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(CASE REPORT)

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Feline sporotrichosis and differential diagnosis in cryptococcosis: Case report

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Abstract

This paper described a case of feline sporotrichosis, characterized as zoonotic subcutaneous mycosis, caused by the dimorphic fungus *Sporothrix brasiliensis*, with the species *Sporothrix schenckii* being the most common. This report demonstrates the clinical pathology, clinical signs, diagnosis, treatment, addressing a possible differential diagnosis of the disease in comparison with cutaneous cryptococcosis, known since 1905, for being a serious disease, caused by cryptococcus neoformans, of extreme importance since the nervous system is involved in almost 90% of cases. Both fungal infections present a considerable level of similarity and deserve attention in their differential diagnosis. The gold standard test for differentiation would be fungal culture, as the cytology test performed is not very conclusive for the morphological differentiation between the two fungi. However, with the anamnesis, history, clinical signs and positive response to the recommended treatment and in pharmacological association, it was confirmed that the patient had acquired a mycotic disease.

Keywords: Sporotrichosis; Cryptococcosis; Cats; Geophilic fungus

1. Introduction

1.1. Fungal infections: sporotrichosis and cryptococcosis

Classified as a subcutaneous mycosis, Sporotrichosis is caused by a dimorphic and geophilic fungus of the *Sporothrix* complex. The disease can evolve subacutely or chronically and can become fatal for affected felines. *Sporothrix schenckii* (agent of feline sporotrichosis) is considered a saprophytic fungus of tree bark and rich soils. Then, when contaminated, felines present subcutaneous granulomatous diseases spread throughout the skin and ulcerated lesions. *Sporothrix* lives in a filamentous form and after inoculation, it will transition to the yeast-like form, where the infection occurs. Sporotrichosis is a disease that has occurred through several epidemic outbreaks, but it is currently considered a public health problem. It is considered a notifiable disease because it is a zoonosis, and the form of transmission between animals and humans occurs mainly through scratches, bites or direct contact with the blood of infected animals [1,2].

Cryptococcosis is a mycosis where the agent is a fungus of the *Bastomycetes* class, *Cryptococcaceae* family, *Cryptococcus* genus, *Cryptococcus* neoformans species. Morphologically, it is a rounded, oval or ellipsoid yeast, usually surrounded by a mucopolysaccharide capsule. The species can be underdeveloped in three varieties and five serotypes; however, the main causes of diseases in humans and animals are *Cryptococcus neoformans* and *Cryptococcus gattii*. It is often reported that aged poultry excreta offer a more favorable organic substrate for the development of the fungus, as they have a

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smaller number of bacteria and, therefore, competition for growth is reduced, thus contributing to the high population density of *C. neoformans* cells in this substrate [2,3,4].

2. Transmission

In general, *Sporothrix* infection occurs through traumatic inoculation, considering that the fungus is not capable of penetrating intact skin. So, when it penetrates deeper layers of the epidermis, its form is modified, becoming a yeast. It can remain in the place where the inoculation occurred, developing nodular lesions and/or spread through the lymphatic system, reaching other organs. Transmission occurs through inoculation of the fungus in cases of perforation by contaminated objects, such as wood chips, thorns, plant cuttings and contaminated straw in the environment. The transmission between animals and zoonotic transmission occurs mainly through bites and/or scratches from infected animals, with penetration of the fungus through the skin. These lesions created by scratching and/or biting are characterized by wounds that do not heal and have a rapid growth period, differing from cryptococcosis where contagion occurs through the inhalation of yeast, present in contaminated soil, in its encapsulated form of the fungus *Cryptococcus neoformans* or *C. gattii* [1, 2, 4].

3. Pathogenesis and clinical signs

In felines, the disease can present in four forms: (i) localized pertinent, (ii) lymphocutaneous, both of which are the most common, (iii) disseminated multifocal and (iv) extracutaneous. The first signs of infection appear within a variable period, from three to 84 days, with an average of 21 days, depending on the patient's immune status [2].

The cutaneous form due to traumatic inoculation of the agent can generate a cutaneous-lymphatic complex or sporotrichosis chancre at the site of the lesion. The disease may be self-limiting and heal spontaneously, or it may spread and generate progressive nodular and ulcerative lesions that do not regress with treatments with ointments or topical and systemic antibiotics. It may affect regional lymphatic vessels, later in the main lymph nodes, and may reach the bones, eyes, lungs, gastrointestinal tract, central nervous system and other organs. However, this is a rare form, occurring mainly in immunosuppressed animals. Studies show that the species *S. brasiliensis* has significant tropism for nervous tissue.

