Structural and functional imaging for the characterization of CNS lymphomas

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Introduction

A few decades ago, Primary Central Nervous System Lymphoma (PCNSL) was considered as an extremely rare neoplasia; currently it is found behind gliomas and meningiomas as the third most frequent Central Nervous System (CNS) primary tumor (1,2).

It is defined as an extranodal malignant lymphoma, located in the CNS in the absence of a systemic disease at the moment of diagnosis.

Its prevalence and characterization have improved considerably in recent times due to immunodepression states, especially with the arrival of the AIDS epidemic and immunosuppressant therapies. Anyway, its incidence has also increased in immuno-competents patients. Systematic use of magnetic resonance imaging (MRI) has also contributed to the increase in the number of detected cases (3).

An overwhelming majority of lymphomas that invade the CNS are comprised of B cells, with an average age of appearance at 61 years, and patients being predominantly males.

CNS Involvement by lymphoma results in varied radiological signs, some of which are quite characteristic (4,5). In this article we describe the major radiological characteristics of lymphoma, emphasizing the contribution of spectroscopy. Through the knowledge from conventional and functional findings this diagnosis can be suggested before surgery and, eventually, it may modify the therapeutic and surgical strategy.

We shall remember that cortico-therapy is not advised in preoperative procedures.

Fig. 1. Parenchymatous pattern characteristic of lymphoma. Axial FLAIR and axial WI T2. Hyperintense formation located at the posterior periventricular region, involving the splenius of the corpus callous. Moderate perilesional edema and mild mass effect can also be observed.

Fig. 2. Deep located lymphoma. Diffusion and Apparent Diffusion Coefficient (ADC) map. A mass centered in the left striate-capsular region that extends to the thalamus with compression of the frontal horn at the lateral ventricle. There is restricted diffusion: high signal in the diffusion sequence and low signal in the ADC map. This finding is characteristic of highly cellular tumors, including lymphoma.

Materials and Methods

Between May of 2003 and June of 2009, 25 patients (16 men and 9 women) aged 37 to 86 years old, with an average age of 69.7, were studied in our institution. The patients selected had been histological diagnosed as non-Hodgkin lymphoma of B cells with CNS
involvement, confirmed by pathological anatomy. All cases involved immune-competent patients and the anatomopathology was obtained by surgery or stereotactic biopsy.

One of the cases included systemic lymphoma with secondary CNS involvement; this patient was included because there was no diagnosis of systemic lymphoma at the time of the study and it emerged with the involvement of the CNS. The rest of the cases were primary CNS lymphomas.

The patients were studied using Siemens Vision and Avanto 1.5T equipments. Our MRI tumor protocol was as follows: FLAIR, T2, GRE, T1, diffusion with ADC map and a post contrast volumetric T1: MPRAGE. In five patients, Magnetic Resonance Spectroscopy (MRS) was also performed. Intermediate and short echo times (135 and 30) were utilized. In all the cases post contrast sequences were obtained after injection of 20 ml of gadolinium. Previously, any type of renal failure was ruled out in our patients.

With the study concluded, the post processing of the MRS was carried out at the Syngo work station, measuring the different metabolites and their relations. Choline (Cho), Creatine (Cr), N-acetylaspartate (NAA), Lipids and Lactate were the main metabolites evaluated. The corresponding curves and metabolic maps were accomplished.

Fig. 3. PCNSL located in the deep white matter. Axial sequence weighted for T1 without and with contrast. A hypointense lesion is evident in weighted T1 sequence in the right medial temporo-occipital sector, adjacent to the convexity. The lesion exhibits intense homogenous increment with the contrast.

Fig. 4. PCNSL with exclusive pachymeningeal affectation. Axial T2-weighted sequence and coronal T1-weighted sequence with contrast. An extra-axial formation, hypointense in T2-weighted sequence with homogenous contrast reinforcement is evident in the anterior sector of the left frontal region. Although the image is suggestive of a meningioma, it can also be seen in the lymphomas.

Fig. 5. Lymphoma with cranial nerves infiltration pattern. Axial view in T1-weighted sequence with contrast. Bilateral infiltration and reinforcement of II, III and low cranial nerves (IX and X).

Fig. 6. Dissemination of the PCNSL across the perivascular spaces. Sagittal view in T1-weighted sequence with the Virchow-Robin perivascular spaces reinforcement. This pattern constitutes the classic dissemination path of this tumor, observed in 20% of our patients.

