

## Meningoencephalomyelitis and pneumonia caused by *Cryptococcus* spp. in a cat – case report

[Meningoencefalomielite e pneumonia causada por *Cryptococcus* spp. em um gato – relato de caso]

A.S. Siviero<sup>1</sup> , B.B. Rivas<sup>2</sup> , R. Redaelli<sup>2</sup> , T.M. Veronezi<sup>2</sup> , M. Slaviero<sup>3,4</sup> ,  
E.C. Oliveira<sup>2</sup> , L. Sonne<sup>3</sup> , F.V.A. Costa<sup>5\*</sup> 

<sup>1</sup>Autonomous Veterinarian, Porto Alegre, Brasil

<sup>2</sup>Veterinarian, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brasil

<sup>3</sup>Faculdade de Veterinária, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brasil

<sup>4</sup>Graduate, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brasil

<sup>5</sup>Universidade Federal do Rio Grande do Sul, Porto Alegre, Brasil

### ABSTRACT

Cryptococcosis is an important systemic mycosis with worldwide distribution that affects men and also domestic and wild animals. The infection is acquired by inhalation of the fungus or basidiospores present in the environment and may manifest as localized nasal or ocular injury, pulmonary illness or, less commonly, as meningoencephalomyelitis. Long-term treatment is necessary, and the prognosis is reserved. This paper aims to report a case of invasive cryptococcosis in a domestic cat that was presented with neurological signs. It is intended to emphasize the systemic nature of the infection and its possible routes of infection, reinforcing the importance of investigating this disease as a differential diagnosis of clinical manifestations with neurological involvement in cats.

Keywords: cryptococcosis, meningitis, systemic mycosis, feline

### RESUMO

A criptococose é uma importante micose sistêmica de distribuição mundial, que acomete homens, animais domésticos e silvestres. A infecção é adquirida pela inalação do fungo ou de basidiósporos presentes no ambiente e pode manifestar-se por lesão nasal ou ocular localizada, por comprometimento pulmonar, ou, menos comumente, como meningoencefalomielite. O diagnóstico definitivo nos casos neurológicos é desafiador, assim como seu tratamento. Este trabalho tem como objetivo relatar um caso de meningoencefalomielite e pneumonia por criptococose diagnosticado por meio de histopatologia, em um felino doméstico. Pretende-se enfatizar o caráter sistêmico da infecção e suas possíveis vias de infecção, reforçando a importância da investigação dessa doença como diagnóstico diferencial de manifestações clínicas com envolvimento neurológico em gatos.

Palavras-chave: criptococose, meningite, neurologia, pneumonia, felino

### INTRODUCTION

Cryptococcosis is a potentially fatal fungal infection that affects animals, and men (Malik, 2003; Marcasso *et al.*, 2005; Queiroz, 2008), but is most seen in the cat (Castellá, 2008; Lester *et al.*, 2011). It is considered a subacute to chronic systemic mycosis, with no evident sex or breed predisposition (Marcasso *et al.*, 2005; Castellá *et al.*, 2008; Queiroz, 2008). Cryptococcosis is

caused by basidiomycetous yeasts of the genus *Cryptococcus* belonging to the *C. neoformans* – *C. gattii* complex (Lester *et al.*, 2011). This organism is cosmopolitan and, can be isolated from the nasal mucosa and the skin of susceptible animals or people. *Cryptococcus* spp. can also be found in the environment, particularly in soil rich in bird droppings, where it can be viable for at least two years if conditions are favorable (Reolon *et al.*, 2004;

\*Corresponding author: fernanda.amorim@ufrgs.br

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Marcasso *et al.*, 2005; Queiroz, 2008). In Brazil, the presence of *C. neoformans* has been also reported in native decaying vegetation (Fortes, *et al.*, 2001). Cryptococcosis is not zoonosis. Susceptible animals are infected mainly by inhaling spores from contaminated environment (Reolon *et al.*, 2004; Marcasso *et al.*, 2005; Castellá *et al.*, 2008; Queiroz, 2008, Lester *et al.*, 2011).

