Epidemiological and Clinical Aspects of Sporotrichosis in Espírito Santo State, Southeast Brazil: A Study of Three Decades (1982–2012)

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Abstract. This study discusses a historical patient series and is designed to describe clinical and epidemiological characteristics of human sporotrichosis in the state of Espírito Santo, Brazil. Data were derived from patients treated at the Infectious Diseases service of Cassiano Antônio Moraes University Hospital in Vitória, the state capital, from July 1982 to June 2012. A total of 171 patients were diagnosed with sporotrichosis, mostly men (80.7%) with a median age of 33 years and 5 months. We can presume an approximate average incidence rate of 4.9 cases per 100,000 inhabitants during the studied period. All the patients were involved in occupational or leisure activities with direct contact with soil or plants. Most cases were recorded in the mountainous region of the state during the hot and rainy periods. The average time elapsed from lesion progression to diagnosis was 3 months, with the lymphocutaneous form being the most common (70.2%), followed by the fixed cutaneous form (28.6%). Diagnosis was confirmed in 93.6% of the cases by culturing *Sporothrix* spp. in Sabouraud dextrose agar, and from the clinical features in the remaining cases. Aspiration of cutaneous nodule secretions was the best method for the collection of clinical specimens for disease diagnosis. A 25% saturated solution of potassium iodide (SSKI) was provided to almost all patients (98.8%), with therapeutic success. In conclusion, in this retrospective study in the state of Espírito Santo, we found that sporotrichosis affects primarily the ≥ 10-year-old population, and the most common presentation is the lymphocutaneous form affecting the lower and upper limbs, and the infection appeared to be acquired predominantly through occupational activities. Treatment with SSKI was safe and effective.

INTRODUCTION

Sporotrichosis is an implantation mycosis of subacute/chronic course, distributed worldwide, especially in tropical and subtropical regions. This infectious disease is caused by the dimorphic fungus *Sporothrix schenckii* sensu lato (s.l.), which comprises 51 taxa, divided into clinical and environmental clades. The clinical clade encompasses mostly human pathogens, including *Sporothrix brasiliensis*, *S. schenckii* sensu stricto (s.s.), *Sporothrix globosa*, and *Sporothrix luriei*. The environmental clade is composed of other species complexes, such as *Sporothrix pallida* and *Sporothrix candida*.^{1–6} Classically, infection occurs after traumatic inoculation of fungus-contaminated organic material into the skin. However, transmission by contact with infected animals (zoonotic pattern, mostly involving cats) and, less frequently, by inhalation of conidia present in the environment has been reported.⁶ Clinically, cutaneous manifestations prevail and are divided into lymphocutaneous (multiple lesions extending to the lymphatic channels), fixed cutaneous (single nodular, ulcerative, or verrucous lesions), multiple inoculation, disseminated infection, and extracutaneous forms (cutaneous disseminated, osteoarticular, and ocular).^{6–8} The latter is rare and usually related with immunosuppression.^{9,10}

Sporotrichosis is considered the main subcutaneous mycosis in Latin America. It is endemic to Mexico, Guatemala, Costa Rica, Panama, Colombia, Venezuela, Brazil, Peru, Bolivia, Argentina, and Uruguay. Mycosis mainly affects low-income, rural populations. Epidemiological information is scarce, as reporting to authorities is not mandatory in most American countries.^{11,12} Sporotrichosis has been recognized

in Brazil since 1907,¹³ with the classical epidemiological pattern of the disease prevailing until the 1990s, specifically a high infection incidence in adult, male rural workers with frequent contacts with the soil.¹¹ However, a zoonotic pattern has emerged in the last two decades, related to domestic or professional contact with infected cats. This type of transmission affects mainly women in urban areas, which has caused a large outbreak in the state of Rio de Janeiro, tending to spread to the states of São Paulo and Rio Grande do Sul. *Sporothrix brasiliensis* is the involved species.^{14–16}

In the local context, the largest sporotrichosis case series have been reported in Southern and Southeastern Brazil, the main endemic areas of the disease.^{17–19} There is little sporotrichosis-related information in the state of Espírito Santo,^{20–23} also located within southeastern Brazil. In this way, our findings could be used in the state health surveillance program, for understanding and comparing the actual disease epidemiological changing pattern in the country. Thus, the main objective of this study was to describe clinical and epidemiological characteristics of human sporotrichosis in the state of Espírito Santo, Brazil.

