

***Sporothrix schenckii* complex in felines: Analysis of clinical, mycological, environmental and epidemiological factors**

Complexo *Sporothrix schenckii* em felinos: Análise dos fatores clínicos, micológicos, ambientais e epidemiológicos

Complejo *Sporothrix schenckii* en felinos: Análisis de factores clínicos, micológicos, ambientales y epidemiológicos

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Abstract

Sporotrichosis is an infectious and chronic fungal disease caused by fungi belonging to the *Sporothrix schenckii* complex that affects humans and animals through traumatic implantation of the fungus in the skin. They are dimorphic, saprophytic and geophilic fungi that are widely distributed in nature, especially in soils rich in organic matter. The aim of this study was to understand the clinical, mycological, environmental and epidemiological aspects of the *Sporothrix schenckii* complex in felines. In order to meet the objectives of this research, a qualitative, descriptive and exploratory data survey was carried out through a bibliographic review based on works published in the last 23 years. *Sporothrix* spp. is considered to be a complex of at least six cryptic species, in other words, they have similar morphological characteristics but different genotypes. In cats, the incubation period is variable; it usually lasts 14 days. On penetrating the tissue, the micellar form transforms into yeast, which generates an inflammatory response and proliferation of the microorganism at the site, causing papular and nodular lesions which, in some cases, heal spontaneously. Therefore, it is clear that sporotrichosis is caused by dimorphic fungi of the *Sporothrix schenckii* complex. It is a zoonotic disease of great importance in the context of public health, since it is still a neglected disease and requires robust measures to control. As well as being the most seriously affected, felines are the main transmitters to humans and animals, making them a key point in controlling outbreaks of the disease.

Keywords: Fungi; Mycology; Sporotrichosis; Veterinary medicine; Zoonoses.

Resumo

A esporotricose é uma doença fúngica infecciosa e crônica, causada por fungos pertencentes ao complexo *Sporothrix schenckii* que afeta humanos e animais por implantação traumática do fungo na pele. São fungos dimórficos, saprófitos e geófilos que estão amplamente distribuídos na natureza, principalmente em solos ricos em matéria orgânica. O objetivo deste trabalho foi compreender os aspectos clínicos, micológicos, ambientais e epidemiológicos do complexo *Sporothrix schenckii* em felinos. Para atender aos objetivos desta pesquisa, foi realizado um levantamento dos dados de natureza qualitativa, caráter descritivo e exploratório através de revisão bibliográfica baseada em obras publicadas nos últimos 23 anos. O *Sporothrix* spp. é considerado um complexo de pelo menos seis espécies crípticas, ou seja, possuem características morfológicas semelhantes, mas genótipos diferentes. Nos gatos, o período de incubação é variável; geralmente dura 14 dias. Ao penetrar no tecido, a forma micelar se transforma em levedura, o que gera resposta inflamatória e proliferação do microrganismo no local, causando lesões papulares e nodulares que, em alguns casos cicatrizam espontaneamente. Portanto, ficou claro que a esporotricose, é causada por fungos dimórficos do complexo *Sporothrix schenckii*, sendo uma doença de caráter zoonótico e que possui grande importância no contexto de saúde pública; uma vez que ainda é uma doença negligenciada e necessita de medidas robustas para seu controle. Como também, os felinos, além de serem os mais gravemente acometidos, são os principais transmissores para humanos e animais, sendo assim um ponto chave no controle de surtos da doença.

Palavras-chave: Esporotricose; Fungos; Medicina veterinária; Micologia; Zoonoses.

Resumen

La esporotricosis es una enfermedad fúngica infecciosa y crónica causada por hongos pertenecientes al complejo *Sporothrix schenckii* que afecta a humanos y animales por implantación traumática del hongo en la piel. Son hongos dimórficos, saprófitos y geófilos que se encuentran ampliamente distribuidos en la naturaleza, especialmente en suelos