The dissemination of *C. neoformans* occurs via hematogenic or lymphatics, with tropism for the central nervous system (CNS) (Malik, 2003; Reolon *et al.*, 2004; Marcasso *et al.*, 2005; Castellá *et al.*, 2008), ocular tissue, lymph nodes, and skin tissue (Pennisi *et al.*, 2013). The establishment of the clinical presentation and the spread of the infection seems to have a relationship with the host immunity (Reolon *et al.*, 2004; Marcasso *et al.*, 2005; Queiroz, 2008). Some predisposing factors include neoplasms, diabetes, surgical interventions, and glucocorticoid treatments. Similarly, some authors suggests that the presence of retroviruses as feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV) can play a role in the course of disease (Malik, 2003; Castellá *et al.*, 2008). However, a retrospective study has shown no significant difference between healthy and FIV infected cats in the outcome of the disease (O'Brien *et al.*, 2006).

Clinical signs can be divided into four main syndromes, and associations of these can be found in the same animal. The respiratory syndrome, more frequent in the cat, is characterized by mucopurulent, serous, or bloody nasal discharge, inspiratory dyspnea, and sneezing. However, pulmonary involvement is not always observed (Marcasso *et al.*, 2005). The neurological syndrome (which can derive from the nasal form or occur independently), can present as meningoencephalomyelitis, with neurological signs related to the injury site (Marcasso *et al.*, 2005; Castellá *et al.*, 2008; Queiroz, 2008). Other presentations of disease are tegumentary or ocular syndrome (Malik, 2003; Queiroz, 2008).

The identification of the etiologic agent is provided by culture of nasal discharge, cytology, and histopathology of tissues such skin and lymph nodes. When disseminating or neurologic disease is suspect, the cryptococcus can be isolated from the cerebrospinal fluid (CSF)

(Honscho *et al.*, 2003; Malik, 2003). Due to the invasive degree of this procedure, CSF collection should be considered when feline cryptococcosis is not confirmed using other suitable biological samples (Sykes, *et al.*, 2010). For identification of the species genotype, isolation and polymerase chain reaction (PCR) are recommended (Pennisi *et al.*, 2013).

This report aims to describe the clinical and pathological aspects observed in a cat with systemic cryptococcosis, emphasizing its importance as a differential diagnosis in cats that present diseases with neurological impairment.

### CASE REPORT

A 12-year-old male cat was presented with prostration and hyporexia for seven days at the Feline Medicine Service at the Veterinary Hospital of the Federal University of Rio Grande do Sul (HCV-UFRGS). The patient also had behavioral changes, with vocalization, aggression, and alterations in balance. The animal was not vaccinated or neutered and had outdoor access. The cat was first seen by another veterinarian, who instituted treatment with prednisolone, 1.5 mg/kg, twice a day, for five days. The clinical signs then worsened, and the cat started showing signs of tetraparesis.

