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Review Article

Feline sporotrichosis: epidemiological and clinical aspects

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Abstract

Feline sporotrichosis, which is caused by species of the *Sporothrix schenckii* complex, is endemic to Rio de Janeiro, Brazil. More than 4000 cases of the disease were diagnosed at Fundação Oswaldo Cruz, Brazil, between 1998 and 2012. Sporotrichosis in cats has been reported in several countries, but nowhere has an outbreak of animal sporotrichosis been as large as that seen in Brazil. The clinical manifestations of the disease range from an isolated skin lesion that can progress to multiple skin lesions and even fatal systemic involvement. Nodules and ulcers are the most common types of lesions, and respiratory signs and mucosa involvement are frequent. The definitive diagnosis depends on isolation of the etiologic agent in culture. Cytology, histopathology, and serology are useful tools for preliminary diagnosis. Severe pyogranulomatous inflammatory infiltrate, high fungal load, and extension of lesions to mucosa, cartilage, and bone in the nose of cats are indicative of an agent of high virulence in this endemic region. Itraconazole is the drug of choice, while, in refractory cases, amphotericin B or potassium iodide might be alternative treatments; however, recurrence after discharge may occur. Sporotrichosis persists as a neglected disease in Rio de Janeiro, and the treatment of cats remains a challenging and long-term endeavor.

Key words: *Sporothrix* sp., cat, zoonosis, diagnosis, therapy.

Epidemiology

Sporotrichosis is a worldwide mycosis that results from implantation of the conidia of four pathogenic thermodimorphic members of the genus *Sporothrix* [1]. The disease has been reported in humans and animals; in the state of Rio de Janeiro, Brazil, it mainly affects cats [2]. In Brazil, the most prevalent etiological agent and primary pathogen of feline sporotrichosis is *Sporothrix brasiliensis* [3].

In the past 16 years, zoonotic transmission of *Sporothrix* from scratches, bites, or contact with sick cats has been reported in Brazil [4]. Sporotrichosis was found in more than 4000 humans [5] and 3804 cats at the Instituto de Pesquisa Clínica Evandro Chagas (IPEC)/Fundação Oswaldo Cruz

(Fiocruz), Rio de Janeiro, Brazil, between 1998 and 2011 [2], emphasizing the importance of this mycosis as a public health problem [4]. Currently, it is very difficult to determine the scale of feline epizootic sporotrichosis because reporting of this disease is not required. In addition, these numbers represent only those feline cases registered at IPEC/Fiocruz, a national reference center of fungal diseases, thus accounting for the probable majority of cases [2]. From January 2012 through December 2012, 320 new feline cases were diagnosed at this institution.

Sporotrichosis in cats has been reported in several countries, but nowhere has an outbreak of animal sporotrichosis been as large as that seen in Brazil [2]. Feline cases have been described in other Brazilian states, especially in Rio Grande do Sul [6,7] and São Paulo [8]. However, the number of cases in these regions is small compared with the epidemiological situation that is occurring in Rio de Janeiro [2].

Clinical aspects

Feline sporotrichosis has a broad spectrum of clinical manifestations, ranging from a subclinical form that can progress to multiple skin lesions to the fatal disseminated systemic forms [9]. A higher occurrence of the disease is found in adult male, mongrel, and unneutered cats [2].

The most frequent clinical manifestations noted in cats are multiple skin lesions with mucosal involvement, especially mucous membranes of the respiratory tract. Clinically, the skin lesions are characterized by nodules and ulcers and can be found at three or more noncontiguous anatomical sites, commonly on the head, especially on the nose (Fig. 1,2), as well as lymphangitis and lymphadenitis [9].

Extracutaneous signs, particularly respiratory signs (sneezing, dyspnea, and nasal discharge) and mucosa involvement, are also frequently noted in cats. The occurrence of respiratory signs is associated with treatment failure and death [10]. However, the isolation of *S. schenckii* from nasal swabs and the occurrence of sneezing may precede the appearance of skin lesions in some cases. Significant clinical and laboratory test results were not found among feline immunodeficiency virus (FIV)– and/or feline leukemia virus (FeLV)–coinfected and non-coinfected animals [9].

Figure 1. Feline sporotrichosis: lesions located on the face.

Figure 2. Feline sporotrichosis: ulcer on the bridge of the nose.

The prognosis for cats depends on the number, extent, and location of the lesions; the occurrence of respiratory signs; and the cat's general medical condition. Feline sporotrichosis is hard to treat and requires a long period of daily care; also, cats do not always respond well to treatment. Owner cooperation and persistence are necessary for successful treatment [11].

