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IMPORTANCE OF DIAGNOSIS OF CRYPTOCOCCOSIS IN COMPANION ANIMALS AIMING AN ALERT TO PUBLIC HEALTH

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ABSTRACT

In this case female canine, Dachshund, at one year and eight months, which initially presented cough, then sudden bilateral blindness, emesis and dyspnea. Evolving to opisthotonos, nystagmus, convulsion, and soon in respiratory arrest and death. Microscopy of lesions found in the central nervous system, peri-bronchial lymph nodes and pulmonary alveoli revealed numerous yeasts. The lesions were associated with the presence of intralesional yeasts, compatible with Cryptococcus neoformans. This disease is uncommon in the Northwest region of the State of Rio Grande do Sul, but should be suspected in future diagnoses and be concerned with the imminent risk to public health.

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INTRODUCTION

Cryptococcosis, also known as Torulosis, European Blastomycosis, Busse-Buschke Disease is a systemic mycosis caused by a complex of pathogenic fungi identified in the genus *Cryptococcus*. This yeast has a worldwide distribution. (MARCASSO *et al*., 2005). Caused by an opportunistic agent, *Cryptococcus neoformans*, a basidiomycete found in several types of soil, fabrics, secretions and excretions (BARONI *et al*., 2006; MARTINS *et al*., 2008). The infection caused by this disease, is acquired by inhalation of spores and yeast present in the soil, especially in environments with birds' feces (KIDD *et al*., 2007; PAPPALARDO *et al*., 2005). These environments are rich in nitrogen sources such as urea and creatinine, which are substrates that allow the abundant growth of yeast and favor the microfocus formation, notably in urban centers, where human exposure to this agent becomes an everyday event. Where viable fungal elements are in the home environment, particularly in the household dust, with high concentration demonstrated in studies carried out in Africa, with 30 to 50% positivity and in the city of Rio de Janeiro, with 13% of the analyzed households were contaminated . In addition to pigeons, other birds are also important reservoirs, especially those related to rearing in captivity in the domestic environment, as the canaries and parakeets (MINISTRY OF HEALTH, 2012). Another important factor to be considered is that this yeast is very resistant, because in its state of desiccation, this measures at most 1 micrometer, and remains viable for up to two years in the environment (TABOADA, 2008). Being considered of low occurrence, but important, in felines, canines, equines, bovines, wild animals and even in humans (MALIK *et al*., 2008). Being classified as an opportunistic disease (CORRÊA *et al*., 1999), cryptococcosis is cosmopolitan and associated to immunosuppression

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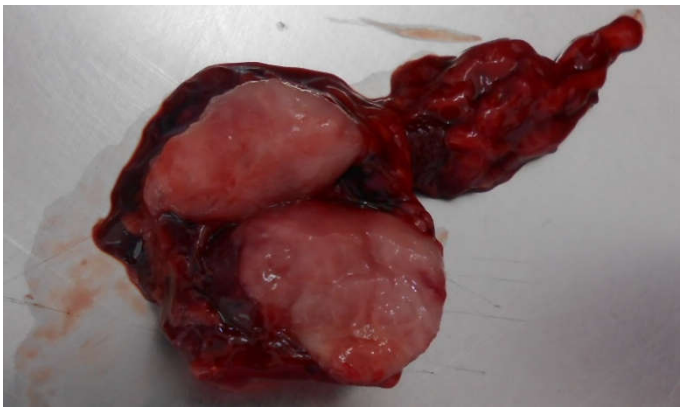
conditions. Caused by *Cryptococcus neoformans* var. *Neoformans* and (CORRÊA *et al*., 2002) primary cryptococcosis, endemic in tropical and subtropical areas, occurs in apparently normal hosts, caused by *Cryptococcus neoformans* var. *Gattii*. Both cause meningoencephalitis, with severe and fatal evolution in humans (MINISTRY OF HEALTH, 2012). Among the systemic mycoses, cryptococcosis has been reported as the most prevalent in terms of hospitalization. Data from the System of Hospitalization Admission of the Single Health System - SIH-SUS demonstrate that cryptococcosis presented the highest number of hospital admissions in the period from 2000 to 2007 (MINISTRY OF HEALTH, 2012). In the South and Southeast regions of Brazil predominates the cryptococcosis by *C. neoformans* var. *Neoformans*, with prevalence of human cases of risk condition, mainly immunosuppression by AIDS, but also by lymphomas, leukemias and use of corticosteroids, being the lethality of approximately 35 to 40%. Cases per *gattii* variety imported or not from other regions of the country also occur sporadically in the South and Southeast regions. Cryptococcus occurs as an opportunistic manifestation in approximately 4.4% of cases of AIDS in Brazil and it is estimated the prevalence of cryptococcosis associated with AIDS between 8 and 12% in referral centers in the Southeastern region (MINISTRY OF HEALTH, 2012).Important disease that endangers public health worldwide. Several factors are implicated in the pathogenesis of yeast, among which are the thermotolerance at 37ºC, synthesis of melanin, presence of capsule and production of Exoenzymes (KULETA *et al*., 2009). According to Santangelo *et al*.,(1999), the capsular polysaccharide acts by inhibiting the phagocytosis. Melanin facilitates the survival of the agent in the central nervous system, for being an antioxidant and eliminate reactive oxygen species (ZACHARY, 2013). The objective of this study is to report a case of cryptococcosis in dogs with systemic involvement, little reported disease in the northwestern region of the state of Rio Grande do Sul, aiming to contribute to the diagnosis of this pathology in dogs and serving as an alert to the occurrence of the disease in immunosuppressed patients.