MATERIAL AND METHODS

Study design and population. Data were derived from patients diagnosed with sporotrichosis, treated at the Infectious Diseases service of the Cassiano Antônio Moraes University Hospital (HUCAM), located in Vitória, state capital of Espírito Santo, from July 1982 to June 2012. The HUCAM Infectious Diseases service is the state's reference center for patients with leishmaniasis and other tropical diseases. The state of Espírito Santo extends over an area of 46,095.583 km² and has an estimated population of 3,929,911 people, distributed among 78 municipalities (Figure 1). Sporotrichosis patients were mostly referred to from health posts and hospitals outside the state capital for diagnosis. Possible risk

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FIGURE 1. Map of the state of Espírito Santo, Brazil. This figure appears in color at www.ajtmh.org.

factors related to the disease were investigated in anamnesis, such as life habits and occupational activities. The detailed clinical examination provided a database with precise notes on the number and distribution of lesions for each patient. Patients were diagnosed with sporotrichosis based on the following criteria: 1) *Sporothrix* spp. isolation from clinical specimen cultures and 2) clinical–epidemiological features, when patients exhibited lesions consistent with sporotrichosis, regardless of history of trauma or contact with diseased animals.⁹

Specimen collection and processing. The clinical specimens for diagnosis were collected by one or more of the following methods: 1) open exudative lesion swab; 2) aspiration of purulent material from cutaneous abscess; and 3) incisional cutaneous biopsy at the margin of the lesions with a 5-mm

punch, followed by grinding of the material in 0.9% saline solution.

All material collected was seeded in test tubes with Sabouraud dextrose agar media and examined daily to assess *Sporothrix* spp. colony growth. Unfortunately, during period of the study, we did not have the laboratory support to perform the molecular identification of *Sporothrix* spp.

Patient treatment. Once diagnosed, patients were treated orally with a 25% saturated solution of potassium iodide (SSKI) at a dose of 40–60 drops/day (1–2 g and 2–4 g/day for children and adults, respectively), until the lesions healed. Patients were examined monthly or in shorter time periods in case of any adverse events or drug intolerance. In such cases, SSKI was replaced with a single daily 200 mg/day itraconazole dose, until lesions healed completely. Patients were considered cured when inflammation was no longer detectable and were subsequently discharged from the outpatient clinic.

Statistical analysis. Statistical package SPSS 16.0 (SPSS, Inc., Chicago, IL) was used for data analysis using the following sociodemographic variables: gender, age, ethnicity, profession, municipality, and state of residency. The clinical presentation of human sporotrichosis was analyzed, characterizing the lymphocutaneous, fixed cutaneous, disseminated, and extracutaneous forms. Lesion location, probable point of initial inoculation of the etiological agent, and time of disease progression until diagnosis were also assessed. Other variables considered in the study were as follows: method of diagnosis, drug treatment, and the time until lesion healing. Socioeconomic, demographic, and environmental data were obtained from the Brazilian Institute of Geography and Statistics (IBGE), demographic census 1980 and 2010 (aggregates by census sector), and the Jones dos Santos Neves Institute (2012).

Variable analysis involved frequencies, measures of central tendency, and variability. Distribution of variables was evaluated by determining their central tendency and variability measures, either as mean and standard deviation (SD) when data fit a Gaussian model, or otherwise as median and interquartile distance (ID). The Kruskal–Wallis nonparametric post hoc test was used to compare processes of collecting clinical specimens for culture, to evaluate colony growth in Sabouraud dextrose agar media, and the time interval between seeding and detection of colony growth. The comparison between the continuous variables involving time and the clinical forms of the disease were calculated using the nonparametric Mann–Whitney test because the normality of the data was rejected by the Kolmogorov–Smirnov test. Linear regression analysis was used to verify the trends of growth (or decrease) of the number of cases during the period studied.