ricos en materia orgánica. El objetivo de este estudio era conocer los aspectos clínicos, micológicos, ambientales y epidemiológicos del complejo *Sporothrix schenckii* en felinos. Para cumplir los objetivos de esta investigación, se llevó a cabo un estudio cualitativo, descriptivo y exploratorio de los datos mediante una revisión bibliográfica basada en trabajos publicados en los últimos 23 años. Se considera que *Sporothrix* spp. es un complejo de al menos seis especies crípticas, es decir, que tienen características morfológicas similares pero genotipos diferentes. En los gatos, el periodo de incubación es variable; suele durar 14 días. Cuando penetra en el tejido, la forma micelar se transforma en levadura, lo que genera una respuesta inflamatoria y la proliferación del microorganismo en el lugar, causando lesiones papulares y nodulares que en algunos casos curan espontáneamente. Por lo tanto, está claro que la esporotricosis es causada por hongos dimórficos del complejo *Sporothrix schenckii*. Se trata de una enfermedad zoonótica de gran importancia en el contexto de la salud pública, ya que sigue siendo una enfermedad desatendida y requiere medidas energéticas para su control. Además, los felinos, además de ser los más gravemente afectados, son los principales transmisores a humanos y animales, siendo por tanto un punto clave en el control de los brotes de la enfermedad.

Palabras clave: Esporotricosis; Hongos; Medicina veterinaria; Micología; Zoonosis.

1. Introduction

Sporotrichosis is an infectious and chronic fungal disease caused by fungi belonging to the *Sporothrix schenckii* complex that affects humans and animals through traumatic implantation of the fungus in the skin. The complex includes six main species, which are: *S. albicans*, *S. brasiliensis*, *S. globosa*, *S. luriei*, *S. mexicana* and *S. schenckii* (Cruz, 2013).

They are dimorphic, saprophytic and geophilic fungi that are widely distributed in nature, mainly in soils rich in organic matter, dry plants, wood and mosses (Lopes-Bezerra et al., 2006; Antunes et al., 2009), as these places are humid, warm and lack light, which favors the growth and reproduction of the fungus (Gusmão, 2017); *S. schenckii* being the most common species in this complex (Lopes-Bezerra et al., 2006; Antunes et al., 2009).

Due to its thermal dimorphism, *Sporothrix* spp. presents in mammals or *in vitro*, yeast-like cells in parasitic form at 35-37°C and filamentous form at 25°C, a range of 30-37°C being considered optimal for this fungus for its growth (Orofino-Costa et al., 2017).

Sporotrichosis has a worldwide distribution, with a predilection for tropical and subtropical areas, and is considered the most important subcutaneous mycosis in Latin America. It is considered a neglected disease and a public health problem, as it results from the absence of a control program or actions at a national level and the lack of diagnostic capacity in most of the municipalities affected (Greene, 2006). The aim of this study was to understand the clinical, mycological, environmental and epidemiological aspects of the *Sporothrix schenckii* complex in felines.

2. Methodology

This work presents a literature review of a qualitative nature, where the procedure is characterized by the author's approach to interpreting phenomena without trying to discover or calculate events, and often without the use of statistical tools to evaluate the information (Pereira et al., 2018). In addition, the research has a descriptive nature that aims to assimilate the phenomenon under study and its specificities in order to accurately specify events and phenomena as established facts (Triviños, 1987; Godoy, 1995). It is also exploratory in that the aim is to broaden the understanding of a phenomenon (Gil, 2002).

The guiding question was: "What clinical, mycological, environmental and epidemiological aspects of the *Sporothrix schenckii* complex in cats have already been addressed in the literature?" The search was carried out in the SciELO database, using the descriptors: "Sporotrichosis", "Feline Sporotrichosis", "Felines", "*Sporothrix schenckii* complex" and "Clinical aspects"; as well as using the Boolean operators AND and OR. Manual searches were also carried out on the Google Scholar website to fill in possible gaps in the data to complement the research.

The inclusion criteria were: course completion papers, dissertations, theses and complete national and international articles, available free of charge, published in the last 23 years. The exclusion criteria were: papers that dealt with another form of sporotrichosis other than feline sporotrichosis; as well as abstracts and studies with a design that did not address the topic in question.