Case Report

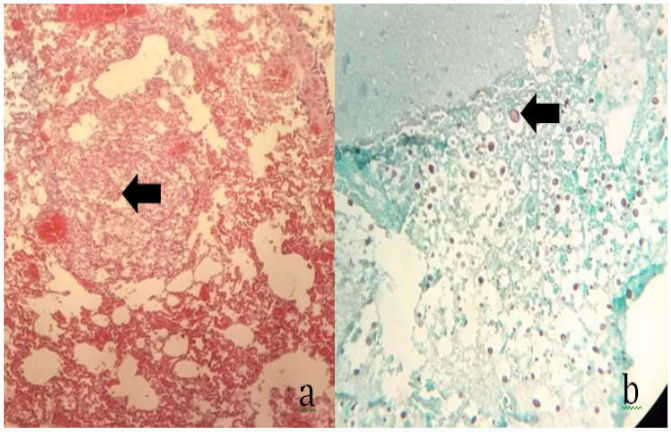
Necropsy was performed at the Laboratory of Veterinary Histopathology of Unijuí, a female dog, breed Dachshund, with one year and eight months of age, which before death had systemic, neurological and respiratory signs. Epidemiology and clinical signs were evaluated as well as in histopathology the macroscopy and microscopy of the case, being used the techniques of the laboratory routine, for necropsy and histopathological exam. In the clinical consultation, this presented cough and from this sign oral medication was prescribed. Without improvement, after two days, the animal returned to the clinic with sudden blindness bilaterally, emesis and dyspnea. The next day, the clinical signs evolved to opisthotonos, nystagmus, seizures, and then respiratory arrest and death. The initial suspicion was intoxication, but for a more accurate diagnosis, the animal was submitted to necropsy and histopathological analysis. Being that in the autopsy of this case, oral hyperemic mucosa, subcutaneous dark red tissue, dehydration and peri-bronchial lymph nodes with gelatinous aspect and increased in volume were evidenced (Figure 1). Animal's samples of the tissues and organs, were collected and immediately immersed in 10% formalin, remaining in the same, for 24 hours to fixation. Afterwards, the process of samples preparation was started for histopathological analysis. After the tissue processing, this was placed in a blade, to then be stained with hematoxylin and eosin using the staining technique of histopathological routine. It was also used in this case, the *Grocott* staining which is used for the fungi detection, being used in the protocol that accompanies the commercial kit of histochemistry used in the laboratory routine. At the end the stained slides were analyzed in light microscope and the main changes were noted, by adding to the photographic record data.



Source: Author's records.

Figure 1. Peri-bronchial lymph nodes with increased volume and gelatinous aspect

In the microscopy of lesions found in the peri-bronchial lymph nodes, numerous yeasts were evidenced, with a diameter from 5 to 10 µm, observed in hematoxylin and eosin (HE) and *in Grocott*. The morphology observed in this case, was compatible with yeasts of *Cryptococcus neoformans*, and these were also observed in the pulmonary alveoli, as well as in the central nervous system (Figure 2), affecting the meninges, brain capillaries, frontal cortex and the cerebellum. In the spleen and kidney, rare yeasts were observed in blood vessels.



SOURCE: Author's records.

Figure 2. Presence of *Cryptococcus neoformans* (a) in the pulmonary alveoli, observed in hematoxylin and eosin in 20 X objective (b) in the nervous system, observed in Grocott staining, objective 40X

The morphological diagnosis of this case was marked diffuse lymphadenitis, moderate multifocal meningoencephalitis and multifocal pneumonia. All the mentioned lesions were associated with the presence of intralesional yeasts, morphology compatible with Cryptococcus. The final opinion

of the case was that the clinical signs of blindness, cough and dyspnea presented by the patient, occurred due to fungal infection, characterizing a systemic cryptococcosis.

