



Histopathology of cutaneous sporotrichosis in Rio de Janeiro: a series of 119 consecutive cases

Background: Sporotrichosis is the most common subcutaneous mycosis in Rio de Janeiro. Histopathological examination reveals diffuse granulomatous and suppurative dermatitis, and the fungus is rarely identifiable in tissue. We describe the histopathological features of cutaneous sporotrichosis, and investigate the association between them and the lack of visualization of the fungus.

Methods: A total of 119 samples of confirmed sporotrichosis cases were studied. The characteristics of the inflammatory infiltrate, the presence of epidermal changes, necrosis and fibrosis, and the parasite burden were analyzed. The association between histopathological changes and the lack of visualization of the fungus was evaluated using prevalence ratios.

Results: Granulomas were observed in all samples, suppurative granulomas in 100 (84%) and diffuse dermatitis in 114 (95.8%). Liquefaction and caseous necrosis were present in 78 (65.5%) and 52 (43.7%) samples, respectively. The fungus was not seen in 77 (64.7%) samples. Epithelioid, tuberculoid or foreign-body-type granulomas, caseous, fibrinoid or absent necrosis, predominance of lymphocytes among nonphagocytic cells and fibrosis were associated with the lack of visualization of the fungus.

Conclusion: The histopathological characteristics of sporotrichosis were variable when the causative fungus was not seen. In a proper context, the diagnosis of sporotrichosis remains a potential consideration even in the absence of demonstrable yeast.

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Sporotrichosis caused by *Sporothrix* species is the most frequent subcutaneous mycosis in Latin America. Clinically, cutaneous sporotrichosis manifests as a fixed form characterized by a single ulcerated lesion or as the lymphocutaneous form characterized by nodular lymphangitis ascending from the initial inoculation lesion. The latter is regarded as the most characteristic and most frequent form. In addition, there is a disseminated form which results from hematogenous dissemination and involves multiple anatomic sites.¹

Isolation of the fungus in culture medium, although not always available, is the gold standard diagnostic method. False-negative results may occur because of the lack of fungal growth or bacterial contamination. Histopathologically, sporotrichosis appears as chronic diffuse granulomatous dermatitis. The most characteristic granulomas are 'suppurative granulomas' or 'pyogranulomas' (abscess-centered granulomas).² The presence of a lymphoplasmacytic infiltrate surrounding the granulomas has also been described. Some investigators refer to pyogranulomas surrounded by this type of infiltrate as 'sporotrichotic granulomas'.³ Other types of granulomas are also observed.⁴

In human tissue, *Sporothrix* can be seen in the form of yeasts or asteroid bodies, which are fungal structures surrounded by radial eosinophilic projections.^{2,5-7} The frequency of detection of *Sporothrix* by histopathological examination is controversial. According to some investigators, the fungus is present in small numbers in the lesions and the search for the agent is frequently negative.⁸ However, others report that asteroid bodies are present in all cases and their detection depends only on the analysis of serial histological sections.⁹

Sporotrichosis has occurred in an epidemic form in the metropolitan region of Rio de Janeiro, since 1998, as a zoonosis associated with the domestic cat: infection commonly results from bites or scratches.¹⁰⁻¹³ Characteristics of the current epidemic, including the mode of transmission and the fungal form transmitted (yeast-like phase), besides fungal virulence and host susceptibility, may theoretically result in peculiar tissue alterations.

The objective of the present study was to characterize the histopathological features of the sporotrichosis epidemic that is occurring in Rio de Janeiro, and to investigate the association between histopathological changes and the lack of visualization of the fungus.

Material and methods

Eligibility criteria and study group

All patients seen in an outpatient clinic between 1998 and 2004 with a diagnosis of cutaneous sporotrichosis

confirmed by isolation of *Sporothrix* species in culture were eligible for the study. Of these patients, were included those who had a skin lesion biopsy sent for histopathological analysis and whose samples were available in the archive (slides and tissue blocks) during the course of this study.

Criteria for exclusion were unsatisfactory histological technique (inadequate fixation, processing or staining), superficial samples (not including at least the reticular dermis), and samples supposedly not representative of a macroscopic lesion (not exhibiting diffuse dermatitis, granulomatous dermatitis or inflammatory infiltration covering more than one third of the surface of the sample).