3. Results and Discussion

3.1 Etiological agente

The causative agent of sporotrichosis is a thermodimorphic fungus of the genus *Sporothrix* spp. The first reported human isolation of *Sporothrix* spp. dates back to 1898, by Benjamin Schenk in the United States. However, it was only in 1900, two years after the isolation, that the fungus was described by Hektoen and Perkins and, in addition to describing its dimorphism, also identified its class and genus (Rodrigues et al., 2020), which was later named *Sporothrix schenckii* (Chakrabarti et al., 2015).

The first cases of sporotrichosis in humans and rodents were described in Brazil in 1907 by Lutz and Splendore. Before the different pathogenic species belonging to the *Sporothrix* genus were known (De Beer, Duong, Wingfield, 2016), sporotrichosis was attributed to a single pathogen, *S. schenckii*, which was considered a fungus with low virulence (López Romero et al., 2011). Subsequently, advances in molecular research have demonstrated the existence of different species, as well as the high capacity of fungi to adapt to the places in which they are isolated, a factor that is capable of influencing the exacerbation of the virulence of some species (Rojas et al., 2018).

Sporothrix spp. is considered to be a complex of at least six cryptic species, i.e. they have similar morphological characteristics but different genotypes. Among them, *Sporothrix brasiliensis* is the most virulent because it has a strong ability to invade tissues and cause death (Marimón Picó et al., 2008; Zhang et al., 2015; Orofino-Costa et al., 2017). The literature reports that the most common species are: *S. brasiliensis*, *S. schenckii*, *S. chilensis*, *S. luriei*, *S. globosa*, *S. pallida* and *S. mexicana* (Brandolt et al., 2019). These species are divided into different clades, with the most aggressive species belonging to the clinically important clade in human infections: *S. brasiliensis* (clade I) and *S. schenckii* (clade II), which are reported most frequently; including *S. globosa* (clade III) and *S. luriei* (clade IV) (Rangel-Gamboa et al., 2016). Other species make up the environmental clade but, to date, are of lesser medical importance (Caus et al., 2019; Paiva et al., 2020).

Belonging to the Kingdom Fungi, the species of the *Sporothrix schenckii* complex have the Division Ascomycota, Class Pyrenomycetes, Order Ophiostomatales, and Family Ophiostomataceae. They are heterotrophic and eukaryotic, have no motility of their own and contain hard, chitinous cell walls. They live saprophytically in nature and are pathogenic to humans and animals (Guarro et al., 1999). They are dimorphic fungi that initially appear as white colonies during the saprophytic stage or when grown at 25°C on media such as malt extract agar or potato dextrose agar after 21 days, gradually turning brown to black as dark conidia form (Figure 1A) (Kwon-Chung & Bennett, 1992).

