



Case report

Feline sporotrichosis successfully treated with methylene blue-mediated antimicrobial photodynamic therapy and low doses of itraconazole

Fernanda V. Cabral^{a,*}, Fábio P. Sellera^{b,c}, Martha S. Ribeiro^a^a Center for Lasers and Applications, Energy and Nuclear Research Institute (IPEN/CNEN), São Paulo, SP, Brazil^b Department of Internal Medicine, School of Veterinary Medicine and Animal Science, University of São Paulo, São Paulo, SP, Brazil^c School of Veterinary Medicine, Metropolitan University of Santos, Santos, SP, Brazil

ARTICLE INFO

Keywords:

Antifungal
 Veterinary medicine
 Rose gardener's disease
 Sporotrichosis
 Pathogenic fungi

ABSTRACT

Sporotrichosis is a mycotic infection of humans and animals caused by different fungal species of the genus *Sporothrix*. Feline sporotrichosis presents a broad spectrum of clinical manifestations and its treatment with classic antifungal drugs is often long and frustrating. Methylene blue-mediated antimicrobial photodynamic therapy (MB-APDT) comes to light as an interesting approach against fungal infections, including sporotrichosis. In this case report, a 1-year-old male cat was diagnosed with sporotrichosis, being confirmed by fungal culture. The cat was treated by MB-APDT combined with oral administration of itraconazole. Following 2 weeks after the end of treatment, the animal was clinically cured, and an additional fungal culture was negative for *Sporothrix* spp., confirming the total remission of sporotrichosis. No side effects and recurrences were observed after a 3-month follow-up. MB-APDT is a promising strategy against feline sporotrichosis, however large-scale studies are welcome to confirm its potential.

1. Introduction

Sporotrichosis, also known as rose gardener's disease, is a mycotic infection of humans and animals (mostly cats) caused by different fungal species of the genus *Sporothrix*, a saprophyte fungus that is endemic mostly in tropical and subtropical regions [1,2]. It affects the skin and subcutaneous tissue, but it can rarely cause other clinical forms of infection [1,2]. In cats, sporotrichosis frequently causes multiple skin nodules and ulcers as a consequence of fights with infected cats or contact with contaminated wounds and soil by *Sporothrix* propagules [1, 2]. Although it has been demonstrated that *in vitro* *Sporothrix* spp. are susceptible to a broad range of antifungal drugs, the treatment of feline sporotrichosis is often long and frustrating [1,2].

Antimicrobial photodynamic therapy (APDT) combines the use of a photosensitizer (PS), light, and molecular oxygen to generate significant amounts of reactive oxygen species (ROS) that are lethal for microorganisms [3]. Methylene blue (MB) is a broad investigated cationic PS in the APDT field, and literature is vast regarding MB-APDT inactivation effects against a broad range of microorganisms, including pathogenic fungi [3,4]. Additionally, MB-APDT is considered cost-effective and safe for the hosts, making this approach interesting for clinical applications in human and veterinary medicine [4]. We describe the successful

treatment of feline sporotrichosis using MB-APDT combined with itraconazole.

2. Case report

A 1-year-old male cat, weighing 3.5 kg, was admitted to a private veterinary clinic presenting a deep ulcer of nearly 3 cm (longitudinal size) surrounded by two nodular lesions measuring 2 cm in the region of the penis (Fig. 1A). The feline's urethra remained intact, thus not affecting his ability to urinate properly. Fungal culture confirmed the presence of *Sporothrix* spp., and medical records suggested that the animal was infected during recovery of a post-operative orchietomy through contact with contaminated soil. A combined treatment using oral itraconazole and topical MB-APDT was performed. Itraconazole was administered at a dose of 10 mg/kg daily (around 35 mg/day) for 50 days. Three sessions of MB-APDT were conducted once a week in the first 3 weeks. Afterward, 2 more sessions were applied every 2 weeks, totaling 5 sessions in 45 days. The cat's owner signed a free and informed consent allowing the treatment.

