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Integrative Therapy with Methylene Blue and PDT in a Feline with Sporotrichosis - Case Study

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Abstract: ***Purpose*: "Sporotrichosis, a zoonotic disease caused by Sporothrix schenckii, poses a significant public health risk, particularly in regions where cats are the primary transmitters. *Methods*: This case study reports the successful integrative treatment of a feline with sporotrichosis using methylene blue (MB) and photodynamic therapy (PDT). *Results*: The patient, previously unresponsive to itraconazole, showed significant improvement after two PDT sessions, with complete resolution of symptoms within 76 days. *Conclusions*: The study concludes that the combination of MB and PDT is a promising, minimally invasive therapy for itraconazole-resistant sporotrichosis, with minimal side effects. This integrative approach may offer a viable alternative for treating resistant fungal infections in both veterinary and human medicine.***

Keywords: sporotrichosis, feline, bio-oxidative therapies, methylene blue, photodynamic therapy

1. Introduction

Sporotrichosis is a zoonotic disease with global epidemiological significance, where cats are the primary transmitters to humans, making it a public health concern [1]. In Brazil, this mycosis mainly affects cats, while the vast majority of cases in humans and dogs have the cat as the transmitter, thus, the cat has assumed an important role in the epidemiological chain of transmission of the disease to humans, representing a substantial risk to public health [2]. Cases in humans are increasingly characterized by being zoonotic, with domestic felines as the transmitter [3]. Sporotrichosis is a subcutaneous mycosis with subacute to chronic evolution, caused by the dimorphic and geophilic fungus *Sporothrix schenckii*. The definitive diagnosis is made through clinical history associated with complementary cytology tests, mycological culture examination [4], histopathology, serological tests, intradermal tests, inoculation in animals and polymerase chain reaction [5]. Zoonotic transmission has been highlighted, with domestic cats playing an important epidemiological role in the disease. Furthermore, the number of cases with therapeutic failures is still increasing, reaffirming the need to review options and forms of treatment [6]. Sporotrichosis can be adequately treated with antifungals and the drug itraconazole is recommended as the first therapeutic option [7]. In cases of resistance to traditional antifungals, new therapeutic alternatives are being sought; Among these, the association with immune system stimulants such as **β**-glucan and traditional antifungals shows promise [8]. Photodynamic Therapy is among the most innovative therapies using a photosensitizing agent, light and molecular oxygen to destroy neoplastic cells [9] as well as microorganisms (bacteria, viruses and fungi) [10]. Among several photosensitizing agents are phenothiazines such as methylene blue (MB) and its light absorption band of 620-700 nm. In the treatment of infections in dogs and cats, it has been found that few or no side effects have been described. This is due to the fact that most photosensitizers used for this type of treatment are more toxic to microorganisms when compared to host cells [11]. Methylene blue (MB) is listed as a contraindicated drug in cats due to potential side effects such as depression, dyspnea, bluish discoloration of urine and feces, and pale or jaundiced mucous membranes [12]. However, there is still a lack of consensus among authors and the therapeutic index is narrow despite the benefits being promising with single doses systemically [13]. The mechanisms of action of photodynamic therapy (PDT) as a photosensitizer consist of the production of reactive oxygen species (ROS), which negatively affected mitochondrial function, resulting in a decrease in membrane potential and cell death, which alters the mitochondrial ultrastructure and physiology of *Sporotrix brasiliensis* and research that highlights the importance of mitochondria as a new therapeutic target in fungal diseases (Figure 1).

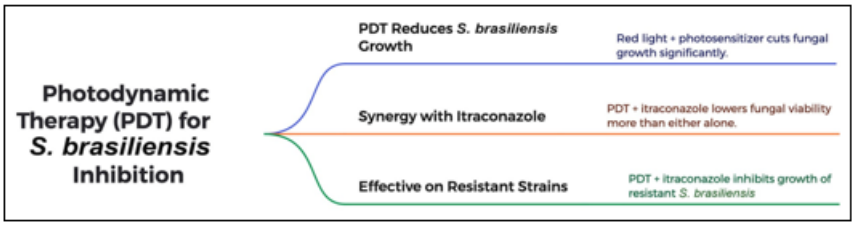

Figure 1: PDT action mechanisms (Source: adapted from Ramos et al, 2024).

2. Material and Methods

Case report

The feline patient, male, SRD, 2 years old, was seen on 07/27/2023 referred by another veterinarian who had already carried out the yeast and fungus culture test (Figure 2) and had already received conventional therapy with itraconazole (ITL) at a dose of 50 mg BID for four months, without response. On 07/27/2023, Photodynamic Therapy (PDT) began, using Genesis Veterinary Phototherapy equipment from Eccovet, class II, Brazil, in the visible red laser pen function (AlGaInP), with λ= 660 nm, continuous emission, DP=20mW/cm^2 and dose= 9 joules/cm^2, associated with the topical photosensitizer methylene blue 1% / 5mL / (Health Tech, Brazil), diluted to 0.1% in physiological solution. Two PDT sessions were conducted 30 days apart. Following a positive response, four additional sessions were performed weekly using a blue/green LED pen. Subsequently, with favorable evolution, 4 sessions were carried out once a week using the blue/green LED pen, λ= 460nm continuous emission and DP= 400mW to complement healing and yeast control. As immunological nutritional support for the patient, two doses of thymomodulin 50mg/5ml ampoule (Health Tech Laboratory) at a dose of 2mg/kg was used subcutaneously, with an interval of 30 days associated with itraconazole orally a dose of 50mg/BID, maintained for 30 days after the lesions disappeared, totaling 210 days of medication.