In cryptococcosis, the main form of infection is via inhalation, both in humans and animals. The yeasts and/or basidiospores of the fungus are inhaled and reach mainly the upper respiratory tract, where large particles are trapped and smaller particles can reach the pulmonary alveoli, potentially causing pulmonary infection. The microorganism spreads to extrapulmonary sites via hematogenous transmission. The central nervous system can also be infected by direct extension through the cribriform plate of the nasal cavity [3].

The clinical signs of the disease and its spread are closely related to the host's immunity and vary according to the organs affected and the lesions caused. Since the disease is transmitted by inhalation of yeasts, it can affect the respiratory tract (mainly the nasal cavity), central nervous system, eyes and skin [4].

Cryptococcosis respiratory syndrome is more common in felines, which present with stertorous breathing, mucopurulent, serous or bloody nasal secretion, inspiratory dyspnea and sneezing. The ocular syndrome manifests with uveitis, chorioretinitis, optic neuritis, corneal opacity, iris edema and hyphen. Neurological syndrome is more common in dogs, but when it affects the central nervous system, the signs are usually chronic. The cutaneous form occurs mainly on the head and neck with several nodules that tend to ulcerate. Infection of the skin and subcutaneous tissue is considered a manifestation of disseminated disease [1,2].

4. Epidemiology

Sporotrichosis is said to be the most prevalent subcutaneous mycosis in Latin America, where the largest proportion of cases occurs in temperate and tropical climates, which provide a better climate for the development of the microorganism. In Rio de Janeiro, it is a very common disease, considered hyperendemic in the state and in feline clinics due to the high number of semi-domiciled and stray animals. The form of transmission combined with the territorial instinct of felines means that the number of animals carrying the fungus is only increasing. In addition, felines mark their territory by sharpening their nails on tree trunks and by urinating and defecating in sand and soil, covering their urine and feces with the substrate [1,4].

Since Cryptococcus neoformans are widely distributed in nature, this makes the environment in general an important form of infection. The etiological agent has also been isolated from fruits and animal feces, mainly pigeons. In addition, it has been observed that the fungus has an opportunistic behavior, making its incidence more present in immunodeficient animals, such as cats carrying the feline immunodeficiency virus (FIV) and feline infectious anemia (FelV) [2,3].

5. Diagnosis

In both diseases, it is necessary to take a good anamnesis and study the patient's history and habits. In addition to issues such as living environments, direct contact with animals, presence of plants, soil and substrates for litter boxes, in addition to the possibility of semi-domiciled breeding. As diagnostic methods for sporotrichosis, the most common to start treatment is cytology, and the material can be collected mainly in three ways, namely: (i) imprint on ulcerated lesions or (ii) FNA (fine needle aspiration) and (iii) FNA (fine needle aspiration) on nodular lesions. However, the diagnostic method considered the gold standard is the fungal culture of material collected from the lesions [2].

The diagnosis of cryptococcosis can be obtained through laboratory tests, such as by searching for circulating polysaccharide antigen in serum or cerebrospinal fluid using the latex test, which has high sensitivity and specificity and is the main form of diagnosis. It can also be obtained using the ELISA immunoenzymatic technique. Hematological and biochemical findings are usually not suggestive. The definitive diagnosis is based on the identification of the agent by cytology and culture of nasal exudate, cerebrospinal fluid, and tissues such as skin. The laboratory test of fungal culture aims to identify the fungus that is causing the disease and, consequently, to differentiate the yeasts from *Sporothrix* and *Cryptococcus neoformans*. However, both have a similar morphology, making it difficult for the pathologist to diagnose [1,2].

6. Treatment

The medication of choice for the treatment of sporotrichosis in felines is itraconazole at a dose of 10 mg/kg/day, combined with potassium iodide 5 mg/kg in cases of resistance to itraconazole. Since itraconazole and potassium iodide are hepatotoxic drugs, monitoring of the biochemical levels of liver enzymes is recommended. In addition to the medication of choice, there are other drugs that can be used for treatment, such as fluconazole, local thermotherapy and surgical resection of the lesions. Fluconazole is not indicated for felines because it is considered a drug that is even more toxic to the feline organism than itraconazole; thermotherapy is excellent when combined with drug treatment, although it is dangerous in cases of felines that do not accept much handling; surgical resection is only indicated for cases in which the lesions do not regress [1,2].