MB-APDT was carried out by the topical administration of MB aqueous solution at a concentration of 500 µM (Sigma-Aldrich, USA). After 10 min, the lesion was irradiated with a diode laser emitting a

* Corresponding author.

E-mail address: fe_vcabral@hotmail.com (F.V. Cabral).<https://doi.org/10.1016/j.pdpdt.2022.103154>

Received 27 July 2022; Received in revised form 23 September 2022; Accepted 7 October 2022

Available online 19 October 2022

1572-1000/© 2022 Elsevier B.V. All rights reserved.

wavelength of 660 nm, delivering radiant exposure of 128 J/cm², 9 J, and 90 s per point, being 5 points in the ulcer and one in each nodule, resulting in a total of 7 points. The output power was 100 mW, and irradiance of 1.4 W/cm² (Therapy XT DMC®, Brazil) (Fig. 1B and C).

After the 7th day of treatment, ulcer size appeared more superficial, while both nodules were reduced by approximately 25% (Fig. 1D). After 2 weeks, we observed a significant clinical improvement, determined by the reduction of the lesion's area in the surrounding external urethral orifice (Fig. 1E).

At the last MB-APDT session, the wound was completely healed, while nodules were substantially smaller, nearly 50% reduced (Fig. 1G). Two-weeks after the end of treatment, the animal was clinically cured, showing a normal anatomical position of the urinary tract opening and hair growth on the site of treatment (Fig. 1H). Moreover, a further fungal culture was negative for *Sporothrix* spp., confirming the total remission of sporotrichosis.

Of clinical importance, no vomit, diarrhea, anorexia, weight loss, or any side effects were noticed throughout treatment. In addition, the animal revealed normal levels of liver enzymes and an active behavior across the entire period. The animal was monitored for 3 months, and no recurrences were noticed during the follow-up period (Fig. 1I).

3. Discussion

Sporotrichosis is a serious zoonotic infection that causes single or multiple subcutaneous lesions that can spread to several organs and cause the disseminated form of the disease [1]. Although itraconazole has been recommended as one of the first-line antifungal drugs, treatment remains a challenge given that most cats might not respond well to this treatment [2]. Moreover, it should be administered for at least 1 month after the clinical cure to avoid the risk of possible recurrences. In general, the recommended dose for cats ranges from 50 to 100

