Primary central nervous system lymphoma and 5-aminolevulinic acid

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INTRODUCTION

Surgical resection of primary central nervous system lymphoma (PCNSL) is not routinely performed as its conventional management has regularly consisted of radiation treatment and chemotherapy after obtaining pathology diagnosis through biopsy. In addition, the role of 5-aminolevulinic acid (5-ALA)-induced fluorescence which has been established almost as protocol for malignant gliomas resection remains unexplored in PCNSL. Here, we describe two cases of PCNSL treated using 5-ALA-induced fluorescence-guided surgical resection with good clinical and radiological outcome.

CASE DESCRIPTION

We present two cases. They were in their sixties, a man (patient 1) and a woman (patient 2) without any significant medical history, who presented to our emergency department with headache.
Neurological examination was normal. Magnetic resonance image (MRI) of the brain demonstrated in both cases a solitary solid intraparenchymal mass in the right frontal lobe with perilesional edema. The lesions were hypointense in noncontrast T1-weighted images and hyperintense in T2-weighted images. After contrast administration, both lesions enhanced with a ring-like pattern [Figure 1]. There was restricted diffusion, and only in case 2, minor increment of relative blood volume on perfusion maps was evident (about 1.6 respect to the healthy contralateral white matter) [Figure 2]. Differential diagnosis included high-grade glioma, metastasis, and abscess; however, the presence of marked restricted diffusion forced us to consider PCNSL as a possible diagnosis as well.

As high-grade glioma leaded the list of differential diagnosis, 5-ALA-guided surgery was recommended. During the intervention, there was strong 5-ALA-induced tumor fluorescence in both cases. Surgery was done with the navigation system StealthStation™ S8 (Medtronic, Minneapolis, USA), and the area of 5-ALA fluorescence corresponds exactly with the gadolinium enhancement on MRI in both cases. Surgery was uneventfully carried on until 5-ALA-induced fluorescence was no longer evident [Figure 3]. Postoperative MRI confirmed total resection, presenting only milimetric remains in the surgical site in patient 2 [Figure 4].

Pathological examination confirms that both tumors were PCNSL. They showed diffuse lymphoid cell proliferation immunoreactive for B-cell marker but not for T-cell marker [Figure 5]. After surgery, an adjuvant chemotherapy treatment started. After an initial slight radiological worsening, whole brain radiotherapy was initiated. The patients presented a very good response to the treatment. After a 1 year follow-up, brain MRI shows no recurrence with complete remission and patients present with a Karnofsky performance status scale of 90.

**DISCUSSION**

PCNSL are rare and aggressive central nervous system (CNS) neoplasms. Radiologically, the lesions may be single or multifocal. The most common locations are subcortical regions (most frequent in frontal lobe) and periventricular structures. They usually enhance homogeneously after contrast administration and have restricted diffusion; however, in case of immunosuppression, the enhancement pattern may be more heterogeneous or even be absent. Neovascularization is not a prominent feature, as seen by low cerebral blood volume on perfusion studies.

Nowadays, the management of PCNSL consists of biopsy to obtain pathological diagnosis followed by chemotherapy and radiation therapy. Some authors have reported worse outcomes in patients who underwent surgical resection. However, these conclusions must be taken cautiously since most of these studies were done previous to the development of modern surgical techniques, chemotherapy and imaging.
New advances in surgical technology and adjuvant treatments have led to more aggressive approaches reconsidering the role of surgical resection in PCNSL. Bellinzona et al. could not demonstrate a clear benefit from surgery in all patients with PCNSL, but they suggested that it might be a subgroup of patients with large single space-occupying lesions and deteriorating neurological status who might benefit from it. Weller et al. performed a secondary analysis of the German PCNSL Study Group-1 trial, and, considering that there were no significant differences in the baselines characteristic of both study groups such as age and Karnofsky performance status, they concluded that progression-free survival and overall survival were significantly shorter in biopsied patients compared to patients.

**Figure 2:** The images a and b correspond to the patient 1. The images c, d, and e correspond to the patient 2. Diffusion-weighted image demonstrate a clear rim of restricted diffusion in its solid marginal components: periphery of the lesion evince hyperintensity on diffusion-weighted imaging (a and c) and very low values on apparent diffusion coefficient map (b and d). In the perfusion study of the patient 2 (e), the peripheral region of the lesion manifests a slight increase in relative cerebral blood volume about 1.6 respect to the healthy contralateral white matter.

**Figure 3:** All images belong to the patient 1. These images correspond to the surgical site (a and b) and the tumor resection (c and d). We can appreciate strong red fluorescence under blue light illumination (OPMI/Pentero, Carl Zeiss, Oberkochen, Germany).

**Figure 4:** Postoperative magnetic resonance image (contrast-enhanced T1-weighted images). Total resection of the tumor was achieved in the patient 1 (a). The patient 2 present milimetric remains in the surgical site (b).
with subtotal or gross total resection (GTR). The impact of extent of resection was similar for progression-free survival but less prominent for overall survival when adjusted for the number of lesions. Interestingly, there was no difference in progression-free survival or overall survival between patients who underwent GTR versus subtotal resection. While this study was limited as a post hoc analysis of randomized data, it suggests a survival benefit associated with cytoreductive surgery for PCNSL. Jelicic et al. published in 2015 a 10-year retrospective series of patients who underwent complete resection and had a significantly longer overall survival than patients who underwent either subtotal resection or biopsy only. Despite limited by its small sample size, retrospective nature, and lack of reported complications, this study suggests a potential benefit not only from surgical resection but also encourages surgeons to achieve GTR to improve prognosis in patients with PCNSL.

While the use of 5-ALA is known to be associated with increased extent of resection that leads to improved progression-free survival in patients with high-grade gliomas, its role in PCNSL remains unclear. Yamamoto et al. reported 41 patients with PCNSL diagnostic biopsies of which 34 (corresponding to 82.9% of the samples) had fluorescence with 5-ALA. This high percentage of fluorescence of PCNSL has been corroborated in other series. To the light of scientific literature and our experience, the use of fluorescence could not be restricted to gliomas. In the case of PCNSL, 5-ALA could provide an increased extent of resection and, according to the latest studies, a longer overall survival.

CONCLUSION

PCNSL is rare primary CNS tumors associated with substantial morbidity and mortality. The field of this tumor management is evolving substantially in recent decades and will continue to do so. These cases add to the growing literature which shows that surgery resection is a safe and effective method that might improve overall survival in patients with accessible PCNSL and single lesions, and it could be optimized by the use of 5-ALA. The follow-up period after treatment was 1 year, so long-term results are needed in future to confirm these good outcomes. In this context, there is a need for prospective studies to investigate the safety and therapeutic benefit of cytoreductive surgery for PCNSL.

Declaration of patient consent

Patient’s consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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