Laboratory diagnosis

The definitive diagnosis of feline sporotrichosis requires isolation of the etiologic agent in culture and its species identification by morphologic studies and physiologic phenotyping of the isolate, as well as by polymerase chain reaction targeting of the calmodulin gene [3,11]. Due to their high sensitivities, cytology and histopathology are very useful tools for obtaining a preliminary diagnosis of this disease in cats. Using skin lesion samples from cats, along with recovery of *Sporothrix* in culture, the sensitivity of cytology using a Romanowsky-type stain is 79% and the sensitivity of histopathology using Grocott methenamine silver (GMS) is 94% [12,13]. Other options for histologically identifying the yeast-like forms or hyphae of *Sporothrix* are by periodic acid Schiff (PAS) and immunohistochemistry; however, their sensitivities in cats have not been evaluated. Histologically, the lesions of feline sporotrichosis are characterized by a pyogranulomatous inflammatory reaction with a low frequency of well-formed granulomas

and high fungal loads [9,13]. These lesions and yeast-like forms are primarily observed in the skin but may also be found in the lungs, liver, lymph nodes, kidney, and adrenal glands [14,15]. The enzyme-linked immunosorbent assay may be used as a sensitive and specific screening tool for the detection of *Sporothrix* antibodies in the serum of cats with sporotrichosis [16].

Histological alterations in the nose

In cats with sporotrichosis, most lesions refractory to antifungal treatment as well as lesions that reoccur after clinical cure are found on the nose [17,18]. Since little is known about the histological lesions in the nasal regions of such infected cats, a study aiming to describe the pathological changes in the nasal region of cats with sporotrichosis from Rio de Janeiro, Brazil, was conducted at IPEC/Fiocruz between 2008 and 2011.

Thirty-three cats with a definitive diagnosis of sporotrichosis that had lesions in the nose were examined. Of these, 17 had no previous history of treatment for sporotrichosis (group 1), and the lesions of 16 were refractory to oral itraconazole (ITZ) at doses of 8.3–27.7 mg/kg every 24 hours (group 2). Ten (62.5%) of the 16 cats with infections that were resistant to ITZ were also found to be refractory to oral potassium iodide (KI; 2.5–20 mg/kg every 24 hours) or ITZ at the same dose in combination with intralesional (IL) or subcutaneous (SC) administration of amphotericin B deoxycholate (AMB; 1 mg/kg and 0.5 mg/g, respectively, either once a week or every other week). The cats were considered resistant to treatment when lesions remained the same or became worse after 8 weeks of treatment. The cats were euthanized and necropsied, including the entire nose, that is, the external nose and nasal cavity, and tissue sections were fixed in 10% buffered formalin and then processed for regular paraffin embedding. Tissue sections were stained with hematoxylin-eosin, PAS, and GMS [19]. Pearson χ^2 test or Fisher exact test was used to evaluate the association between both groups and the variables of the type of granuloma, extension and intensity of inflammatory infiltrate, fungal load, and frequency of hyphae. A P value <0.05 indicated a statistically significant association.

Pyogranulomatous dermatitis and rhinitis were observed in 100% of the cats examined. Poorly organized granulomas were noted in 94.1% of cats in group 1 and in 93.8% of cats in group 2; this is in contrast with well-organized granulomas in 5.9% of cats in group 1 and in 6.3% of cats in group 2. In the group 1cats, the intensity of inflammatory infiltrate was severe (more than 30 inflammatory cells per high-power field) in the skin and nasal mucosa of 100% of cats. The pyogranulomatous inflammatory infiltrate with the presence of *Sporothrix* extended to the dermis in 94.1%, subcutaneous tissue in 82.4%, subjacent skeletal muscles in 64.7%, bone in 41.2% (Fig. 3A), bone marrow in 58.8% (Fig. 3B), hyaline cartilage of vestibule in 23.5% (Fig. 3C), mucosa of vestibule in 82.4%, respiratory mucosa in 52.9%, and mucosa of nasal concha in 41.2%. In group 2 cats, the intensity of the inflammatory infiltrate was severe in the skin of 93.8% and in the nasal mucosa of 100%. The pyogranulomatous inflammatory infiltrate with *Sporothrix* present extended to the dermis in 93.8%, subcutaneous tissue in 93.8%, subjacent skeletal muscles in 56.3%, bone in 12.5%, bone marrow in 18.8%, hyaline cartilage of vestibule in 18.8%, mucosa of vestibule in 100.0%, respiratory mucosa in 68.8%, and mucosa of nasal concha in 37.5%. The following were observed in cats from both groups: ulcers, degeneration of collagen, hemorrhages and dermatofibrosis in the skin; osteomyelitis with lyses of bone (Fig. 3A,B); necrosis of hyaline cartilage of the vestibule (Fig. 3C); ulcers, thickening (Fig. 3D), microabscesses, hemorrhages, and necrosis of mixed glands in the nasal mucosa. Cigar-shaped or round to oval and budding yeast-like forms of *Sporothrix* were observed in 100% of cats examined. A high fungal load (more than 25 yeast-like forms per high-power field) was observed in 82.4% of cats in group 1 and 93.8% of cats in group 2. Hyphae (Fig. 3E) were found in 11.8% of cats in group 1 and in 62.5% of cats in group 2. The hyphae were localized within macrophages and extracellular in the dermis, subcutaneous tissue, nasal mucosa (Fig. 3E), and bone marrow. The yeast-like forms were observed intracellularly within neutrophils, macrophages, giant cells, and osteoclasts (Fig. 3F) or extracellularly. The only statistical difference between both groups was observed in the frequency of hyphae, which was higher ($P = 0.004$) in group 2.

