Epidemic sporotrichosis

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Purpose of review

Epidemic sporotrichosis is rare and has been related to an environmental source of infection. There were no reports of epizootics before a cat-transmitted epidemic was reported in Rio de Janeiro, Brazil. In the present paper we review the data published on this epidemic.

Recent findings

From 1998 to 2004, 759 humans, 64 dogs and 1503 cats were diagnosed with sporotrichosis in the Evandro Chagas Clinical Research Institute. Of them, 85% of dogs and 83.4% of patients were reported to have had contact with cats with sporotrichosis, and 55.8% of the latter reported cat bites or scratches. Unusual manifestations were diagnosed in humans. Canine sporotrichosis presented as a self-limited mycosis. Feline sporotrichosis varied from subclinical infection to severe systemic disease with hematogenous dissemination of *Sporothrix schenckii*. Sporotrichosis in cats always preceded its occurrence among their owners and their domiciliary canine contacts. The zoonotic potential of cats was demonstrated by the isolation of *S. schenckii* from skin lesion fragments, and from material collected from their nasal and oral cavities.

Summary

Thus far it is not known why sporotrichosis takes on the proportion of an emergent zoonosis in Rio de Janeiro. We alert physicians and veterinarians working outside the epidemic area to the diagnostic challenges involved with sporotrichosis.

Keywords

cat, epidemic, *Sporothrix schenckii*, sporotrichosis, zoonosis

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Introduction

Sporotrichosis is caused by the dimorphic fungus *Sporothrix schenckii*, widely distributed all over the world, especially in tropical and temperate climates. Classically, the infection is acquired through traumatic implantation of *S. schenckii* present in organic matter. The most frequent clinical presentations are the cutaneous and subcutaneous forms with or without regional lymphatic involvement [1,2•].

Sporotrichosis usually occurs in isolated cases or in small family or professional outbreaks [3,4]. Human sporotrichosis has sporadically been related to the scratch or bite of animals [5]. The role of felines in the transmission of the mycosis to humans has, however, gained importance [1,6–9]. Up to now, there was no description of epizootics before a cat-transmitted epidemic was reported in Rio de Janeiro, Brazil [10]. In the present paper we review the data published on this epidemic.

Cat-transmitted sporotrichosis epidemics in Rio de Janeiro

The Evandro Chagas Clinical Research Institute [Instituto de Pesquisa Clínica Evandro Chagas (IPEC)] is a reference center for infectious diseases in Rio de Janeiro. During the period just before the onset of the present emergence of sporotrichosis, from 1987 to 1997, only 13 cases of human sporotrichosis had been recorded at the IPEC. Two of these patients, diagnosed in 1991 and 1997, respectively, reported that their lesions had arisen at a site previously scratched by a cat [11]. In 1998, the first year of the present outbreak, nine cases of human sporotrichosis were seen, three of them reporting a scratch from a cat with cutaneous lesions. Isolation of *S. schenckii* from the cutaneous lesions and from nail fragments of the cats of these domiciliary foci supported the hypothesis of transmission through a scratch in these cases [12].

Since then the number of cases increased steadily [13–16], reaching a total of 1503 cats, 64 dogs and 759 human cases from 1998 to 2004 [17]. Curiously, 85% of dogs and 83% of patients were reported to have had contact with cats with sporotrichosis, and 56% of the latter reported cat bites or scratches [17].

Human sporotrichosis

From 1998 to 2001, 178 human cases of sporotrichosis from this epidemic were described. In that series of cases

there was a predominance of women ($n = 122$; 68%) and age ranged from 5 to 89 years, with a median of 39 years. Domestic activities (30%), followed by students (18%), were the most prevalent occupations and 5% of the patients were veterinarians [16]. The predominance of adult females involved in domestic activities suggests that it is the group most exposed to the fungus by caring for the animals [18•].

Patients infected with HIV either had systemic sporotrichosis or cutaneous sporotrichosis, or did not become ill after exposure to cats with sporotrichosis [17].