Data including age, gender, duration of the lesion, clinical form and outcome were collected from the medical records. The epidemiological and clinical characteristics of these patients, as well as basic histopathological features, have been previously reported.¹⁴

The study was approved by the Institution Ethics Committee and all patients signed a free informed consent form.

Histopathological analysis

The original hematoxylin/eosin (H/E)-stained slides retrieved from the archive were examined by a pathologist who was unaware of the original histopathological report. The following microscopical changes were analyzed: composition, distribution and organization of the inflammatory infiltrate and the presence of necrosis, ulceration and epidermal changes as shown in Table 1. These changes were classified as present or absent. For 'distribution of inflammation', 'type of granuloma', 'cells of the mononuclear phagocytic system', 'inflammatory cells, nonmononuclear phagocytic system', 'type of necrosis' and 'location of necrosis', more than one alternative was accepted within the same group, and for these a predominant category was also registered when it was more extensive than others.

Parasite burden was semiquantitatively evaluated in Grocott's silver-stained slides using an arbitrary scale as shown in Table 1. All fields of at least two histological sections of the fragments were examined at high magnification ($\times 400$). Asteroid body-like structures were also investigated in H/E-stained sections.

Data analysis

The data were entered into the EpiData Entry program, version 3.1, and analyzed using the Statistical Package for the Social Sciences (SPSS), version 16.0. Simple frequencies and measures of central tendency, and dispersion of the histopathological changes and

Table 1. Definition of histopathological changes

Organization of the inflammatory infiltrate	
Nonspecific	Absence of granulomas
Poorly formed granuloma	Macrophages or poorly cohesive epithelioid cells in poorly delimited aggregates
Well-formed granuloma	Cohesive epithelioid cells in round and well-delimited aggregates
Type of granuloma*	
Foreign body	Predominance of activated macrophages compared to epithelioid cells and presence of foreign body-type giant cells
Tuberculous	Well-formed granulomas with central caseous necrosis, Langhans giant cells and surrounding lymphoplasmacytic infiltrate
Sarcoidal	Juxtaposed, small, round granulomas composed of epithelioid cells, Langhans and foreign body-type giant cells, without a lymphocytic halo
Palisaded	Granulomas with a necrotic center and histiocytes arranged in a palisade around this
Suppurative	Neutrophils permeating a histiocytic aggregate
Epithelioid NOS	Poorly formed granulomas without necrosis or suppuration
Ulceration	
Present	Loss of epithelial lining, exudate forming a crust or necrotic material on granulation tissue
Supposed	Only granulation tissue or exudate
Absent	Intact epidermis
Squamous hyperplasia	
Absent or minimal	Epidermis of normal thickness
Regular	Epidermal cones of similar width and height
Irregular	Wide variation in the width and height of epidermal cones
Pseudocarcinomatous	Lumps of squamous hyperplasia of variable shape, width and height extending deep into the dermis and showing an infiltrative aspect
Parasite burden	
0	No fungus
1+	Up to five fungal elements per section (standard: 5 mm punch)
2+	From six fungal elements per section to five per field at high magnification ($\times 400$)
3+	From 6 to 50 per field at high magnification
4+	More than 50 per field at high magnification

*The same granuloma may receive more than one classification, except for those classified as epithelioid NOS (not otherwise specified).

clinical variables were obtained. For the variable 'lesion duration', the normal distribution was rejected by the Kolmogorov–Smirnov test and means of this variable were compared by the nonparametric Mann–Whitney test between cases with and without visualization of the fungus. The chi-square test with continuity correction was used to compare proportions of the histopathological changes between cases with and without visualization of the fungus. The level of significance was set at 5% for all tests. Prevalence ratios and the respective 95% confidence intervals were calculated as measures of association.

Results

Sample

A total of 759 patients with a final diagnosis of cutaneous sporotrichosis were seen between January 1998 and December 2004. Of these, 128 patients fulfilled the inclusion criteria and were selected for preliminary evaluation. More than one skin biopsy was obtained from some patients for a total of 144 samples. Twenty-five samples were excluded:

1 because of unavailability of archival material, 22 for nonrepresentative nature, and 2 for unsatisfactory histological technique. None was considered superficial. Finally, 119 skin samples from 110 patients were studied.