Results

The conventional MRI and 5 cases with additional MRS findings were able to be completely accomplished. We detected three patterns of presentation of this pathology amongst the findings of the structural MRI.

The parenchymatous pattern was observed in 21 patients (84%). Lesions were mainly iso/hypointense in T2WI, located in the periventricular region. In 9 patients (36%) there was involvement of the splenius of corpus callosum. We found moderate to severe
perilesional edema. When this is more evident, a hyperintense signal from the tumor can be apparent in sequence weighted in T2 and Flair (Fig. 1). Both cerebellar hemispheres were affected in two cases (8%) and extension to the brainstem in other two cases. The tumor shows mild increment post-contrast and restriction in diffusion sequence (Figs. 2 and 3).

The meningeal pattern has been found in three patients (12% of the cases). It was observed in systemic lymphoma with CNS involvement as well as in a PCNSL, where it was found associated with the parenchymatous pattern. In the remaining case, involvement was exclusively pachymeningeal, simulating a meningioma (Fig. 4).

Extension to cranial nerves was detected in two of the PCNSL cases (8%) with orbital involvement and second pair affected in one of them and involvement of multiple cranial nerves in the others (Fig. 5).

In addition to these three patterns, five patients with PCNSL exhibited contrast enhancement of the Virchow-Robin perivascular spaces, which represents a known characteristic in the dissemination of this tumor, observed in 20% of the cases (Fig. 6).

Although the described findings are characteristics of lymphoma, other tumors like glioma can depict very similar images to the parenchymatous pattern presented by the PCNSL. Therefore, in some cases, the results of the MRI were not conclusive, particularly in two of the presented cases with an extensive perilesional edema.

**SPECTROSCOPY**

Functional MRS sequences where obtained with echo time of 135 and 30, in patients who presented a parenchymatous tumor pattern (5 of 25), including the patient who was afterwards detected with a systemic lymphoma. In the intermediate echo times sequences a Choline (Cho) peak and a NAA decrease were detected. These findings constitute a nonspecific proliferative MRS pattern (evident in the majority of CNS tumors). The lipids peak was present in both sequences, being more prominent when short echo time was used. This finding, besides being a lymphoma characteristic, can also be seen in high grade primary necrotic tumors (glioblastoma multiforme) or in metastasis (Figs. 7 and 8). The described pattern (Cho increase, NAA decrease and lipid increase) was seen in the 5 patients studied with MRS.

**Fig. 7.** Spectroscopy with intermediate echo time 135 programmed over a volume with contrast. A Cho peak has been observed with NAA decrease which is a characteristic pattern of tumoral process. A lipid peak is also shown, which is more visible in short echo time 30. This peak in a solid tumor is highly suggestive of lymphoma.

**Fig. 8** Spectral maps with echo times 135 and 30 of the same patient. In the colored map, observed in red there is the localization site of the Cho peak in intermediate echo time and the lipid peak in short echo time.

**Discussion**
General characteristics

The PCNSL is one of the most enigmatic tumors of the CNS. Due to its origin and cause, continues to be uncertain and also presents a high mortality rate (8).

Currently, it is the third most frequent among CNS primary tumors, reaching 5%, and its frequency is increasing due primarily to the immunodepression states (3).

Even though PCNLS can develop at any age, the prevalence peak occurs between the sixth and seventh decades of life, and affects more men than women (2:1) (2). These findings are similar to those observed in our series.

It is considered that the majority of the CNS lymphomas (90%) are primary lesions (PCNSL), and that supratentorial affection is much more frequent than posterior fossa affection. Spinal cord is very seldom involved (1%).

PCNSL has a great prevalence in immunosuppressed patients, a group that includes renal transplant states, immunodeficiency syndromes (Wiskott-Aldrich, etc.), rheumatoid arthritis and acquired immunodeficiency syndrome (AIDS). In this last condition, PCNSL constitutes the second cause of cerebral mass in adults (after toxoplasmosis) and the first in the pediatric population (9,10).

At the present time, CNS involvement by a systemic lymphoma is extremely infrequent due to, amongst other causes, the effectiveness of chemotherapy in controlling this disease. When present, it is determined by dissemination across the neural axis and the meninges are affected more commonly than the cerebral parenchyma.