Histopathology of 73 biopsy fragments showed a granulomatous infiltrate in 66 (90.4%) and the fungus was visualized in 21 (28.8%) – an unusually high frequency in human tissue lesions [16]. The most frequent clinical presentation was the lymphocutaneous form ($n = 59$; 55.6%), followed by the localized cutaneous form ($n = 45$; 25.3%) and widespread cutaneous lesions ($n = 29$; 16.3%) [16,19]. Five (2.8%) patients presented mucosal involvement, including the nasal cavity in one case and the conjunctiva in four cases [16,20,21]. The lesions were characterized by a wide variety of morphologies: nodules, tubercles, pustules, cysts, gummy lesions, ulcers, ulcerovegetative lesions, verrucose lesions and plaques, accompanied or not by lymphangitis. Lesions were more frequent on the upper limbs (65.2%), followed by the lower limbs (12.9%) and the face (6.2%) [16]. Cutaneous leishmaniasis was the main differential diagnosis [22]. Arthralgia was an associated symptom in 53 (29.8%) patients and five of them presented signs of arthritis [16,23]. Erythema nodosum [24] and erythema multiforme [25] were first associated with sporotrichosis. These exceptional presentations may be explained by different mechanisms such as repeated inoculation during long-lasting contact with sick animals, self-inoculation, bloodstream dissemination, or aspiration of conidia and/or yeast forms from cat lesions or sneezes [19,26]. Additionally, continuous exposure to large amounts of fungi and subclinical reinfection may have resulted in hypersensitivity [24]. The enzyme-linked immunosorbent assay has been used for the serodiagnosis of several clinical forms of sporotrichosis and to monitor therapeutic response to itraconazole treatment [27,28•,29•].

Of the 178 patients, 13 (7.3%) presented spontaneous regression of the lesions and 165 (92.7%) started specific treatment with itraconazole administered orally at the dose of 100 mg/day for 4–36 weeks (median 12 weeks), with rare adverse effects. Of these 165 patients, 149 (90.3%) were cured and 16 (9.7%) were lost to follow-up. In five of nine diabetic patients, treatment lasted 16–24 weeks and three required higher itraconazole doses of 200–400 mg/day. Four other patients with chronic obstructive pulmonary disease and nine alcoholic patients presented a satisfactory response to treatment with 100 mg/day itraconazole. All patients were followed-up for 6 months to 1 year after the end of therapy and many of them remained in contact with cats with sporotrichosis. Only two patients relapsed and were treated again, both of them being cured after retreatment with itraconazole [16].

Between 1998 and 2004, 81 cases of sporotrichosis were diagnosed in children younger than 15 years. There was a predominance of girls aged 10–14 years. Thirty-three (41%) of the patients reported some type of injury, including the scratch or bite of a cat with sporotrichosis in 29 (36%) and diverse injuries in four (5%). Of the 48 (59%) children without a history of trauma, 42 (52%) had domiciliary contact with a cat with sporotrichosis. A cat was the probable source of infection in 73 (90%) of these 81 patients and the most frequent clinical presentation was the lymphocutaneous form located on the upper limbs. Itraconazole was used as the first-choice treatment. Sixty-six patients were cured, nine were lost to follow-up and six had spontaneous regression of the lesions [30].

Canine sporotrichosis

Forty-four dogs with sporotrichosis were described. Twenty-five (56.8%) animals had single ulcerated skin lesions on the nose and nine (20.5%) showed nasal mucosal involvement. Respiratory symptoms were observed in 17 (38.6%) dogs and were found to be the most common extracutaneous signs of infection. Yeast-like cells were observed in seven (16.7%) of 42 dogs examined histologically. During the study, eight (18.2%) animals were lost to follow-up and three (6.8%) were submitted to euthanasia. Of the remaining 33 dogs, five (15.2%) presented spontaneous regression of the lesions, 26 (78.8%) were cured after treatment and two (6%) continued to be treated [14]. As was observed in human cases, cutaneous leishmaniasis was the main differential diagnosis [31,32].