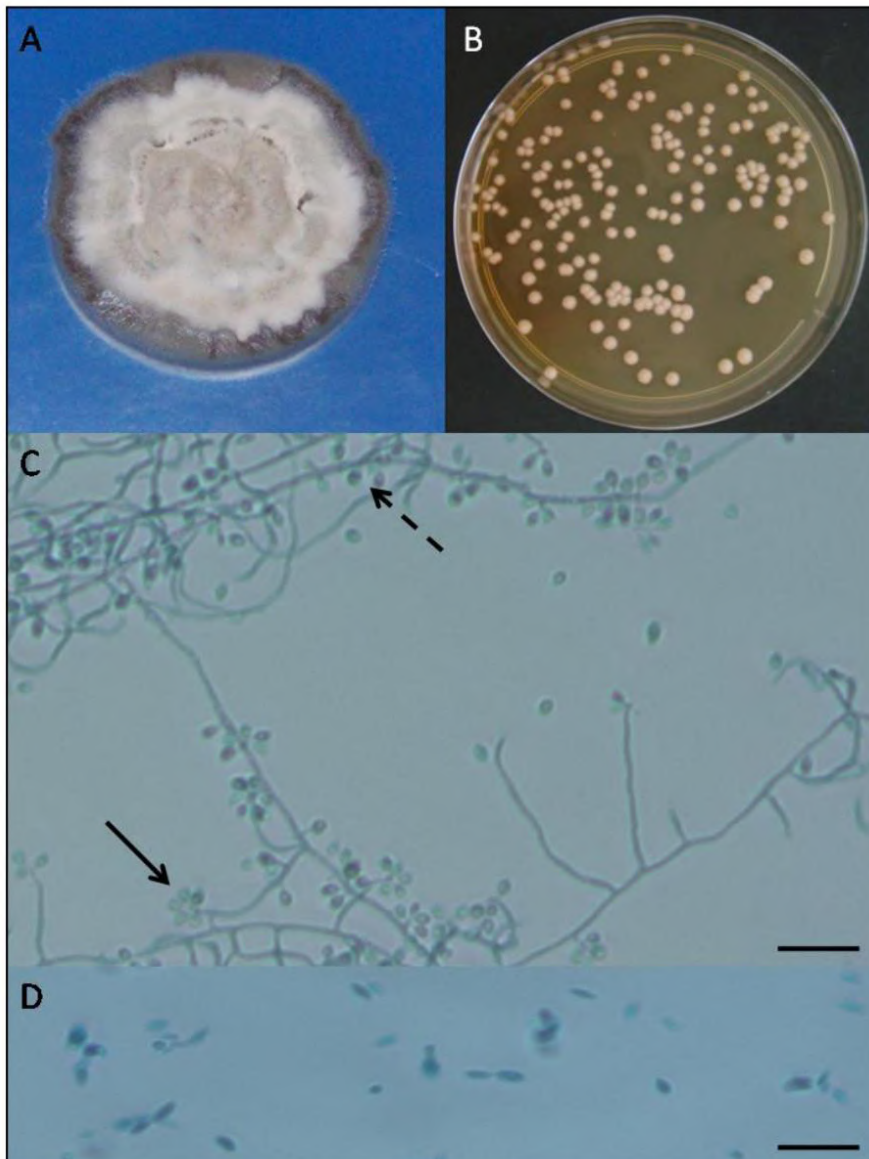
However, some strains have the ability to form dark colonies from the start of growth (Zancopé-Oliveira et al., 2011). Colonies of *Sporothrix* spp. in filamentous form will never become cottony or floccose (Kwonchung & Bennett, 1992). Microscopically, they appear as hyaline, septate hyphae and unicellular conidia, either dematiaceous or not, sessile or arranged in conidiophores (ST-Germain & Summerbell, 1996), in (Figure 1C) a microculture of the filamentous form stained with lactophenol cotton blue at (400X magnification). The solid arrow shows a sympodial conidiophore and the dashed arrow points to a dematiaceous conidium.

The species of *Sporothrix* spp. cultivated or parasitized at 35-37°C have yellowish-beige colonies with a creamy appearance (Rippon, 1988), where in (Figure 1B) yeast-like colonies are observed on BHI (Brain Heart Infusion) agar after 10

days of incubation at 36°C. Microscopically, they appear as oval, globose or cigar-shaped unicellular yeasts that may have one or more buds (Zancopé-Oliveira et al., 2011), as in (Figure 1D) there is a microscopy of yeast cells stained with lactophenol cotton blue showing cigar-shaped buds at (400X magnification).

Sporothrix spp. grown or parasitized at 35-37°C have yellowish-beige colonies with a creamy appearance (Rippon, 1988). The transition of *Sporothrix* spp. from filamentous to yeast-like form can be achieved by culturing fragments of mycelia and conidia at 35-37°C in a rich medium such as BHI agar. This transformation process also occurs when patients are infected with the filamentous form (Freitas, 2014).

Figure 1 - Morphology of the genus *Sporothrix* spp.



Source: Adapted from Almeida-Paes, 2012, p. 3. Note: Bars: 10 µm.

3.2 Clinical aspects of the *Sporothrix schenckii* complex in felines

In cats, the incubation period varies. The process usually lasts 14 days, but in some cases it can take several months for clinical symptoms to appear (Gremião et al., 2021). The agent does not penetrate intact skin and requires continuous solution for infection to occur (Santos et al., 2018). Therefore, this condition often occurs after a traumatic event, such as bites

and scratches from cats, which harbor the fungus in their nails and oral cavity (Lecca et al., 2020).