Clinical and epidemiological variables

Sixty-four (52.8%) of the 110 patients were females. Patient age ranged from 6 to 89 years (mean: 41; median: 43). Sixty-two (56.4%) patients had the lymphocutaneous form, 28 (25.4%) the fixed cutaneous form and 20 (18.2%) the disseminated form. The duration of the lesions at the time of diagnosis ranged from 1 to 108 weeks (mean: 12; median: 6). Seventy-nine (71.8%) patients were clinically cured and no recurrence was observed during a six-month follow-up period after the end of treatment. Eleven (10.0%) patients abandoned follow up after clinical cure and 18 (16.4%) abandoned treatment before cure. One patient presented spontaneous cure and abandoned follow up. One patient's condition worsened, with dissemination to the mucosa four months after the beginning of treatment.

Table 2. Frequency of histopathological changes analyzed as present and predominant in the 119 cases of sporotrichosis

	Present*	Predominant†
Distribution of inflammation		
Diffuse	114 (95.8%)	103 (86.6%)
Interstitial	53 (44.5%)	5 (4.2%)
Hypodermic	32 (26.9%)	5 (4.2%)
Perivascular	64 (53.8%)	3 (2.5%)
Band-like	9 (7.6%)	2 (1.7%)
Periadnexal	29 (24.4%)	1 (0.8%)
Vasculitis type	8 (6.7%)	0 (0%)
Perineural	5 (4.2%)	0 (0%)
Total	—	119 (100%)
Type of granuloma		
Suppurative	100 (84.0%)	65 (54.6%)
Epithelioid NOS	71 (59.7%)	30 (25.2%)
Tuberculoid	49 (41.2%)	19 (16.0%)
Palisaded	27 (22.7%)	3 (2.5%)
Foreign body	25 (21.0%)	2 (1.7%)
Sarcoidal	1 (0.8%)	0 (0%)
Total	—	119 (100%)
Cells of the MP system		
Epithelioid cells	118 (99.2%)	99 (83.2%)
Macrophages	87 (73.1%)	18 (15.1%)
Langhans giant cells	95 (79.8%)	1 (0.8%)
Foamy cells	18 (15.1%)	1 (0.8%)
Foreign body-type cells	63 (52.9%)	0 (0%)
Total	—	119 (100%)
Inflammatory cells, non-MP system		
Lymphocytes	119 (100.0%)	66 (55.5%)
Plasma cells	109 (91.6%)	33 (27.7%)
Neutrophils	104 (87.4%)	20 (16.8%)
Eosinophils	36 (30.3%)	0 (0%)
Absent or rare	0 (%)	0 (0%)
Total	—	119 (100%)
Type of necrosis		
Liquefaction	78 (65.5%)	59 (49.6%)
Caseous	52 (43.7%)	34 (28.6%)
Fibrinoid	40 (33.6%)	10 (8.4%)
Coagulative	3 (2.5%)	1 (0.8%)
Absent	15 (12.6%)	15 (12.6%)
Total	—	119 (100%)
Location of necrosis		
Center of granuloma	83 (69.7%)	59 (49.6%)
Associated with granuloma‡	74 (62.2%)	36 (30.3%)
Associated with ulceration	19 (16.0%)	6 (5.0%)
Associated with nongranulomatous infiltration	19 (16.0%)	3 (2.5%)
No apparent association	1 (0.8%)	0 (0.0%)
Absent	15 (12.6%)	15 (12.6%)
Total	—	119 (100%)

MP, mononuclear phagocytic; NOS, not otherwise specified.

*More than one alternative accepted.

†Only one alternative accepted.

‡except center.