The high frequency of severe pyogranulomatous inflammatory infiltrates, high fungal loads, and extension of lesions to mucosa, cartilage, and bone associated with *Sporothrix* spp. in the nose of cats in both groups indicate that the fungus was highly virulent in the endemic region of Rio de Janeiro. In addition, the antifungal treatment used in this study did not minimize the severity of lesions and did not prevent multiplication of fungal elements in the noses of the cats examined. The higher frequency of hyphae in the noses of cats of group 2 may be related to the use of antifungal drugs. These results indicate that lesions on the nose of cats with sporotrichosis are difficult to treat and that the severity and extension of the lesions observed may hinder their healing.

Therapy

Treatment of feline sporotrichosis presents a challenge, as there are a limited number of oral antifungal agents,

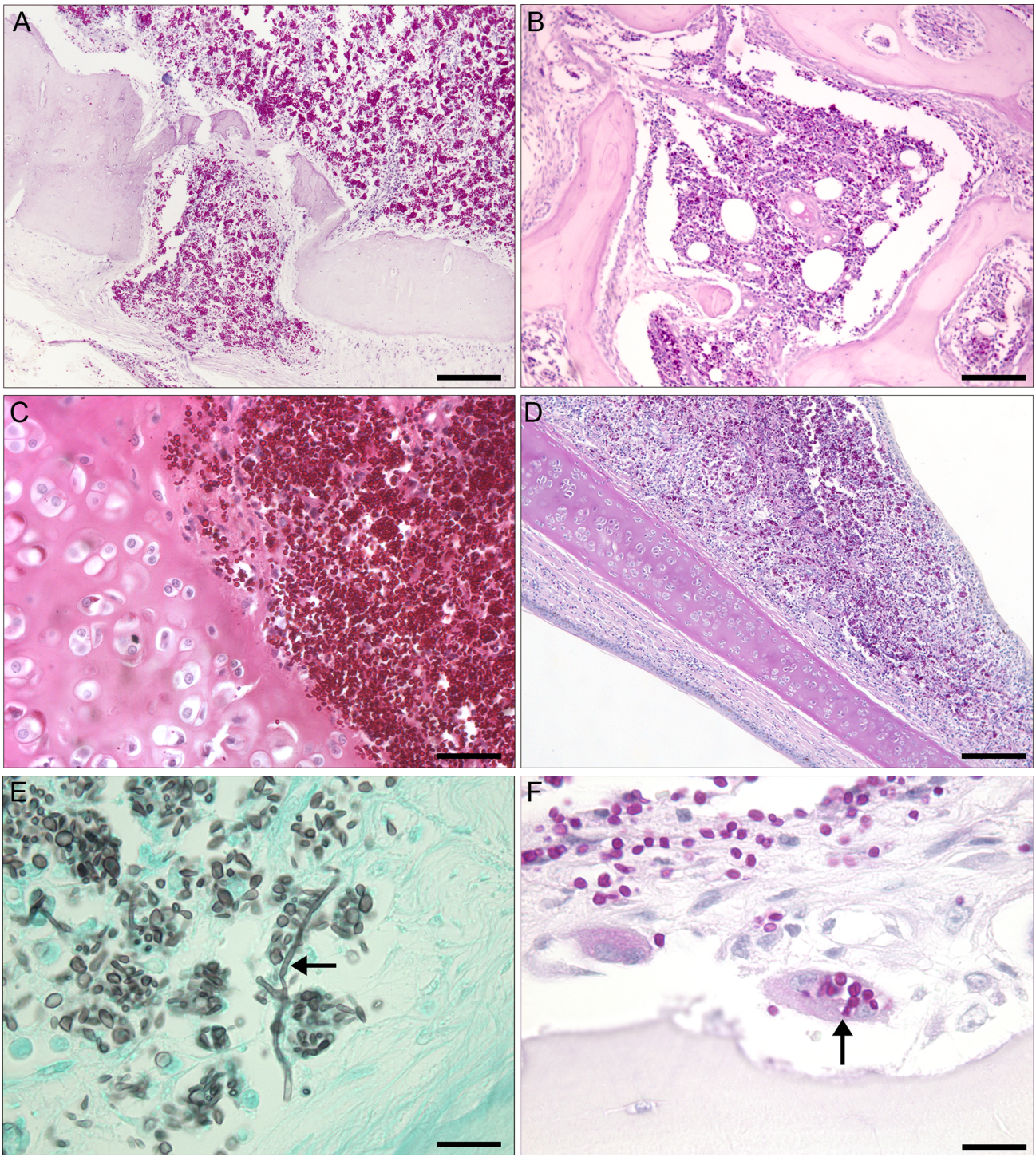

Figure 3. Histological alterations in the nose of cats with sporotrichosis. (A–C) Cats receiving no treatment. (A) Severe pyogranulomatous rhinitis showing lyses of osseous tissue and several yeast-like forms within macrophages; periodic acid Schiff (PAS), bar = 0.15 mm. (B) Severe pyogranulomatous osteomyelitis showing several yeast-like forms of *Sporothrix* within macrophages in the bone marrow; PAS, bar = 0.15 mm. (C) Mucosa of vestibule showing several yeast-like forms within macrophages or extracellular invasion and causing necrosis of hyaline cartilage; PAS, bar = 0.04 mm. (D, E) Cats refractory to treatment with itraconazole. (D) Severe pyogranulomatous rhinitis showing unilateral thickening of the mucosa of the vestibule and several yeast-like forms; PAS, bar = 0.15 mm. (E) Several cigar-shaped or round to oval yeast-like forms and a hypha (arrow) in the mucosa of the vestibule; Grocott methenamine silver, bar = 0.01 mm. (F) Cat with no previous history of treatment for sporotrichosis. Osteomyelitis showing cigar-shaped or round to oval yeast-like forms that were located extracellularly or within an osteoclast (arrow) and macrophages; PAS, bar = 0.01 mm.

