Original Article

Acute pulmonary histoplasmosis in the state of Rio Grande do Sul, Brazil

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Background: Acute pulmonary histoplasmosis is a respiratory infection occurring when an otherwise healthy individual inhales a large quantity of fungal propagules. Length of exposure determines disease severity. An epidemic is influenced by factors affecting the growth and transmission of *Histoplasma capsulatum var. capsulatum* in nature.

Objective: To identify epidemiological and clinical aspects of patients with acute pulmonary histoplasmosis in the state of Rio Grande do Sul (RS) and compare these aspects with those of other cluster outbreaks reported in Brazil.

Method: The charts of 212 patients diagnosed with histoplasmosis over a 25-year period (1977-2002) were obtained from the archives of the Laboratório de Micologia from Complexo Hospitalar Santa Casa (Santa Casa Hospital Mycology Laboratory), in the city of Porto Alegre (RS). In reviewing these patient charts, we identified and included in the study cases of acute pulmonary histoplasmosis in which there was a positive culture and/or histopathological findings consistent with the diagnosis. Outbreaks were defined as one confirmed case or positive immunodifusion *Histoplasma capsulatum* with compatible clinical history. All reported Brazilian outbreaks were reviewed.

Results: Of the 212 patient charts reviewed, 18 (8.5%) were selected for inclusion in the study. Among those 18 patients, ages ranged from 8 to 63 years (median, 35.4), and 67% were male. Epidemiological histories were suggestive of the disease in 11 patients (61%). The most common disease type, seen in 17 patients (95%), was primary acute pulmonary histoplasmosis, and there was a predominance of isolated cases.

Conclusion: The identification of isolated cases and the presence of cluster outbreaks demonstrate the abundance of *H. capsulatum* in the soil and, together with the occurrence of all forms of the disease, confirms the assumption that Rio Grande do Sul is a hyperendemic region for histoplasmosis.

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Key words - Histoplasmosis/epidemiology. Histoplasmosis/diagnostic. Histoplasma. Medical records. Retrospective studies.

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INTRODUCTION

Human infection with *Histoplasma capsulatum* var. *capsulatum* (*H. capsulatum*) is benign and regressive[1]. Clinical manifestations of the disease are dependent on the immunological status and anatomy of the host, as well as on the concentration of fungal propagules inhaled. Cellular immunodeficiency predisposes to the disseminated form of the disease, which is potentially fatal if not treated. Structural changes in the lung parenchyma (emphysema) propitiates colonization of the airways when there is prolonged exposure to the fungus, and, via an allergic mechanism, leads to the chronic form of the disease, accompanied by pulmonary fibrosis[2]. However, in healthy hosts, acute pulmonary histoplasmosis only occurs when a substantial quantity of fungal propagules is inhaled[3].

The objective of the present study was to identify epidemiological and clinical aspects of patients diagnosed with acute pulmonary histoplasmosis over a 25-year period in the state of Rio Grande do Sul (RS), Brazil and to briefly review this presentation of the mycosis in Brazil.

METHODS

Diagnosis of acute pulmonary histoplasmosis and inclusion in the study were based on the following criteria: residence in the state of Rio Grande do Sul; clinical evidence of histoplasmosis (culture positive for *H. capsulatum*), histopathological findings showing fungal elements consistent with *H. capsulatum* or immunodiffusion test results revealing H or M bands; culture or histopathological evidence of *H. capsulatum* located exclusively in the lungs of patients presenting no structural defects in lung anatomy. Materials used for diagnosis were sputum, bronchoalveolar lavage fluid or lung biopsy sample. The smears on the slides were stained with silver methenamine according to the Grocott-Gomori technique. Cultures were grown on Sabouraud agar (DIFCO, Detroit, MI, USA), 1% chloramphenicol (União Química Farmacêutica Nacional S.A., São Paulo, Brazil), and Mycosel® (BBL) media, processed in a model FVL, series 636 Class II biosafety laminar flow hood (Trox do Brasil Ltda., São Paulo, Brazil), and incubated at 25°C. Cultures testing positive for *H. capsulatum* were confirmed by the micromorphological aspect (tuberculate macroconidia), and thermal dimorphism was characterized through conversion to the yeast phase on brain heart infusion (BHI) agar at 37°C.

Outbreaks were defined as one confirmed case or positive mycological blood culture (immunodiffusion) with compatible clinical history. Patient charts were obtained from the archives of the *Laboratório de Micologia do Complexo Hospitalar Santa Casa* (Santa Casa Hospital Mycology Laboratory), in the city of Porto Alegre. These charts were reviewed regarding age, gender, race, epidemiological history, origin of referral, signs and symptoms, concomitant or predisposing condition, mycological blood culture, treatment and evolution. All reported Brazilian outbreaks were reviewed.

