

## CASE REPORT

# Therapeutic efficacy of isavuconazole and potassium iodide in a cat with refractory sporotrichosis

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**Abstract**

A seven-month-old, male, domestic short-hair cat was presented with nodular and ulcerative lesions, as well as respiratory signs, caused by *Sporothrix brasiliensis* infection. Owing to lack of response to oral itraconazole and potassium iodide, isavuconazole was substituted for itraconazole, leading to clinical cure after three months of treatment without adverse effects.

**KEYWORDS**

cat, isavuconazole, potassium iodide, *Sporothrix brasiliensis*, sporotrichosis

## INTRODUCTION

Sporotrichosis is a chronic infection affecting humans and animals caused by *Sporothrix* species. The pathogenic group of *Sporothrix* consists of four species which include *S. brasiliensis*, *S. schenckii*, *S. globosa* and *S. luriei*.<sup>1</sup> The main aetiological agent affecting cats in Brazil is *S. brasiliensis*, which represents an endemic subcutaneous mycosis in this country.<sup>2</sup> *Sporothrix brasiliensis* may cause both zoonotic and cat-to-cat transmission, with infection occurring mainly through scratches, bites or direct contact with exudates of cutaneous lesions.<sup>2</sup> A higher prevalence of the disease is reported in young adult male and unneutered cats.<sup>2</sup>

Cutaneous lesions appear as nodules and ulcers, usually located on the head and most frequently affecting the nasal region and pinnae. Extracutaneous signs, particularly respiratory (sneezing, dyspnoea and nasal discharge) often are observed.<sup>2</sup>

Treatment options for feline sporotrichosis include antifungal drugs such as itraconazole, ketoconazole, potassium iodide and amphotericin B.<sup>3</sup> Although itraconazole is considered to be the drug of choice for the treatment of *S. brasiliensis* infections in cats, in vitro studies have reported the emergence of strains with tolerance to high minimum inhibitory concentrations (MIC) of this drug in southern Brazil, which is characteristic of antifungal resistance.<sup>3</sup>

Isavuconazole is a second-generation broad-spectrum triazole with activity against yeasts, dimorphic fungi and moulds, which exhibits a favourable safety profile when used in people.<sup>4</sup> It was approved by the U.S. Food and Drug Administration (FDA) in 2015 for the treatment of invasive aspergillosis and

mucormycosis, and its clinical use has been expanded to include a wide array of fungal infections.<sup>4</sup> This report aims to describe, for the first time in veterinary medicine, the use of isavuconazole in combination with potassium iodide, for the successful treatment of feline sporotrichosis refractory to conventional treatment.

## CASE REPORT

A seven-month-old, 3.5 kg, intact male, domestic short-hair cat from southern Brazil was presented for evaluation of nodular and ulcerated skin lesions affecting the nose and limbs, along with respiratory signs. Dermatological examination revealed a cutaneous ulcerated nodular lesion affecting the bridge of the nose, philtrum and nostrils, measuring approximately 3 cm in diameter (Figure 1a,b), and ulcerative lesions of the distal regions of the right forelimb and right hind limb. Sneezing and inspiratory dyspnoea also were evident. The cat lived outdoors and had direct contact with other cats. A fine-needle aspirate was collected for cytological examination from the nasal lesion and swabs were obtained from both limbs and the nasal lesions for culture on Sabouraud-dextrose agar medium. Feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV) tests (SNAP FIV, FeLV comb test; IDEXX Veterinary Diagnostics) were both negative. Molecular analysis to identify *Sporothrix* species also was performed.

Cytopathological examination using a modified Wright–Giemsa stain revealed numerous cigar-shaped to oval or round budding yeast-like organisms, with blue cytoplasm and a single round pink nucleus surrounded



**FIGURE 1** (a) Intact male, domestic short-hair cat with sporotrichosis caused by *Sporothrix brasiliensis*, showing an ulcerated nodular lesion affecting the bridge of the nose, philtrum and nostrils; (b) lateral view.