Feline sporotrichosis

During the period from 1998 to 2001, feline sporotrichosis was studied in 337 cats with mycologically proven sporotrichosis. The fungus was isolated from 100% of cutaneous lesions, 66.2% of swabs of the nasal cavity, 41.8% of swabs of the oral cavity and 39.5% of pools of nail fragments of cats with sporotrichosis [15]. Additionally, *S. schenckii* was isolated from the oral and nasal cavities of 10 apparently healthy cats that lived with cats with sporotrichosis. Six of them developed cutaneous lesions. Three of these animals presented sneezing before the occurrence of lesions [15]. Isolation of the fungus from the nails and oral cavity of cats supports evidence indicating that transmission can occur through a

scratch or bite, while isolation from the nasal fossae and cutaneous lesions indicates the possibility of infection through secretions [5,15]. These observations, together with the high frequency of respiratory signs and pulmonary and nasal mucosal lesions, in addition to the isolation of *S. schenckii* from bronchoalveolar lavage collected *in vivo* and from the lung of autopsied cats, suggest the epidemiologic importance not only of the cutaneous trauma route, but also of the inhalatory route in the current epidemic [15,33,34•]. Molecular typing of *S. schenckii* strains isolated from humans and animals reinforces that hypothesis [35].

A broad spectrum of clinical presentations was observed, which ranged from a single cutaneous lesion with spontaneous regression to fatal systemic forms. A predominance of males of reproductive age was observed among the animals studied. A history of fights as a possible mode of infection was more common among males than among females. In contrast to humans [16], the lymphocutaneous form was observed in only 19.3% of cases, while mucosal involvement of the upper respiratory and digestive tracts was observed in 34.9% and multiple cutaneous lesions in 39.5% cases [15]. Multiple cutaneous lesions might have been the result of both self-inoculation and bloodstream dissemination from the lungs or from an initial cutaneous lesion [15,36,37].

Systemic disease was demonstrated by the detection of *S. schenckii* in different internal organs obtained from autopsied cats. In these animals, respiratory signs were related to the presence of interstitial pneumonia and alveolar edema [33,34•,37]. To diagnose bloodstream dissemination of the fungus *in vivo*, peripheral blood from 49 cats with no signs suggestive of sepsis was cultivated, *S. schenckii* being isolated from 17 animals (34.4%) [37].

Yeast forms of *S. schenckii* were identified in 62.2% of 90 histopathologic examinations performed with biopsy material obtained from the cutaneous lesions of the cats [15]. In contrast to humans, the absence of asteroid bodies together with the low frequency of granuloma (12%) and the high parasite burden observed in the skin histopathologic examinations in cats demonstrates their high susceptibility to *S. schenckii*.

Some investigators believe that the severity of feline sporotrichosis is related to immunodepression caused by coinfection with feline immunodeficiency virus (FIV) or feline leukemia virus (FeLV), although reports of coinfection with FIV/FeLV and *S. schenckii* are rare [7,26]. In one study, 21.8% of 142 animals tested were coinfected [15]. In another investigation, coinfection with FIV was demonstrated in 18.7% of cats with a positive blood culture and in 22.2% of those with a negative blood culture [37]. No significant differences in clinical or laboratory findings were observed between animals coinfected or not with FIV/FeLV [15,26,33]. In contrast to humans, in whom disseminated sporotrichosis usually affects immunocompromised individuals [5], bloodstream dissemination was frequent in the studied cats and no association with FIV/FeLV-caused immunodeficiency was observed [33].

Treatment was conducted by the household persons responsible for the animals. Failure to comply with the proposed regimen seems to have been the major obstacle to successful treatment. Although medications were supplied free of charge, the high percentage of drop-outs and deaths, mainly before completing 1 month of treatment, suggests difficulties in the handling of these animals. One important cause for the request of euthanasia was the onset of human sporotrichosis in the family. Clinical cure was obtained with itraconazole, ketoconazole or sodium iodide as long as the medications were used regularly and for a prolonged period of time, irrespective of the initial clinical presentation or coinfection with FIV/FeLV. Spontaneous cure was observed in one cat, while six other treated animals relapsed after discharge. In the last cases, the possibility of reinfection cannot be excluded.

