PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Cryosurgery for the treatment of cutaneous sporotrichosis in four pregnant women

Vivian Fichman[1☯]*, Antonio Carlos Francesconi do Valle[1☯], Priscila Marques de Macedo[1☯], Dayvison Francis Saraiva Freitas[1☯], Manoel Marques Evangelista de Oliveira[2☯], Rodrigo Almeida-Paes[2☯], Maria Clara Gutierrez-Galhardo[1☯]

1 Laboratory of Clinical Research on Infectious Dermatology, Evandro Chagas National Institute of Infectious Diseases, Oswaldo Cruz Foundation (Fiocruz), Rio de Janeiro, Brazil, **2** Laboratory of Mycology, Evandro Chagas National Institute of Infectious Diseases, Oswaldo Cruz Foundation (Fiocruz), Rio de Janeiro, Brazil

☯ These authors contributed equally to this work.
* vivianfichman@gmail.com

Check for updates

OPEN ACCESS

Citation: Fichman V, Valle ACFd, de Macedo PM, Freitas DFS, Oliveira MMEd, Almeida-Paes R, et al. (2018) Cryosurgery for the treatment of cutaneous sporotrichosis in four pregnant women. PLoS Negl Trop Dis 12(4): e0006434. https://doi.org/10.1371/journal.pntd.0006434

Editor: Todd B. Reynolds, University of Tennessee, UNITED STATES

Received: December 5, 2017

Accepted: April 6, 2018

Published: April 23, 2018

Copyright: © 2018 Fichman et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: The authors received financial support from the Evandro Chagas National Institute of Infectious Diseases, Oswaldo Cruz Foundation (Fiocruz), which provided infrastructure and paid for publishing expenses. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Background

Pregnant women with sporotrichosis should not receive systemic antifungal therapy except in severe cases when amphotericin B is recommended. Thermotherapy is the most reported treatment described in this group of patients. It entails weeks of daily self-application of heat to the lesions, requires that the patient faithfully apply it, and it could cause skin burns. Cryosurgery is a useful therapeutic tool for many cutaneous infectious diseases, safe for pregnant women, but not well evaluated for sporotrichosis treatment in this group.

Methodology

The authors conducted a retrospective study describing epidemiological, clinical, and therapeutic data related to four pregnant patients with sporotrichosis treated with cryosurgery. The authors reviewed the clinical records of four pregnant patients diagnosed with cutaneous sporotrichosis and treated with cryosurgery. The sessions were carried out monthly up to clinical cure. Molecular identification of the *Sporothrix* species was performed in two cases using T3B PCR fingerprinting assays.

Principal findings

All patients were in the second trimester of pregnancy and their age ranged from 18 to 34 years. With regard to clinical presentation, two patients had lymphocutaneous and two had the fixed form. *S. brasiliensis* was identified in two cases as the causative agent. Cryosurgery was well tolerated and the number of sessions ranged from 1 to 3. All the patients reached a complete clinical cure.

Conclusions

Cryosurgery was a safe, easy to perform and well tolerated method, and therefore it is suggested to be a suitable option for the treatment of cutaneous sporotrichosis in pregnant women.

Competing interests: The authors have declared that no competing interests exist.

Author summary

Sporotrichosis is a cosmopolitan disease, considered the most important subcutaneous mycosis in Latin America. Since 1998, there is an ongoing cat-transmitted zoonotic epidemic of sporotrichosis occurring in Rio de Janeiro, Brazil. Pregnant women are a vulnerable population occasionally affected that require special attention regarding sporotrichosis treatment. Antifungal drugs should be avoided because of their potential risks to the fetus, unless in severe cases when amphotericin B (an intravenous antifungal drug) can be indicated. In this context, local measures are the treatment of choice. Cryosurgery consists in local application of intense cold using liquid nitrogen to destroy some infectious, tumoral and inflammatory cutaneous diseases. It is scarcely reported in the literature for the treatment of sporotrichosis, especially in pregnant women for whom local heat is most used. This works aims to describe the clinical response and outcome of cryosurgery for the treatment of sporotrichosis in four pregnant women. All patients reached clinical cure after one to three sessions. These results suggest that cryosurgery can be a well-tolerated, safe, and efficient method for the treatment of sporotrichosis in pregnancy.