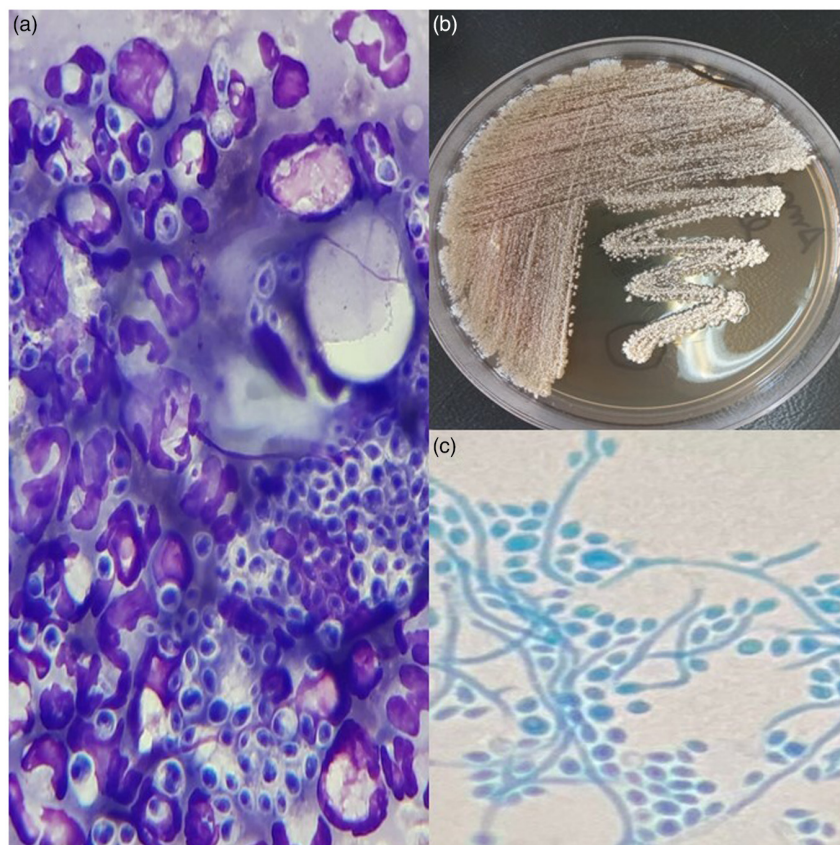
by a nonstaining cell wall, located within macrophages and extracellularly, consistent with *Sporothrix* spp. (Figure 2a). Fungal culture produced filamentous hyaline colonies with dark colour (Figure 2b), after seven days of incubation at 25°C. Lactophenol blue staining of the colonies showed hyaline hyphae forming conidiophores, which produced numerous conidia compatible with *Sporothrix* spp. (Figure 2c). DNA was extracted and purified directly from the fungal colonies using the MagNA Pure 96 DNA, following the Pathogen 200 SV protocol (Roche Diagnostics GmbH), as described previously.<sup>5</sup> A PCR amplifying introns and exons of the calmodulin gene was used for species identification. Resulting calmodulin sequences were compared with NCBI GenBank sequences using the BLAST programme,<sup>5</sup> identifying the species *S. brasiliensis*.

Treatment with human generic itraconazole capsules (Itraconazol; EMS Brazil), 50 mg/cat and compounded potassium iodide capsules, 5 mg/kg orally, once daily, was initiated. Both medications were administered at the same time directly into the cat's mouth, using a pill dispenser. Following five months of therapy, the cat did not exhibit clinical improvement and worsening of the lesions was evident. An increase in serum alanine aminotransferase (ALT; 210 U/L) and anorexia also were present. Hence, treatment was interrupted and the patient was maintained on fluid therapy for two days until appetite was recovered. Subsequently, isavuconazole capsules (Cresemba; United Medical Brazil) 50 mg/cat was substituted for the itraconazole, and the potassium iodide dose was maintained. The isavuconazole

dose was calculated based on the manufacturer's recommended oral dosing for humans, through allometric scaling for the cat's body weight (3.5 kg). Monthly blood tests, including complete blood count and serum biochemistry, revealed no significant changes. After one month of treatment, significant improvement of the lesions was observed (about 70%); therefore, therapy was maintained for two additional months after which time complete resolution of the cutaneous and respiratory signs was achieved (Figure 3a,b). No adverse effects were noted during this period. The cat subsequently was followed for one year, with recheck examinations scheduled every three months. There has been no evidence of lesion recurrence.

