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CASE REPORT

MENINGOENCEPHALITIS AND OPTICAL NEURITIS CAUSED BY *Cryptococcus gattii* IN AN IMMUNOCOMPETENT PATIENT

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ABSTRACT

The following case is of a 59-year-old man, undergoing no medication, with no pathological history or others risk factors, who presented dizziness, fever and asthenia twenty days before admission. The patient was admitted for investigation when the asthenia intensified, followed by seizures. On admission, blood count, biochemical tests and chest computed tomography were normal, a serological test for anti-HIV proved negative, while the magnetic resonance of the brain showed signs suggestive of meningoencephalitis. Cerebrospinal fluid (CSF) analysis suggested bacterial meningitis due to increased leukocytes with a predominance of polymorphonuclear cells, reduced glucose and increased proteins as well as positive Gram cocci in pairs by Gram and negative fungi by India ink test. Treatment with ceftriaxone was started. Since there was no significant improvement, CSF analysis was repeated on the seventh day of treatment. Intracranial pressure was measured by manometry (29 mmHg) and CSF analysis showed the presence of encapsulated yeasts similar to *Cryptococcus neoformans* by the India ink test. The treatment was modified to liposomal amphotericin B and flucytosine; the intracranial hypertension was controlled by repeated CSF punctures. After fourteen days of antifungal treatment, the patient presented visual turbidity and bilateral papillar edema, so corticosteroid therapy was prescribed. The evolution was favorable, with progressive resolution of symptoms, improvement of CSF parameters and visual acuity. The patient was discharged eight weeks after admission, with outpatient guidance. Corticosteroid therapy associated with antifungal therapy proved to be beneficial in this case, since following the introduction of corticosteroids there was progressive visual improvement.

KEY WORDS: Neurocryptococcosis; *Cryptococcus gattii*; ocular involvement; optic neuritis

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INTRODUCTION

Cryptococcosis is a systemic infection caused by fungi of the genus *Cryptococcus*. Usually, two species of *Cryptococcus* cause disease in humans: *Cryptococcus neoformans* and *Cryptococcus gattii* (May et al., 2016; Maziarz & Perfect, 2016; Beardsley et al., 2019). The infection is acquired through the respiratory tract, by inhalation of basidiospores or dehydrated yeasts (Moretti et al., 2008). Due to the high tropism of the fungus for the central nervous system, the most prevalent form of the disease is meningitis or meningoencephalitis (neurocryptococcosis).

The manifestations are directly related to the host's immunological state. In immunocompromised subjects it is an opportunistic infection, in most cases caused by *Cryptococcus neoformans*; in the immunocompetent *Cryptococcus gattii* has been considered the predominant pathogen (Sloan & Parris, 2014). The clinical manifestations of neurocryptococcosis include a variety of signs and symptoms such as headache, fever, cranial neuropathies, changes in level of consciousness and signs of meningeal irritation. Symptoms usually develop over a period of several weeks; eventually patients have a more acute form or even no typical symptoms, such as headache (Maziarz & Perfect, 2016). The pulmonary form is asymptomatic in 1/3 of the affected immunocompetent patients. When symptomatic, the patient may have fever, night sweat, hemoptoic sputum and chest pain. The radiological picture shows a localized pattern, with nodules, predominantly solitary or multiple subpleural, and pleural effusion in less than 10% of cases (Moretti et al., 2008).

Antifungal therapy is based on a three-step strategy, including induction, consolidation and maintenance phases. The combination of intravenous amphotericin B, preferably one of lipid formulation, with oral flucytosine is considered the first choice for treatment in the induction phase, over a period of two to six weeks. After the induction phase, triazole antifungal (fluconazole has the best action) is used in high doses in the consolidation phases, for eight weeks, and for suppression or maintenance for six to twelve months (Chammard et al., 2018; Mourad & Perfect, 2018). In addition to antifungal treatment, other important aspects must be considered for the adequate and successful management of neurocryptococcosis. These include early diagnosis, identification of risk factors and complications, such as increased intracranial pressure and the development of inflammatory immune reconstitution syndrome (IIRS), which may require the use of immunomodulatory drugs and is mostly observed in AIDS patient (Mourad & Perfect, 2018).