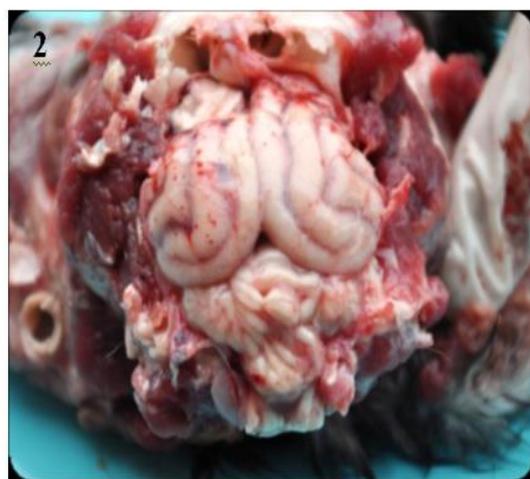
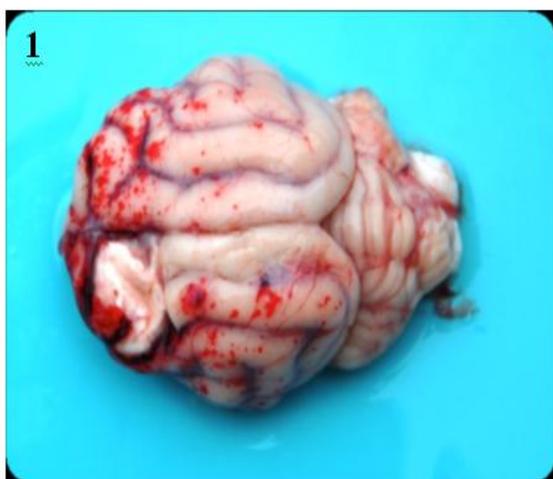
On clinical evaluation, the cat was at lateral recumbency, making alternating pedaling movements with excitement, aggression, and vocalization. The cat had no pupillary, eyelid, or menace reflexes. The rectal temperature was 35.5°C, with moderate dehydration. The animal was hospitalized for initial support therapy, including warming, nutrition support, fluid therapy and anticonvulsants. Once the patient was stable, hematologic analysis and imaging tests were performed. Despite mild lymphopenia, no changes were observed in the biochemical analysis, cervical and skull radiography, or abdominal ultrasound. The animal died 18 hours after hospitalization.

On necropsy, gross examination showed multifocal petechiae in the cerebral cortex and meninges, cornification of the cerebellum (Figures 1 and 2) and mild emphysema in the pulmonary lobes. On microscopic examination, a large amount of circular ovoid structures with a thick, slightly colored halo (yeast) with approximately 10-20 µm in diameter, compatible with *C. neoformans* were observed in the

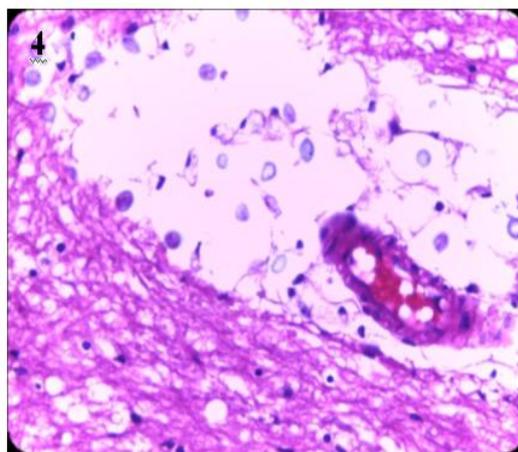
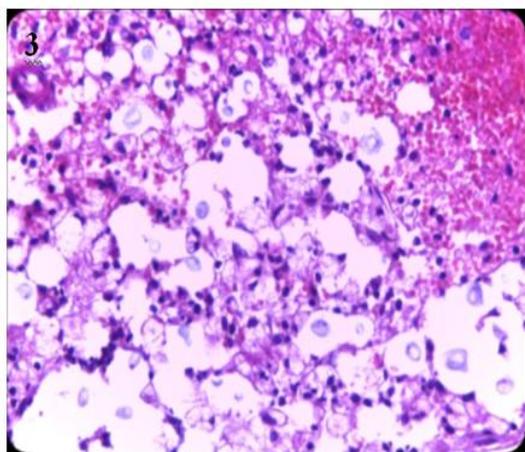
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leptomeninges of the brain. Sometimes, this finding was also seen associated with a mild inflammatory infiltration of macrophages and lymphocytes (Fig. 3 and 4). The presence of yeast structures was confirmed through special stains of Periodic Acid Schiff (PAS) (Fig.5) and Alcian Blue (AB). Areas of marked and multifocal hemorrhage in the leptomeninges, perivascular edema, and mild congestion have

also been identified. Slightly stained circular structures were rarely seen in the meninges of the spinal cord in the thoracic segment. In the lungs, slightly colored yeast forms were identified, similar to those observed in the CNS, often associated to a mild inflammatory infiltrate of macrophages and lymphocytes well as chronic mild emphysema and moderate congestion.