## DISCUSSION

Feline sporotrichosis caused by *S. brasiliensis* is a neglected mycosis in several regions of Brazil, representing a serious public health concern as a consequence of its zoonotic potential and rapid distribution among feline populations.<sup>2</sup> *Sporothrix brasiliensis* is considered to be the most virulent species within its genus and is often associated with severe lesions of the nasal mucosa and upper respiratory signs in cats, which have often resulted in treatment failure and death of affected animals.<sup>6</sup> This clinical presentation was observed in the cat reported here, which exhibited advanced cutaneous lesions and severe respiratory signs (sneezing and inspiratory dyspnoea).



**FIGURE 2** (a) Cytopathological examination of a fine-needle aspirate. Numerous cigar-shaped to oval or round budding yeast-like organisms, with blue cytoplasm and a single round pink nucleus surrounded by a nonstaining cell wall, within macrophages and extracellularly (modified Wright–Giemsa stain,  $\times 100$ ). (b) Fungal culture demonstrates growth of filamentous hyaline colonies with dark colour, after seven days of incubation at 25°C. (c) Hyaline hyphae forming conidiophores, which are producing numerous conidia. Lactophenol blue staining,  $\times 100$ .

*Sporothrix* infection is often acquired through scratches and bites acquired during fighting or mating, so is most frequently observed in young, intact cats (particularly males) residing outdoors,<sup>2,7</sup> as was the case in the cat reported here. The standard method for diagnosis of sporotrichosis is mycological culture.<sup>2</sup> However, cytological examination is a low-cost technique which is simple to perform and provides immediate results. Molecular tests, such as PCR, are best suited for identifying the *Sporothrix* species.<sup>2</sup>

Therapy of feline sporotrichosis usually is a challenge. The high cost of medications, risk to human handlers and need for long-term treatment in which the animal is confined to prevent the spread of the disease, are frequently associated with therapeutic failure.<sup>7</sup> Itraconazole remains the drug of choice for the treatment of sporotrichosis in cats and is reported to be effective as a monotherapy.<sup>2</sup> For cases refractory to itraconazole monotherapy, the addition of potassium iodide, which increases fungicidal activity within phagocytes,<sup>8</sup> should be considered, especially for cats with nasal lesions and/or respiratory signs.<sup>2,8</sup> The prognosis for cats with sporotrichosis depends on several factors, including the number, extent and location of the lesions, the occurrence of respiratory signs and the cat's general medical condition. Moreover, owner cooperation and persistence are necessary for successful treatment.<sup>9</sup>

In the case reported here, failure of itraconazole and potassium iodide therapy was evident after several

months. This may have been a result of the presence of upper respiratory tract disease, which is usually the result of infection spreading through the nasal and frontal sinuses where only low concentrations of antifungals are achieved.<sup>9</sup> In addition, the emergence of *S. brasiliensis* with high MIC values for itraconazole has been reported in southern Brazil.<sup>3</sup> Susceptibility testing for itraconazole was not performed in this case, yet antifungal susceptibility tests must be interpreted with caution because clinical breakpoints are not yet established for *Sporothrix* species.<sup>3,7</sup>

