REVISTA DO INSTITUTO DE MEDICINA TROPICAL DE SÃO PAULO
JOURNAL OF THE SÃO PAULO INSTITUTE OF TROPICAL MEDICINE

ORIGINAL ARTICLE
http://doi.org/10.1590/S1678-9946202365041

Severe form of lymphocutaneous sporotrichosis: a case report

Ezequias Batista Martins[1], **Sandra Maria Barbosa Durães**[2], **Julia de Abreu Teixeira**[3], **Remberto Maurício de La Cruz Vargas Vilte**[1], **Aline Schultz Klitzke**[2], **Thainá Busque dos Santos**[2], **Karla Regina Oliveira de Moura Ronchini**[1], **Laura da Cunha Ferreira**[1], **Natália Chilinque Zambão da Silva**[1], **Ianick Souto Martins**[1], **Billy McBenedict**[1], **Carolina Romero Cardoso Machado**[3], **Patrícia Yvonne Maciel Pinheiro**[3]

ABSTRACT

Sporotrichosis is the most frequent subcutaneous mycosis in Latin America. It is caused by species of the genus *Sporothrix*. Infection in humans occurs through the entry of the fungus into the skin. Zoonotic outbreaks involving cats in the transmission of the disease have been frequently reported. The lymphocutaneous form is the most commonly observed and the upper limbs are the most affected sites. We report a case of a 64-year-old healthy female patient with a lymphocutaneous form with rapid progression of lesions, which was refractory to initial treatment with itraconazole. Treatment with liposomal amphotericin B was performed with a satisfactory resolution, but aesthetic and functional sequelae in the left upper limb were installed.

KEYWORDS: Sporotrichosis. *Sporothrix* species. Treatment. Lymphocutaneous. Immunocompetent patient.

[1]Universidade Federal Fluminense, Faculdade de Medicina, Niterói, Rio de Janeiro, Brazil

[2]Universidade Federal Fluminense, Faculdade de Medicina, Hospital Universitário Antônio Pedro, Serviço de Dermatologia, Niterói, Rio de Janeiro, Brazil

[3]Universidade Federal Fluminense, Faculdade de Medicina, Hospital Universitário Antônio Pedro, Serviço de Infectologia, Niterói, Rio de Janeiro, Brazil

Correspondence to: Ezequias Batista Martins
Universidade Federal Fluminense, Faculdade de Medicina, Av. Marquês do Paraná, 303, Centro, CEP 24220-000, Niterói, RJ, Brazil
Tel: +55 21 2629-9317

E-mail: ezequiasm@id.uff.br

Received: 27 March 2023

Accepted: 18 May 2023

INTRODUCTION

Sporotrichosis is a fungal disease caused by species of thermodimorphic fungi of the genus *Sporothrix*. The ancient classification of the species that cause this disease was based on the classification of the *Sporothrix schenckii* complex[1].

The taxonomic classification of *Sporothrix* was modified in 2016, leading to the categorization of the following species *Sporothrix schenckii*, *Sporothrix globosa*, *Sporothrix brasiliensis* and *Sporothrix luriei* as those of public health importance[2]. The disease is commonly observed in gardeners following *Sporothrix* species fungal penetration into the skin after injury caused by thorns. The parasite spreads through the lymphatic circulation, simultaneously causing skin lesions. The infection affects the skin, subcutaneous tissues, the lymphatic system, and rarely the deep-seated organs[3]. Zoonotic outbreaks have been described in Brazil, where the disease is transmitted by cats, with *S. brasiliensis* being the species involved[3,4].

Clinically, the disease manifests itself as lesions limited to skin, or with lymphatic involvement (lymphocutaneous forms). Atypical clinical manifestations are described with systemic involvement, affecting the mucosa, eyes, bones, joints, lungs, and the central nervous system. The gold standard for sporotrichosis diagnosis is the isolation and identification of *Sporothrix* spp. from clinical specimens[5].

The main drugs used to treat sporotrichosis are itraconazole, terbinafine, potassium iodide, and amphotericin B[5]. Cryosurgery has been used as an adjuvant

treatment for sporotrichosis, mainly in residual lesions or in cases of thick ulcerovegetative or nodular ulcerovegetative lesions[6]. For cutaneous and lymphocutaneous forms, oral itraconazole is considered the first choice of treatment[5]. Terbinafine is indicated for the cutaneous forms of sporotrichosis, in refractory cases or those intolerant to itraconazole, and has less potential for interaction[7]. For severe forms of the disease, amphotericin B deoxycholate or the liposomal version has been used for treatment and reportedly yields favorable results. However, after the improvement of lesions, amphotericin B deoxycholate or liposomal amphotericin B should be replaced by oral itraconazole and treatment continued until the lesions are completely healed[5].