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17741033
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Destino de Laudo: EMAI
ESPOROTRICOSE CULTIVO
Local de Coleta:
Amostra: FELINA
Material: Swab
Resultado: Positivo
Microorganismo(s):
Sporothrix sp

Figure 2: Result of the fungal culture of the feline SRD. Source: Salto/SP Zoonosis Surveillance Unit

3. Results

In Figure 3 (07/27/23) the patient with the original lesions before the start of the integrative therapy of PDT associations with topical 0.1% (MB) photosensitizer, demonstrating the areas of highest concentration of lesions on the left side of the face where the animal had intense itching.

Figure 3: Patient on the day of clinical examination before therapy

Application of 0.1% methylene blue photosensitizer with gauze to the entire area affected by the yeast and immediately performing PDT in laser mode in the red region, λ= 660 nm, dose= 9 joules/cm^2, for 3 minutes) (Figure 4).

Figure 4: During the photodynamic therapy of first application

The initial results were obtained from 08/02/2023, six days after the first PDT session (Figure 5). The last evaluation carried out was on 10/13/2023 where no session was carried out and there was another return on 02/05/2024, totaling two applications of PDT with (MB), in addition to 4 sessions of green/blue LED, totaling 76 days of treatment. After the lesions disappeared, only maintenance of itraconazole 50mg/BID, orally, was prescribed for 30 days.

Figure 5: After 6 days of treatment

Clinical evolution: upon return on 02/05/2024, the patient underwent a complete skin assessment, with no further signs of fungal lesion. On this day the animal was discharged without the need for new applications (Figure 6).

Figure 6: Revaluation with clinical discharge

4. Discussion

In a study carried out with 100 felines with suspected lesions, it was found that 65.2% had focal lesions and 34.8% disseminated lesions, 75.5% on the front limbs and only 9% on the face, in contrast to the patient in the clinical report who presented a lesional topography exclusively on the face [14]. Itraconazole is the most used drug and has fewer side effects when compared to other antifungals, and should be used for up to 30 days after symptoms disappear. Potassium iodide is an important option for the treatment of cases refractory to itraconazole, especially for those cats that present lesions in the nasal mucosa and/or respiratory signs [14]. With the development of several integrative techniques in Veterinary Medicine, the use of ozone gas for the treatment of wounds is an economically accessible possibility that has shown positive results when used by rectal, topical insufflation and through the ``bag'' method [15]. Biooxidative therapy using methylene blue is widely studied and used in humans with onychomycosis and yeast [16]. The use of MB in felines remains controversial, particularly concerning its intravenous administration. The study carried out with 40, divided into 4 groups, 1 being a control group and the others with sodium nitrite compared to (MB), concluding that only a therapeutic dose of 1.5mg/kg intravenously was sufficient to reverse the induced intoxication and its consequence methemoglobinemia (MTH) without increasing circulating red blood cells with hemoglobin and there was no hemolytic anemia in any of the groups of cats [17]. The (MB) 1% can be used to reverse (MTH) in dogs and cats. Despite having a narrow therapeutic index in dogs and cats, it has shown promise for treating animals with methemoglobinemia syndrome (MS) at a dosage of 1.0 to 1.5 mg/kg IV in a single dose [13]. Methylene blue has affinity for NADPH reductase present in erythrocytes and causes reduction of MHb to Hb, and generates leucomethylene blue, which reduces MHb to Hb again and alleviates cyanosis and dyspnea [18]. However, in addition to respecting the therapeutic dose, it is recommended to perform a blood count and blood gas analysis with drug-induced feline (MS), serial oximetry in order to avoid drug intoxication and its use should be in a hospital environment and the in vitro efficacy of PDT using a diode laser (InGaAIP) in combination with the topical (MB) photosensitizer for the treatment of yeast strains *Sporotrix brasiliensis*, including a non-wild strain to itraconazole, concluding be very favorable for combating yeast without causing side effects[19].

5. Conclusion

It is concluded that the applied integrative therapeutic model of the association of photodynamic therapy, a topical 0.1% methylene blue and to complement healing and yeast control was effective in eliminating the inflammatory condition with pharmacological resistance to itraconazole after 76 days of therapy, since the evolution of the disease is reserved for unfavorable. The safety and effectiveness of using methylene blue in felines was verified, without side effects, as long as it is used within the therapeutic window. This study suggests that the combination of therapies may also be favorable in humans.

6. Future Scope

This clinical study on felines is a stimulus for other researchers to feel encouraged to use it in other diseases

Consent to Participate Informed: consent was obtained from all individual participants included in the study.

Consent to publish: The authors affirm that human research participants provided informed consent for publication of their data.

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