RESULTS

The charts of 212 patients diagnosed with histoplasmosis over a 25-year period (1977-2002) were obtained from the archives of the laboratory. Of the 212 patient charts, 18 (8.5%) presented acute pulmonary histoplasmosis. Among those 18 patients, ages ranged from 8 to 63 years (median, 35.4; mean, 34.5), and 12 (67%) were male. Epidemiological histories were suggestive of exposure to a fungal ecological niche in 11 patients (61%), of which 8 had been exposed to chicken feces and 3 to bat feces. The interval between exposure and symptom development ranged from 7 days to 11 months. The most common disease type, seen in 17 patients (95%), was primary acute pulmonary histoplasmosis, with acute development of respiratory and systemic symptoms, in combination with diffuse micronodular infiltrate seen on the chest X-ray. One patient (Case 17) presented an uncommon radiological pattern with nodular opacities, 3 presented bilateral mediastinal adenopathy, and 7 were diagnosed in groups: 3 (Cases 6, 7 and 8) belonging to the same family; a couple (Cases 12 and 13); and 2 brothers (Cases 1 and 2). The rest were isolated cases. One patient presented the recurrent form of the disease due to exposure to the same hen house where he had been infected a year ago.

Histological pattern: tissue sections from lung biopsies, stained with hematoxylin and eosin, showed tuberculoid granuloma with caseous necrosis in all (13) cases in which this procedure was performed (Figure 1A). The Grocott-Gomori

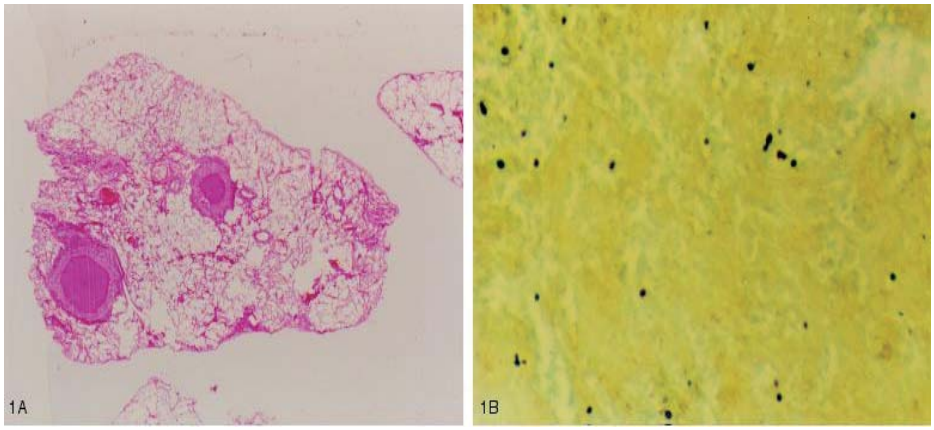

Figure 1 – A. Tuberculoid granuloma with caseous necrosis, hematoxylin-eosin staining (x100); B. Presence of small and budding oval yeast-like cells, Grocott-Gomori methenamine silver staining (x400)

methenamine silver stain showed small, oval yeast-like cells suggestive of *H. capsulatum* and budding in the center of the caseous necrosis (Figure 1B). The remaining 5 patients were group cases, among which 3 were diagnosed through immunodiffusion assay. Culture was performed in 6 patients and was positive in 3.

Ten patients (56%) presented spontaneous cure, and 8 (44%) were treated with ketoconazole or itraconazole for a period that ranged from two months to one year and presented favorable evolution (Table 1). Among these 18 patients, 4 (22%) had been treated for tuberculosis prior to diagnosis.

Cases of acute pulmonary histoplasmosis from a recent cluster outbreak in the state of Rio Grande do Sul are shown below:

Case 6, 34-year-old white male:

Epidemiological history: exposure to chicken feces brought from the city of São Gabriel (RS).

Symptomatology: dyspnea caused by physical effort, ventilatory-dependent chest pain, dry cough, fever, prostration and sudden weight loss.

Imaging: ill-defined nodular lesions, predominantly in the lower halves of the lungs, seen on the chest X-ray.

Mycological evaluation: mycological blood culture with immunodiffusion was positive for *H. capsulatum* and the M band was present; histopathology of the lingula segment (obtained through lung biopsy) stained with hematoxylin and eosin showed granuloma with hemorrhagic necrosis and vasculitis in the lung parenchyma; and Grocott-Gomori methenamine silver staining revealed small, budding yeast-like organisms suggestive of *H. capsulatum*.