CASE REPORT

A 64-year-old healthy woman developed a small ulcerated lesion on the second finger of her left hand on March 5, 2022. The initial lesion was nodular and eroded within a few days, evolving into a painful and bleeding ulcer with raised edges. Approximately five days earlier, she was providing care to a sick cat with ulcerated lesions all over the body. The patient reported that the cat died within a few days. Occasionally, the patient performed gardening activities without personal protective equipment (e.g., gloves), and thus had frequent direct hand contact with the soil and plants. The patient had no comorbidities, and did not report the use of any medications or alcohol consumption before the onset of lesions. The patient came from an urban area.

The ulceration of the finger had a progressive increase in diameter, with drainage of serosanguineous secretion, accompanied by intense local pain. After medical evaluation during the first month of evolution, the patient was treated with oral cephalexin for 10 days, intramuscular benzylpenicillin (single dose) and topical chloramphenicol antibiotics, but this treatment still lacked clinical efficacy.

In April, approximately one month after the onset of the disease, the clinical and epidemiological diagnosis of sporotrichosis was confirmed and treatment with itraconazole (100 mg, twice a day) was prescribed. Despite the continued use of itraconazole, in the third month of the disease, several nodules appeared in an ascending direction on the left forearm and upper arm following the patterns/ramifications of lymphatic drainage.

On July 1, corresponding to four months after the onset of symptoms, the patient had a consultation at the dermatology outpatient clinic. The physical examination showed fistulas, which arose from nodules, and confluent ulceration from proliferation throughout the left upper limb (Figure 1). The lesions were covered by a single crust with a "verrucous" aspect, where the presence of purulent secretion was evidenced in some ulcers. Treatment with itraconazole (100 mg, twice a day) was continued, and cephalexin (500 mg, four times a day, for 10 days) was added to treat the associated bacterial infection. Figure 1 shows the characteristics of the patient's lesions in the four months of disease prior to hospital admission.

Figure 1 - Patient evolution in the fourth month of disease, with confluent ulcers throughout the left upper limb covered by crust with a verrucous aspect.

On August 29, the patient was hospitalized. This occurred after four months of treatment with itraconazole, during which the wounds had formed an extensive and continuous verrucous plaque from the dorsum of the left hand to the proximal third of the left arm. The laboratory diagnosis of sporotrichosis was confirmed on July 4, through culturing of *Sporothrix* sp. from the material collected from the lesion. Unfortunately, we were unable to identify the species of the parasite.

The diagnosis of sporotrichosis was confirmed by the histopathological examination of a fragment of the lesion on the left hand, showing a chronic granulomatous inflammatory process of the suppurative type, compatible with pathologies that produce verrucous skin lesions.

The patient was hospitalized for 31 days, and treated with liposomal amphotericin B (3 mg/kg/day), which was administered for 21 days, and thereafter replaced by itraconazole (100 mg, twice a day), with an expected treatment duration of four months. The skin lesions had a relevant improvement during hospitalization (Figure 2), evidenced by a progressive healing process after the use

of amphotericin B. However, the hematology and blood biochemistry laboratory tests showed no relevant changes during this period. After hospital discharge, the patient continued with a maintenance treatment of oral itraconazole (100 mg, twice a day) for another four months without any adverse reaction to the drug. The skin lesions were almost completely healed, leaving only aesthetic sequelae and a slight functional limitation of the second left finger.

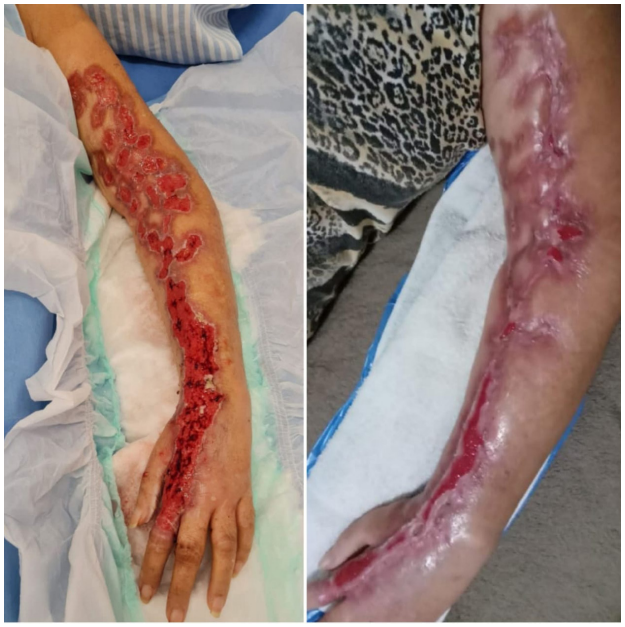

Figure 2 - Progressive healing process of skin lesions. Left image taken after treatment with amphotericin B. Right image taken one month after hospital discharge (seven months after the initial injury).

