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Experience of Non-Hodgkin's Lymphoma in the Central Nervous System Presented as Neurological Deficit from 2017-2021 in a Medical Center in Mexico City

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ABSTRACT

AIM: Primary central nervous system lymphoma (PCNSL) is a neoplastic entity associated with B symptoms. Note that the prevalence of intramedullary presentation is 0.02% of reported cases.

Aim: This study was designed to show the oddity of PCNSL and illustrate the histopathological and magnetic resonance imaging (MRI) characteristics of this disease entity.

MATERIAL and METHODS: We obtained the histopathological diagnosis through stereotactic biopsy, and all lesions were resected at the Department of Neurosurgery, Centro Medico Nacional 20 de Noviembre.

RESULTS: We identified and included six lymphoma cases in a 5-year period: none of the patients had human immunodeficiency virus (HIV) infection; none were Epstein–Barr virus (EVB)-positive; all of them received chemotherapy and radiotherapy; and the survival rate was ≥1 year.

CONCLUSION: Regarding the clinical data, the symptoms entirely depended on the location of the lesions. If the symptoms suggest malignancy, such as fever, weight loss, and night sweats, we searched for causes, other than the usual ones, to find a diagnosis. This is a rare disease, which responds well to medical treatment and has a survival greater than 5 years in some cases.

KEYWORDS: B symptoms, Biopsy, Central nervous system lymphoma, Hodgkin's lymphoma

ABBREVIATIONS: CNS: Central nervous system, **PCNSL:** Primary central nervous system lymphoma, **PISCL:** Primary intramedullary spinal cord lymphoma, **DLBCL:** Diffuse large B-cell lymphoma, **MRI:** Magnetic resonance imaging

INTRODUCTION

The most frequent lymphoma in the central nervous system is the non-Hodgkin type variety, of which the variant with B cells stands out among the others. The incidence of this pathology is approximately 2–3 per 100,000 inhabitants, according to the literature. Primary central nervous system lymphoma (PCNSL) is a rare and aggressive disease. New information is acquired as this pathology is confined to the brain parenchyma, eyes, spinal cord, or leptomeninges without systemic involvement. On magnetic resonance spectroscopy, lymphomas differ from other glial tumors, including glioblastomas, by massively increased lipid resonances and markedly higher choline/creatine and choline/N-acetyl-aspartate ratios. This study was designed

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to determine the oddity of Hodgkin's lymphoma and illustrate its histopathological and magnetic resonance imaging (MRI) characteristics.

MATERIAL and METHODS

In this study, we report a series of patients with lymphomas, all of which have affected the central nervous system and one included the spinal cord. We collected the data using our computer-based system (SIAH) and obtained the images using TESI, an Internet-based software in our medical center. All biopsy procedures were performed by only one personnel, and all biopsy materials were evaluated by one neuropathologist. Stereotactic ring fixation was performed under local anesthesia (0.4-mL dexmedetomidine, 10-mL bupivacaine, and 4-mL lidocaine 2%) using the scalp block technique. An 8–10-mm burr hole was used as the entry point, the pial surface was observed, and biopsy samples were obtained using a standard sedan-type needle.

RESULTS

The patients evaluated in this study included five men and one woman, aged between 40 and 85 years. The initial imaging study used was simple computed tomography (CT). All patients underwent MRI; however, no spectroscopy was performed.

All patients had arterial hypertension; their symptoms started 1–6 months before they received a clinical diagnosis; they presented with motor deficits; and they had blood cell alterations, such as anemia, thrombocytopenia, and pancytopenia.

None of the patients had human immunodeficiency virus infection; none were Epstein–Barr virus (EVB)-positive; however, the overexpression of T-cells was observed, which might have been a risk factor for PCNSL. All patients received chemotherapy and radiotherapy, and the survival rate was ≥1 year. All samples (only six patients in a 5-year period) were evaluated by the same neuropathologist, and in most cases, the neuropathologist could perform the procedures using the same stains. Our outcomes are similar to those of other manuscripts: this disease is rare and can involve the spinal cord. PCNSL involving the spinal cord is infrequent; in a 5-year period, we could only identify one patient.

