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Intraparenchymal Primary CNS Marginal Zone Lymphoma: A Rare Disease or Rather a Highly Misdiagnosed Condition? A Case Report and a Literature Review

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Marginal zone lymphoma; MALT lymphoma; primary CNS; Intraparenchymal

1. Abstract

1.1. Context: Marginal zone lymphoma, also known as mucosa associated lymphoid tissue (MALT) lymphoma, is a low-grade neoplasm generally with good prognosis and treatable with radiotherapy – rarely has its initial presentation in the CNS. When it does, a dural presentation is more common. However, it represents an even more infrequent condition when it appears as a primary intraparenchymal lesion and tends to be misdiagnosed: a potential problem because, almost always, a less invasive approach is adequate as treatment.

1.2. Goal: This article brings forward a rare case of intraparenchymal primary CNS marginal zone lymphoma (PCNS MZL), aiming to add information to the literature about this atypical case and its diagnostic and therapeutic approach.

1.3. Method: We made a case report and a literature review.

1.4. Results: This article describes a rare condition that was reported only in few other studies, as well as the process of diagnosis and treatment, which led to a partial remission of the lesion and to a reduction of clinical features.

1.5. Conclusion: Intraparenchymal PCNS MZL is a rare and, possibly, underdiagnosed condition and should be remembered when facing an intraparenchymal brain mass. Further studies are required to develop protocols that ensure a more precise diagnostic reasoning considering this condition.

2. Introduction

Primary CNS lymphomas are rare. The vast majority of cases in immunocompetent patients comprise the high grade Diffuse large B-cell lymphomas (DLBCLs), that typically are intraparenchymal. Accounting for the minority of lymphoma cases with initial presentation in the CNS, we have low grade lymphomas, that typically do not involve cerebral tissue and have predominant dural location, resembling meningiomas. [1, 2] [5]. This article is about an extremely rare presentation of an intraparenchymal primary CNS lymphoma: Primary CNS Marginal Zone Lymphoma (PCNS MZL) with no dural presentation – an indolent, low-grade lymphoma. [1-3] [5] MZL is also known as Mucosa Associated Lymphoid Tissue (MALT) lymphoma [11].

We provide a case report and a literature review of intraparenchymal PCNS MZL with a search that included all combinations of the following terms in the baselines PUBMED, MEDLINE and LILACS: ((marginal zone lymphoma) OR (mucosa-associated lymphoid tissue lymphoma) OR (MALT-type lymphoma) OR (MALT lymphoma) OR (MALToma) OR (low grade B cell lymphoma)) AND ((CNS) OR (Central Nervous System)) AND ((primary) OR (initial presentation)) AND (case report). After the primary selection, we excluded articles that didn´t fit the criteria "intraparenchymal marginal zone lymphoma with initial presentation in the CNS" by analyzing titles and abstracts – that resulted in just five case reports.

3. Case Report

The patient is a 40-year-old woman HIV negative with a history of seizure and headache. At admission, she presented with right frontoparietal headache and focal seizure with motor activity in the left upper limb, without impairment of awareness. At physical examination, no abnormalities but the focal seizure were found. Enhanced MRI disclosed a right frontoparietal lesion with the following features: infiltrative and expansive cortical-subcortical formation with high signal intensity on T2 and FLAIR (Figures 1A and 2-a). Enhanced MRI also showed high signal intensity on

