information, such as tumor vascularization and cellularity, potential of malignancy, cell membrane integrity.

**Imaging findings OR Procedure details**

**Patients:**

Retrospective study over a period of 9 years, consisting of imaging exams (CT and / or MRI) performed for pretherapeutic diagnosis and posttherapeutic follow-up of 88 patients hospitalized in the Hematology Clinic Fundeni Hospital with a diagnosis of Hodgkin lymphoma (HL) or non-Hodgkin's lymphoma (NHL) who presented clinical manifestations of neurological disease.

**TECHNIQUES**

**CT protocol:**

CT exams were performed on sequential mode, with 5 mm sections, slices parallel with orbito-meatal plane, without contrast injection, most of these exams were followed by iodate contrast injection.

**MR protocol:**

MR examinations included axial or coronal T2 and or T2 FLAIR weighted images, diffusion weighted images, axial T1weighted images without contrast injection and axial and sagital or coronal contrast enhanced T1 weighted images. MRS (MR spectroscopy) was performed only in 7 cases with cranio-cerebral lymphomatous
disease. We performed MRS with PRESS (point-resolved spectroscopy) sequence (single voxel \( n = 2 \)) with a TE of 144 msec.

**IMAGING ANALYSIS:**

Based on conventional computed tomography (CT) and resonance magnetic imaging (MRI), we evaluated: tumor location (leptomeningeal or intraaxial location, supra/or infratentorial, white matter or deep grey nuclei involvement), number, density on CT / MR signal on conventional sequences, structure (presence of calcifications, intratumoral hemorrhages or necrosis, enhancement patterns), associated edema. Diffusion restriction and tumor signal on ADC map were also analyzed. And finally, we attempt a brief analysis of MR spectrogram.

The main features found will be presented, analysed, and discussed in comparison with proven literature data.

As previously stated, cranio-cerebral lymphomatous involvements includes 2 major subtypes: PCNSL (primary central nervous system lymphomas), in which the lymphoma is restricted to the brain, leptomeninges, spinal cord, or eyes, without evidence of it outside the CNS at primary diagnosis and secondary central nervous system (CNS) involvement by systemic lymphoma (Hodgkin or nonHodgkin lymphoma).[9]

**Location:**

In first subgroup (patients with PCNSL), parenchymal mass is by far the most frequently encountered pattern (in our study, as in previous reports) , while in secondary lymphomatous CNS involvement most studies reports leptomeningeal metastases as the most common [1,8,10]. Leptomeningeal involvements, including diffuse or focal leptomeningeal, subependymal, dural, or cranial nerve enhancement are best imaged on contrast-enhanced MR imaging. (Fig. 1 on page 7)

Patients with PCNSL usually have supratentorial mass, most of them in the white matter of the frontal or parietal lobes. [8,10, 19]. Periventricular location (abutting the ventricular/ependymal surfaces), either white matter or deep gray structures (Fig. 2 on page 7 ) are considered one of the most typical neuroradiologic signs which may suggest the diagnosis of PCNSL.[19]

Secondary cranio-cerebral involvements, more common than primary CNS lymphoma, are uncommon in Hodgkin Lymphoma, much more rare than in NonHodgkin Lymphoma. [16]
Fewer than 0.5% of patients with Hodgkin’s lymphoma and 5-9% of systemic non-Hodgkin’s lymphoma have CNS involvements [1]. Parenchymal secondary lymphomatous lesions often appear as single or multiple lesions and can be accompanied by leptomeningeal metastases. Most typically they are located in periventricular white matter (Fig. 3 on page 8) and deep grey nuclei.

Secondary lymphomatous involvements of corpus callosum and infratentorial parenchyma are also common. (Fig. 4 on page 9)

Whereas cavernous sinuses lymphomatous involvements are extremely rare, intraorbital lymphomatous masses are frequently described. (Fig. 5 on page 10).

