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Case Report

Brain cryptococcoma mimicking a glioblastoma in an immunocompetent patient: A rare case report and comprehensive review

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ABSTRACT

Background: Cryptococcosis is an invasive fungal infection primarily affecting lungs and potentially spreading to the central nervous. This fungal infection might be misdiagnosed as other infection diseases, such as tuberculosis; granulomatous diseases, like sarcoidosis; and even neoplastic diseases. Some previous reports described cases of cryptococcomas resembling brain tumors. In this paper, we present a very rare presentation of brain cryptococcoma mimicking a malignant glioma. To the best of our knowledge, this is the third case description in the literature.

Case Description: A 64-year-old male patient presented at the hospital with a history of progressive frontal headache for 1 month, becoming moderate to severe, associated with visual changes, without nausea or vomiting. No fever was reported. He was a heavy smoker and denied other relevant previous medical data. Neuroimage disclosed a right temporal expansive lesion initially considered a malignant glioma. The patient underwent a right temporal craniotomy and biopsy revealed a cryptococcoma.

Conclusion: Cryptococcomas characteristics in magnetic resonance are quite nonspecific. They should always be included in differential diagnosis of expansive brain lesions, both malignant and benign. Therefore, once cryptococcomas may resemble like other intracranial expansive lesions, biopsy should always be carried out to clarify diagnosis and avoid inadequate treatment and definition of prognosis only based on radiological patterns.

Keywords: Brain neoplasm, Differential diagnosis, Neurocryptococcosis, Surgery

INTRODUCTION

Cryptococcosis is an invasive fungal infection primarily affecting lungs and potentially spreading to the central nervous.[3] It can be caused by *Cryptococcus neoformans* or *Cryptococcus gattii*.[4] Epidemiological studies suggest that a large part of the population is exposed to the fungus, with a small percentage developing clinically evident disease.[15]

Cryptococcosis is the most common opportunistic fungal infection in the central nervous system in patients with human immunodeficiency virus (HIV) or other immunodeficiencies.[5,7] Infection usually begins with meningitis; however, cerebral parenchyma may also be involved, which

may present as cryptococcoma, dilation of Virchow-Robin spaces, or gelatinous cortical nodules. Cryptococcomas are more common in immunocompetent patients, generally presenting intense contrast enhancement, related to a greater immune response.[16]

Diagnosis of neurocryptococcosis is usually done based on clinical picture and typical association with HIV. Cerebrospinal fluid (CSF) evaluation and neuroimage methods may also help. Once diagnosis is established, treatment is potentially successful with antifungal therapy.[1-3] On the other hand, neuroimage may be challenging due to nonspecific characteristics, especially in immunocompetent subjects.

This fungal infection might be misdiagnosed as other infection diseases, such as tuberculosis; granulomatous diseases, like sarcoidosis; and even neoplastic diseases. Cryptococcoma presentation in neuroimage methods may also be indistinguishable from other mass lesions such as metastasis, malignant gliomas, and pyogenic abscesses. Thus, cryptococcoma should always be included in the differential diagnosis of expansive brain lesions, both malignant and benign.[1-6] In this paper, we present a very similar presentation of brain cryptococcoma mimicking a malignant glioma. To the best of our knowledge, this is the third case description in the literature. We additionally review literature and discuss learning points.

CASE DESCRIPTION

A 64-year-old male patient presented at the hospital assistance with a history of progressive frontal headache for 1 month, becoming moderate to severe, associated with visual changes, without nausea or vomiting. No fever was reported. He was a heavy smoker and denied other relevant previous medical data.

An outpatient investigation had carried out with a neurologist. A skull tomography computerized tomography (CT) was done and showed a right temporo-parieto-occipital hypodensity [Figure 1], associated with a temporo-occipital isointense lesion, suggestive of neoplastic lesion. He was then referred to the hospital emergency department, with physical admission examination pointing Glasgow Coma Scale 15, left homonymous hemianopsia, and no motor deficits. Visual field defects were evaluated by confrontation. We did not perform visual charting. We did not perform any preoperative broader neuropsychological assessment. In our routine neurosurgical evaluation, we could not identify any other symptoms regarding lobar functions. Initial laboratorial evaluation was unremarkable, including a blood count with 15.6 g/dL hemoglobin, 11,000/mm^3 leukocytes, 0.7 mg/dL creatinine, and 47 mg/dL Urea. Other laboratorial data were unremarkable.