When it penetrates the tissue, the micellar form turns into yeast, which generates an inflammatory response and proliferation of the microorganism at the site, causing papular and nodular lesions that in some cases heal spontaneously (Jericó et al., 2015). Initially, the lesions may resemble a bite abscess or cellulitis and are sometimes treated incorrectly with antibiotics, and consequently unsuccessfully. Subsequently, these lesions become ulcerated wounds that drain purulent or reddish-brown exudate (Santos et al., 2018).

Large, painless crusts form, with raised edges that drain the exudate. The inflammation is usually pyogranulomatous, containing multinucleated and epithelioid macrophages in the center of the lesion; as well as lymphocytes and plasma cells in the periphery (Mcvey et al., 2016). Normally, in cats, the fungus reaches the lymphatic and hematogenous pathways, causing lymphadenitis and spreading to other organs, which is characteristic of the cutaneous-disseminated form of the disease (Santos et al., 2018). The pathogen has been isolated from the lungs, heart, spleen, liver, lymph nodes, brain, kidneys and adrenal glands in autopsies of infected cats (Gremião et al., 2021).

Sporotrichosis has the potential to be transmitted by inhalation, as the fungus has been isolated from the nasal cavity, lungs and bronchoalveolar lavage of infected animals. In addition, cats often develop respiratory symptoms and lesions on the nasal mucosa membrane (Gremião et al., 2021). The clinical manifestations of the disease in cats vary and can appear as mild lesions, as single cutaneous lesions, or as systemic lesions through hematogenous spread (Jackson & Marsella, 2012).

Clinical manifestations are divided into cutaneous and extracutaneous based on their distribution. Cutaneous infections can be localized, lymphocutaneous and disseminated. Extracutaneous infections mainly affect the lungs or can affect other areas such as the joints, kidneys and liver, eyeballs and nervous system. Infected animals often show more than one clinical manifestation at the same time (Megid et al., 2016).

The disseminated cutaneous form is more common in cats with sporotrichosis and also involves the nasal mucosa membrane. The oral mucosa membrane, genitalia and conjunctiva can also be involved. In addition, lymphadenomegaly is frequently observed in these cases (Gremião et al., 2021). According to a 2004 study by Schubach and collaborators, they evaluated 347 cats with sporotrichosis, with most of the skin lesions located in the head region, specifically on the muzzle, ears and thoracic extremities, although they can also be present in any other part of the body, (Figure 2).

Figure 2 - Felines with characteristic lesions for sporotrichosis.



Source: Adapted from Sales (2021, p. 69).

When cats get into fights, usually over territorial disputes or for mating, they tend to bite and scratch the facial region, showing a higher incidence of lesions in this area (Santos et al., 2018). The wound has an ulcerated appearance, with raised

edges and an ulceronecrotic center, and may be covered by a bloody-purulent crust and secretion of purulent exudate. In addition, they can have the appearance of a nodule, tumor, evolving to liquefaction necrosis and acquiring a gummy appearance (Megid et al., 2016). The areas of necrosis can be severe, exposing muscle and bone tissue in some cases (Greene, 2006). In general, despite the severity of the lesions and mucosal involvement, the feline's general health is good (Gremião et al., 2021).

In the extracutaneous form of the disease, the main problem is the respiratory system, with sneezing and difficulty breathing being the most common symptoms (Schubach et al., 2004). These symptoms can occur even in animals without skin lesions, and may even precede their appearance. In addition, respiratory involvement is associated with cases of treatment failure and death, resulting in a poor prognosis for affected animals. Other non-specific signs, such as lethargy, anorexia, fever and apathy, should draw attention to the possibility of a systemic form of the disease (Gremião et al., 2021).

Immunocompromised animals may be associated with a greater likelihood of developing the disease systemically (Megid, Ribeiro, Paes, 2016). However, in the aforementioned study by Schubach et al. (2004), cats co-infected with retroviruses such as feline immunodeficiency virus (FIV) or feline leukemia virus (FeLV) did not show significant clinical and laboratory changes; for those without concomitant medical conditions.