and these agents have adverse effects and high cost. Iodides, ketoconazole (KTZ), ITZ, AMB, terbinafine, local heat therapy, and surgical removal of lesions are the current treatment options available for treating this infection in cats [20]. The azoles and KI are the most common drugs used to treat feline sporotrichosis [10,18], and clinical cure is observed regardless of the initial clinical findings or coinfection with FIV and/or FeLV. Treatment may take a few weeks to several months (median time, 4–9 months) and must be continued for at least 1 month after clinical cure. Recurrence may occur, demonstrating the possibility of reactivation of the lesions in spite of ending treatment [10,17,21].

In the past, KI (10–20 mg/kg every 12–24 hours) was used to treat the infection; however, there were serious adverse effects associated with its use in cats that, in turn, led to its replacement with safer and more effective antifungal drugs such as the azoles. In feline sporotrichosis, there are few reports of cases having been treated with a supersaturated solution of potassium iodide (SSKI), the results being inconclusive [18,20].

In order to evaluate the effectiveness of KI, a study was conducted of 48 cats with sporotrichosis. KI was manipulated in capsules, as it is convenient and easy to administer when compared with SSKI. The median dose used was lower (15 mg/kg every 24 hours) than that established in the literature. The KI cure rate was 47.9% and clinical adverse effects were observed in 52.1% of cases. Compared with previous studies with ITZ and SSKI, KI capsules are an effective alternative for feline sporotrichosis treatment, and its low cost greatly favors its use [18].