CASE REPORT

Male patient, 59 years old, physician, living in an urban area, denied travel for the previous six months, claimed no previous contact with wood or vegetable debris, no pre-existing disease or past use of any medication and pathological history or risk factors. The patient presented low-grade fever twenty days before hospitalization, as well as dizziness and asthenia which progressed to incapacitation associated with absence crises like convulsive seizures. The patient was subsequently admitted for investigation presenting a generally compromised condition and repeated seizures, requiring sedation. During the physical examination, the patient's axillary temperature was 38.2ºC, there were no signs of meningeal irritation or motor deficiencies. The patient did not present a respiratory clinical picture or other abnormalities. The chest computed tomography scan was normal and a magnetic resonance imaging (MRI) of the skull showed small alterations in the cortical signals in the parietal lobes associated with a discreet prominence of cortical vessels in parietal and posterior fossa regions, findings which are suggestive of meningoencephalitis. A serological test for anti-HIV proved negative (fourth generation immunoassay for detection of HIV 1 p24 antigen and antibodies).

The patient underwent a lumbar puncture where liquor alterations suggested acute bacterial meningitis due to pleocytosis (426 cells µ/L) with a predominance of polymorphonuclear cells (72%) reduced glucose (9 mg/dL), increased protein (147 mg/dL), positive gram cocci in pairs by Gram method and negative fungi by Ink test. Treatment began with ceftriaxone, corticosteroids, anticonvulsants and symptomatic medication. As there was no significant improvement, on the seventh day of treatment CSF was obtained again, presenting pleocytosis (67 cells µ/L) with a predominance of mononuclear cells (67%), as well as reduced glucose (14 mg/dL) and increased protein (133 mg/dL), positive fungi with the presence of encapsulated yeasts, similar to *C. neoformans* by the India ink test; 427 yeasts were counted. To quantify the yeasts present in the CSF, the Fuchs-Rosenthal camera was utilized. In this technique, slightly homogenized but not concentrated pure CSL is used. The material is placed in the counting chamber and after 2 minutes of sedimentation it is examined under a microscope. The count is performed across the camera, that is, 256 quadrants and then dividing the result found by 3.2. This factor is used to correct the height of the camera volume and obtain real values per µL. Subsequently, the result of the culture of this liquid on Agar Sabourad and the biochemical test using the canavanine-glycine-bromothymol blue agar (CGB) confirmed infection by *Cryptococcus gattii*.

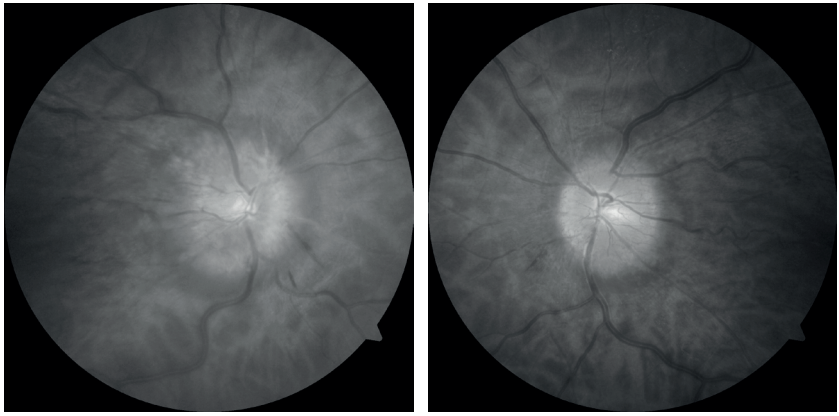
The molecular analysis using restriction fragment length polymorphism (RFLP– URA5) showed that the isolate of *C. gattii* belonged to the genotype VGII.

The treatment was changed to liposomal amphotericin B associated with flucytosine. Corticosteroid therapy was suspended, and anticonvulsants and symptomatic medication was continued. Aiming at controlling intracranial hypertension, repeated lumbar punctures were performed, this procedure stabilized the condition. Direct search and quantification of yeasts were performed on all CSF samples obtained during treatment. Two weeks after the beginning of antifungal treatment, a liquid culture proved negative, a result that was confirmed in a second test. During this period, the clinical picture evolved favorably with the disappearance of fever and seizures, in addition to significant decrease in dizziness.