DISCUSSION

This case represents an unusual evolution of sporotrichosis, with rapid dissemination of lymphocutaneous lesions in an immunocompetent patient without comorbidities. It demonstrates that the clinical evolution of this disease has varied presentations and can be a challenge to achieving success with medical treatment.

Human sporotrichosis manifestations mainly occur in the skin and subcutaneous tissues, and the lymphocutaneous form is responsible for more than 80% of the cases. Depending on the immunological status of the host, the presentation of the disease can take different forms[8]. Our patient had a classic presentation of the lymphocutaneous form, but also had a rapid evolution of the lesions despite the initiation of treatment in the second month after disease onset. No impairment of immunity was observed in this case.

Usually, the diagnosis of sporotrichosis takes several months, due to the numerous possible differential diagnoses, especially for bacterial skin infections[9]. In regions of endemic transmission, such as Brazil, where zoonotic transmission is frequent, the diagnosis tends to be earlier. The admission to the first consultation in cases that require hospitalization usually occurs within 90 days after the onset of symptoms[10]. Our patient had a clinical and epidemiological diagnosis in the second month of the disease, demonstrating an ideal period for intervention with oral itraconazole. However, after four months of treatment, the disease progressed in a devastating way, covering the entire left upper limb. We cannot say that the transmission of the disease was zoonotic, because despite the history of helping to take care of the neighbor's sick cat, the patient had the habit of taking care of the plants in her garden, where there were many rose bushes. Uncertainties arise in classifying it as a case of zoonotic sporotrichosis or saprophytic disease. However, considering that the fungal burden of a sick cat is much higher when compared to environmental sources, the zoonotic transmission is more probable.

The 3-to-6-month treatment time for sporotrichosis remains arbitrary, but any treatment should be continued for a period of at least four to six weeks after complete clinical remission to achieve mycological cure[11]. It is recommended to take itraconazole with citric juices to increase gut absorption, and consequently, better clinical response. The consumption of alcohol or concomitant use of some drugs may impair the absorption of itraconazole (such as antacids)[11]. Our patient received adequate guidance for the use of the medication and did not consume alcohol.

Queiroz-Telles *et al.*[12] described a case of disseminated sporotrichosis in an immunocompetent man, but the diagnosis was late, as it took 4 years after the onset of the lesions. Our patient had an early diagnosis and was treated immediately even though the clinical course of the disease was unfavorable. We assume that if the time for diagnosis of our patient was prolonged, the outcome could have been the manifestation of a more severe form, producing more relevant sequelae in the affected limb.

Oral itraconazole remains the treatment of choice for cases of lymphocutaneous sporotrichosis[13,14] and amphotericin B has been shown to be a first-choice drug for the treatment of severe cases or cases that are refractory to treatment with itraconazole[10]. In a recently published case report[15] a patient with a similar case to ours could not tolerate the initial treatment with itraconazole, due to adverse drug effects, and was cured with the use of amphotericin B. However, the case had eight months of evolution and did not show rapid dissemination of the disease. Our patient was able to tolerate treatment with oral itraconazole for almost four months and her diagnosis

occurred earlier. Undoubtedly, the clinical manifestation exhibited by our patient was aggressive and the delay for initiating treatment with amphotericin B may have represented a factor that favored the progression of skin lesions. It was not prudent to have prolonged the use of itraconazole, since the lesions were not regressing.

The combination of infectious pathogens has negative effects on the prognosis and the possibility of clinical recovery from skin lesions, crusts are foci of drug resistance and secondary infection[16]. We believe that proper care of the wound, the use of antibiotics and the removal of crusts from the lesion during the patient's hospitalization contributed to the great improvement of the disease.

When a drug that is approved for treatment induces the opposite of what is intended, such as a recurrence of inflammation or exacerbation of a predisposed disease, it is referred to as a paradoxical reaction[17]. The paradoxical response to treatment has been reported in patients with other mycoses[18]. It can be argued or hypothesized that this could have been the case in our patient, since all mycoses share similar immunopathogenic mechanisms.

CONCLUSION

This work showed that the treatment of sporotrichosis can be challenging. Even in cases of early diagnosis, the lymphocutaneous form can evolve aggressively, causing deformities and functional limitations. In the first hypothesis, when the first-line treatment is not effective, amphotericin B should be the immediate option, to prevent the rapid spread of the disease.

ACKNOWLEDGMENTS

The authors would like to thank the patient, who consented to the publication of this clinical case, and all the employees of Hospital Universitario Antonio Pedro.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

FUNDING

Hospital Universitario Antonio Pedro – Faculty of Medicine of the Universidade Federal Fluminense.