Histopathological changes

The frequencies of the histopathological changes analyzed as present and predominant are shown in Table 2. Changes classified only as present or absent

Table 3. Frequency of histopathological changes classified only as present in the 119 cases of sporotrichosis

Organization*	
Nonspecific	0 (0%)
Poorly formed granuloma	74 (62.2%)
Well-formed granuloma	45 (37.8%)
Total	119 (100%)
Ulceration	
Present	22 (18.5%)
Absent	83 (69.7%)
Supposed	14 (11.8%)
Total	119 (100%)
Squamous hyperplasia	
Absent or minimal	39 (32.8%)
Regular	9 (7.6%)
Irregular	22 (18.5%)
Pseudocarcinomatous	41 (34.5%)
Not analyzable	8 (6.7%)
Total	119 (100%)
Epidermal changes	
Spongiosis	34 (28.6%)
Parakeratosis	56 (47.1%)
Exocytosis	77 (64.7%)
Other changes	
Fibrosis	55 (46.2%)
Hemorrhage	72 (60.5%)
Thrombosis	7 (5.9%)
Vascular proliferation	103 (86.6%)
Parasite burden	
0	77 (64.7%)
1+	16 (13.4%)
2+	11 (9.2%)
3+	8 (6.7%)
4+	7 (5.9%)
Total	119 (100%)

*Organization of the inflammatory infiltrate considering the highest degree of organization present.

are shown in Table 3. Among the 119 samples examined, there was a predominance of diffuse dermatitis and suppurative granulomas associated with a lymphoplasmacytic and neutrophilic infiltrate and with liquefaction necrosis in the center of the granuloma (Table 2).

Granulomas were detected in all samples, with a predominance of poorly formed granulomas (Table 3). Suppurative granuloma was the most frequent type, although all types of granulomas studied were detected as predominant or only present (Table 2).

Up to five different granuloma types were observed in the same sample (mean: 2.29; median: 2). Only one type of granuloma was detected in 39 (32.8%) samples, two types in 29 (24.4%) and three types in 31 (26.1%). Four and five different types of granulomas were seen in 17 (14.3%) and 3 (2.5%) samples, respectively.