3.3 Mycological aspects of the *Sporothrix schenckii* complex in felines

In laboratory diagnosis, the components of *Sporothrix* spp. are rarely visible on direct examination (Kwon-Chung & Bennett, 1992; Zancopé-Oliveira et al., 2011). Sometimes, in Giemsa-stained smears, a yeast-like cigar or navette shape can be seen with a halo around it. The isolation of *Sporothrix* spp. from the culture of clinical samples, such as exudate, scrapings from lesions or sputum, is the gold standard (Rippon, 1988; Kwon-Chung & Bennett, 1992; Penha & Bezerra, 2000; Lacaz, 2002; Zancopé-Oliveira et al., 2011).

Megid, Ribeiro and Paes, 2016, state that mycological culture is the gold standard for diagnosis. Samples are preferably obtained by biopsy, but curettage and swabs from lesions can also be used. And to obtain a positive result, the growth of the agent must occur in both morphological forms of *Sporothrix* spp. On BHI agar at 37°C, the fungus develops into yeast, with moist and creamy colonies, white or yellow in color (Megid et al., 2016).

When the fungus is sown on Sabouraud agar (containing antibiotics), colonies will appear within three to five days, but this period can be extended to four weeks. When observing the culture under a microscope at room temperature, one sees the mycelial form, with thin, hyaline, septate and branched hyphae, and oval or pyriform unicellular conidia, arranged along the hyphae in the form of a cluster or bouquet; these conidia are dematiaceous or hyaline. As *Sporothrix* spp. exhibit reversible thermal dimorphism, they become yeasts when grown at 35-37°C (Rippon, 1988; Kwon-Chung & Bennett, 1992; Penha & Bezerra, 2000; Lacaz, 2002; Zancopé-Oliveira et al., 2011).

In this form, the fungus reproduces by budding and does not form conidia. In order to confirm the diagnosis, the dematiaceous conidia-producing fungus must be converted from a filamentous to a yeast-like form (Rippon, 1988; Kwon-Chung & Bennett, 1992; Penha & Bezerra, 2000; Lacaz, 2002; Zancopé-Oliveira et al., 2011). The disadvantages of this methodology include contamination of cultures with other pathogens, time-consuming results and the need for a biosafety level II laboratory to handle the agents (Gremião et al., 2021).

3.4 Environmental aspects of the *Sporothrix schenckii* complex in felines

Sporotrichosis falls within all the areas offered by One Health, considering that the fungus is transmitted via zoonotic agents and present in nature. Recognizing this, greater coverage of human and animal populations in diagnosis, assistance and

awareness to prevent and control the occurrence of diseases can only be achieved through public policies and multidisciplinary teams (Gremião et al., 2020).

For this scenario to become a reality, one of the relevant issues is public awareness; this includes responsible guardianship. Research carried out in Belo Horizonte - Minas Gerais, Brazil, showed that cats on the streets were three times more likely to test positive than animals confined at home. In addition to management, responsible ownership also comes from taking care of the animals' health, controlling their numbers in the same place and neutering them as a way of avoiding future litters. And due to behaviors such as aggression and the possibility of running away, habits that increase the risk of exposure and transmission of pathogens (Lecca et al., 2020).

3.5 Epidemiological aspects of the *Sporothrix schenckii* complex in felines

Sporotrichosis is a worldwide fungal disease, with cases reported on all continents except Antarctica (Santos et al., 2018). It is more common in countries in tropical and subtropical regions where temperature and humidity conditions favor saprophytic forms of the fungus in the environment, although studies have reported resistance in species of *Sporothrix* spp. to drastic changes in temperature (Ramírez-Soto et al., 2018).

Cases of feline sporotrichosis have been reported in Argentina, Australia, Brazil, Japan, Malaysia, Mexico, Paraguay, Spain, the United Kingdom, Thailand and the United States of America (Gremião et al., 2021). In Brazil, *S. brasiliensis*, discovered in 2007, is the most reported zoonotic pathogen and is commonly found in feline and human lesions, but no isolated strains have been found in studies of soil samples (Orofino-Costa et al., 2017). This pathogen is associated with high virulence, systemic and exacerbated disease, antifungal resistance in cats and severe cases in human patients, leading to hospitalization and death (Gremião et al., 2021).