Limitations

Retrospective design, single center experience were major limitations of the present study. In addition, the sample size was only 6 patients not all our patients had all the MRI sequences, none had spectroscopy.

DISCUSSION

Central nervous system lymphomas are primarily categorized into two groups: secondary and primary. The most frequent type is the secondary type, and the primary one, known as PCNSL, is a very specific type of lymphoma that only appears in few tissues, such as the eyes, leptomeninges, spinal cord, and brain. The main criterion for diagnosis is that there is no evidence of it outside the CNS at the primary diagnosis. The exact incidence of PCNSL may vary according to region in America and accounts for approximately 1%–5% of brain tumors; this rate increases among immunocompromised patients (7).

The pathology of PCNSL has the following features: the distinctive histological features include perivascular tropism and centroblastic cytology (Figure 1). As expressed by Citterio, most PCNSL (>95%) are diffuse large B-cell lymphomas (DLBCL) (Figure 2); express B-cell markers, such as CD20, CD19, and CD79a, and monotypic surface immunoglobulin light chains; and correspond to the non-germinal center B-cell-like DLBCL subtype with a CD10– BCL6+ IRF4/MUM1+ pattern (6) (Figure 3).

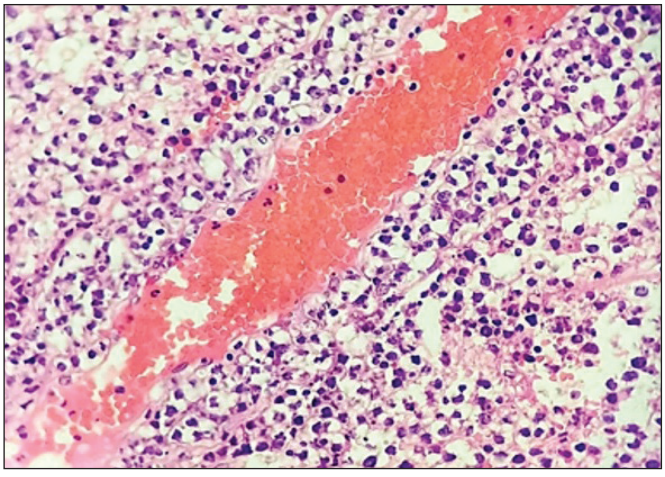

Figure 1: Hematoxylin and eosin stain 40×. Presence of a hypercellular lesion, with atypical lymphocytes, which at higher magnification show an angiocentric and angioinvasive arrangement, with surrounding eosinophilic areas of intact brain parenchyma.

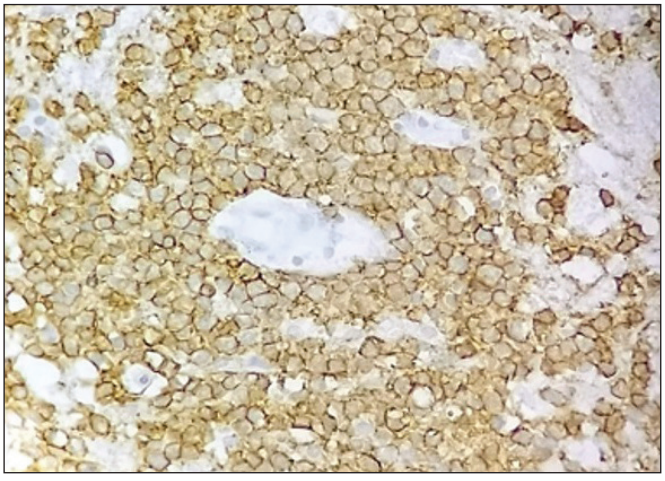

Figure 2. CD20 immunostaining, 40×. Immunostaining antibodies against CD20 highlight the atypical and large lymphoid cells around the vessels, favoring the diagnosis of diffuse large B-cell lymphoma (DLBCL).