Figures 1 and 2. CNS of feline affected by cryptococcosis in necropsy. Grossly, there were multifocal petechiae in the cerebral cortex and meninge and cornification of the cerebellum.



Figures 3 and 4. Histological examination of the feline CNS. The leptomeninges had round to ovoid structures (yeasts) with thin eosinophilic walls and clear centers surrounded by clear space (capsule), compatible with *C. neoformans*, sometimes associated with a discreet inflammatory infiltrate of macrophages and lymphocytes. H.E. Staining, Obj. 40x.

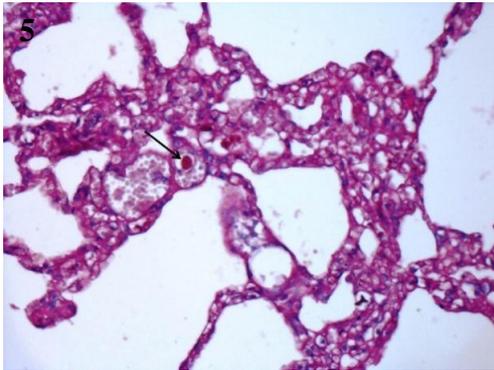


Figure 5. Microscopy of affected feline lung evidenced yeast structures, characteristics of *C. neoformans* (arrow). PAS Staining, Obj. 40x.

## DISCUSSION

Cryptococcosis affects several species of animals, with cats being the most susceptible (McGill *et al.*, 2009). It can appear at any age, with no predilection for gender or breed (Lester *et al.*, 2011). However, McGill *et al.*, (2009) reported a higher incidence in male cats. Exposure and self-limiting infection may occur in the first years of life, and the disease in elderly cats can reflect the reactivation of the agent presented in residual granulomas (Malik, 2003). Considering the age of the patient in this report, a reactivation of an old infection could be possible.

The environment in which the animal lives can enhance the risk of cryptococcosis, as the fungus is often isolated in bird excreta and wood products (Moretti *et al.*, 2008). According to the owner, the cat in this report was intact and had outdoor access and free-roaming habits. These factors may contribute to a major contact with contaminated environments.

According to Trivedi *et al.*, (2011), the most common sites of infection are the nasal cavity, skin, lymph nodes, brain, meninges, and eyes in cats. An infection of the respiratory system can lead to hematogenous dissemination of *C. neoformans*, achieving diverse tissues. The spread of the upper respiratory disease through the cribriform plate may result in meningitis. The local dissemination seems to be the most likely path for the development of CNS cryptococcosis (Sykes *et al.*, 2010). The neurological signs presented by this animal, such as paresis, changes in behavior, dementia, and cranial nerve deficit (II, VII, VIII) were reported previously in the literature (Malik, 2003; Moretti *et al.*, 2008).

According to Sykes, *et al.* (2010), behavioral changes can occur in 40% of cats, and the presence of extraneural signs may precede the appearance of neurological signs in 72% of feline patients. As related by the owner, the cat in this report was lethargic for at least seven days before the CNS signs appeared.

The yeasts and/or basidiospores of the fungus inhaled by felines, can reach the upper respiratory tract, which can produce pulmonary infection (Moretti *et al.*, 2008). The clinical signs of the lower respiratory tract are not very frequent (Honsho *et al.*, 2003), but Sykes *et al.*, (2010), found that approximately 8% of the cats may show any low respiratory tract signs, such as dyspnea or tachypnea. They can reflect the presence of cryptococcal pneumonia, pleuritis, or a mediastinal mass (Trivedi *et al.*, 2011). None of these symptoms were related by the owner in the present case, but some mild alterations in respiratory patterns can be subtle for the owner perception.

Most cases of cryptococcosis affect immunocompromised individuals (Honsho *et al.*, 2003). Malnutrition, weakness, intercurrent illnesses and immunosuppression can compromise the immunity of animals and act as a trigger for the occurrence of cryptococcosis (Marcasso *et al.*, 2005; Castellá *et al.*, 2008). In this case, a worsening of the clinical signs was observed after the institution of treatment with prednisolone, suspecting iatrogenic immunosuppression. However, the use of glucocorticoids to treat CNS cryptococcosis can be indicated as a secondary treatment to modulate the inflammatory response after fungal death. Sykes *et al.*, (2010) showed that judicious

glucocorticoid use in conjunction with antifungal drugs after diagnosis was associated with improved survival of the cats in the first 10 days.