Four years ago, the fungus was associated with localized cases in Argentina and there were warnings about the possibility of it spreading across borders (Gremião et al., 2020). The disease is popularly referred to as "gardener's mycosis" or "rose mycosis", because human cases have been correlated to activities such as handling plants and soil; exposure to saprophytic forms of the pathogen and creating pathogen inoculation through incisions in the skin and subcutaneous tissue (Orofino-Costa et al., 2017; Podestá Junior et al., 2022).

Domestic cats are the most affected and are considered the largest reservoir of disease among animals and a key point for zoonotic transmission (Gremião et al., 2017). Domestic cats have a habit of scratching and climbing trees, digging and hiding feces on the ground, rubbing against objects in the environment and getting into fights. Therefore, in addition to the large amount of agents already contained in the lesions, infected cats also carry the fungus on their teeth and nails, making them the main spreaders of sporotrichosis (Larsson, 2011).

Healthy cats do not have large populations of the fungus in the oral cavity and nails, so they do not appear to have zoonotic potential (Gremião et al., 2021). Males who have not been neutered and are allowed out on the streets are of greater epidemiological importance, because they are more likely to be involved in fights over territory and females. In addition, bites and scratches can occur during mating, increasing the likelihood of inoculation (Andrade et al., 2021).

The first case of feline sporotrichosis in Brazil occurred in 1950 and, until the 1990s, reports of the disease were sporadic and did not appear to be a public health problem. Since then, cases have increased significantly, with outbreaks involving dogs, cats and humans reported in various locations, mainly in the south and southeast of Brazil (Gremião et al., 2021). Although the disease also affects other states, none has a similar situation to Rio de Janeiro, Brazil, which is considered to be highly endemic for sporotrichosis (Gremião et al., 2017).

According to the Evandro Chagas National Institute of Infectious Diseases, 5,113 cases were recorded in cats between

1998 and 2017, and 244 cases in dogs between 1998 and 2014. The number of cases in dogs is high, but no zoonotic transmission involving them has been documented, possibly because the affected dogs usually only have localized lesions with a reduced presence of infectious agents (Gremião et al., 2021).

The epidemic in Rio de Janeiro (Brazil) is evidenced by the massive expansion of the city in recent decades and the increase in interactions between humans and animals. There are a large number of cats living on the streets, most of which are not vaccinated, neutered, dewormed or ectoparasitically controlled. In this case, the possibility of other concomitant infectious diseases contributing to susceptibility to sporotrichosis cannot be ruled out (Gremião et al., 2017). The state of Rio de Janeiro did not include sporotrichosis on the list of notifiable diseases until 2013, so the prevalence and incidence data may be underestimated and lack information from previous years (Gremião et al., 2021).

And with the awareness and dissemination of the seriousness of sporotrichosis in Brazil, some states and cities have also adopted the same measures, among them: Mato Grosso do Sul, Paraíba, Pernambuco, São Paulo and Guarulhos (SP), Belo Horizonte and Conselheiro Lafaiete (MG) and Camaçari (BA) (Falcão et al., 2019). Sporotrichosis is therefore a serious public health problem in Brazil. In addition to the proper disposal of carcasses, outbreaks need to be combated and contained through awareness programs on responsible ownership and health education, feline neutering, diagnosis, treatment and affordable monitoring of affected individuals. It is also important to keep cats indoors and limit their access to the streets and contact with other animals (Santos et al., 2018).

4. Final Considerations

It is concluded that the study achieved the proposed objectives, without generating any gaps in the research and succeeding in solving the study problem. Therefore, it became clear that sporotrichosis is caused by dimorphic fungi of the *Sporothrix schenckii* complex. It is a zoonotic disease of great importance in the context of public health, since it is still a neglected disease and requires robust measures for its control.

As well as being the most seriously affected, felines are also the main transmitters to humans and animals, making them a key point in controlling outbreaks of the disease. In addition, unneutered males with access to the street are the most affected, as they are more likely to get involved in fights over females or territory disputes. Given that urban sprawl and the increase in the feline population in cities show that sporotrichosis could become an even bigger problem in the future.

In addition, feline neutering campaigns and education on responsible guardianship are essential to prevent and contain new outbreaks. Finally, it is essential to fund and encourage research into sporotrichosis in cats, which will lead to the discovery of new drugs and therapeutic protocols that are more effective and have fewer adverse effects.

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