For the treatment of cryptococcosis, itraconazole is also the drug of choice for dogs and cats when there is no imminent risk of death or neurological signs. For those who present neurological signs, the indicated drug is fluconazole, as it crosses the blood-brain barrier. Ketoconazole is effective in some felines, but it has several adverse effects such as vomiting, diarrhea, weight loss and loss of appetite. And although amphotericin B is a potent, broad-spectrum, fast-acting antifungal drug, for cryptococcosis as a single medication it has a moderate effect. This drug is only recommended in situations where the disease is disseminated, and the patient is at risk of death [4].

7. Case report

The selected case is about a feline named Antônio Francisco, male, P.C.B., black and white fur, neutered, approximately 5 (five) years old, with no previous history of previous illnesses, vaccinations, diet, among other important information. The animal was rescued and arrived at the clinic for the first time on 04/30/2021 weighing 2.8 kg, with fleas, lesions suggestive of sporotrichosis on various parts of the body and myiasis in the left eye, with affected hind limbs. The animal was dehydrated, pale, with a fever, with signs of acute pain and very responsive to handling when food was offered (Figure 1).

Figure 1 Rescue Day and first appointment at the vet

The lesions initially suggestive of sporotrichosis were located on the right front paw, on both hind paws, on the ends of both ears, on the back of the ear, nostrils (characterizing the “clown nose” lesion) and around the right eye. Lesions ranged from ulcerations to edema with cutaneous dissemination (Figure 2)

Figure 2 A) Ulcerative lesions in the head region with the presence of myiasis; B) Feline in the adopted therapeutic protocol

Upon arrival, the patient was given only medication for myiasis (nitenpyram), injectable analgesic medications (dipyrone monohydrate and tramadol hydrochloride), antibiotic therapy (benzylpenicillin benzathine) and hospitalization was recommended for monitoring and stabilization of the condition, which was denied due to the owner's inability to bear the costs.

According to the patient's condition, he was advised to seek public care for diagnosis and free treatment from the Zoonosis Control Centers of the State of Rio de Janeiro. At the Municipal Institute of Veterinary Medicine, wounds with necrosis were debrided, subcutaneous serum therapy was continued, analgesia was administered and diagnostic tests for fungal infection were performed.

Supportive treatment was maintained, mainly at the veterinary clinic where the first appointments were made, but the treatment and diagnostic tests to identify the type of lesions affecting the entire body were carried out at the Jorge

Vaitsman Municipal Institute of Veterinary Medicine. The institute used an imprint method of ulcerated lesions on the nose and ear to collect material and perform microscopic analysis, where fungal yeasts with characteristics suggestive of *Sporotrhix sp*. were found. With the diagnosis of mycosis, treatment was started with itraconazole 100 mg SID, associated with liver protector (Hepvet) ¼ of the SID tablet.

After two months, the treatment was effective, with ulcerated lesions no longer present and edema significantly reduced with the use of itraconazole. However, the patient was removed from the hospital due to reports of indigestion and diarrhea. A protocol of pre-surgical tests (blood count, biochemistry, and electrocardiogram) was initiated for enucleation of the right eye and two phalanges of the right paw affected by myiasis, in which there were no changes other than a decrease in platelets (82,000 µl). After five days of corticosteroid use, the platelet count returned to normal, and the patient was fit for surgery (Figure 3).