However, three weeks after admission and two weeks after antifungal treatment, the patient began to complain of visual changes (diplopia and blurred vision). An ophthalmological evaluation revealed blurring on the edge of the optical disc associated with protrusion obscuring the superficial vessels when crossing the disc margin; alteration of the arterio-venous relationship, with venous engorgement and tortuosity of vessels and peri papillary retinal edema (Figure 1A). A new brain MRI showed a prominent subarachnoid space around the optic nerves (Figure 1B) and intraocular protrusion of the optic nerve head denoting a case of bilateral optic papillitis. In view of the ocular condition and the two negative liquid cultures for fungi and the fact that the patient remained stable, with progressive improvement while adhering to antifungal treatment, corticosteroid therapy was introduced (prednisone 1 mg/kg/day) to control and reduce eye inflammation and, consequently, vision improvement (Figures 1C e 1D).

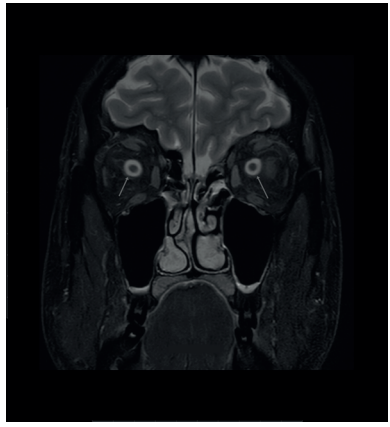
The patient was discharged seven weeks after admission and six weeks using amphotericin B and flucytosine and was instructed to return monthly for outpatient follow-up and treatment with fluconazole plus anticonvulsant medication. The patient followed the directions given, presenting favorable evolution, with progressive improvement and, in the last evaluation, performed twelve months after hospital discharge, the patient was asymptomatic, with total recovery of vision without sequelae and no other complications, maintaining regular use of fluconazole 300 mg/ day and an anticonvulsant.

Figure 1. Retinography and brain MRI before and after corticosteroid therapy

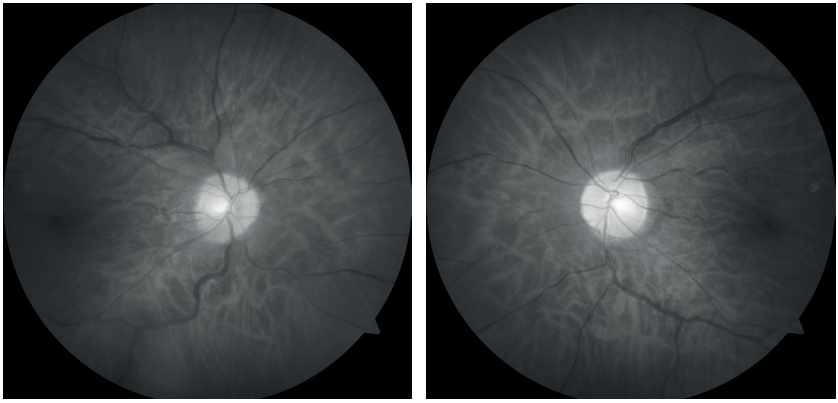


A: Retinography before corticosteroid therapy

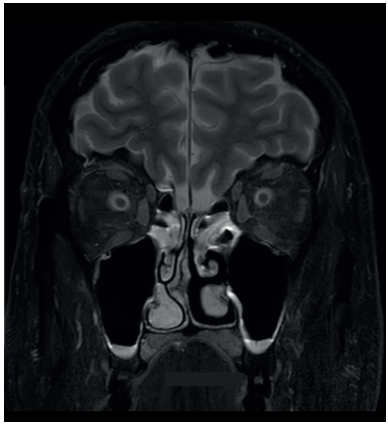
Blurring of the edge of the optical disc associated with its protrusion and obscuring the superficial vessels when crossing the disc margin; alteration of the arteriovenous relationship, with venous engorgement and tortuosity of the vessels; peri papillary retinal edema.



B: prominent subarachnoid space around the optic nerves.