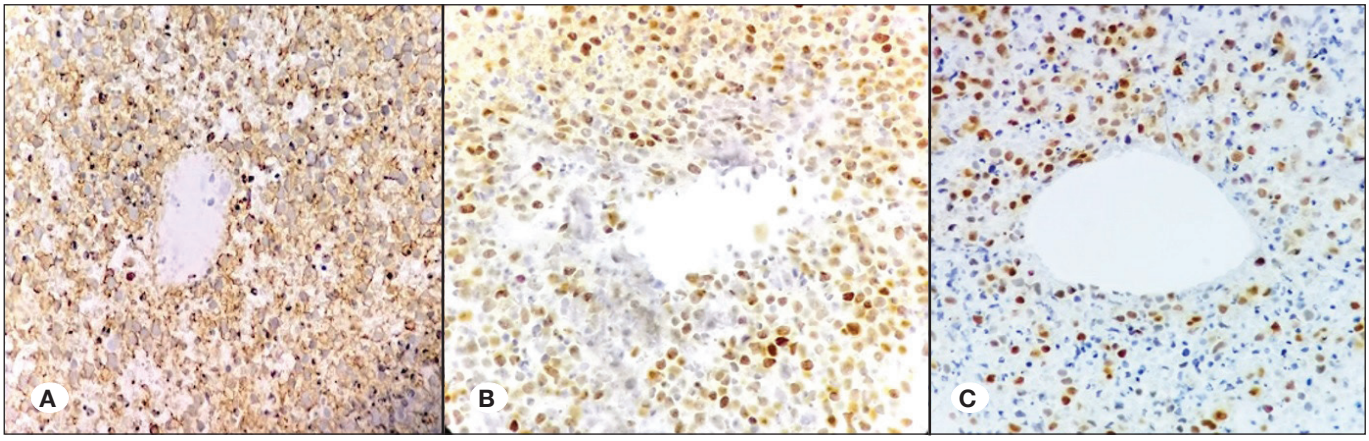

Figure 3: Positive immunostaining with CD20 **(A)**, Bcl6 **(B)**, and MUM1 **(C)**, in neoplastic cells, showing an angiocentric arrangement, 40×. Immunohistochemical staining with antibodies against CD20, Bcl6, and MUM1 highlights the atypical and large lymphoid cells around the vessels, favoring the diagnosis of diffuse large B-cell lymphoma, with an activated phenotype (without germinal center), because the expression of MUM1 supports this phenotype, regardless of Bcl6 expression.

The timely diagnosis of lymphoma is critical for decision-making for patients. According to the immune status of the patients (immunocompromised or immunocompetent), PCNSL often has a distinctive appearance because of its hypercellularity, high nuclear/cytoplasmic ratio, disruption of the blood–brain barrier, and its predilection to the periventricular and superficial regions, often in contact with the ventricular or meningeal surfaces (9).

Lesions are typically hypointense or isointense on unenhanced T1-weighted MRI and isointense to hyperintense on T2-weighted MRI but are often hypointense to gray matter. Most lesions show moderate to marked contrast enhancement on CT and MRI—the so-called ring enhancement. In our patients, we found the following: intramedullary hypointense T2 image (Figure 4), and we demonstrated that after treatment (Figure 5), T1-weighted imaging with gadolinium enhancement showed some ring enhancement, peripheral edema not corresponding to the size of the lesion, and restricted diffusion visible in the apparent diffusion coefficient (ADC) map in the same patient (Figure 6). In the first left image in Figure 6, a hyperintense lesion with ring enhancement was observed on a T1-weighted image, which does not displace the midline but lowers the posterior horns of the lateral ventricles, predominantly the right one, and a patchy pattern was observed.

In the middle figure, on axial fluid-attenuated inversion recovery (FLAIR), abundant perilesional edema was observed, with central necrosis. On the ADC map, restriction to diffusion was observed; ADC is a sensitive measure of microscopic diffusion of unbound extracellular water molecules and is an extremely sensitive test to detect cerebral ischemia (2).