Sporothrix schenckii

The virulence of two strains of *S. schenckii* isolated from patients with lymphocutaneous or disseminated sporotrichosis was examined in BALB/c mice inoculated subcutaneously into the footpad with *S. schenckii* yeast. The development of cutaneous lesions, signs of inactivity, weight loss, survival rates, number of viable yeast cells in lung and spleen, splenic index, organ lesions, and immunological responses were evaluated in those mice. The comparison of the two groups showed more severe disease in the mice infected with the strain isolated from disseminated sporotrichosis. The histopathology and the great number of viable microorganisms isolated from the spleen confirmed the higher invasive ability of this strain. In addition, both specific and unspecific cellular immune response measured by in-vitro tests showed a decrease over time. These results suggest the existence of different virulence profiles in *S. schenckii* strains [38]. Other authors found similar results and suggest that different genotypes may be associated closely with the virulence of different clinical forms of *S. schenckii* infection [39]. Another study aimed to evaluate the virulence of two different isolates of *S. schenckii* from cutaneous and systemic forms of feline sporotrichosis injected in the pads of Swiss albino mice. Curiously, the group inoculated with cutaneous isolates demonstrated a more evident clinical evolution of the disease [40].

Drug resistance has not been a major problem in Rio de Janeiro epidemics [15,16,17]. This observation was in accord with in-vitro antifungal susceptibilities of

S. schenckii isolates [41]. There is, however, no consensus about quantitative antifungal methods correlating with clinical findings in *S. schenckii* infection [42–44,45•,46].

To verify whether different virulence of individual *S. schenckii* strain as well as immune status of the host could contribute to give such different clinical manifestations, other authors investigated the interactions between human monocyte-derived dendritic cells (MoDCs) and *S. schenckii*. They found that *S. schenckii* isolates obtained from cutaneous lesions were more potent to activate MoDCs to induce a strong T helper-type 1 response, while the *S. schenckii* isolates obtained from internal organs induced only minimal dendritic cell activation and T helper-type 1 induction [47].

Phenotypic and genotypic evaluation of clinical and environmental isolates of *S. schenckii* has been used for diagnosis, epidemiological and taxonomic purposes [35,48–50].

Final comments on the present epidemic of zoonotic sporotrichosis

Sporotrichosis probably has been occurring in an insidious manner in Rio de Janeiro, reaching epidemic proportions in recent years, and it is still ongoing to date. By December 2006, a total of 1137 humans with culture-proven sporotrichosis had been recorded, so far representing the largest epidemic of this mycosis in the form of a zoonosis.

Despite that, a major question remains: why did sporotrichosis take on the proportion of an emergent zoonosis in the metropolitan region of Rio de Janeiro? To date, we know that the typical patients involved in this epidemic were inhabitants of dwellings located in areas of underprivileged socioeconomic conditions and with precarious health services [18•]. The absence of a feline sporotrichosis control program and various feline behavioral factors (e.g. intimately cohabiting with human beings, frequent cat fights in the neighborhoods, and coming in to contact with soil and plants) may have contributed to the spread of the mycosis. The reviewed series mainly consisted of patients, dogs and cats with chronic cutaneous lesions, who themselves or their owners sought specialized care at a reference center. In transmission areas, many cases of subclinical infection and spontaneous cure may have gone unnoticed. Since it is not mandatory to report sporotrichosis cases, it is difficult to assess its occurrence and distribution, and the incidence certainly may have been underestimated [13].

Conclusion

For public health purposes and to control the current epidemic, an effective and viable therapeutic regimen applied to cats under field conditions is necessary. In addition, public awareness programs on sporotrichosis prophylaxis are required, encouraging the following: responsible ownership, castration, cremation of dead cats, confinement of cats inside the home, limitation of the number of cats per household, regular cleaning of the dwellings and proper healthcare for the animals, as well as general public health measures such as basic sanitation, regular garbage collection and cleaning of empty lots [13]. Further epidemiological and environmental studies are needed to better understand this epidemic.

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