The cases were georeferenced from patients' residence address to map the approximate spatial distribution of sporotrichosis in the municipalities of Espírito Santo throughout the 30 years of the study. The incidence rate of the disease per 100,000 inhabitants throughout the studied period was calculated to better estimate the human sporotrichosis incidence rate in the municipalities of Espírito Santo. The approximate population used as a basis for calculation was obtained as the arithmetic mean of the populations of the municipalities of the demographic censuses of 1980 and 2010, according to IBGE, and considered the changes in the geographical structure and the population difference of the municipalities from 1982 to 2012.

Ethical considerations. This study was submitted to and approved by the Research Ethics Committee of the Health Sciences Center of the Federal University of Espírito Santo, Brazil (124/11).

RESULTS

Epidemiological aspects. A total of 171 cases of human sporotrichosis were diagnosed in the HUCAM Infectious Diseases service from 1982 and 2012, 160 of which (93.6%) were confirmed by laboratory diagnosis with *Sporothrix* spp. isolation and 11 (6.4%) by clinical-epidemiological diagnosis (culture was not performed). Some of these cases were partially described in previous publications.^{20–23} The majority of the patients were male (80.7%, 4:1 male-to-female ratio); most patients were Caucasian (86.5%), and showed an age range from 6 to 77 years. Only six patients (3.5%) were younger than 12 years old (Table 1). The median age was 33 years and 5 months, with an ID between 24 and 47 years. Most patients were individuals who worked in direct contact with plants and soil and included farmers (68.4%), and people who, despite being in a domestic environment for an extended period, performed agricultural or gardening activities (e.g., housekeepers, students, and housewives). Other occupational activities are also listed in Table 1.

Most patients were from the state of Espírito Santo (155, 90.6%), nine (5.3%) were from Minas Gerais, two (1.2%) from Bahia, and one (0.6%) from Rio de Janeiro. The state of origin

of four patients (2.3%) was unknown. A total of 109 (63.7%) patients came from 10 of the 78 municipalities of the state of Espírito Santo (Table 2), showing a trend toward a higher clustering of cases in the Serrana region (Figure 2). Although it contemplates only the cases referred to the HUCAM, we can presume an approximate average incidence rate of 4.9 cases per 100,000 inhabitants for the state of Espírito Santo, during the studied period.

The number of notifications per year varied widely during the period of study, with an annual average of six cases (5.4 cases per year, *P*-value 0.682). There were no statistically significant differences in trends of growth or decrease in the number of cases (Figure 3). A greater clustering of cases was observed in the hot and dry (October–January) and hot and humid (February–May) seasons, according to the expected climatic features of the Serrana region.²⁴ Compared with the two hot periods (both with similar higher number of cases), the cold and dry period (June–September) had a lower average number of cases (*P*-value 0.027) (Figure 4).

Clinical aspects. The average time elapsed from lesion progression to diagnosis ranged between 15 days and 10 years, with a mean value of approximately 3 months. The

TABLE 1

Sociodemographic characteristics of human sporotrichosis cases in the Cassiano Antônio Moraes University Hospital's Infectious Diseases service, Espírito Santo, 1982–2012

Variables	n	%
Gender		
Male	138	80.7
Female	33	19.3
Age group (years)		
0–9	4	2.3
10–19	25	14.6
20–29	40	23.4
30–39	29	16.9
40–49	31	18.1
50–59	20	11.7
≥ 60	11	6.4
ND	11	6.4
Ethnicity		
Caucasian	148	86.5
“Pardo”	12	7.0
Black	6	3.5
ND	5	2.9
Occupation		
Farmer	117	68.4
Housekeeper	14	8.2
Student	13	7.6
Housewife	9	5.3
Stonemason	3	1.7
Mechanic	2	1.2
Agronomical engineer	1	0.6
Teacher	1	0.6
Rural entrepreneur	1	0.6
Miner	1	0.6
Painter	1	0.6
Welder	1	0.6
Gold miner	1	0.6
ND	6	3.5

ND = no data.