**Number:**
PCNSL tends to present as a homogeneously enhancing solitary periventricular mass, but multiple lesions were also described [9, 19]. Multifocal tumors are more common on secondary CNS lymphomatous involvement (which in turn can be solitary) and are frequently seen in immunocompromised patients. [1, 8]

**Conventional CT/ MR features**

Imaging features of secondary lymphomatous parenchymal lesions are quite similar to the PCNSL findings; this similarity makes it impossible to discriminate these 2 entities on the basis of neuroimaging.[8]

**CT attenuation**

On noncontrast CT scans, both on primary and secondary CNS lymphoma may appear isoattenuated or more frequently - hyper attenuated masses relative to white matter (due to the high nucleus-to-cytoplasm ratio), with minimal or moderate surrounding edema. [1,5,14,16]. (Fig. 6 on page 11)

**MR signal intensity:**

At MR imaging, tumors usually have intermediate-to-low signal intensity on T1-weighted images and are either isointense or hypointense relative to the gray matter on T2-weighted images. Isolated hyperintens lesions on T2-weighted MR imaging has also been described.[8]

Calcifications or hemorrhage within the tumor are rarely seen [8,9]. (Fig. 7 on page 12)
Enhancement:

We found few studies [1,8, 15], which reports enhancement in all lymphomatous lesions examined after administration of a contrast agent (both on CT and MR image), with variable pattern, but there are some papers that report enhancement in 97%-99%. [9]. Ring enhancement, which could represent central necrosis, occur in immunocompromised patients (AIDS-related) with lymphomatous lesions.[8, 9, 14] (Fig. 8 on page 13).

Advanced MR techniques

DWI/ ADC

Similar to previous reports, we emphasize the most constant feature of lymphomatous masses as restricted water diffusion, with high signal on DWI and low signal on ADC map. Diffusion within the tumor is considered a surrogate marker of tumor cellularity because intact cells constitute a barrier to water diffusion. Because CNS lymphomas are highly cellular tumors, water diffusion is often restricted, making them to appear hyperintense on DWI and hypointense on ADC maps. This characteristic may help to differentiate high-grade gliomas and metastases from lymphomatous lesions (that show more restricted diffusion and lower ADC values) [8, 10, 12]. (Fig. 9 on page 14).

MR spectroscopy

MR spectroscopy obtains biochemical information noninvasively from biologic tissue. [8]. The NAA decrease reflects decreased neuronal density and variability in the tumor, the creatine decrease suggests higher tumor metabolism and energy consumption, and the choline increase indicates phosphorylcholine and glycerophosphorylcholine release by cell membrane destruction or synthesis. Lymphoma typically shows decreased NAA, decreased creatine, increased choline, and present lipid-lactate peaks. Often because of the very high cellularity of lymphoma, the Cho concentration can be very high, even greater than in high-grade gliomas. [10, 12, 13]. So, spectroscopy is helpful in initial imaging diagnosis of cranio-cerebral lymphomatous disease. [8, 13] (Fig. 10 on page 15).

Follow up

Different types of treatment are available for patients with CNS lymphoma: radiation therapy, chemotherapy and steroid therapy, making necessary a careful post-therapy follow-up of these lesions. Residual contrast enhancement may rarely be observed in CNSL patients after successful therapy and does not necessarily indicate residual lymphoma. [18]

On the basis of the morphology of the non-progressive residual lesions in the patients described above, W. Küker et al. proposed, at ECR 2006, MRI response criteria for
PCNSL, applying a treatment response evaluation system established for malignant gliomas. (Fig. 11 on page 16)

We also tried to evaluate posttreatment response using contrast enhancing T1 sequences, where we have found it useful.

W. Küker’s proposed modification of Macdonald criteria for response evaluation in PCNSL [18]. We have introduced as well, new techniques (DWI and ADC) in CNS lymphomatous lesions follow up and we can see that a decreased contrast enhancement together with a significant appropriate reduction of hypersignal on DWI and hyposignal on ADC map appears on posttreatment evaluations. (Fig. 12 on page 17).