Treatment and evolution: outpatient observation with no antifungal therapy; subsequent spontaneous regression of symptoms and eventual clinical cure.

Case 7, 29-year-old white female:

Epidemiological history: exposure to chicken feces brought from the city of São Gabriel (RS).

Symptomatology: dry cough, dyspnea, chest pain, fever, cephalgia, prostration and sudden weight loss.

Imaging: both lungs presenting diffuse micronodular infiltrate on the chest X-ray.

Mycological evaluation: mycological blood culture with immunodiffusion negative for *H. capsulatum*; histopathological examination not performed.

Treatment and evolution: outpatient observation with no antifungal therapy; subsequent spontaneous regression of symptoms and eventual clinical cure.

Case 8, 18-year-old white female:

Epidemiological history: exposure to chicken feces brought from the city of São Gabriel (RS).

Symptomatology: cough with purulent expectoration, dyspnea, fever, prostration, sudden body aches and sore throat.

Imaging: both lungs presenting diffuse interstitial infiltrate on the chest X-ray.

Mycological evaluation: not performed.

Treatment and evolution: outpatient observation with no antifungal therapy; subsequent

TABLE 1

Cases of acute pulmonary histoplasmosis diagnosed in the *Laboratório de Micologia do Complexo Hospitalar Santa Casa* (Santa Casa Hospital Mycology Laboratory), in the city of Porto Alegre, from 1997 to 2002

Case	Age	Gender	Symptoms T	R	S	Radiological study of the chest	Diagnosis	H&E	GMS	Cult	IDh	Specific treatment	Evolution
1*	24,	M	60	+	+	Bilaterally disseminated micronodular infiltrate	TGCN	+	NP	NP	No		Cure
2*	35,	M	60	+	+	Bilaterally disseminated micronodules	NP	NP	NP	+M	No		Cure
3	8,	M	90	+	+	Diffuse micronodular interstitial pulmonary infiltrate and hilar	TGCN	+	-	NP	No		Cure
4	23,	M	21	+	+	Nodules and micronodules disseminated in both lungs and probable enlargement of interlobular and paratracheal lymph nodes	TGCN	+	+	+M	No		Cure
5	46,	M	15	+	+	Numerous nodules of acinar or lobular extension, disseminated in both lungs	TGCN	+	+	+M	No		Cure
6*	34,	M	16	+	+	Nodular bilateral lesions of acinar or lobular extension	TGCN	+	NP	+M	No		Cure
7*	29,	F	12	+	+	Diffuse bilateral micronodular infiltrate	NP	NP	NP	-	No		Cure
8*	18,	F	27	+	+	Diffuse bilateral interstitial infiltrat	NP	NP	NP	NP	No		Cure
9	51,	M	7	+	+	Diffuse bilateral pulmonary infiltrate	TGCN	+	NP	-	Keto 6 m		Cure
10	59,	M	120	+	+	Interstitial infiltrate with granular pattern, bilateral interlobar lymph node enlargement	TGCN	+	+	NP	Keto 6 m		Cure
11	54,	F	180	+	+	Thin reticular diffuse pulmonary infiltrate, bilateral, symmetric	TGCN	+	NP	-	Keto		Cure
12*	23,	F	14	+	+	Limited bilateral infiltrative lesions, some of them nodular, with possible bilateral enlargement of interlobular lymph nodes	NP	NP	NP	+M	Keto 2 m		Cure
13*	23,	M	14	+	+	Multiple ill-defined nodular lesions, micronodules and striation, disseminated bilaterally and symmetrically. Slight bilateral enlargement of the mediastino-pulmonary lymph nodes	NP	NP	NP	+M & H	Keto 2 m		Cure
14	38,	M	45	+	+	Symmetrically bilateral, diffuse reticulonodular pulmonary infiltrate	TGCN	+	NP	-	Keto 15d Itra 6 m		Cure
15	39,	F	730	+	-	Diffuse bilateral pulmonary infiltrate	TGCN	+	NP	-	Itra 12 m		Cure Reinfection
16	31,	F	150	+	+	Micronodular and nodular infiltrate predominatly in the lower two-thirds of the lungs	TGCN	+	NP	+M	No		Good
17	63,	M	330	+	+	Chest CT-proven diffuse bilateral pulmonary infiltrate with granular zones and some central nodular opacities.	TGCN	+	-	-	Itra		Cure
18	40,	M	15	+	+	Bilateral micronodular lesions predominantly in the more caudal areas of both lungs, some confluent, possible paratracheal adenopathy	TGCN	+	-	NP	No		Cure