In contrast, one of the rarest cases of lymphoma is the primary intramedullary spinal cord lymphoma (PISCL). The incidence of this pathology is approximately 1% of all lymphomas involving the central nervous system. It is mentioned that the age range is associated with the fifth decade of life. In this study, one of the patients presented with PISCL in the fourth decade of life, involving the thoracic region. In Moussaly's study, 403 patients were reviewed, of whom only one had non-Hodgkin's lymphoma, which corresponded to 0.3%. Regarding their findings, the most frequent subtype of lymphoma was DLBCL, corresponding to 40% of all cases reviewed (8).

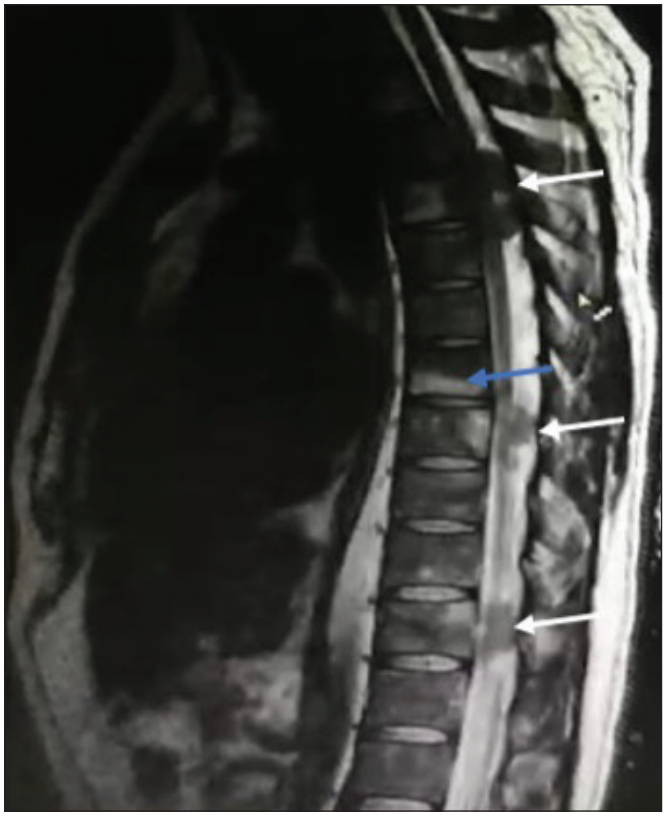

Figure 4: Sagittal MRI, T2-weighted, thoracic intramedullary hypointense image (white), and hyperintense image in vertebral bodies (blue).

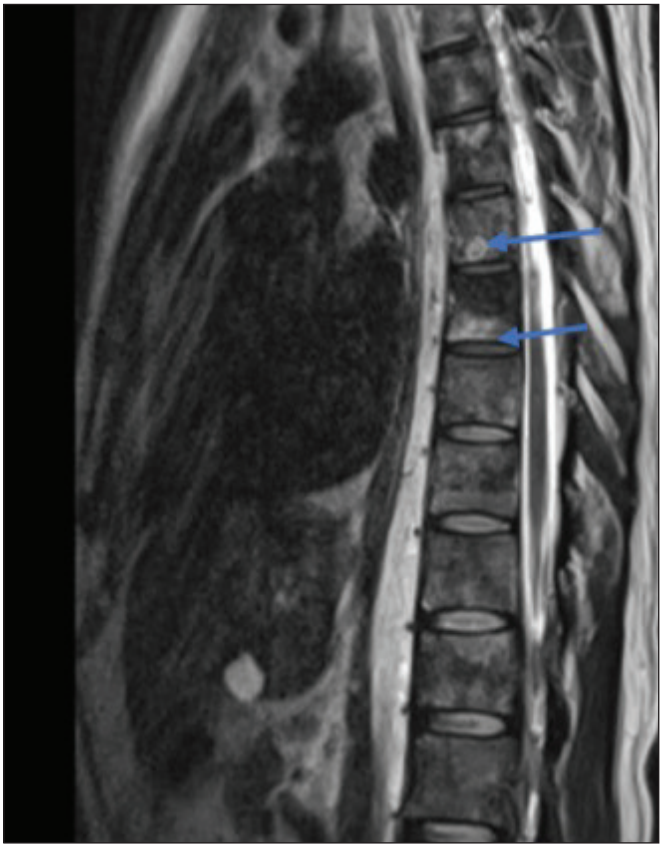

Figure 5: Sagittal MRI, T2-weighted, 1 month after treatment, without the presence of intramedullary images, even with the presence of a hyperintense image in vertebral bodies (blue).