Images for this section:

Fig. 1: Diffuse, homogeneous leptomeningeal enhancement or nodular enhancement of bilateral temporal leptomeninges seen in 2 patients with NHL.
**Fig. 2:** Median deep hypointense T2 polilobular mass, with biemisferic evolution, with moderate enhancement, surrounded by moderate edema.
Fig. 3: Two cases with single white matter nodular lesion at patients with secondary CNS involvements in NHL. In the first case: left frontal mass with low signal on T2 and T2 - FLAIR, surrounded by moderate edema, isointense with gray matter on T1 weighted image and in second case: nodular hyperattenuated mass in right fronto-parietal white matter with moderate surrounding edema and marked homogeneous enhancement on contrast-enhanced CT scan.
**Fig. 4:** Polilobulated mass with marked enhancement located at corpus callosum level and left peduncular little infiltrative lesion with small focal enhancement.
Fig. 5: A right cavernous mass with intrasellar evolution, manifesting marked enhancement and two cases of intraorbital masses: unilateral mass (in first case), with wide bone destruction or bilateral homogenous intraorbital masses appearing hyperintense on T2 image and hypointens on T1 image.
Fig. 6: A, B: Nodular isoattenuated masses involving right frontal white matter and left fronto-parietal white matter, both with moderate surrounding edema and marked homogeneous enhancement. C, D: two nodular mass in right frontal white matter and in right talamo-lenticular region, both appearing hyperattenuated on noncontrast CT, with moderate surrounding edema and manifesting marked contrast enhancing on postcontrast CT.
Fig. 7: A: Nodular right cerebelar lymphomatous mass appear hyperintense on T2 weighted image and hypointense on T1, surrounded by minim edema, with restricted diffusion and homogeneous, moderate mass enhancement B: Nodular superficial right frontal lymphomatous mass appear hypo-isointense on T2 with gray matter, hypointense on T1 (with small focus hyperintens T1, T2 relevant for a small intratumoral hemorrhage), surrounded by moderate edema, with marked, homogenous mass enhancement
Fig. 8: Multiple nodular and micronodular lesions disseminated biemisferic, same of that with ring-like enhancement.
Fig. 9: Homogeneously enhancing masses in the right frontal white matter and right basal ganglia, that manifest marked restriction of water diffusion on DWI sequences and marked low signal on ADC map.
**Fig. 10:** MR spectroscopic (MRS) markers of lymphoma include increase in choline, decreased creatine, decrease in NAA (N-Acetyl Aspartate) and presence of lipid and lactate.
<table>
<thead>
<tr>
<th>Classification</th>
<th>Complete remission (CR)</th>
<th>Partial remission (PR)</th>
<th>Stable disease (SD)</th>
<th>Progressive disease (PD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macdonald et al., 1990</td>
<td>Complete absence of contrast enhancement</td>
<td>Contrast enhancing lesion with a volume less than 50% of the pre-treatment lesion</td>
<td>Volume change between 50% decrease and 25% increase</td>
<td>Volume increase of more than 25% of the initial lesion or new lesions</td>
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**Complete Response (CR) may be assumed even in the presence of residual enhancing lesions if:**

1. No perilesional oedema, and
2. Contrast-enhancing lesion/s < 3 mm, or
3. Contrast-enhancing lesion <5 mm in the region of previous biopsy, or if tumour >5cm before treatment.

Caution also needed in interpretation of small foci of enhancement in areas of previous infection or haemorrhage.

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**Fig. 11:** Proposed modification of Macdonald criteria for response evaluation in PCNSL
Fig. 12: Pretreatement MR examination: homogeneously enhancing mass (arrow) in the right thalamus and basal ganglia, with bright signal on DW image and very low signal on ADC map. First MR examination after 2 months from start of therapy - show a small CE area, wich are also hiperintense on DWI but not hypointense on ADC map; MR exam after another 5 month of chemotherapy show decrease of tumor volume with complete disappearance of contrast enhancement and diffusion restriction.
Conclusion

- Although cranio-cerebral lymphomatous disease is conservatively treated, it is necessary to thoroughly image these lesions.
- Contrast-enhanced MR imaging is preferred to CT for detecting cranio-cerebral lymphomatous involvement. Nevertheless, imaging features in cranio-cerebral lymphomatous disease on CT and conventional MRI vary considerably.
- New MR imaging techniques (DWI, ADC) and metabolic imaging (MRS) demonstrates characteristic findings in cranio-cerebral lymphomatous disease, aiding in its differentiation from other CNS lesions, also in monitoring treatment response.

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