Introduction

Sporotrichosis is caused by dimorphic fungi of the genus *Sporothrix*, found in its filamentous form as saprophytes on decaying and living vegetation, and soil [1]. However, since the late 1990s, sporotrichosis in the state of Rio de Janeiro, Brazil, has become an urban-epidemic phenomenon, being transmitted from naturally infected cats to humans [2]. The most affected population is characterized by having poor socioeconomic backgrounds and low access to health services. In this zoonotic scenario of sporotrichosis transmission, female patients with a median age of 39 years predominate, and most of them acquire the disease through bite or scratches from infected cats [2]. In this context, women in childbearing age are an at-risk population to acquire this mycosis.

Sporotrichosis in pregnancy is a therapeutic challenge. Pregnant women should not receive azole therapy due to the potential teratogenic effects, as well as potassium iodide saturated solution (SSKI), because of its toxicity to the fetal thyroid. Although terbinafine is classified by the US Food and Drug Administration (FDA) as a category B drug, there is no sufficient clinical experience in pregnancy. Besides that, terbinafine passes into the breast milk, which could have an effect on a nursing baby. For severe sporotrichosis cases that need to be treated during pregnancy, amphotericin B is recommended [3–5].

Since systemic treatment is hardly possible, local alternative treatment plays an important role in pregnancy. Thermotherapy is the most reported therapeutic option described in this group of patients entailing weeks of daily self-application of heat to the lesions, and requires a faithfully application with a certain caution to avoid skin burns [3–7]. Cryosurgery is an effective and safe method, when applied by well-trained staff, being a useful therapeutic resource for many infectious skin diseases [8, 9]. Regarding the treatment of cutaneous sporotrichosis, it has already been reported as an effective adjuvant therapy when associated with oral antifungals [9–11]. However, to the best of our knowledge, has not yet been evaluated in pregnant women. The authors report four cases of pregnant women with cutaneous sporotrichosis that were successfully treated with cryosurgery.

Materials and methods

The study was approved by the Ethical Committee of the INI, Fiocruz, Rio de Janeiro, Brazil (CAAE 55348416.5.0000.5262). The patients' data were anonymized/de-identified to protect patients' privacy/confidentiality.

The authors reviewed the clinical records of pregnant patients diagnosed with cutaneous sporotrichosis who were treated at the cryosurgery outpatient clinic of the Laboratory of Clinical Research in Infectious Dermatology, Evandro Chagas National Institute of Infectious Diseases (INI), Oswaldo Cruz Foundation (Fiocruz) from 2006 to 2016. Briefly, the protocol of pregnant women with sporotrichosis included isolation of *Sporothrix* spp. in clinical specimens [2], complete blood count, and biochemical tests. They were instructed to perform thermotherapy with warm compresses for 20 minutes 3 times a day [7]. Subsequent follow-up was scheduled monthly or anytime in case of worsening of the lesions. For non-adherent patients or those who did not desire to perform thermotherapy for sporotrichosis treatment, cryosurgery was offered, and that was the case of the patients included in this work. Patients that received any other type of treatment for sporotrichosis besides cryosurgery were excluded. Cryosurgery sessions were carried out monthly, performed by dermatologists, up to clinical cure. In each session, lesions were treated with two cycles of 10 to 30 seconds of freeze time with liquid nitrogen in spray form. Clinical cure was defined as complete healing of the lesions. In a general way, once *Sporothrix* spp. was isolated, molecular identification of the species was performed using the T3B PCR fingerprinting method [12].

Results

From 2006 to 2016, 218 adult patients diagnosed with sporotrichosis, by fungal isolation in culture, were treated with cryosurgery. From these 218 patients, 8 were pregnant women, and 4 of them were treated exclusively with cryosurgery. These 4 patients were at the second trimester of pregnancy and their age ranged from 18 to 34 years. All of them lived in Rio de Janeiro state, Brazil. Two of them worked with domestic duties. The patients presented ulcerovegetative or nodular ulcerovegetative lesions (Fig 1).