C: restoration of papillary contours and remission of peri-disc edema



D: normal subarachnoid space around the optic nerves

DISCUSSION

Cryptococcus gattii is the cause of most cases of neurocryptococcosis in immunocompetent patients or with no evidence of immune impairment (Maziarz & Perfect, 2016; Beardsley et al., 2019). This fungus was found in our patient, who was previously healthy without respiratory symptoms and normal chest tomography. Sequencing identified the molecular type VGII currently considered, together with VGI, the most common in clinical isolates and the most frequent in environmental isolates (Chen et al., 2014; Nakao et al., 2016). Regarding the clinical picture, it is important to highlight that the manifestations of the disease are related to the patient's immune

condition, although, especially in patients with no HIV infection, there is little data regarding the dynamics of this immune response and how it could be optimized to benefit the patient (Panackal et al., 2015; Marr et al., 2020). In immunocompetent individuals, the pulmonary form is asymptomatic in 1/3 of those affected; in the present case, chest tomography at admission was normal. Neurocryptococcosis, which is the most common form, can develop with nausea, vomiting, seizures (tonic-clonic seizures and/or absence crises), visual deficit or amaurosis, diplopia, behavioral changes, fever and headache (Ramírez-Ramos et al., 2018).

The patient had low-grade fever, asthenia, dizziness and seizures. Intracranial hypertension, which was evidenced in the CSF opening pressure in our case, is common in patients with neurocryptococcosis, and is associated with increased morbidity and, due to cranial nerve involvement, as well as auditory and visual changes. Ocular involvement occurs in about 30% of cases and may manifest as papilledema, optic atrophy and ophthalmoplegia, secondary to intracranial hypertension or by direct infiltration of the optic nerve.

The immune response plays an important role in the pathogenesis of optic neuropathy associated with cryptococcal meningitis and, for this reason, corticosteroid therapy can be beneficial, as observed in the outcome of our case; other authors have also described benefits of corticosteroid therapy in reducing optic neuritis due to neurocryptococcosis (Ghatalia et al., 2014; Portelinha et al., 2014).

The improvement obtained with corticosteroid therapy is thought to be due to its anti-inflammatory or immunomodulatory effects, associated with specific antifungal treatment and the proper handling of intracranial pressure (Palau et al., 2014; Perfect & Bicanic, 2015; Marr et al., 2020). The treatment of the reported case was carried out with liposomal amphotericin B associated with flucytosine, a therapeutic regimen considered the first choice and used for six weeks. Flucytosine is unavailable in Brazil and was therefore purchased by the patient.

The patient underwent daily CSF punctures to control intracranial pressure, a measure that contributed to stabilizing the condition and avoiding the need for CSF derivation. The inflammatory response triggered in neurocryptococcosis determines the reduction and elimination of the fungus, however, it can also promote cell destruction. Understanding the variables that lead to these results can optimize therapeutic strategies and, in this context, harmful inflammatory responses can be controlled by the administration of corticosteroids (Marr et al., 2020). Quantitative CSF yeast counts have been used for evaluation of antifungal therapy to determine the impact of various treatments on the yeast load (Day et al., 2013; Jarvis et al., 2014). In the reported case, a progressive reduction in the amount of fungi was observed in successive CSF samples.

Elevated intracranial pressure (>19 mmHg, reaching up to 230 mmHg in severe cases) is a frequent complication in neurocryptococcosis caused by obstruction of arachnoid villi, impairing CSF reabsorption. Frequent lumbar punctures to remove CSF are effective in controlling intracranial hypertension, reducing sequelae and lethality. However, frequency has not been defined and depends on individual response (Chen et al., 2014; Mourad & Perfect, 2018). When CSF pressure remains high and symptoms persist for a long period of time, despite CSF punctures, or if the patient does not tolerate this daily procedure, CSF derivation (ventriculoperitoneal shunt – DVP) should be considered. For patients presenting increased intracranial hypertension and hydrocephalus, early DVP is indicated (Moretti et al., 2008; Perfect & Bicanic, 2015).

The present case shows that a cure without neurocryptococcosis sequelae is possible when an early diagnosis is made, along with adequate antifungal therapy, correct handling of complications and possible complications, including the safe use of corticosteroids to reduce inflammation resulting from the host's immune response to the fungus.

CONFLICT OF INTEREST

The authors state that the content of this article presents no conflicts of interest.

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