Isavuconazole is a novel triazole with a broad spectrum of antifungal activity, administered as a water-soluble prodrug, isavuconazonium sulphate. In vitro and animal studies have demonstrated potential utility in the treatment of invasive aspergillosis, mucormycosis, candidiasis and certain endemic mycoses in human medicine.<sup>10</sup> Isavuconazole inhibits cytochrome P450-dependent lanosterol 14 $\alpha$ -demethylase, which is essential for the synthesis of ergosterol, a component of the fungal membrane. This disruption leads to alterations in the structure and function of the fungal membrane leading to cell death.<sup>4</sup> This medication is well-tolerated with a favourable adverse effect profile when compared to other agents in the azole class. The most commonly reported adverse effects in people are nausea, vomiting and diarrhoea and to a lesser extent drug-related hepatotoxicity.<sup>4</sup> Evaluation of isavuconazole pharmacokinetics in healthy cats demonstrated that both oral and



**FIGURE 3** (a) Intact male, domestic short-hair cat exhibiting clinical resolution of the nasal lesion after three months of combined therapy with oral isavuconazole and potassium iodide; (b) closer view.

intravenous routes of administration result in high serum concentrations and are generally well-tolerated.<sup>11</sup> In the case reported here, the addition of this antifungal agent resulted in clinical resolution of all lesions and clinical signs after three months of therapy, without adverse effects and no evidence of recurrence for a one-year follow-up period. To the best of the authors' knowledge, this is the first documented report of the clinical use of isavuconazole in veterinary medicine. While it was well-tolerated in this one cat, controlled studies will be required to comprehensively evaluate the safety and efficacy of isavuconazole for long-term use in animals.

#### AUTHOR CONTRIBUTIONS

**Wendie Roldán Villalobos:** Conceptualization; investigation; writing – original draft; methodology; validation; writing – review & editing; supervision. **Fabiana Monti:** Conceptualization; investigation; methodology; validation; writing – review & editing. **Tássia Ferreira:** Investigation; methodology; writing – review & editing. **Sabrina Sato:** Investigation; methodology. **Flávio Telles:** Investigation; methodology; validation; conceptualization. **Marconi Farias:** Conceptualization; investigation; methodology; validation; writing – review & editing; supervision.

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#### CONFLICT OF INTEREST STATEMENT

None declared.

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## 摘要

一只7月龄雄性家养短毛猫，出现结节性和溃疡性病变，以及由巴西孢子丝菌感染引起的呼吸道症状。由于口服伊曲康唑和碘化钾治疗无效，艾沙康唑替代伊曲康唑，治疗3个月后临床治愈，无不良反应。

## Résumé

Un chat domestique mâle à poil court de 7 mois est présenté avec des lésions nodulaires et ulcéreuses, ainsi que des signes respiratoires, causés par une infection à *Sporothrix brasiliensis*. En raison de l'absence de réponse à l'itraconazole oral et à l'iodure de potassium, l'isavuconazole est substitué à l'itraconazole, ce qui conduit à une guérison clinique après 3 mois de traitement sans effets indésirables.

## 要約

*Sporothrix brasiliensis* 感染による結節性、潰瘍性病変および呼吸器症状を呈した7カ月齢の雄のドメスティック・ショートヘアが受診した。イトラコナゾールおよびヨウ化カリウムの経口投与が無効であったため、イトラコナゾールに代えてイサブコナゾールを投与したところ、副作用なく3カ月で治癒した。

## Resumo

Um gato doméstico de pelo curto de sete meses de idade foi apresentado com lesões nodulares e ulcerativas, bem como sintomas respiratórios, causados por infecção por *Sporothrix brasiliensis*. Devido à pobre resposta ao tratamento com itraconazol oral e iodeto de potássio, itraconazol foi substituído por isavuconazol, levando à cura clínica após três meses de tratamento, sem efeitos adversos.

## Resumen

Un gato doméstico de pelo corto, macho, de 7 meses de edad, se presentó con lesiones nodulares y ulcerativas, así como signos respiratorios, causados por infección por *Sporothrix brasiliensis*. Ante la falta de respuesta a itraconazol y yoduro potásico orales, se sustituyó itraconazol por isavuconazol, con curación clínica tras 3 meses de tratamiento sin efectos adversos.

## Zusammenfassung

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