TABLE 2

Distribution of human sporotrichosis cases in Espírito Santo, according to the municipality of residence of the patients, 1982–2012

Municipalities	N	%	Estimated population	Approximate incidence rate per 100,000 inhabitants
Afonso Cláudio	39	25.2	39,690.5	98.3
Domingos Martins	19	12.2	29,715.5	63.9
Brejetuba	10	6.4	9,961.5	100.4
Santa Maria de Jetibá	10	6.4	28,722	34.8
Santa Leopoldina	8	5.2	18,452	43.3
Venda Nova do Imigrante	5	3.2	14,454.5	34.6
Muniz Freire	5	3.2	18,680.5	26.8
Mimoso do Sul	5	3.2	29,793	16.8
Laranja da Terra	4	2.6	10,470	38.2
Alfredo Chaves	4	2.6	12,340.5	32.4
Baixo Guandu	4	2.6	27,507	14.5
Viana	4	2.6	44,220.5	9.0
Conceição do Castelo	3	1.9	10,273.5	29.2
Santa Teresa	3	1.9	23,907	12.5
Ilúna	3	1.9	32,475	9.2
Alto Rio Novo	2	1.3	7,305.5	27.4
Irupi	2	1.3	9,643	20.7
Aracruz	2	1.3	58,811.5	3.4
Cachoeiro do Itapemirim	2	1.3	156,787.5	1.3
Serra	2	1.3	245,917.5	0.8
Cariacica	2	1.3	268,918.5	0.7
São Roque do Canaã	1	0.6	7,378	13.5
Atílio Vivacqua	1	0.6	7,901	12.6
Itarana	1	0.6	9,902	10.0
Rio Novo do Sul	1	0.6	10,142.5	9.8
Iconha	1	0.6	10,402.5	9.6
Marechal Floriano	1	0.6	10,567.5	9.5
Itaguaçu	1	0.6	13,700	7.3
Vargem Alta	1	0.6	14,769.5	6.8
Anchieta	1	0.6	17,657.5	5.7
Ibatiba	1	0.6	21,300	4.7
Pancas	1	0.6	25,821.5	3.9
Castelo	1	0.6	30,316	3.3
Itapemirim	1	0.6	33,050.5	3.0
São Gabriel da Palha	1	0.6	37,077.5	2.7
Barra de São Francisco	1	0.6	46,084	2.2
Guarapari	1	0.6	71,893	1.4
Vila Velha	1	0.6	308,993.5	0.3

FIGURE 2. Spatial distribution of sporotrichosis cases per municipality of residence, in the state of Espírito Santo, 1982–2012. This figure appears in color at www.ajtmh.org.

clinical forms of sporotrichosis included 120 patients (70.2%) who presented with the lymphocutaneous form and 49 (28.6%) with the fixed cutaneous form. The lymphocutaneous form was diagnosed approximately 9 months faster than the fixed cutaneous form (P -value 0.012). Only two patients (1.2%) developed extracutaneous sporotrichosis: one with osteoarticular involvement (disseminated infection) and the other with ocular mucosa involvement (disseminated infection).²³ The lower and upper limbs were mostly affected by the disease (157 cases, 92%), as shown in Figure 5, whereas

the hand (45 cases, 26.3%) was the initial inoculation point of the etiological agent (Table 3).

Lesion biopsies were performed in 60 (35%) patients, followed by open wound swab in 38 (22.2%) and aspiration of cutaneous nodule secretion in 37 (21.6%). Some patients underwent more than one diagnostic method, whereas 11 (6.4%) were diagnosed solely by clinical features. Aspiration of cutaneous nodule secretion provided a greater number of *Sporothrix* spp. colonies, in addition to significantly less colony detection time compared with other methods (Table 4).

FIGURE 3. Number of cases of human sporotrichosis in Espírito Santo per year and its trend line along the studied period, 1982–2012. This figure appears in color at www.ajtmh.org.

Treatment with 25% SSKI was established for all but four patients: one was already using terbinafine, and the medication was maintained under our service; one pregnant woman received 200 mg/day itraconazole; one patient had osteo-articular disease in the knee and wrist and received SSKI, itraconazole, and amphotericin B; and the fourth patient, who exhibited multifocal lesions involving the cephalic segment and upper limbs, also received itraconazole. All patients revisited after 4 and 8 weeks of treatment. All achieved therapeutic success. However, 36 patients (21%) did not return for the final visit, acknowledging that they were cured.

The average treatment time until complete healing of lesions was 48 days (SD = 15) for all the clinical forms of the disease, with no statistically significant difference between them (P -value 0.884). Despite some reports of nausea, vomiting, bitter taste in the mouth, diarrhea, abdominal pain, and gastric discomfort with the use of 25% SSKI, only two cases (1.2%) needed to interrupt treatment, with subsequent administration of 200 mg/day itraconazole, also with therapeutic success.