Clinical symptomatology is usually unspecific, showing symptoms of intracranial mass and, less frequently, encephalitis and cranial nerves involvement. Very seldom the lymphoma exhibits extension towards the cranial cavity. In our study, as previously described, the patients experienced migraine and other nonspecific symptoms, according to the tumor topography, and a case of ocular involvement with II and III pair extension and low cranial nerves involvement has been observed.

These lesions are supratentorial in a 78% of the patients, usually unique and with hemisphere localization. In 55% of the cases the PCNSL are found in the deep white matter, 18% at the corpus callosum (11,12).
Likewise in the literature cited we have found 80% supratentorial solitary lesions with 66% of them with hemisphere localization (2-3). Affection of the deep gray matter (basal ganglia, thalamus, and hypothalamus) was observed in the present work in a similar percentage to that reported in the literature. Nevertheless, we found a slightly higher corpus callosum affection. The average size of the PCNLS was 30 mm, but due to its infiltrative pattern the mass effect of this neoplasia was less than expected for the lesion size, comparing with other tumors. Perilesional edema was observed in 90% of the cases, the majority being between mild and moderate, and it was severe only in two cases.

Lesions were multiple in 16% of the patients. This finding is more common in immunodepressed subjects, who were not included in this study.

Conventional images

In computed tomography (CT) the invasion of the CNS by lymphoma is usually seen as a spontaneous dense lesion (which can even simulate a hematoma), with well-defined edges and reinforcement after the administration of the contrast. However, negative results in a CT don't rule out the diagnosis of lymphoma (8).
With MRI, we can observe 3 imaging patterns described for this tumor:

- **Parenchymatous pattern**: lesions well-defined, in round or oval configuration. In T1-WI they are slightly hypointense or isointense in relation to gray matter and produce minimal mass effect in relation to their size. In T2-WI, iso/hypointense signal is commonly surrounded by hyperintense edema. The presence of intratumoral necrosis is a rare finding, more likely detected in immunosuppressed patients. Areas of hemorrhage or calcification have not been seen.

  High cellular tumors usually show restricted diffusion (they are hyperintense in diffusion and hypointense in ADC maps), this is an useful characteristic for distinguishing them from glial tumors and the majority of metastatic tumors.

  The post-contrast enhancement tends to be nodular and homogenous in immune-competent patients, in contrast to irregular and heterogeneous enhancement in immune-compromised patient.

- **Meningeal pattern**: is less frequent than the parenchymatous pattern. It is produced by involvement of the intracranial or intradural pachymeninges or leptomeninges. It is most likely to be detected in secondary lymphoma or in immunocompromised patients. When PCNSL involve the dura, can simulate a meningioma because their extra-axial location and appearance.

- **Cranial nerves affection pattern**: it is infrequent pattern, only described for the PCNSL. They can be solitary or multiple lesions.

  One of the characteristics of lymphoma dissemination is its tendency to occupy the Virchow-Robin spaces, from where it extends towards the ependyma, the meninges or both. Even when this is a characteristic invasion pattern of PCNSL, is also common in other tumoral or infectious pathologies.

**MRS**

Although lymphomas may show some radiological signs that are quite characteristic (localization, post-contrast homogenous enhancement, diffusion restriction and involvement of the Virchow-Robin perivascular spaces), in some cases, the findings from the conventional MRI are inconclusive (atypical localization, extensive peritumoral edema, etc.). In these situations, advanced MRI techniques (diffusion, perfusion and MRS) can substantially increase the sensitivity and specificity of the diagnosis and are useful in the differential diagnosis with other entities like glioblastoma multiforme (GBM).

MRS Spectroscopy is a technique that permits determining of the tumor's biochemical profile and provides physiological data, as well as the information of its chemical composition. From the integration of this functional information and the data provided by conventional MRI, a better tumor characterization may be obtained that eventually can be used as a guide for the biopsy.

The sequences most frequently performed in the tumor protocol are multivoxel with TE intermediate 135 and TE short 30. The acquisition data obtained are analyzed at a work station and the metabolites most commonly evaluated are: Creatine (Cr), N-acetylaspartate (NAA), Choline (Cho), Lactate and Lipids.

  The characteristic neo-proliferative pattern consists of a decrease in NAA (neuronal integrity marker) and an increase in Cho (associated with the increase in cellularity and
membrane biosynthesis). Although it is not histological specific to a given tumor lineage, the degree of increase in Cho may be related to the histological tumor aggressivity (15).