REFERENCES

1. Lopes-Bezerra LM, Mora-Montes HM, Zhang Y, Nino-Vega G, Rodrigues AM, Camargo ZP, et al. Sporotrichosis between 1898 and 2017: the evolution of knowledge on a changeable disease and on emerging etiological agents. Med Mycol. 2018;56 Suppl 1:S126-43.
2. Rodrigues AM, Della Terra PP, Gremião ID, Pereira SA, Orofino-Costa R, Camargo ZP. The threat of emerging and re-emerging pathogenic Sporothrix species. Mycopathologia. 2020;185:813-42.
3. Mora-Montes HM. Special issue "Sporothrix and Sporotrichosis 2.0". J Fungi (Basel). 2022;8:821.
4. Boechat JS, Oliveira MM, Gremião ID, Almeida-Paes R, Machado AC, Zancopé-Oliveira RM, et al. Sporothrix brasiliensis and feline sporotrichosis in the metropolitan region of Rio de Janeiro, Brazil (1998-2018). J Fungi (Basel). 2022;8:749.
5. Rabello VB, Almeida MA, Bernardes-Engemann AR, Almeida-Paes R, Macedo PM, Zancopé-Oliveira RM. The historical burden of sporotrichosis in Brazil: a systematic review of cases reported from 1907 to 2020. Braz J Microbiol. 2022;53:231-44.
6. Fichman V, Valle AC, Macedo PM, Freitas DF, Oliveira MM, Almeida-Paes R, et al. Cryosurgery for the treatment of cutaneous sporotrichosis in four pregnant women. PLoS Negl Trop Dis. 2018;12:e0006434.
7. Kauffman CA, Bustamante B, Chapman SW, Pappas PG. Clinical practice guidelines for the management of sporotrichosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis. 2007;45:1255-65.
8. Rodrigues AM, Gonçalves SS, Carvalho JA, Borba-Santos LP, Rozental S, Camargo ZP. Current progress on epidemiology, diagnosis, and treatment of sporotrichosis and their future trends. J Fungi (Basel). 2022;8:776.
9. Sendrasoa FA, Ranaivo IM, Sata M, Razanakoto NH, Andrianarison M, Ratovonjanahary V, et al. Osteoarticular sporotrichosis in an immunocompetent patient. Med Mycol Case Rep. 2021;32:50-2.
10. Fichman V, Freitas DF, Valle AC, Souza RV, Curi AL, Valete-Rosalino CM, et al. Severe sporotrichosis treated with amphotericin B: a 20-year cohort study in an endemic area of zoonotic transmission. J Fungi (Basel). 2022;8:469.
11. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Articulação Estratégica de Vigilância em Saúde. Guia de vigilância em saúde. 5ª ed. rev. atual. Brasília: Ministério da Saúde; 2022. [cited 2023 May 18]. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/guia_vigilancia_saude_5ed_rev_atual.pdf
12. Queiroz-Telles F, Cognialli RC, Salvador GL, Moreira GA, Herkert PF, Hagen F. Cutaneous disseminated sporotrichosis in immunocompetent patient: case report and literature review. Med Mycol Case Rep. 2022;36:31-4.
13. Sharma B, Sharma AK, Sharma U. Sporotrichosis: a comprehensive review on recent drug-based therapeutics and management. Curr Dermatol Rep. 2022;11:110-9.
14. Sharma R, Mahajan VK, Singh Chauhan P, Mehta KS, Sharma

A, Sharma J. The clinico-epidemiological characteristics and therapeutic experience of 152 patients with cutaneous sporotrichosis: a 10-year retrospective study from India. Int J Dermatol. 2021;60:99-106.

15. Belda Jr W, Passero LF, Casolato AT. Lymphocutaneous sporotrichosis refractory to first-line treatment. Case Rep Dermatol Med. 2021;2021:9453701.
16. Fonder MA, Lazarus GS, Cowan DA, Aronson-Cook B, Kohli AR, Mamelak AJ. Treating the chronic wound: a practical approach to the care of nonhealing wounds and wound care dressings. J Am Acad Dermatol. 2008;58:185-206.
17. Kremenevski I, Sander O, Sticherling M, Raithel M. Paradoxical reactions to biologicals in chronic inflammatory systemic diseases. Dtsch Arztebl Int. 2022;119:88-95.
18. Gryschek RC, Pereira RM, Kono A, Patzina RA, Tresoldi AT, Shikanai-Yasuda MA, et al. Paradoxical reaction to treatment in 2 patients with severe acute paracoccidioidomycosis: a previously unreported complication and its management with corticosteroids. Clin Infect Dis. 2010;50:e56-8.