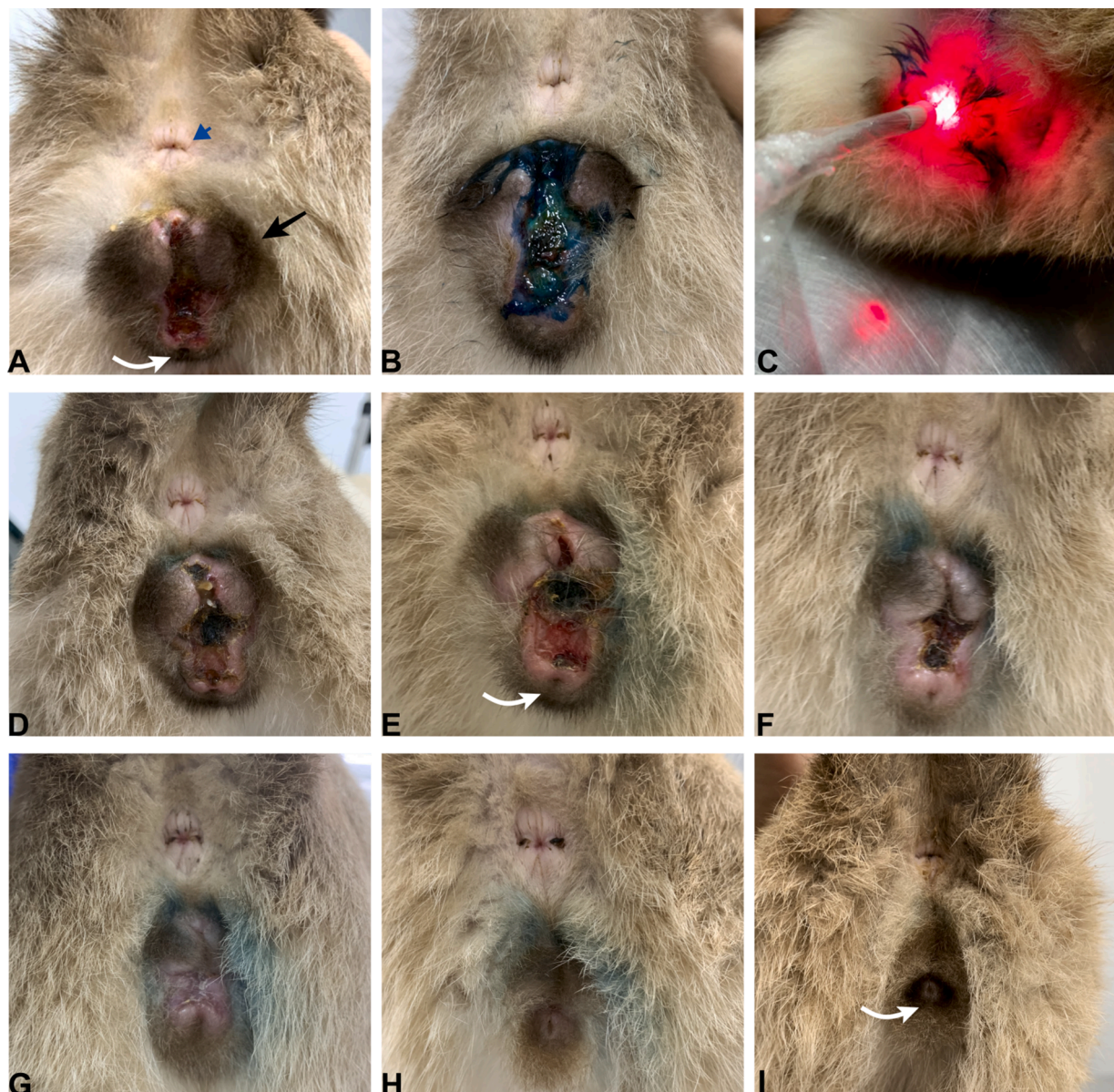


Fig. 1. Representative images of sporotrichosis in a cat infected with *Sporothrix* spp. Clinical presentation of the lesion throughout the course of treatment. (A) Before MB-APDT. (B) MB applied in the lesion's area prior to irradiation. (C) First MB-APDT session. (D) One week after the first MB-APDT session. (E) Two weeks after the first MB-APDT session and one week after the second one. (F) Four weeks after the first MB-APDT session and one week after the third one. (G) Six weeks after the first MB-APDT session and two weeks after session four. (H) Eight weeks after the first MB-APDT session and two weeks after session five. (I) Three months after the end of treatment. Blue arrow represents the cat's anus. Black arrow points to the nodular lesion around the ulcer. White arrow points to external urethral orifice.

mg/animal daily, and the whole treatment course could take several months (from 2 to 12 months), with an average rate of 4 months in most cases [2,5]. This results in poor owner compliance, fungal resistance, and increased toxicity, which can lead to treatment failure. More critically, in severe cases euthanasia may be recommended [2].

In this study, we demonstrated for the first time a successful case of MB-APDT in combination with oral antifungal drugs to treat feline sporotrichosis. Although none of the lesions were exclusively treated with MB-PDT, the possibility of combining a topical therapy that enables decreasing antifungal concentration and hastens the cure is quite innovative. Light parameters and MB concentration used here were based on previous clinical studies that successfully used MB-APDT against bacterial and fungal infections [3,4,6]. As a result, a favorable clinical outcome with complete healing was noticed in just 50 days, without any side effects or recurrences in a 3-month follow-up period.