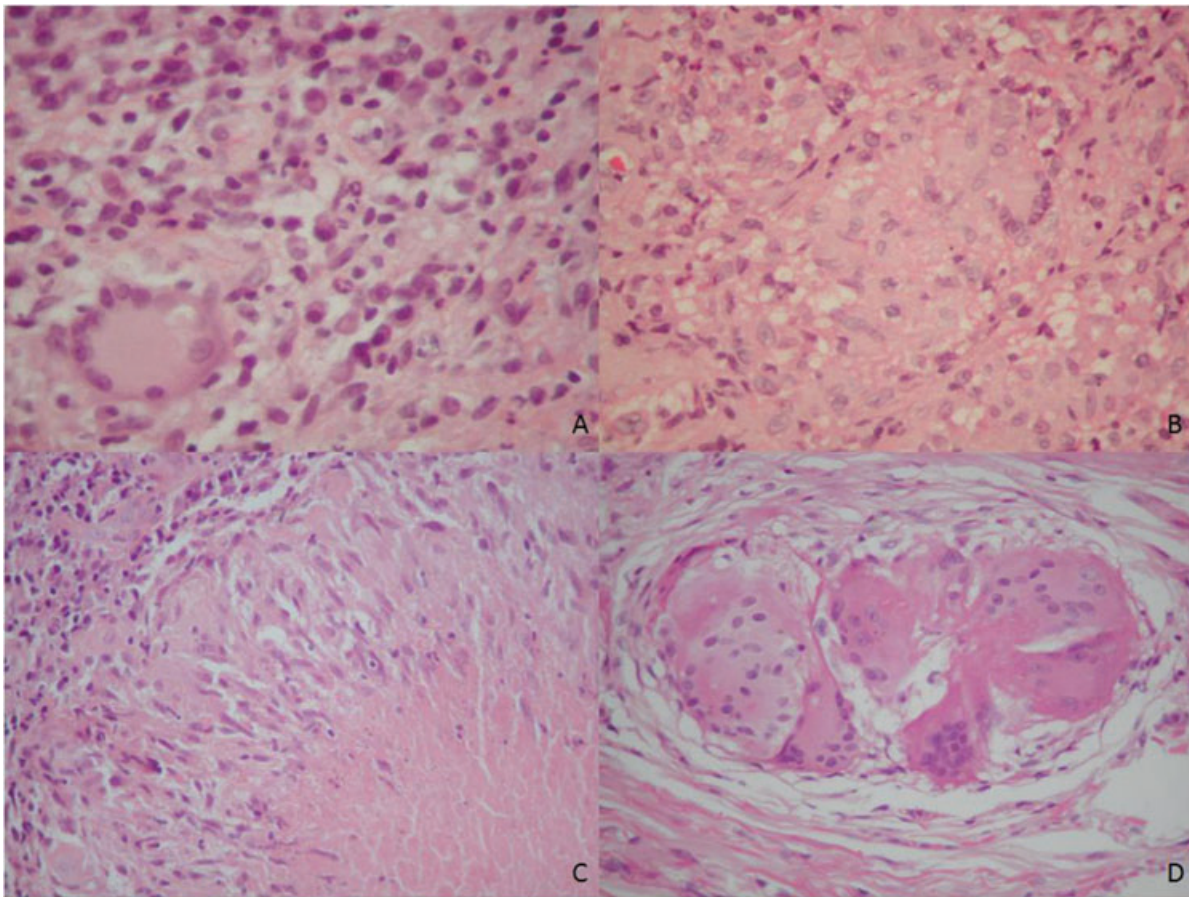


Fig. 1. A) Suppurative granuloma, B) epithelioid granuloma, not otherwise specified, C) tuberculoid granuloma, D) foreign body granuloma. 254 × 191 mm (96 × 96 DPI).

Necrosis was detected in most cases ($n = 104$, 87.4%) and liquefaction necrosis was the most frequent type. Up to three different types of necrosis were found in the same sample (mean: 1.45; median: 1), with two types in 41 (34.5%) and three types in 14 (11.8%) samples.

The fungus was not visualized in 77 (64.7%) cases. The frequency of the lack of fungal visualization significantly differed depending on the observation of some histopathological changes (Figs. 1 and 2 and Table 4). Lack of visualizable fungus was associated with the following factors: presence or predominance of epithelioid (not otherwise specified) granulomas, predominance of tuberculoid granulomas, presence of foreign body-type granulomas, predominance of lymphocytes, presence or predominance of caseous necrosis, predominance of fibrinoid necrosis and fibrosis. When the fungus was not observed, the suppurative granulomas, neutrophils and liquefaction necrosis and exocytosis were uncommon. The mean duration of the lesion did not differ between cases with and without fungal visualization (six weeks in both cases, $p = 0.73$). No asteroid bodies were observed.

Discussion

A comprehensive, detailed and systematic histopathological study of cutaneous sporotrichosis lesions was performed. To the best of our knowledge, this study analyzed the largest sample of sporotrichosis cases that has been presented in the literature. A classical, qualitative and poorly systematized description of sporotrichosis histopathology was published in 1907.⁴ Another classical study described 12 different histopathological variables in 63 cases.³ A large series of 2441 cases originating from a sporotrichosis outbreak in South Africa¹⁵ provided only a brief description of the histopathology of 15 cases.¹⁶ Most clinical series or reports of outbreaks, epidemics and endemics provide short descriptions of the histopathological changes or simply report the sensitivity of histopathological analysis in the detection of the fungus in tissue.^{8,14,17–22}

In the samples studied, sporotrichosis was characterized by chronic, diffuse granulomatous and suppurative necrotizing dermatitis, which was commonly associated with a lymphoplasmacytic infiltrate and epidermal changes, as described by other investigators.^{3,4,9} Although histopathological