The lipids peak can be observed in the lymphomas, as well as in necrotic glioblastomas and in the vast majority of the metastases, but not in the solid areas of glioblastomas (GBM).

It is believed that the lipids are related to the high membrane turnover; therefore, their finding in a solid tumor without necrosis and with post-contrast enhancement is highly suggestive of lymphoma (16).

Lymphomas and GBM share a similar spectroscopic pattern at the peritumoral level; that is, in the peritumoral regions, a Cho peak is visible as well as a NAA decrease outside the margins of the focal enhanced tumor. This peritumoral pattern indicates diffuse infiltration and it is not observed in metastasis (15).

As a result, when conventional MRI is inconclusive, through MRS it is possible to differentiate lymphomas from other tumors like GBM, because this highly aggressive tumor does not present a lipids peak in its solid portion, and from metastasis, because they do not display peritumoral infiltration.

After quantifying the metabolites, the metabolic color maps can be used as a guide for biopsy.

Conclusion

The characterization of PCNSL has become of particular interest in recent years due to the incidence increase in the immune-competent and the immune-suppressed patients. Although this tumor may present characteristic radiological findings in conventional MRI (localization, imaging patterns, restricted diffusion), radiologists should be aware of advanced MRI techniques (perfusion, spectroscopy) that can provide complementary information useful in diagnosis.

MRS Spectroscopy by MRI can be of great help as a complement in these situations due to the characteristic presence of the lipids peak. This spectroscopic information in a solid intra-axial tumor with contrast enhancement, would suggest the possibility of a lymphoma. Early diagnosis of this pathology is of vital importance to avoid the use of steroid medication before doing the biopsy with no need of surgical resection which in this tumor does not improve the prognosis.
Fig. 1. Patrón parenquimatoso característico del linfoma. Axial FLAIR y axial en secuencia ponderada para T2 donde se observa una formación hiperintensa a nivel de la región periventricular posterior que compromeete el espleno del cuerpo calloso. También se aprecia moderado edema perifocal y escaso efecto de masa.

Fig. 2. Linfoma de localización profunda. Difusión y ADC. Se observa una masa centrada en la región esástico-capsular en el hemisferio izquierdo que se extiende comprometiendo el tálamo y produciendo compresión de la prolongación frontal del ventrículo lateral. La imagen presenta restricción de la difusión, observándose hiperintensidad en la secuencia de difusión e hiperintensidad en su correlato ADC, lo que es característico de los tumores densamente celulares, entre ellos el linfoma.
Fig. 3. Linfoma con localización en la sustancia blanca profunda. Axial en secuencia ponderada para T1 sin y con contraste. Se evidencia una lesión hipointensa en secuencia ponderada para T1 en el sector medial temporoparietal derecho, adyacente a la convexidad. Ella presenta un intenso refuerzo homogéneo con el contraste.

Fig. 4. IPSNC con afectación paraimpígena exclusiva. Axial en secuencia ponderada para T2 y coronal en secuencia ponderada para T1 con contraste. Se observa en el sector anterior de la región frontal izquierda una formación extracortical, hipointensa en secuencia ponderada para T2 que presenta un refuerzo homogéneo con el contraste. Si bien la imagen es sugestiva de un meningioma, también puede observarse en los linfomas.
Fig. 5. Linfoma con patrón de afectación de pares craneanos. Corte axial en secuencia ponderada para T1 con contraste donde se observa afectación del II y III par y de pares craneanos bajos (IX y X) en forma bilateral, evidenciada por un refuerzo a ese nivel.

Fig. 6. Diseminación del LPNSNC a través de los espacios perivascularares. Corte sagital en secuencia ponderada para T1 con contraste donde se evidencia un refuerzo siguiendo los espacios perivascularares de Virchow-Robin. Constituye una vía de diseminación clásica de este tumor que en nuestro trabajo se observó en un 20% de los pacientes.
Fig. 7. Espectroscopia con tiempo de eco intermedio 135 programada sobre un volumen con contraste. Se observa un pico de Cho con disminución del NAA, patrón característico de proceso neoformativo. También se visualiza un pico de Ttp, el cual es más evidente en el tiempo de eco corto 30. Este pico en un tumor sólido es altamente sugestivo de infarcta.

Fig. 8. Mapas espectrales con tiempo de eco 135 y 30 del mismo paciente. En el mapa color se observa en rojo el sitio de localización del pico de colina en el tiempo eco intermedio y del pico Ttp, lo que es característico de un infarcta.