T2 and FLAIR that could correspond to edema or infiltration extending to the right posterior internal capsule and right putamen (Figure 2-A). PET-SCAN revealed neither bone lesions or hypercaptating images. SPECT (single-photon emission computed tomography) showed low metabolic activity in the area of the tumor as well as erasement of the sulcus in the cortical related area (Figure 3). The search for HIV, Hepatitis B and C, Syphilis, and Tuberculosis was negative. Serum and urine protein electrophoresis revealed no monoclonal spike. Measurement of serum IgG, IgA and IgM revealed normal levels. The levels of serum beta-2 microglobulin and LDH were respectively 2,02 (nl) and LDH 170 (nl). Immunophenotyping of bone marrow also was revealed normal. The analysis of the CSF showed the following features: Immunoelectrophoresis with no monoclonal band; AFB negative; panel-based PCR for multiple viral pathogens negative; and biochemical tests (glucose and protein levels) normal. Genetic analysis revealed absence of the mutation p.L265P in the gene MYD88. Pathologic examination of a core needle biopsy sample revealed lymphoid proliferation with plasm cell differentiation and atypia – a result that, combined with SPECT images, is consistent with low-grade lymphoma.

Immunohistochemical assays showed that the tumor cells were: positive for Kappa; positive on numerous cells for BCL-2, CD20 and MUM; diffusely positive for CD79a; and negative or non-significant for BCL-6, CD10, CD23, CD3, CD5, CD56, Ciclina D1, c-Myc, Lambda and SOX-11. Also, the assay showed that plasm cells were positive on numerous cells for CD138. The immunohistochemical assay report highlighted: occurrence of small lymphocitic infiltration in the perivascular compartment of the brain tissue sample; evidence of light-chain restriction for Kappa immunoglobulins of the plasma cells in the tumor; Ki-67 labeling index of 15%; high lymphoid expression of CD20; plasm cell component showing co-expression of CD138 and MUM1; and no abnormal expression of CD10, CD5, D1 cyclin or SOX-11 (Table 1). The differential diagnosis after immunohistochemical assay included intraparenchymal primary CNS marginal zone lymphoma (PCNS MZL) and lymphoplasmacytic lymphoma (LPL). After integrating the results of all the exams, the tumor was then diagnosed as a probable PCNS MZL. The patient was then started on corticosteroids (to control the perilesional edema) and antiseizure medicines. Also, started on focal radiotherapy (4000 CGY). The treatment occurred during 8 weeks, with no complications reported. Following 7 months from the first MRI and the SPECT (Figures 1-A, 2-A and 3) – performed in June, 2020 –, new imaging exams showed that the tumor has stabilized and the enhancement and the edema have reduced (Figures 1-B and 2-B).

After 3 months from the initial presentation, the patient demonstrates a regression in clinical features, without seizures or headaches.

Antibody	Result
BCL-2 (124)	Positive on numerous cells
BCL-6 (PG-B6P)	Negative (internal control positive)
CD 10 (56C6)	Negative (internal control positive)
CD 138 (M115)	Positive on numerous plasm cells
CD20 (panB) (L26)	Positive on numerous lymphocytes
CD 23 (CD23)	Weakly positive on rare cells (non significant)
CD 3 (pan T)(policlonal rabbit)	Negative (internal control positive)
CD 5 (4C7)	Negative (internal control positive)
CD56 (123C3)	Negative (internal control positive)
CD 79a (JCB117)	Diffusely positive
Ciclina D1 (EP12)	Negative (internal control positive)
c-Myc (EP121)	Positive on rare cells (less than 5%) (non significant)
Kappa (policlonal rabbit)	Positive
Ki67 (MIB-1)	Positive on 15% of cells
Lambda (Policlonal rabbit)	Negative (internal control positive)
MUM (MUM 1P)	Positive on numerous cells
SOX-11 (MRQ 58)	Negative (internal control positive)