T: time (months); R: respiratory; S: systemic; CT: computed tomography; H&E: hematoxylin-eosin; GMS: Grocott-Gomori methenamine silver. Cult: culture; IDh: immunodiffusion for histoplasmosis; TGCN: tuberculoid granuloma with caseous necrosis; Keto: ketoconazole; Itra: itraconazole; ND: no data; NP: not performed *cluster outbreaks

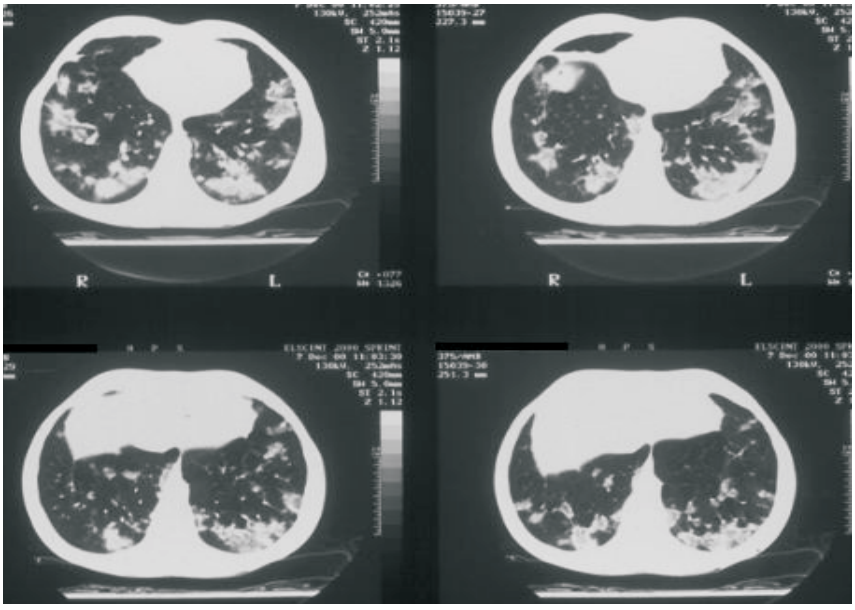

Figure 2 – Bilateral diffuse pulmonary infiltrate with granular areas and some central nodular opacities

spontaneous regression of symptoms and eventual clinical cure.

These three cases occurred simultaneously. The individuals lived in an apartment in the urban area of the city of Porto Alegre (RS). They used chicken feces from the city of São Gabriel as an organic fertilizer for the soil in their apartment flowerbox.

The next case, also a case of acute pulmonary histoplasmosis, was an isolated case.

Case 17, 63-year-old white male:

Epidemiological history: not referred.

Symptomatology: anterior chest pain, dyspnea upon significant exertion, cough with purulent expectoration, anorexia and a 9-kg weight loss in 11 months.

Imaging: bilateral diffuse micronodular infiltrate, with granular areas and some central nodular opacities, on the computed tomography scan of the chest. There was no evidence of lymph node enlargement in the mediastinum (Figure 2).

Mycological evaluation: mycological blood culture with immunodiffusion negative for *H. capsulatum*; histopathology of lingula sample (obtained through lung biopsy) stained with hematoxylin and eosin showing tuberculoid granuloma with caseous necrosis and fibrosis in the lung parenchyma; the Grocott-Gomori methenamine silver staining revealing numerous small, round or oval budding yeast-like cells suggestive of *H. capsulatum*; culture was negative.

Treatment and evolution: itraconazole 200 mg/day, resulting in regression of the symptoms and clinical cure.

This unusual radiological pattern is suggestive of massive inoculation in a non-endemic area, causing a severe inflammatory reaction[1]. Culture is positive in only 15% of cases of the self-limited forms[4].

Up until 1978, only five cluster outbreaks, involving a total of 50 patients and one dog, had been reported in Brazil[7]. Subsequently, it was reported that thirteen cluster outbreaks (involving 102 patients) occurred in the state of Rio de Janeiro[8-12], one each occurred in the states of Paraíba[13], Amazonas[14], Minas Gerais [15], and Bahia[16], and two occurred in the state of Rio Grande do Sul[17,18] (Chart 2). In addition to the two cluster outbreaks documented in the literature[17,18], a new outbreak was reported during the present study period (Cases 6, 7 and 8).