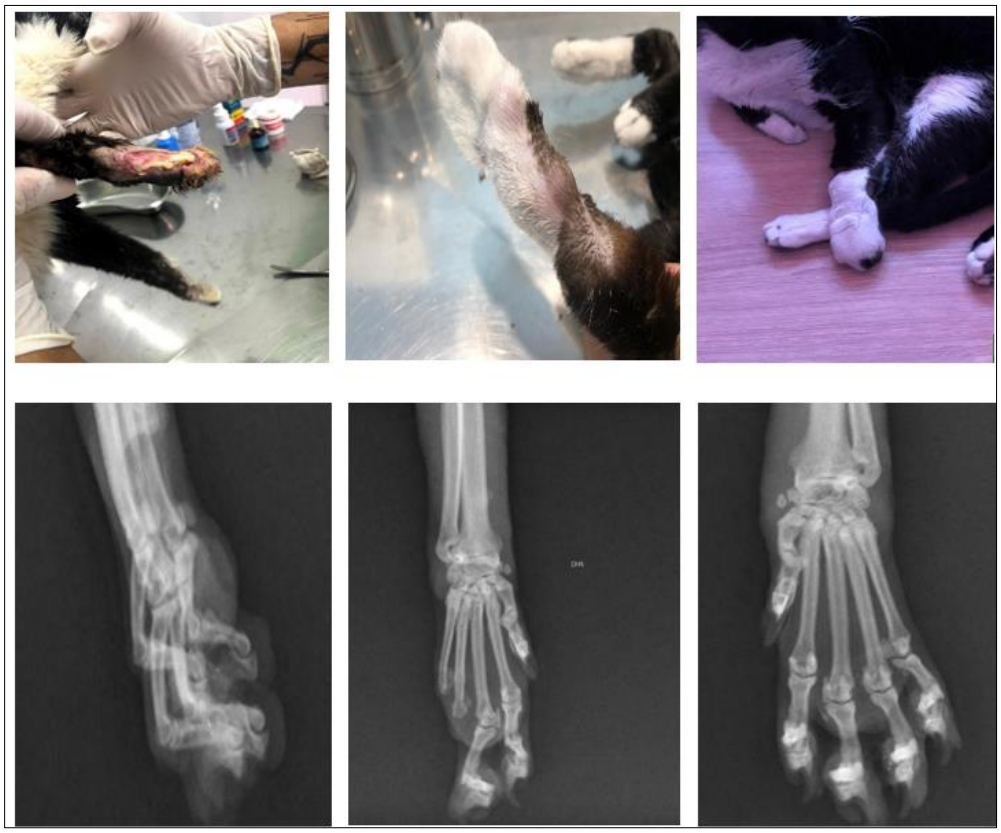

Figure 3 Monitoring of the phases related to the treatment described

The surgeries were performed on June 30, 2021, and there was difficulty in healing the enucleation stitches. There was regression of the treatment, with small ulcerations near the right eye socket and tip of the ears. There was dehiscence of the enucleation suture, and it was necessary to undergo another surgery to close it again. Throughout the surgical and post-surgical process, treatment with itraconazole was maintained.

In the 4th month of treatment with itraconazole, another blood test was performed to monitor the liver levels, which remained stable and within the standards and reference values. At that time, the ulcerated lesions healed and some of the edematous lesions remained, mainly in the ears and "clown nose". In the 6th month of treatment, still with edematous lesions and small ulcerations in the ears and swollen nose, it was then decided to combine Potassium Iodide 20mg SID with treatment with itraconazole 100mg SID, where improvement of the lesions was noted. And after the following five months of treatment combining itraconazole with Potassium Iodide, the patient was considered clinically cured on 03/11/2022.

Antônio Francisco, in November 2022, began immunosuppression treatment with Methylprednisolone for gingivitis-stomatitis complex and consequently immunosuppression. After approximately 10 days of application, his left front paw presented lameness and edema at the height of the metacarpal. An X-ray was performed on November 20 to

investigate any trauma or fracture, without identifying any changes. Then, synovial fluid was collected by FNA from the same joint for microscopic analysis, where yeasts suggestive of *Sporothrix sp*. were found again.

Figure 4 Feline treated in recovering (before and after)

At that time, treatment with methylprednisolone was interrupted and treatment with Itraconazole in combination with Potassium Iodide (80mg and 40mg, respectively) SID was resumed, as it was a relapse. After that, the beginning of this treatment, a significant improvement in edema and pain in the affected area can be noted between the first and second week of continuous medication. The treatment was continued for another 6 months with medical monitoring at a new veterinary clinic where no new blood tests were requested. After six months of treatment, three of which still had joint pain and lameness and three months without any pain, lameness, edema or any other clinical signs, the medication was again withdrawn and since then the sporotrichosis has been considered cured

8. Conclusion

The fungal diseases sporotrichosis and cryptococcosis, although similar, could be differentiated in the case of the feline Antônio due to striking factors in his protocol. Through the history of the location where Antônio was rescued, it was an endemic region of sporotrichosis and there were many active cases at the same time, and it was not an area with a large concentration of birds. Sporotrichosis and cryptococcosis are fungal, zoonotic diseases, which depending on their clinical manifestation may have clinical signs that are confusing at first glance. However, as in the case report of the feline Antônio, the diagnosis of sporotrichosis and not cryptococcosis was made, mainly through some contextual analyses: environment where he lived/was found at the rescue, clinical signs and response to treatment. Through the history of the location where Antônio was rescued, it was an endemic region of sporotrichosis, it was not an area with a large concentration of birds to have a substrate for the proliferation of *Cryptococcus sp*.; the clinical signs, although similar to cryptococcosis, are suggestive of sporotrichosis due to the "clown nose"; the response to treatment, especially the combination of itraconazole and potassium iodide, is suggestive of infection by *Sporothrix sp*.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

Statement of ethical approval

Ethical clearance was obtained from the ethical review committee of Department of Sciences Medicine University.

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