He performed a magnetic resonance [MR-Figure 1] which disclosed an expansive right temporal lesion. It was solid-cystic, hyperintense at T1, and hypointense at T2 [Figure 1], with heterogeneous enhancement after gadolinium injection. There was edema involvement of corpus callosum, thalamus, and ventricular ependymal walls [Figure 1]. Spectroscopic analysis revealed a reduction in N-acetyl aspartate levels with an increase in choline levels and an increase in lactate levels [Figure 2]. Perfusion study displayed increased cerebral perfusion in this region [Figure 3].

Clinical picture and radiological findings pointed to a case of cerebral malignancy, being a malignant glioma the probable diagnosis. Therefore, microsurgical resection was planned. In the preoperative investigation, a routine thoracic and cardiological screening with a chest CT revealed an oval lesion with regular shape in the posterior segment of the upper lobe of the right lung, measuring 0.9 cm, suggestive of a lymph node. This lesion was considered unspecific and benign.

Surgery

Surgical planning and execution occurred as usual. The patient was positioned in supine position and head rotation of 90°. We routinely use neuronavigation in neuro-oncological surgeries to improve approach and decrease complications. The patient underwent a right temporal craniotomy, approaching lesion through middle temporal gyrus, to the temporal horn of the ventricle. Lesion had a hardened aspect and when it was dissected, it released a yellowish pasty content, which resembled an exudative content. In addition, the area around the lesion had an infiltrative or edematous aspect. Lesion had normal bleeding, not suggestive of malignant glioma. Main precaution during surgery was to preserve arachnoidal plane and work in an intrapial plane, especially in mesial portion of tumor.

Frozen resection was performed and partial report was of inflammatory unspecific process. Material was sent for pathological analysis.

Pathological report

Histology revealed in hematoxylin-eosin stain a moderate mixed inflammatory infiltrate with a foreign body-type giant cell reaction permeating capsulated structures. In Gomori-Grocott stain, it was possible to see multiple capsulated structures, round to oval with thin cell walls of variable size [3.5–8 μm in diameter – Figure 4].

Treatment

After histopathological results, treatment was initiated with amphotericin B and flucytosine. The patient underwent postoperative magnetic resonance with good surgical results ([Figure 5]. After hospital treatment for 14 days with

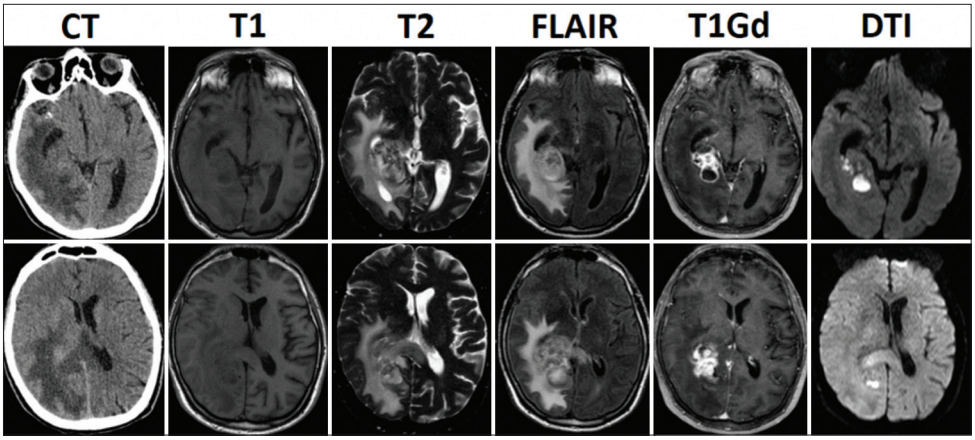

Figure 1: Preoperative neuroimage of patient. We present preoperative computed tomography and MR in sequences T1, T2, FLAIR, and T1 with gadolinium and diffusion. MR disclosed an expansive right temporal lesion. It was solid-cystic, hyperintense at T1, and hypointense at T2, with heterogeneous enhancement after gadolinium injection.