Due to technical reasons, molecular identification of the agent was feasible in two patients (cases 3 and 4—Table 1), and the isolates were identified as *S. brasiliensis*. Complete blood count, and biochemical tests performed before, during, and after the treatment were within the normal ranges. Cryosurgery was well tolerated with no need for local anesthesia. The number of cryosurgery sessions ranged from 1 to 3. All the patients were discharged after a complete cure. No adverse reactions were observed during the treatment as well as no relapses

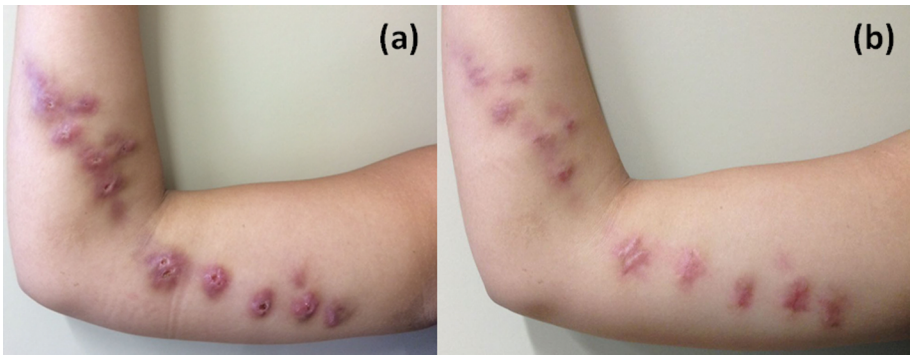

Fig 1. a) Case 2 presenting lymphocutaneous sporotrichosis in the arm; b) The same patient with complete healed lesions after 2 sessions of cryosurgery.

https://doi.org/10.1371/journal.pntd.0006434.g001

Table 1. Epidemiological, clinical and therapeutic aspects of four pregnant patients with sporotrichosis treated with cryosurgery.

Case	Age (years)	Gestational age (weeks)	Transmission form	Clinical presentation	Lesion Sites	Number of cryosurgery sessions
1	18	20	Contact with infected cat	Fixed cutaneous Ulcerovegetative	Thigh	2
2	22	16	Unknown	Lymphocutaneous Nodular ulcerative	Arm	2
3	34	20	Contact with cat	Fixed cutaneous Ulcerovegetative	Shoulder	1
4	32	24	Scratch from infected cat	Lymphocutaneous Ulcero vegetative and nodular lesions	Hand and forearm	3

https://doi.org/10.1371/journal.pntd.0006434.t001

were documented after delivery. Epidemiological, clinical, and therapeutic data of the patients are detailed in Table 1.

Discussion

Despite the low number of pregnant women affected and the benign clinical course, the treatment of sporotrichosis in pregnancy can be always considered challenging. In these cases, topical alternative therapeutic resources are safer than systemic drugs and should be considered whenever possible. Since the 1950s, thermotherapy was reported as the unique topical method for the treatment of sporotrichosis in pregnancy, with a strength of recommendation and quality of evidence considered as BIII [4]. Cryosurgery emerges as a useful tool for many infectious skin diseases, with effects of local cellular and humoral inflammatory response induction in the tissue, with its necrotic effect and, consequently, destructive for the infectious agents [8, 9].