PCNSL is a rare extranodal lymphoma; this pathology constitutes a diagnostic challenge because it can resemble other pathologies, which makes it impossible to take biopsies in some cases, and even taking the biopsy may have an inconclusive result. Yet, as mentioned by several authors, when biopsies were performed, they were inconclusive or the material was insufficient. In the case presented (3), decompressive laminectomy was performed and showed positivity for CD20, contrasting with our patient. Differences were found in the aforementioned phenotypes CD30+, CD20+, and CD3–, which were the result of immunohistochemistry. For the clinical data, neurocognitive symptoms are the most common presenting clinical features; for instance, lymphomas with ocular involvement may present with eye pain, blurred vision, and floaters; other symptoms entirely depend on the lymphoma's location. A lumbar puncture should be performed if not contraindicated, and cerebrospinal fluid should be assessed by flow cytometry, cytology, and immunoglobulin heavy-chain gene rearrangement (4).

In our patients, a histopathological diagnosis was made using stereotactic biopsy, and one lesion that was accessible was resected. Defining the response to treatment in PCNSL requires the assessment of all sites involved. The International PCNSL Collaborative Group has established response criteria that have been adopted by most prospective clinical trials (Table I) (3).

Surgical resection is a controversial topic, considering the infiltrating and multifocal nature of PCNSL; however, surgery can be used to reduce intracranial pressure in patients with brain herniation associated with large lesions. In contrast, radiotherapy and chemotherapy are the initial treatment modalities with efficacy for systemic lymphomas, such as