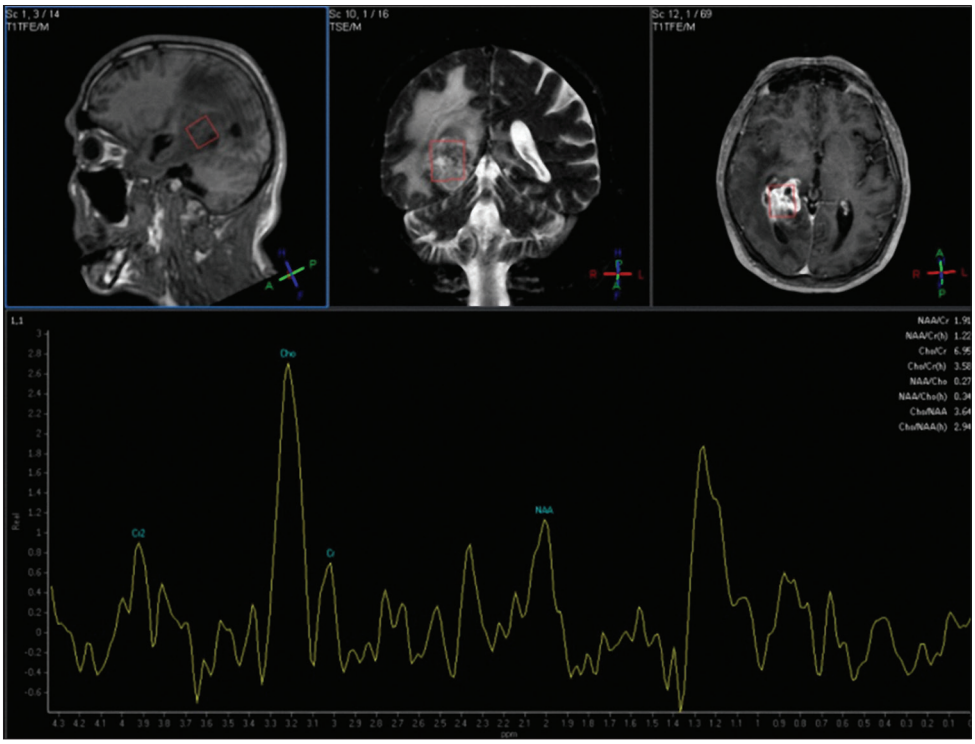

Figure 2: MR spectroscopy evaluation showing reduction in N-acetyl aspartate levels with an increase in choline levels and an increase in lactate levels.

amphotericin and flucytosine, the patient was discharged receiving oral fluconazole, as an outpatient maintenance treatment, which has continued for 6 months. Nowadays, the patient is ongoing a normal life.

DISCUSSION

Cryptococcosis is an invasive fungal infection primarily affecting lungs and potentially spreading to the central nervous.[4,5] The subject immunological status is determinant as to the evolution to latent or disseminated infection, being much more prevalent in patients with immunodeficiency.[10-13] With the increase in the number of immunocompromised patients after the HIV epidemic, cases of clinical and extrapulmonary pulmonary cryptococcosis have become more prevalent. It is estimated that 90% of cases of cryptococcal meningoencephalitis are related to HIV and a CD4 count <100.[8,9]

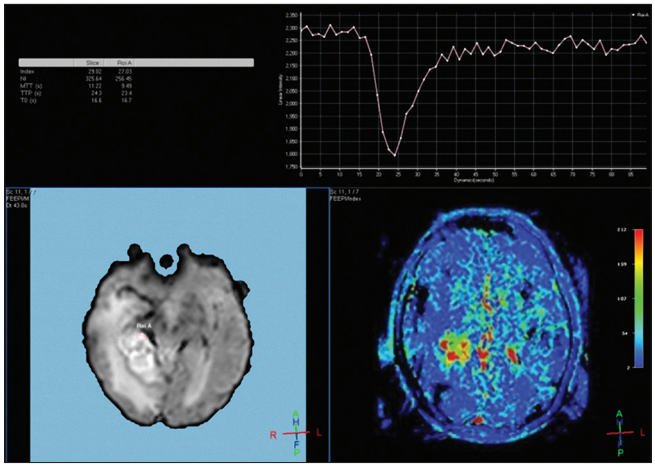

Figure 3: MR perfusion evaluation displaying increased cerebral perfusion.