The number of MB-APDT clinical studies in Veterinary Medicine has significantly increased over the last years, which indicates that this approach could be a great ally for veterinary clinicians. Indeed, some recent studies have demonstrated the ability of MB-APDT to treat dermatological diseases in companion animals, including other fungal and bacterial infections [4,6]. Specifically for sporotrichosis, recent reports have demonstrated that APDT could be safely associated with antifungals for the treatment of sporotrichosis in humans and in mouse models [3], which makes this approach promising for feline sporotrichosis.

A new avenue for feline sporotrichosis treatment is opened. Testing different MB concentrations and light parameters is also worthy of investigation since this variable could optimize MB-APDT. Additionally, the additive or synergistic effect of MB-APDT combined with classic antifungal drugs should also be addressed because this kind of association would improve clinical outcomes and reduce side effects. We hope this case report motivates further large-scale studies of MB-APDT for

feline sporotrichosis.

CRediT authorship contribution statement

Fernanda V. Cabral: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Fábio P. Sellera:** Writing – review & editing, Writing – original draft, Investigation. **Martha S. Ribeiro:** Writing – review & editing, Supervision.

References

- [1] B. Sharma, A.K. Sharma, U. Sharma, Sporotrichosis: a comprehensive review on recent drug-based therapeutics and management, *Curr. Dermatol. Rep.* 11 (2022) 110–119, <https://doi.org/10.1007/s13671-022-00358-5>.
- [2] I.D.F. Gremião, E. Martins da Silva da Rocha, H. Montenegro, A.J.B. Carneiro, M. O. Xavier, M.R. de Farias, F. Monti, W. Mansho, R.H. de Macedo Assunção Pereira, S. A. Pereira, Lopes-Bezerra LM. Guideline for the management of feline sporotrichosis caused by *Sporothrix brasiliensis* and literature revision, *Braz. J. Microbiol.* 52 (2021) 107–124, <https://doi.org/10.1007/s42770-020-00365-3>.
- [3] B.C. Legabão, J.A. Fernandes, G.F. de Oliveira Barbosa, P.S. Bonfim-Mendonça, T.I. E. Svidzinski, The zoonosis sporotrichosis can be successfully treated by photodynamic therapy: a scoping review, *Acta Trop.* 228 (2022), 106341, <https://doi.org/10.1016/j.actatropica.2022.106341>.
- [4] F.V. Cabral, F.P. Sellera, M.S. Ribeiro, Methylene blue-mediated antimicrobial photodynamic therapy for canine dermatophytosis caused by *Microsporum canis*: a successful case report with 6 months follow-up, *Photodiagn. Photodyn. Ther.* 36 (2021), 102602, <https://doi.org/10.1016/j.pdpdt.2021.102602>.
- [5] C.C.T. Nakasu, S.B. Waller, M.K. Ripoll, M.R.A. Ferreira, F.R. Conceição, A.D. R. Gomes, L.D.G. Osório, R.O. de Faria, M.B. Cleff, Feline sporotrichosis: a case series of itraconazole-resistant *Sporothrix brasiliensis* infection, *Braz. J. Microbiol.* 52 (2021) 163–171, <https://doi.org/10.1007/s42770-020-00290-5>.
- [6] F.P. Sellera, M.R. Fernandes, C.P. Sabino, L.M. de Freitas, L.C.B.A. da Silva, F. C. Pogliani, M.S. Ribeiro, M.R. Hamblin, N. Lincopan, Effective treatment and decolonization of a dog infected with carbapenemase (VIM-2)-producing *Pseudomonas aeruginosa* using probiotic and photodynamic therapies, *Vet. Dermatol.* 30 (2019), <https://doi.org/10.1111/vde.12714>, 170–e52.