DISCUSSION

The occurrence of cryptococcosis in dogs is less common, but when this happens, is usually associated to multiorganic dissemination with clinical presentation, associated to neurological and ocular symptoms, which may occur at any age, (QUINN *et al*., 2005), or it may also be in asymptomatic form of the disease (LÓPEZ, 2013). According to Bosco *et al*. (2016) & Ferreira *et al*.(2010), neurological and/or ocular signs have been observed more frequently, as well as the initial clinical manifestations. The involvement of the CNS (Central Nervous System) is observed in 80% of cases with variable neurological signs, depending on the location of the lesions that may occur in the meninges, brain, spinal cord or peripheral nerves (PEREIRA, 2003; QUEIROZ *et al*., 2008). Whereas the apathy and weight loss may occur in approximately 25% of the infections, in addition to being observed, mild fever. The clinical signs of the central nervous system impairment, are multifocal or arising from meningoencephalomyelitis and include seizures, tilt of the head, nystagmus, facial paralysis, walking in circles, paraplegia, quadriplegia, ataxia and cervical hyperesthesia. The diagnosis of this disease is accomplished mainly through the agent visualization in cytological or histopathological exam, but it is also possible to identify it from the post-mortem findings (RONDELLI *et al*., 2010).

The diagnosis can be performed by the fungal cultivation, by means of routine testings , or by serological exam through the test of latex antigen, which can also be obtained with samples of urine and cerebrospinal fluid , in addition to serving as a monitoring method of the patient's response to treatment, by titration of Cryptococcus (FERREIRA *et al*., 2007). In the blood smear, it is possible to identify the fungus and diagnose the disease, by the presence of numerous isolated or grouped yeasts. According to Martins *et al*. (2008) this agent presents itself in the cytological samples with oval, rounded or ellipsoid shape, measuring from 4 to 10 μm and surrounded by a mucopolysaccharide capsule . In the hemogram, there may be the presence of macrophages, lymphocytes, and multinucleated giant cells (LÓPEZ, 2013). The histopathological examination is fundamental to the diagnosis, and one of the stainings employed is the Mayer's mucicarmine, with which it is observed the capsule stained in red, facilitating the Cryptococcus recognition in the lesion. The staining in periodic Schiff acid and Groccot are also great alternatives for the demonstration of the agent because they highlight the yeast in the midst of the lesions. The hematoxylin-eosin should be routinely used for location and analysis of cellular pattern of lesions previously to special stainings (BOSCO *et al*., 2016).
At the autopsy performed by Marcasso *et al*. (2005), visceral pleura was observed with thickened areas, of firm consistency, frontal sinus with purulent content, and discrete leptomeninges hemorrhage in the encephalic trunk, being characteristics similar to those reported in relation to the patient of this case.
The systemic mycoses, are frequent causes of severe uveitis in geographical areas where the organisms are common environmental contaminants, since the lesions are predominantly in the retina, choroid and optic nerve. The ocular involvement is part of the systemic disease, which constitutes the most characteristic clinical signs of this disease in dogs (NJAA and WILCOCK, 2013). The main problem of cryptococcosis regarding aspects of public health, concerns the environmental exposure which is difficult to control, since contact with infective sources is omnipresent and common in most urban centers, either among animals or humans. Areas with aggregation of birds in urban constructions should be cleaned regularly, trying to keep them illuminated and ventilated (BOSCO *et al*., 2016). The majority of cases affects immunocompromised animals and humans, then the treatment for this disease, is performed with antifungal agent, which is efficient for the patient's improvement, if the disease is diagnosed and treated while still in the initial phase of the disease, where treatment may be imposed on the basis of fluconazole, amphotericin B, flucytosine, ketoconazole or itraconazole (NOBRE *et al*., 2002). The course of treatment is usually long (3 months to 1 year) and in some cases, for life (FERREIRA *et al*., 2007). However, even after the treatment, there may be progression of neurological clinical signs presented by the patient (MARTINS *et al*., 2008). The prophylaxis of cryptococcosis is difficult to be performed, since it is recommended that the access of animals to locations with birds' excreta be avoided, especially pigeons, which are becoming an increasing problem in urban centers, due to possibly affect the animals and people's health. But, the amount of environmental fungi may be reduced after successive washes with calcium hydroxide solution 40 g/l associated to sodium hydroxide 1.5 g/L (BOSCO *et al*., 2016). Due to the great importance of cryptococcosis as a public health problem, the Ministry of Health (2012), through the Department of Health Surveillance, has been implementing the program for the monitoring and control of systemic mycoses, being included the cryptococcosis.

Conclusion

After the histopathological analysis of the animal's organs subjected to autopsy, it was found that the injuries occurred due to fungal infection. Highlighting that the lesions were associated with the presence of intralesional yeasts, morphology compatible with Cryptococcus neoformans. The present case has characteristics of an episode of canine systemic cryptococcosis, which had not been suspected in the clinical course, with rapid evolution to patient's death. Considering that such disease is uncommon in the Northwestern region of the state of Rio Grande do Sul, and which should be suspected in future diagnoses of animals with clinical signs similar to those reported in this case. Also, helping to demonstrate the presence of the disease in this region, in terms of imminent risk to public health, especially in immunocompromised patients.

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