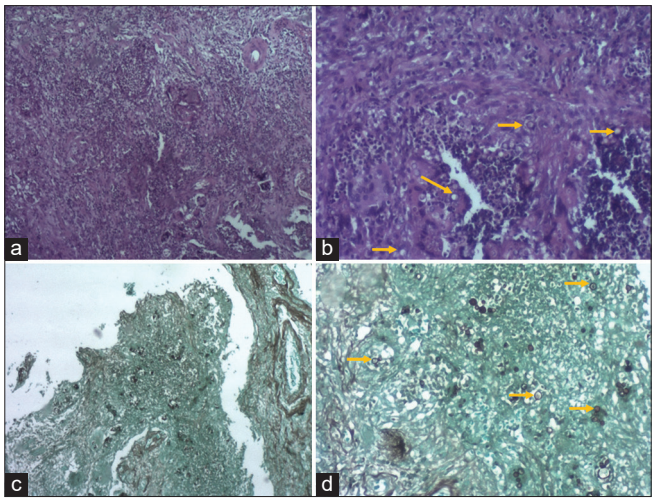

Figure 4: Histology image. In (a), histological section stained by H and E ×40, brain parenchyma is shown, showing a moderate mixed inflammatory infiltrate with a foreign body-type giant cell reaction permeating capsulated structures. (b) This same cut, enlarged at 100×, revealing a moderate mixed inflammatory infiltrate and round to oval capsulated structures. In (c), a Gomori-Grocott stain, enlarged by ×40, reveals the silver impregnation, showing multiple capsulated structures. Finally, (d), in the same coloration, at 100×, it is possible to notice capsulated structures, round to oval with thin cell walls of variable size (3.5–8 μm in diameter). Arrows show inflammatory infiltrate and round to oval capsulated structures compatible with cryptococcoma.

Another important factor related to presentation is the cryptococcal variety involved. *C. neoformans* is more prevalent in immunocompromised individuals, usually presenting with meningitis, while *C. gattii* has a higher incidence in immunocompetent individuals, more related to cryptococcoma.[13-16]

Radiologically, despite having a more frequent pattern of presentation, cryptococcomas characteristics in magnetic

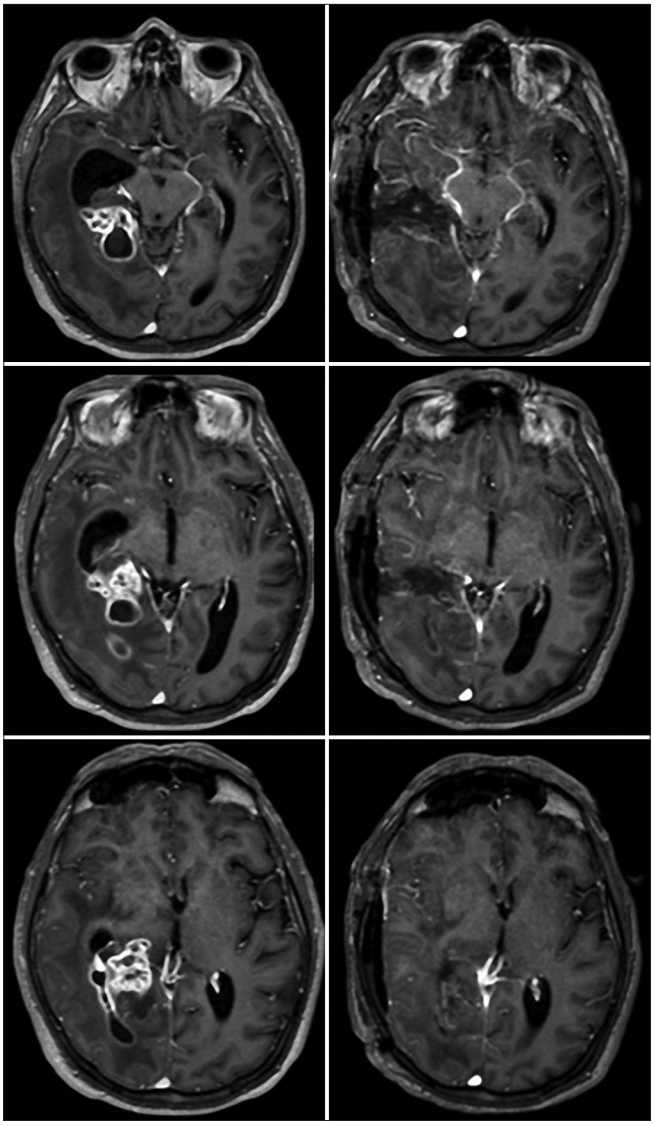

Figure 5: Comparison of preoperative MR (left) and postoperative MR (right). MR revealed good surgical resection of lesion.