The definitive diagnosis of cryptococcosis is straightforward, based on obtaining representative tissue specimens for cytology, culture and/or histology. Deep nasal swabs, nasal washings, needle aspirates from cutaneous nodules or lymph nodes, bronchoalveolar lavage material, pleural fluid and CSF can be used as samples for tests (Malik, 2003). When neurological cryptococcosis is suspected, the diagnosis is established after identification of the agent in CSF by direct microscopy, fungal isolation from CSF culture or detection of capsular antigens in latex agglutination test (Marcasso *et al.*, 2005; Castellá *et al.*, 2008). According to Sykes *et al.*, (2010), magnetic resonance imaging (MRI) can contribute to the diagnosis of CNS cryptococcosis. Although the imaging features are quite variable in cats (Stevenson *et al.*, 2004), the presence of meningitis with gelatinous pseudocyst formation, granulomatous mass lesions, and peripherally enhancing brain lesions can predict the cryptococcal infection (Sykes *et al.*, 2010).

The detection of cryptococcal capsular antigen by the latex agglutination procedure is the most widely utilized serological test and can be very useful, as it can be realized using serum or CSF. They provide a rapid diagnostic method in suspected cases where CSF collection may be an unacceptable risk, and diagnosis of cryptococcosis should be excluded (Malik, 2003). CSF analysis and serology were not performed due to the rapid deterioration in this patient. These tests could reveal the diagnosis in time to institute a treatment. Therefore, neoplasia was the main suspected diagnosis.

The definitive diagnosis was based on histopathological findings. The evaluation of the brain, cerebellum, and spinal cord was compatible with granulomatous meningoencephalomyelitis. The pneumonia presented by the animal suggests that the airway was the portal of entry for the microorganism. Inhalation is generally the most common route for contamination (Marcasso *et al.*, 2005). Hematological and biochemical changes are usually not suggestive of cryptococcosis, and the erythrocyte and leukocyte counts are commonly

within normal values for the species (Queiroz, 2008). This patient only had lymphopenia, and it may be explained by the previous corticosteroid therapy. As observed by Sykes *et al.*, (2010), when CNS injury is present, the patient may have a rapid deterioration, sometimes before achieving a diagnosis.

Even in patients that are diagnosed *ante mortem* and treated accordingly, there are limitations to treatment. The main problem in treating cryptococcosis cases is the high cost of therapy and the requirement for medication through a long-term period (Malik, 2003). Amphotericin B, ketoconazole, fluconazole and itraconazole have all been used to treat cats (Pennisi, 2013). Among them, itraconazole seems to be the most used drug for cryptococcosis treatment, although CNS penetration is inferior to fluconazole and adverse effects are more common (Trivedi *et al.*, 2011). It is reported that response to treatment can vary according to the injuries already established on CNS (Pennisi, 2013).

The prognosis for most affected cats is favorable, related to early diagnosis and owner's compliance to treatment, which is prolonged (Malik, 2003; Pennisi, 2013). In patients whose diagnosis is delayed or have disseminated disease, the prognosis can be worse (Malik, 2003); Also, neurological disorders were associated with a negative outcome. (Sykes *et al.*, 2010). However, the same author reports that survival three days after diagnosis of CNS cryptococcosis was associated with dramatic prolongation in the mean survival time in cats.

## CONCLUSIONS

Neurological cryptococcosis is a potentially fatal infection and the investigation of this disease as a possible diagnosis for clinical manifestations compatible with CNS involvement is of fundamental importance, even if the diagnosis of cryptococcosis in cats is uncommon. Veterinarians should tell owners to avoid free roaming habits for cats to minimize the chances of exposure to cryptococcosis infection due to environmental contamination.

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