DISCUSSION

The HUCAM Infectious Diseases Outpatient Clinic is a state reference service, with the appropriate infrastructure to

FIGURE 4. Average number of cases of human sporotrichosis in Espírito Santo according to three seasonal periods: cold and dry (June–September), hot and dry (October–January), and hot and humid (February–May), 1982–2012. This figure appears in color at www.ajtmh.org.

perform tropical disease diagnoses, where patients from all municipalities of the state and from neighboring states are referred to, especially those with suspected leishmaniasis and sporotrichosis. Thus, we consider that the patients studied from 1982 to 2012 represent the full clinical–epidemiological profile of sporotrichosis in the state of Espírito Santo. We can presume an approximate average incidence rate of 4.9 cases per 100,000 inhabitants; nevertheless, because sporotrichosis patients were mostly referred to from health posts and hospitals outside the state capital, the incidence rates in the municipalities of Espírito Santo only provide an approximate estimate. Therefore, these findings can constitute underestimations or overestimations of the true incidence rates of sporotrichosis in the state of Espírito Santo, Brazil.

The classic rural disease pattern was observed in our case series, with a higher incidence in men engaged in agricultural work and in constant contact with plants and soil, which are sources of infection by the fungus.¹¹ De Araujo et al.²² characterized molecular isolates from patients with sporotrichosis in Espírito Santo (most of which originated from our case series), identifying *S. schenckii* s.s. as an etiological agent. This species is closely associated with the classical pattern of the disease in Brazil.¹⁶

The demographic characteristics of patients with sporotrichosis in this study were similar to those reported in most endemic regions of Latin America (including other Brazilian states), where men in the age group of 15 years and older account for 56–97% of the cases.^{12,17,19,25–28} An exception is the hyperendemic province of Abancay in Peru, where children aged less than 14 years are the most affected population.²⁹ However, the demographic profile is similar to that of the state of Espírito Santo, where patients come from the mountainous region, with altitudes between 450 and 1,200 m, and the incidence rates approach 100 cases per 100,000 inhabitants in the most affected municipalities.^{30,31} By contrast, Rio de Janeiro shows a different epidemiological profile from the other Brazilian states, where sporotrichosis urbanization is observed, maintained in the enzootic form by domestic cats.¹⁸

Our study showed that most cases occurred in the hot and humid period of the year, similar to the case series described in Mexico and Australia,^{11,32} but the incidence in our study was

FIGURE 5. Lesion location vs. sporotrichosis clinical forms (lymphocutaneous and fixed). This figure appears in color at www.ajtmh.org.

in contrast to that reported in other countries such as Peru and India,^{29,33} where the disease incidence was higher in the dry periods of the year.

The clinical characteristics of sporotrichosis exhibited by our patients are consistent with previous findings that revealed an average period of 2–10 months from lesion progression to disease diagnosis.^{17,28,32,34} Our results on the most frequent clinical forms of the disease also agree with previous studies demonstrating that the prevalence of the lymphocutaneous form was between 52% and 92%, followed by the fixed cutaneous form (13–48% of the cases).^{12,19,25–27,29} In our study, we observed a similar involvement of lower and upper limbs (46.2% versus 45.6%, respectively). This result is in contrast to most studies reported in the literature, which demonstrated that 52–92% of lesions were located in upper limbs.^{12,17,19,26–28,32} Of note, only 0.6% of the patients exhibited facial lesions, a finding similar to previous reports^{12,17,19,26–28} and in contrast to the clinical pattern described in the province of Abancay in Peru, where 44% of the patients, mostly aged less than 14 years, presented with facial lesions.²⁹

Sporothrix spp. culture, which is considered the diagnostic gold standard,⁹ was the most commonly used method in our study, showing a sensitivity of more than 90%, similar to that of other case studies.^{14,17,27} Cutaneous nodule aspirate, open

lesion swab, and lesion biopsy were effective specimen collection methods for fungus culture. Importantly, cutaneous nodule aspirate allowed the growth of more colonies over a shorter time, a result similar to that reported by Oyarce et al.²⁸ in Peru. The superiority of this method can be explained by the absence of bacteria and other contaminants that could prevent or delay *Sporothrix* spp. growth.