resonance end up being quite nonspecific. In general, cryptococcoma presents as an expansive lesion, hypo or isointense in T1, and hyperintense in T2. Enhancement to gadolinium is variable, generally related to the host response.[4,15] In diffusion tensor imaging, it shows an intense aspect, more likely to be a cerebral neoplasm, than a pyogenic abscess. Such features are usually hard to differentiate from other expansive lesion including malignant gliomas and metastases and make that cryptococcoma should always be included in differential diagnosis of expansive brain lesions, both malignant and benign.

There have been some reports of brain lesions suggestive of neoplasms (both primary and secondary) which turned to be finally diagnosed as cryptococcoma.[4-10] In most cases, patients had no evidence of immunodeficiency and

Table 1: Data of the previous published papers discussing image differential diagnosis of neurocryptococcomas with neoplasms.

Author/year	Patient	Localization	Cryptococcosis diagnosis	Subtype	Immunodeficiency signs	Suspected diagnosis
Yu *et al.*, 1995[16]	Male 31 years	Sellar contrast- enhancing mass, extending to the floor of the third ventricle	Cerebral biopsy Cerebrospinal fluid Cryptococcal antigen test	Not reported	Negative HIV No signs of immunodeficiency	Pituitary Adenoma
Oliveira *et al.*, 2007[8]	Male 64years	Right cystic temporal lobe mass and multiple nodules throughout brain parenchyma.	Cerebral Biopsy Serum Cryptococcal antigen test Blood culture positive for Cryptococcus gattii	Cryptococcus gattii	Negative HIV No signs of immunodeficiency	Metastasis
Li *et al.*, 2010[6]	Female 49 years	MR large right occipital lesion	Cerebral biopsy	Cryptococcus neoformans	Negative HIV No signs of immunodeficiency	High-grade glioma
Chen *et al.*, 2011[3]	Male 47 years	Brainstem mass with an contrast-enhancing rim and nonenhancing core	Histopathology indicative of cryptococcosis	Not reported	Not reported	Not reported Suspected neoplasm
Ang *et al.*, 2017[1]	Male 59 years	Pulmonary mass suggestive of a primary bronchogenic carcinoma two nodules in the right frontal lobe	Pulmonary Biopsy Serum Cryptococcal antigen test	Cryptococcus neoformans	Negative HIV No signs of immunodeficiency	Metastasis
Ulett *et al.*, 2017[15]	Male 55 years	Heterogeneous right frontoparietal lesion with enhancement	Cerebral Biopsy Superior lobe lesion in thorax CT CSF Cryptococcal antigen test	Cryptococcus gattii	Negative HIV No signs of immunodeficiency	High-grade glioma
Paiva *et al.*, 2018[9]	Female 54 years	Two left occipital lesions, with gadolinium enhancement, and perilesional edema	Cerebral Biopsy Normal thorax CT C. neoformans detected in CSF	Cryptococcus neoformans	Negative HIV No signs of immunodeficiency	Not reported Suspected neoplasm
Santander *et al.*, 2019[14]	Female 41 years	Intraventricular attached to the posterior third of the septum pellucidum and the fornix commissure with hydrocephalus	Cerebral Biopsy CSF culture positive for Cryptococcus neoformans	Cryptococcus neoformans	Negative HIV No signs of immunodeficiency	Not reported Suspected neoplasm
Misra *et al.*, 2020[7]	Male 55 years	Left frontal lesion enhancing lesion with the central necrosis and peripheral edema	Histopathology indicative of cryptococcal granuloma CSF Cryptococcal antigen India ink stain revealed presence of yeast	Cryptococcus neoformans	Negative HIV No signs of immunodeficiency	Metastasis

neuroradiological findings were completely compatible with brain neoplasms [Table 1].

Ang *et al.*[1] described a patient in which a lung lesion suggestive of bronchogenic carcinoma and multiple brain lesions led to the presumptive diagnosis of brain metastasis with a primary pulmonary site. Oliveira *et al.*[8] described a similar case, with an atypical lung lesion suggestive of primary lung cancer, with another expansive lesion in the right temporal lobe, suggesting secondary involvement. In both cases, the final diagnosis was cryptococcoma.