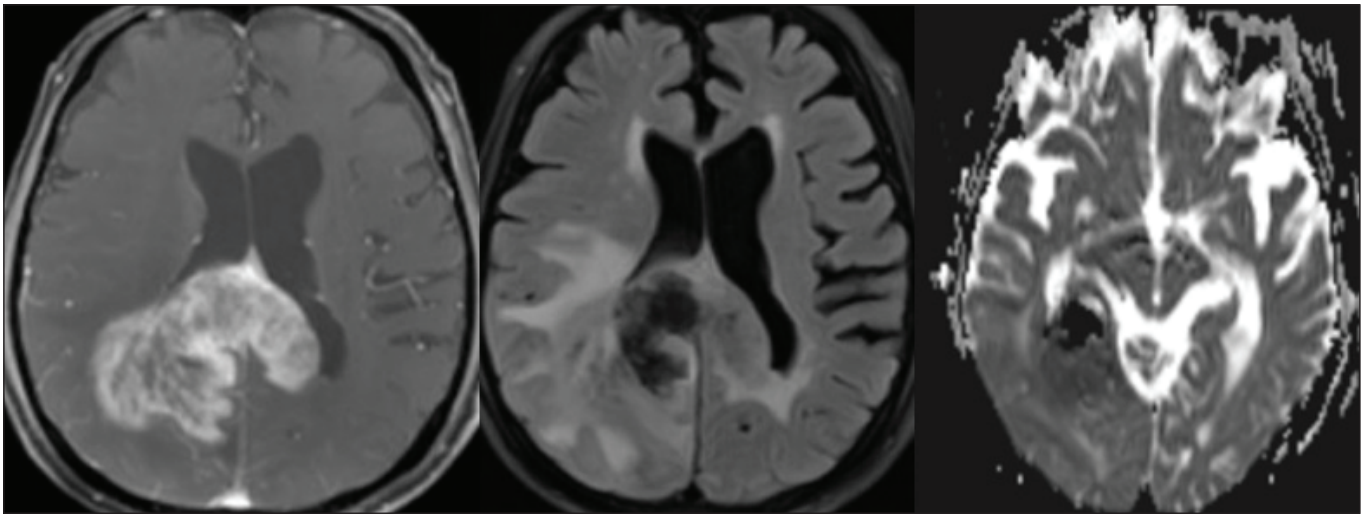

Figure 6: T1-weighted imaging. We identify a lesion that stands out and is observed to be hyperintense to the administration of gadolinium, which does not displace the midline but lowers the posterior horns of the lateral ventricles, predominantly the right one. A patchy pattern is observed. On the middle, on axial FLAIR, abundant perilesional edema is observed, with central necrosis. In the ADC map, restriction to diffusion is observed, corresponding to a lymphoma. ADC is a sensitive measure of microscopic diffusion of unbound extracellular water molecules and is an extremely sensitive test to detect cerebral ischemia.

Table I: International PCNSL Collaborative Group Consensus Guidelines for the Assessment of Response in PCNSL5

Response	Brain Imaging	Steroid Dose	Ophthalmologic Examination	CSF Cytology
Complete response	No contrast enhancing disease	None	Normal	Negative
Unconfirmed complete response	No contrast enhancing disease	Any	Normal	Negative
	Minimal enhancing disease	Any	Minor RPE abnormality	Negative
Partial response	50% decrease in enhancement	NA	Normal or minor RPE abnormality	Negative
	No contrast enhancing disease	NA	Decrease in vitreous cells or retinal infiltrate	Persistent or suspicious
Progressive disease	25% increase in enhancing disease Any new site of disease	NA	Recurrent or new disease	Recurrent or positive
Stable disease	All scenarios not covered by responses above			

Table II: Imaging, Clinical, and Demographic Aspects of Our Case Series

Patient	Lymphoma localization	Age	Gender	Comorbidities	Clinical Data
Case 1	Corpus callosum	59	Male	Arterial Hypertension	Motor
Case 2	Corpus callosum	85	Male	Arterial Hypertension	Motor
Case 3	Periventricular	63	Male	Arterial Hypertension	Motor
Case 4	Periventricular	64	Female	Arterial Hypertension	Motor
Case 5	Occipital lobe	54	Male	Arterial Hypertension	Visual
Case 6	Spinal cord	41	Male	Arterial Hypertension	Inferior Motor Neuron

cyclophosphamide, doxorubicin, vincristine, and prednisone. We showed post-treatment images of the intramedullary lymphoma with great results. In a trial of a combination of chemotherapy and radiotherapy, no difference in survival was observed between patients aged ≥60 years who decided to undergo radiotherapy and those who chose to delay it.

Note that relapse was observed less frequently in patients who received upfront radiotherapy (1 of 12) than in those who delayed it (10 of 22) (10). Finally, there are many case reports involving lymphoma in uncommon brain areas, such as a mass in the cerebellopontine angle, which is an exceptional site affected by this entity. It is estimated that there is a leptomeningeal infiltration in 20% of patients (5). PCNSL is extremely rare; of all our patients, none had HIV and none were Epstein–Barr virus-positive, even though the overexpression of T-cells might have been a risk factor for PCNSL (1).

CONCLUSION

Considering that the incidence for PCNSL is 2.4 per 100,000, it is important to mention the particularity of this lesion, particularly those involving the spinal cord. The imaging characteristics of the lesions are of great help to reach a clinical diagnosis. PISCL is a pathology that mimics other similar ones, such as spinal compression because of disk protrusion, tumors, meningiomas, metastases, or infectious diseases. Therefore, the treatment is focused on identifying comorbidities and signs and symptoms early. Regarding the clinical data, it is imperative to show that these signs and symptoms entirely depend on the location of the lesion (Table II). If symptoms suggest malignancy, such as fever, weight loss, and night sweats, we should search for causes, other than the usual ones, to find a diagnosis.

AUTHORSHIP CONTRIBUTION

Study conception and design: PCO
Data collection: PCO
Analysis and interpretation of results: GHKP
Draft manuscript preparation: GHKP
Critical revision of the article: SOL
All authors (PCO, GHKP, MBA, JAA, PMA, SOL) reviewed the results and approved the final version of the manuscript.

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