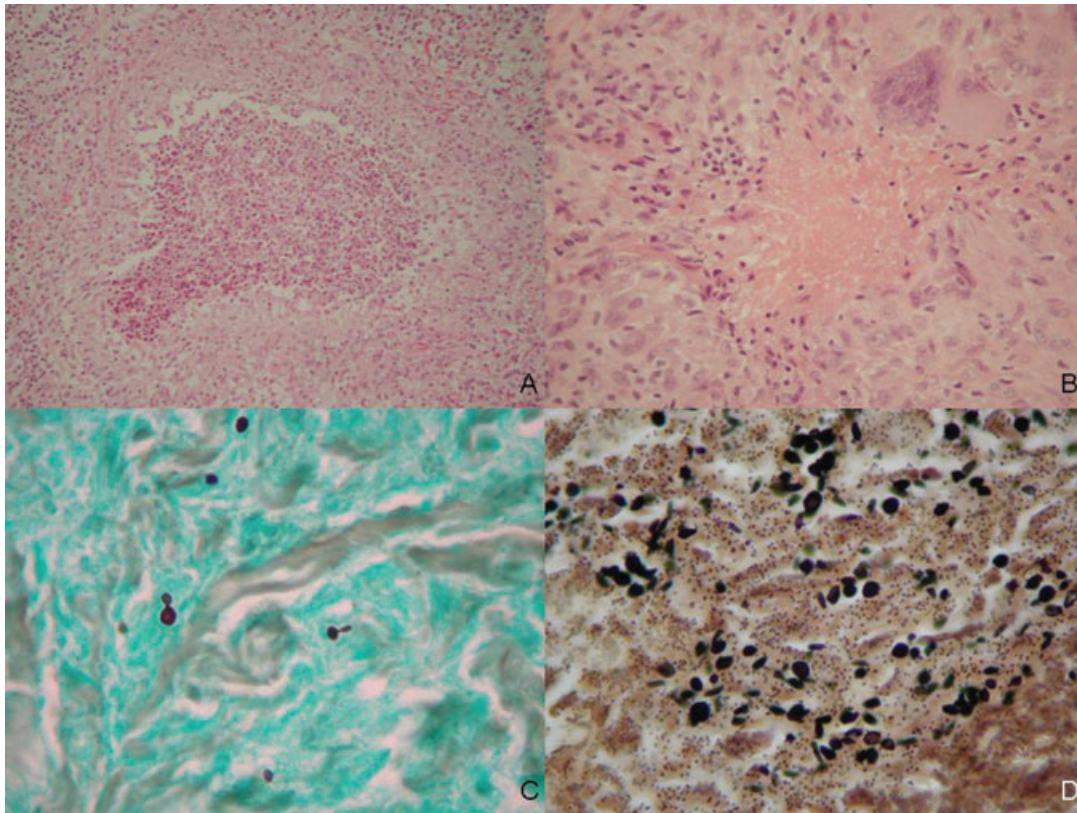


Fig. 2. A) Liquefaction necrosis, B) fibrinoid necrosis, C) positive case (3+), D) positive case (4+). 254 × 190 mm (96 × 96 DPI).

examination is interpretative and subjective, the adoption of definitions for the most complex histopathological changes might have contributed to the uniform interpretation of the present findings.

In the present study, two silver-stained histological sections were examined per sample and the fungus was detected only in a minority of cases (35.3%). Organisms, when detectable, were generally present in small numbers. This low sensitivity is in agreement with a previous report on the current epidemic in Rio de Janeiro.^{8,14} Studies reporting a high sensitivity of histopathological examination report analysis of multiple serial H/E-stained sections⁹ or up to 60 periodic acid-Schiff (PAS)-stained sections.²² The mean number of fungal elements can be as low as 1 per 15 sections depending on the size of the tissue fragment examined.⁹ The discrepancy in the sensitivity of histopathology between different studies might be explained, at least in part, by the method used for detection of the fungus in tissue, which is not always mentioned or not reported in sufficient detail. Search for the fungus in multiple serial sections, although adequate in experimental studies, is difficult to be successfully implemented in routine diagnostic laboratories.

Asteroid bodies may be the result of the deposition of immunoglobulins on the surface of the parasite³

and are frequently observed in sporotrichosis,² either by histopathological examination^{4,9,18,23} or in smears obtained from skin lesions.^{5,6} No asteroid bodies were found in the present study. Similar findings have been reported in a Mexican study including 50 cases¹⁹ and in cases studied in Rio de Janeiro.⁸ The variability between studies might be attributed to different antigenic properties of the fungus or to immunological factors of the host populations investigated, but the issue is yet to be adequately analyzed.