Table 1: Immuno histochemical assays

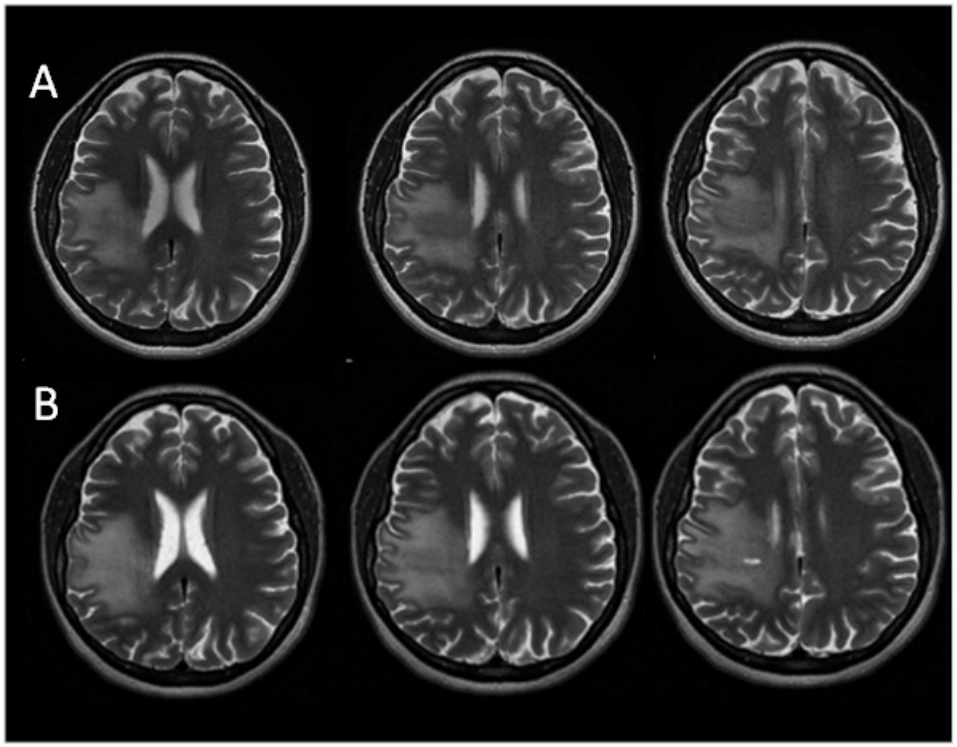

Figure 1: Axial T2 MRI images with enhancement. A: Images before treatment, showing infiltrative and expansive cortical-subcortical formation with high intensity. B: Images after treatment, showing that the tumor has stabilized and that the edhema and the enhancement have reduced.