Misra *et al.*[6] reported the case of a 55-year-old patient with an expansive frontal lesion. The preoperative radiological evaluation suggested a metastatic lesion, with no defined primary site. After surgery, cryptococcal granuloma was found followed by CSF with positive antigen and suggestive Chinese ink.

Previously, only two cases in the literature mimicked high-grade glial neoplasia. Ulett *et al.*[15] reported a case whose characteristics were very similar to high-grade glioma, as well as the case reported in this study. A 55-year-old male

with a history of increasing headache for one month. His HIV test was negative. On examination, he had papilledema on the right and a drop in pronation to the left. Radiological evaluation disclosed an extensive right temporal tumor, with gadolinium enhancement. Lesion was predominantly cystic and with surrounding edema. Preoperative pulmonary imaging identified a lesion at the apex of the left lung. Final biopsy revealed *Cryptococcus*.[15]

Li *et al.*[6] described the case of a 49-year-old female patient who had developed dizziness, vomiting, and headache for 1 month. On examination, the only altered factor was homonymous left hemianopsia. Laboratory evaluation showed a slight increase in leukocytes. Magnetic resonance imaging was performed, pointing to an extensive occipital lesion on the right, lobulated, presenting heterogeneous enhancement to the gadolinium, associated with adjacent edema, occluding the right ventricular atrium, with a slight deviation from the midline. After total resection of the lesion through occipital craniotomy, a pathological study identified *C. neoformans* and granuloma.[6]

There are also other cases of cryptococcomas mimicking cerebral neoplasm. Yu *et al.*[16] describes a sellar lesion suggestive of pituitary adenoma, while Santander *et al.*,[14] Chen *et al.*,[3] and Paiva *et al.*[9] did not suggest a differential diagnosis between primary and secondary lesions. In all cases where cryptococcoma simulated brain tumors, patients were HIV negative, with no signs of immunodeficiency, except for Chen *et al.*,[3] in which this information was not described.

In addition, none of the reports in the literature had a description of the pattern of cryptococcoma neuroimage concerning spectroscopy, which could potentially help diagnostic differentiation. Theoretically, spectroscopy would be one of the fundamental points in differentiating other brain disorders. Classically, it presents an important increase in the lactate peak, in contrast to the reduction in N-acetyl aspartate, choline, and creatine.[7,14]

In our case, a 61-year-old man presenting with holocranial headache presented with a right temporal contrast-enhancing expansive lesion suggestive of neoplasm. MR features were indistinguishable from a malignant glioma, including spectroscopy and perfusion studies, which revealed increase in choline similarly to malignant gliomas. Only after surgical approach, it was possible to settle diagnosis of neurocryptococcoma and the preoperative chest CT image was interpreted as a lung cryptococcoma. His HIV test was negative. To the best of our knowledge, our case is the third to present cryptococcomas mimicking glioblastomas in this manner. Moreover, considering spectroscopy pattern, which was also undistinguishable to glioblastoma, it is the first description available.

Although potentially harmful and a life-threatening condition, the central nervous system cryptococcosis is amenable to treatment and cure, even in immunodeficient subjects. Meanwhile, malignant gliomas and other neoplasms including metastases are neoplastic diseases with poor prognosis, leading patient to death, despite of surgical, chemotherapy, and radiotherapy treatment.[14-16]

In some cases, including low clinical performance patients harboring malignant gliomas, biopsy may even be not considered due to low oncological benefit. In such cases, there might be a venue for intersection of oncological diagnosis with neurocryptococcoma. Thus, it is possible that a patient considered "palliative" and oncological might have a treatable diagnosis. Therefore, a proper diagnostic workout including biopsy must be posed for all patients, to properly perform diagnosis and guide treatment.

The main learning point is that once cryptococcomas may resemble like other intracranial expansive lesions, biopsy should always be carried out to clarify diagnosis and avoid inadequate treatment and definition of prognosis only based on radiological patterns.

CONCLUSION

Cryptococcomas characteristics in magnetic resonance are quite nonspecific. They should always be included in differential diagnosis of expansive brain lesions, both malignant and benign. Therefore, once cryptococcomas may resemble like other intracranial expansive lesions, biopsy should always be carried out to clarify diagnosis and avoid inadequate treatment and definition of prognosis only based in radiological patterns.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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