Cryosurgery has been used as an adjuvant treatment in sporotrichosis, especially in residual lesions or in cases of ulcerovegetative or nodular ulcerovegetative thick lesions since it allows a good penetration of liquid nitrogen in spray form [13]. In other subcutaneous mycoses such as chromoblastomycosis, cryosurgery has been indicated as an isolated method or associated to systemic antifungal agents with good results [14]. Some authors have warned about the risk of lymphatic dissemination with invasive methods performed without systemic drugs in cases of chromoblastomycosis [15, 16]. In contrast with other procedures, cryosurgery is not only an ablative technique but also promotes an immune response, what could reduce this risk. A recent study with murine model found that cryosurgery was responsible for an increase in antigen-presenting dendritic cells (DCs), neutrophils and macrophages in subcutaneous tissue, as well as migration of DCs to regional lymph nodes [17]. Cryosurgery is contraindicated for patients who are sensitive to cold (cold urticaria, cryoglobulinemia, or cryofibrinogenemia) and should be avoided in extensive lesions or flexor surfaces due to the risk of fibrosis [18]. Until now, cryosurgery for sporotrichosis treatment has been poorly explored and documented especially considering cases that involve a supposed more virulent phylogenetic species such as *S. brasiliensis*.

All patients herein reported came from hyperendemic areas of sporotrichosis in Rio de Janeiro state, and become infected during pregnancy. None referred prior trauma with plants, but only contact and/or trauma with cats, in agreement with the zoonotic epidemic profile reported in the literature [2]. Although *S. brasiliensis*, could be identified in only two cases, it is well known that it is the main species involved in Rio de Janeiro epidemic. All patients presented cutaneous-limited clinical forms on the extremities, similar to previous publications [3, 5], in contrast with other mycoses, which can be more aggressive during pregnancy [19]. This work suggests that cryosurgery is a safe and well-tolerated method, easy to perform, being a promising alternative in the treatment of cutaneous sporotrichosis in pregnant women.

Further studies with a larger number of patients are necessary to confirm efficacy of cryosurgery for sporotrichosis in pregnant patients.

Supporting information

S1 Checklist. STROBE checklist.
(DOC)

Author Contributions

Conceptualization: Vivian Fichman, Antonio Carlos Francesconi do Valle, Maria Clara Gutierrez-Galhardo.

Data curation: Vivian Fichman, Maria Clara Gutierrez-Galhardo.

Formal analysis: Vivian Fichman, Maria Clara Gutierrez-Galhardo.

Investigation: Vivian Fichman, Antonio Carlos Francesconi do Valle, Manoel Marques Evangelista de Oliveira, Rodrigo Almeida-Paes, Maria Clara Gutierrez-Galhardo.

Methodology: Vivian Fichman, Antonio Carlos Francesconi do Valle, Priscila Marques de Macedo, Dayvison Francis Saraiva Freitas, Maria Clara Gutierrez-Galhardo.

Project administration: Maria Clara Gutierrez-Galhardo.

Supervision: Antonio Carlos Francesconi do Valle, Maria Clara Gutierrez-Galhardo.

Writing – original draft: Vivian Fichman, Antonio Carlos Francesconi do Valle, Priscila Marques de Macedo, Dayvison Francis Saraiva Freitas, Manoel Marques Evangelista de Oliveira, Rodrigo Almeida-Paes, Maria Clara Gutierrez-Galhardo.

Writing – review & editing: Vivian Fichman, Antonio Carlos Francesconi do Valle, Priscila Marques de Macedo, Dayvison Francis Saraiva Freitas, Manoel Marques Evangelista de Oliveira, Rodrigo Almeida-Paes, Maria Clara Gutierrez-Galhardo.