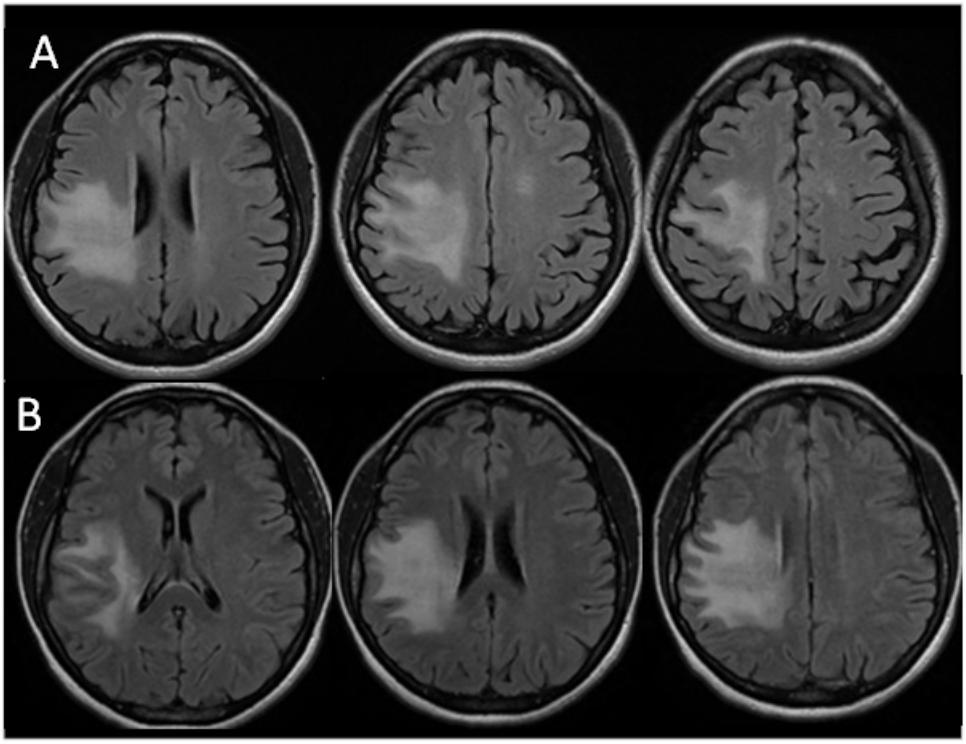

Figure 2: Axial T2-flair MRI images with enhancement. A: Images before treatment, showing infiltrative and expansive cortical-subcortical formation and a high signal (arrow) that could correspond to edhema or infiltration extending to the right posterior internal capsule or right putamen. B: Images after treatment, showing that the tumor has stabilized and that the edhema and the enhancement have reduced.

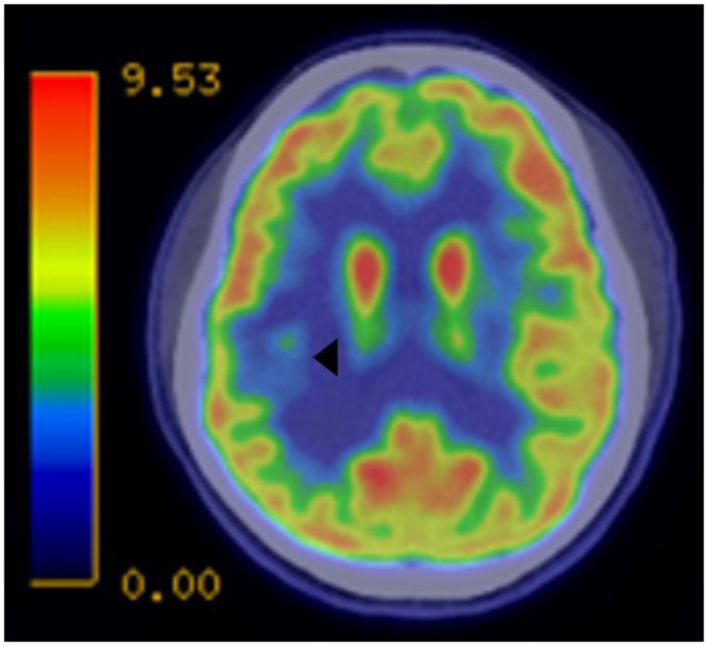

Figure 3: Axial SPECT image obtained at the time of diagnosis, showing low metabolism in the anatomic localization of the tumor, pointed out with the balck arrow. Notice the erasement of the cerebral sulcus in the cortical area, indicating occurrence of edhema.

4. Discussion

PCNS MZLs are a rare type of low-grade non-Hodgkin lymphoma and are usually indolent neoplasms with favorable prognosis. They can be divided according to the location of the mass in the CNS: extra-axial dural-based, resembling meningiomas (the most common presentation); or intraparenchymal. [8] When compared with secondary CNS MZL, the primary presentation features as a lower-grade disease at diagnosis, without B symptoms and with better therapeutic response and outcomes. [9] Women represent the majority of described cases of PCNS MZL, with a median age at diagnosis around 60-year-old. [8, 9] In general, most common presenting features are headaches, seizures and visual changes. [8] It is important to highlight that an Extranodal MZL, also known as MALT lymphoma, is composed of neoplastic B-cells that typically infiltrate epithelial tissues, generating "lymphoepithelial lesions". The infiltrating cells consist of small lymphocytes, marginal zone cells, monocytoid B-cells and often plasm cells. [11] But, as PARK et al (2008) point out, the CNS has no mucosa nor MALT tissue. So, to explain the initial presentation of MZL as intraparenchymal, it has been hypothesized that the epithelial substract for the tumor could come from choroid plexus or, for a dural presentation of MZL, from meningothelial cells. [1] It has been reported that MALT-type tissue can be formed under inflammatory conditions in the CNS, leading to a potential site for MALT-lymphoma in association with choroid plexus or meningothelial cells. [2,8] Cook et al (2019) points out that there is a strong association between MZL and some infections and autoimmune disorders. [11] In this sense, PONZONI et al (2011) presented a case of PCNS MZL in the setting of an infection of Chlamydophila psittaci and ITOH et al (2001) reported another in the setting of Sjogren´s syndrome. [4,3] To our knowledge, only seven cases of intraparenchymal PCNS MZL (included ours) have been reported in the literature. [1-5] [7] Among them, initial presentation varied: facial nerve palsy, right-sided weakness, dizziness, dysarthria, memory disturbance, gait disturbance, urinary incontinence, tinnitus, nausea, vomiting, gradually progressing headache, buccal rim deviation, fever, progressively worsening dysnomia, numbness of arms and legs, slurred speech, blurry vision and hearing loss. [1-5]