An experimental study of cutaneous sporotrichosis lesions showed that the onset of evolution of these lesions is characterized by suppuration and a large number of fungi. Granulomatous formations and plasma cells appear over the following 28 days, accompanied by an increase in lymphocytic infiltration and a reduction in the number of neutrophils and fungal elements.²⁴ In the present study, no correlation was observed between the clinical variable 'lesion duration' and the presence of the fungus. However, histopathological changes related to older lesions or to a specific, more developed immune response (epithelioid or tuberculoid granulomas, epithelioid cells, lymphocytes, caseous or fibrinoid necrosis and fibrosis) were directly associated with the absence of the fungus. In contrast, an inverse relationship with the absence of the fungus was observed in

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Table 4. Histopathological changes significantly associated with the lack of the visualization of the fungus, prevalence of the lack of visualization of the fungus according to histopathological changes, respective prevalence ratios (PR) and 95% confidence intervals (95% CI) in the 119 cases of sporotrichosis

	Histopathological change		Prevalence	PR (95% CI)
Type of granuloma	Suppurative (present)	Yes	60/100 (60.0%)	0.67 (0.54–0.84)
		No	17/19 (89.5%)	
	Suppurative (predominant)	Yes	30/65 (46.2%)	0.53 (0.40–0.70)
		No	47/54 (87.0%)	
	Epithelioid NOS (present)	Yes	55/71 (77.5%)	1.69 (1.21–2.36)
		No	22/48 (45.8%)	
	Epithelioid NOS (predominant)	Yes	26/30 (86.7%)	1.51 (1.20–1.90)
		No	51/89 (57.3%)	
	Tuberculoid (predominant)	Yes	16/19 (84.2%)	1.38 (1.08–1.77)
		No	61/100 (61.0%)	
Foreign body (present)	Yes	22/25 (88.0%)	1.50 (1.20–1.88)	
	No	55/94 (58.5%)		
Non-MP cells	Lymphocytes (predominant)	Yes	49/66 (74.2%)	1.40 (1.05–1.88)
		No	28/53 (52.8%)	
	Neutrophils (present)	Yes	64/104 (61.5%)	0.71 (0.55–0.91)
		No	13/15 (86.7%)	
	Neutrophils (predominant)	Yes	6/20 (30.0%)	0.42 (0.21–0.83)
		No	71/99 (71.7%)	
Type of necrosis	Liquefaction (present)	Yes	41/78 (52.6%)	0.60 (0.47–0.76)
		No	36/41 (87.8%)	
	Liquefaction (predominant)	Yes	27/59 (45.8%)	0.55 (0.41–0.74)
		No	50/60 (83.3%)	
	Caseous (present)	Yes	40/52 (76.9%)	1.39 (1.07–1.81)
		No	37/67 (55.2%)	
	Caseous (predominant)	Yes	27/34 (79.4%)	1.35 (1.06–1.73)
		No	50/85 (58.8%)	
	Fibrinoid (predominant)	Yes	9/10 (90.0%)	1.44 (1.12–1.86)
		No	68/109 (62.4%)	
	Absent	Yes	13/15 (86.7%)	1.41 (1.10–1.81)
		No	64/104 (61.5%)	
Location of necrosis	Associated with granuloma (present)	Yes	43/74 (58.1%)	0.77 (0.60–0.99)
		No	34/45 (75.6%)	
Epidermal changes	Exocytosis	Yes	42/77 (54.5%)	0.66 (0.51–0.84)
		No	35/42 (83.3%)	
Other changes	Fibrosis	Yes	43/55 (78.2%)	1.47 (1.12–1.93)
		No	34/64 (53.1%)	

MP, mononuclear phagocytic; NOS, not otherwise specified.

cases in which the changes found suggested a recent lesion associated with inflammatory activity or the development of specific ongoing immunity (presence of neutrophils or abscesses and predominance of macrophages). These results suggest that objectively evaluated histopathological changes are more important predictors of the absence of the fungus than the subjective variable of lesion duration obtained based on the clinical history.

Conclusion

The histopathological characteristics observed in skin lesions of sporotrichosis patients with detectable fungi from the current epidemic in Rio de Janeiro

are similar to those described previously. However, in samples in which these characteristics were not observed, the fungus was less frequently visualized by histopathological examination. Familiarity with a spectrum of histopathology may suggest a diagnosis of sporotrichosis in the absence of visualization of yeast.

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