References

1. Barros MB, de Almeida Paes R, Schubach AO. Sporothrix schenckii and Sporotrichosis. Clin Microbiol Rev. 2011; 24: 633–654. https://doi.org/10.1128/CMR.00007-11 PMID: 21976602
2. Barros MB, Schubach AO, Valle AC, Gutierrez-Galhardo MC, Conceição-Silva F, Schubach TM, et al. Cat-transmitted sporotrichosis epidemic in Rio de Janeiro, Brazil: description of a series of cases. Clin Infect Dis. 2004; 38: 529–535. https://doi.org/10.1086/381200 PMID: 14765346
3. Orofino-Costa R, Bernardes-Engemann AR, Azulay-Abulafia L, Benvenuto F, Neves ML, Lopes-Bezerra LM. Sporotrichosis in pregnancy: Case reports of 5 patients in a zoonotic epidemic in Rio de Janeiro, Brazil. An Bras Dermatol. 2011; 86: 995–998. PMID: 22147042
4. 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: 1255–1265. https://doi.org/10.1086/522765 PMID: 17968818
5. Ferreira CP, Valle ACF, Freitas DFS, Reis R, Galhardo MC. Pregnancy during a sporotrichosis epidemic in Rio de Janeiro, Brazil. Int J Gynaecol Obstet. 2012; 117: 294–295. https://doi.org/10.1016/j.ijgo.2012.02.003 PMID: 22445393
6. Doherty CB, Doherty SD, Rosen T. Thermotherapy in dermatologic infections. J Am Acad Dermatol. 2010; 62: 909–927. https://doi.org/10.1016/j.jaad.2009.09.055 PMID: 20466169
7. Bustamante B, Campos PE. Sporotrichosis: a forgotten disease in the drug research agenda. Expert Rev Anti Infect Ther. 2004; 2:85–94. PMID: 15482174
8. Kuflik EG. Cryosurgery updated. J Am Acad Dermatol. 1994; 31: 925–944. PMID: 7962774
9. Moraes AM, Velho PENFV, Magalhaes RF. Criocirurgia com nitrogênio líquido e as dermatoses infecciosas. An Bras Dermatol. 2008; 83: 285–298.

10. Ferreira CP, Galhardo MC, Valle AC. Cryosurgery as adjuvant therapy in cutaneous sporotrichosis. Braz J Infect Dis. 2011; 15: 181–183. PMID: 21503410

11. Bargman H. Successful treatment of cutaneous sporotrichosis with liquid nitrogen: report of three cases. Mycoses. 1995; 38: 285–287. PMID: 8559191

12. Oliveira MM, Franco-Duarte R, Romeo O, Pais C, Criseo G, Sampaio P, et al. Evaluation of T3B fingerprinting for identification of clinical and environmental Sporothrix species. FEMS Microbiol Lett. 2015; 362(6). pii: fnv027. https://doi.org/10.1093/femsle/fnv027 PMID: 25714550

13. Almeida-Paes R, Oliveira MME, Freitas DFS, Valle ACFD, Gutierrez-Galhardo MC, Zancopé-Oliveira RM. Refractory sporotrichosis due to Sporothrix brasiliensis in humans appears to be unrelated to in vivo resistance. Med Mycol. 2017; 55(5): 507–517. https://doi.org/10.1093/mmy/myw103 PMID: 27771622

14. Castro LG, Pimentel ER, Lacaz CS. Treatment of chromomycosis by cryosurgery with liquid nitrogen: 15 years' experience. Int J Dermatol. 2003; 42(5): 408–412. PMID: 12755986

15. Bonifaz A, Paredes-Solís V,Saúl A. Treating chromoblastomycosis with systemic antifungals. Expert Opin Pharmacother. 2004; 5: 247–254. https://doi.org/10.1517/14656566.5.2.247 PMID: 14996622

16. Queiroz-Telles F, Santos DW. Challenges in the therapy of chromoblastomycosis. Mycopathologia. 2013; 175:477–488. https://doi.org/10.1007/s11046-013-9648-x PMID: 23636730

17. Kasuya A, Ohta I, Tokura Y. Structural and immunological effects of skin cryoablation in a mouse model. PLoS One. 2015; 10(3):e0123906. https://doi.org/10.1371/journal.pone.0123906 PMID: 25821968

18. Bonifaz A, Martinez-Soto E, Carrasco-Gerard E, Peniche J. Treatment of chromoblastomycosis with itraconazole,cryosurgery, and a combination of both. Int J of Dermatol.1997; 36: 542–47.

19. Sampaio FM, Galhardo MC, de Farias Cardoso R, de Oliveira Coelho JM, Lyra MR, do Valle AC. Eumycetoma on the foot caused by Madurella mycetomatis: amputation after significant worsening during pregnancy. Acta Derm Venereol. 2015; 95: 374–375. https://doi.org/10.2340/00015555-1963 PMID: 25178425