KTZ may be used to treat feline sporotrichosis, but it is associated with a high occurrence of adverse effects in cats. ITZ is currently considered the drug of choice. Oral solution is preferred to capsules because it permits more accurate dose measurement and improved absorption and bioavailability at the recommended dose. Consequently, dosages per unit body weight are lower when compared with those for ITZ capsules. However, this formulation is not available in Brazil [11]. The effectiveness and safety of treatment with KTZ (13.5–27.0 mg/kg every 12 or 24 hours) and ITZ (8.3–27.7 mg/kg every 24 hours) were compared in 773 sporotrichosis-infected cats. Treatment was successful in 30.8% of the cats, and the therapeutic response to ITZ was better than to KTZ. Adverse effects were reported in 39.6% of the cats, and there were fewer gastrointestinal adverse effects in cats treated with ITZ. Higher doses were used because of the difficulty in achieving clinical cure with the doses recommended in the literature (5–10 mg/kg every 24 hours) [10].

During the past 16 years that the IPEC/Fiocruz has been monitoring the sporotrichosis epidemic, several cases of cats with refractory lesions have been seen despite conventional oral antifungal treatment. In those cases, KI capsules as monotherapy [Reis EG, Kitada AAB, Carvalho BW, Ornellas RO, Petry LC, Gremião IDF. Treatment of refractory feline sporotrichosis with potassium iodide capsule. XVIII International Congress for Tropical Medicine and Malaria, Rio de Janeiro, Brazil, 2012] or associated with ITZ [Rocha RFDB, Pereira SA, Carvalho BW, et al. Potassium iodide and itraconazole in the treatment of refractory feline sporotrichosis. 1st International Meeting on *Sporothrix* and Sporotrichosis, Rio de Janeiro, Brazil, 2013], as well as IL or SC AMB, might be considered as alternatives [17,20,22].

Reports on the administration of AMB for treatment of feline sporotrichosis are scarce. Intravenous administration (IV) of the drug in cats is limited because of serious adverse effects and because there are no reports of clinical cure through the use of this drug in cats with sporotrichosis. IL administration of AMB, rather than IV administration, was successful when used in combination with oral ITZ in a cat with a skin lesion in the nasal region refractory to triazole without adverse effects [17]. The same therapeutic protocol was used in 26 cats with residual localized skin lesions refractory to ITZ. Clinical cure was achieved in 72.7% of the cats; however, in 27.3%, lesions reoccurred at the same site [22]. The therapeutic response of the SC AMB associated with oral ITZ was described in 17 cats with sporotrichosis presenting with skin and/or mucosal lesions refractory to oral ITZ. The treatment was effective in 35.3% of cases, but relapse, lack of clinical response, and worsening of the lesions also occurred, as did the formation of local sterile abscess [Rodrigues AM, Carvalho BW, Rocha RFDB, Pereira COA, Viana PG, Gremião, IDF. Treatment of feline sporotrichosis with subcutaneous amphotericin B. XXXIII Brazilian Anclivepa Congress, Curitiba, Brazil, 2012].

Lipid formulations of AMB are less nephrotoxic than the conventional drug and their use is indicated for treatment of disseminated forms of sporotrichosis [23]. The use of IV liposomal AMB combined with oral ITZ was successful in a case of feline sporotrichosis refractory to oral ITZ [Pereira AV, Gremião IDF, Pereira SA, et al. Treatment of feline sporotrichosis using itraconazole and liposomal amphotericin B. XXXII Brazilian Anclivepa Congress, Goiânia, Brazil, 2011]. However, the cost of this formulation may be prohibitive [23].

Terbinafine has been effective in the treatment of feline dermatophytosis and other superficial mycoses. However, results are inconclusive regarding its use in the treatment of feline sporotrichosis [11].

Thermotherapy, adjunctive surgical therapy, and cryosurgery are other options for the treatment of feline sporotrichosis [20]. Local hyperthermia was successfully described in a cat presenting with a single ulcer in the

thoracic region [24]. The surgical resection of lesions combined with antifungal therapy can be an alternative after failed medical treatment [25,26]. Use of cryotherapy has been encouraged as a complementary therapy [22,27], and its use in addition to oral ITZ was effective in a cat with sporotrichosis that presented with a persistent refractory skin lesion [Pereira AV, Daiha MC, Pereira SA, et al. Cryosurgery in a cat with localised sporotrichosis refractory to oral itraconazole. 1st International Meeting on *Sporothrix* and Sporotrichosis, Rio de Janeiro, Brazil, 2013].

Specific biosafety procedures to reduce risks during the handling of cats with potential sporotrichosis, such as personal protective equipment, should be followed by veterinarians, technicians, caretakers, and cat owners [28].

To conclude, sporotrichosis persists as a neglected disease in Rio de Janeiro, Brazil, and the treatment of cats remains a challenging and long-term endeavor.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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