It is crucial to point out that, for immunocompetent patients, the most common low-grade lymphomas of the CNS are LPLs and MZLs [5]. They are similar and must remain as differential diagnosis for each other. [2] [5] In this case, the diagnosis of LPL was excluded because no monoclonal spike was found in the blood stream and in the CSF. Furthermore, the search for MID-88 was negative.

Also, regarding the diagnosis, the results of SPECT (Single-photon emission computed tomography – a nuclear medicine technique used for neuromolecular imaging, that is useful to study some tumor biological behaviors [10]) were critical to determine the metabolism degree of the neoplasm cells in a noninvasive way and then to establish its classification as a low-grade lymphoma – a very important data with respect to diagnosis, treatment and prognosis.

Typically, patients with PCNS MZL undergo surgery for biopsy, followed by treatment after the histological diagnosis is established. Treatment depends on the case and could be surgery, radiation, chemotherapy or a combination of them. [1][6] Sato et al (2020) point out that, among these options, radiation therapy has been reported as the favorable and definitive treatment, with a total dose recommended of 30-36 Gy. The group also points out that for well-defined CNS-MZL, focal radiation therapy has been indicated but, for ill-defined tumor, with potential dissemination due to leptomeningeal involvement, whole brain radiotherapy (WBRT) or intrathecal chemotherapy should be indicated. [6] PARK et al (2008) cite as chemotherapeutic agents commonly used: fludarabine or methotrexate as single agent or the combinations of cytarabine with methotrexate or procarbazine with vincristine, cytarabine and methotrexate. [1]

According to ITOH et al (2001), many cases of pseudolymphomatous lesions (plasma cell granuloma; pseudolymphoma; atypical plasma cell granuloma; atypical lymphoid hyperplasia and inflammatory pseudotumor) could be reclassified into MALT lymphoma if immunochemistry and molecular studies were correctly performed. That´s why, although it is rare, the group defend the need to keep in mind a diagnosis of MALT lymphoma as a differential diagnosis in these cases. [3] Also, as a dural presentation, MALT lymphomas are very similar to meningiomas. [1] So, it is possible that PCNS MZL is a highly misdiagnosed condition. If so, it could lead to potential iatrogenic outcomes because in most cases the

condition is indolent and the treatment could be less invasive.

5. Conclusion

The case presented here represents one of those rare cases of intraparenchymal primary CNS marginal zone lymphoma. When we consider the characteristics of affected people (gender and age of onset, for example), the presenting features at diagnosis, the exams that were performed and the treatment modalities that were used, it corroborates with most of the findings in other articles about primary CNS MZL [8,9]. Nevertheless, considering the rarity of intraparenchymal presentation, the actual diagnostic reasoning usually omits this condition when facing a mass inside the brain tissue. In summary, besides its uncommonness, the intraparenchymal form of primary CNS MZL should be considered in the differential diagnosis of a brain mass.

6. Conflict of Interest

There are no potential conflicts to declare.

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