Treatment with potassium iodide resulted in a cure rate of more than 90% in an average time of 48 days, with mild adverse events that resulted in the suspension of treatment in only two patients. Similar results have been reported in other developing countries where scarce economic resources hinder the use of itraconazole as first-line medication.^{17,25–28,34} However, other authors reported an adverse effect rate of 60% due to the use of SSKI,³⁰ thus recommending the use of itraconazole for disease treatment.³⁵ In view of this controversy, a modification of the daily dose intervals has been suggested to reduce adverse events.^{36,37}

Saturated solution of potassium iodide treatment in a series of 102 patients with sporotrichosis resulted in a 77% cure rate, 15.7% treatment withdrawal, side effects in 64.7% of the participants, and therapeutic failure in 2.9%.³⁷ The mean treatment time was 8 weeks. Another cohort study with 645 patients treated with itraconazole³⁸ reported a healing rate of

TABLE 3

Localization of human sporotrichosis lesions in patients treated at Cassiano Antônio Moraes University Hospital, Espírito Santo, 1982–2012

Variables	n	%
Inoculation point		
Hand	45	26.3
Foot	32	18.7
Leg	23	13.4
Forearm	17	9.9
Arm	14	8.2
Knee	12	7.0
Thigh	12	7.0
Face	5	2.9
Anterior thorax	2	1.2
Back	2	1.2
Neck	1	0.6
Shoulder	1	0.6
Foot and forearm	1	0.6
Leg and hand	1	0.6
Eye, face, and arm	1	0.6
Joint	1	0.6
Location of lesions		
Lower limb	79	46.2
Upper limb	78	45.6
Cephalic segment	6	3.5
Torso	4	2.3
Upper and lower limbs	2	1.2
Cephalic segment and upper limb	1	0.6
Joint	1	0.6

94.6%, with only 4% of treatment withdrawal. However, 40% of the patients reported side effects and 24.1% had alterations in laboratory tests. Furthermore, the average treatment period was 14 weeks.

The American Society of Infectious Diseases has considered itraconazole as the top-line drug for sporotrichosis treatment.³⁹ However, our results show a high healing rate and satisfactory tolerance to SSKI treatment, corroborating results obtained by other authors.^{17,25–28,34} Saturated solution of potassium iodide has been proposed as the first option for regions with limited economic resources because of its low cost.

The two main limitations of our study were the lack of information on the type of trauma or contact that triggered the disease in patients, and the impossibility of characterizing the species in the *S. schenckii* s.l. complex in clinical isolates at the molecular level. This information would be important in view of the emerging changes in the epidemiological profile of

TABLE 4

Average number of *Sporothrix schenckii* s.l. colonies that grew in Sabouraud dextrose agar media and average time from early emergence of colonies, according to the method of collection of clinical specimens, to diagnose human sporotrichosis in patients treated at HUCAM, Espírito Santo, 1982–2012

Variables	Mean	P-value
Clinical specimen collection method	Mean colony number	
Aspiration of cutaneous nodule	47.0	0.000
Open wound swab	22.6	
Biopsy	25.1	
Clinical specimen collection method	Mean colony growth time (days)	
Aspiration of cutaneous nodule	6.6	0.018
Open wound swab	9.5	
Biopsy	8.0	

the disease in the last decades in Brazil.^{11,14–16} However, although we have reported few autochthonous cases of zoonotic sporotrichosis caused by *S. brasiliensis*, related to contact with cats in the state of Espírito Santo (some of which were included in this study),^{20,21} our results suggest the occurrence of the “classic disease transmission pattern,” probably caused by *S. schenckii* s.s.²² between 1982 and 2012.

In conclusion, this is the first retrospective study to describe the clinical–epidemiological characteristics of sporotrichosis in the state of Espírito Santo over a period of three decades, highlighting the involvement of the rural population in mountain areas. We found that sporotrichosis affects primarily the ≥ 10 -year-old population, and the most common presentation is the lymphocutaneous form affecting the lower and upper limbs, and infection appeared to be acquired predominantly through occupational activities. Treatment with SSKI was safe and effective.

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