DISCUSSION

Acute pulmonary histoplasmosis is characterized by the development of respiratory symptoms from one to three weeks after substantial exposure to *H. capsulatum*[2]. Duration of exposure determines

CHART 1
Goodwin & Des Prez classification

	PRIMARY	REINFECTION
Incubation period	10-18 days	3-7 days
Disease severity	More severe	Less severe
Geographical location	Periphery of the endemic area	Highly endemic area
Population of the endemic area	Immigrants	Natives
Radiological findings	Bronchopneumonia	Miliary nodulation
	Hilar adenopathy	No adenopathy
	Possible pleural involvement	No pleural involvement
Late calcification	Usual	None

Source: Goodwin RA, Des Prez RM[3]

disease severity: short exposure times (20 minutes or less) produce mild symptoms, whereas a 50- to 60-hour exposure time results in severe illness[5]. There are three radiological patterns that appear after massive inoculation: nodular pneumonia, micronodular infiltrate and miliary pattern. The first one is the least common, and is suggestive of a pronounced inflammatory reaction, located on the periphery of the endemic area, in hosts with no previous infection. The second pattern is the most frequent, and the third one is suggestive of re-exposure of previously infected hosts who maintained a high level of immunity[1]. The course of the disease is self-limited, with spontaneous regression of the symptoms[3]. Whether the host has been previously infected or not differentiates the findings. Chart 1 shows the principal differences between primary infection and reinfection.

Clinical presence of cough, fever, dyspnea and asthenia in a previously healthy individual may, in most cases, be associated with epidemiologically relevant episodes[1]. In 11 patients (61%), onset of the disease can be related to a specific activity (such as the exposure to chicken or bat feces observed in the representative cluster outbreak). Due to the simultaneous occurrence of the cases and the facility of identifying the source of exposure, cluster outbreaks are more easily recognized than are isolated cases. In the latter, significant clinical suspicion or, preferably, routine mycological investigation including mycological blood culture (immunodiffusion), fungus-specific staining of the histological sections, and fungi culture of the tissue samples obtained through biopsy, is needed[2].

Systemic mycoses, especially histoplasmosis, mimic tuberculosis in terms of clinical, radiological and histopathological aspects since they are granulomatous diseases. Diagnostic differentiation demands special stains as well isolation of the etiologic agent in culture. The presence of tuberculoid granuloma with caseous necrosis on tissue sections from lung biopsies, stained with hematoxylin and eosin, misleads the physician into the diagnostic hypothesis of tuberculosis. In fact, the term *tuberculoid* comes from the word *tubercle,* meaning small and round in shape, and not from *tuberculosis*, the disease. In the present study, 22% of patients were subject to the complications from and deleterious effects of a treatment for tuberculosis, as well as to delayed diagnosis of the disease. A diagnostic routine that includes the Grocott-Gomori methenamine silver stain technique or immunodiffusion for histoplasmosis, or both, in patients with a presumptive diagnosis of tuberculosis reveals unsuspected cases[6].

Many factors indicate that Rio Grande do Sul is a hyperendemic region for histoplasmosis, as are other regions of the country. Such factors include the types of histoplasmosis cases found, the fact that the acute pulmonary form was seen, the presence of isolated cases and cluster outbreaks, isolation of the etiologic agent in the soil[19], the strong cutaneous reactivity to histoplasmin[20], the large number of cases of the disseminated form in patients with acquired immunodeficiency syndrome[21], the presence of the acute disseminated disease in infants[22], and the presence of the chronic pulmonary form[21].

CHART 2

Year	Reference city	State	Source of infection	Activity	Cases	Sero-logy	Histo-logy	Isolation in soil	
1958	Paraíba do Sul	RJ	Cave with bats	Leisure/study	13 *	0	1	NP	Paula, 1959[23]
1959	Santa Teresa	RJ	Water reservoir	Leisure	7	ND	ND	NP	Paula, Aidé, 1979[9]
1966	Ubatuba	SP	House ceiling	Cleaning	8	6	7	(+) Bat feces	Fava Netto *et al.*, 1967[24]
1967	Brasília	DF	Cave with bats	Leisure	14	8	13	(+) Soil	Schmidt *et al.*, 1973[25]
1971/73	Ubatuba	SP	Cave with bats	Leisure	10	10	9	NP	Fava Netto *et al.*, 1976[26]
1972	Vassouras	RJ	Cave with bats	Prospecting	5	ND	ND	NP	Paula, Aidé, 1979[9]
1975	Rio de Janeiro	RJ	Cave with bats	Leisure	5	0	5	NP	Rêgo *et al.*, 1976[27]
1978	Angra dos Reis	RJ	Cave	Leisure	8	ND	8	NP	Paula, Aidé, 1985[10]
1978	Canoas	RS	Hollow tree trunk with bats	Guano harvest	2*	1	ND	NP	Severo *et al.*, 1981[17]
1981	Rio do Ouro	RJ	Cave	Leisure	10**	ND	ND	(+) Soil	Paula, Aidé, 1985[10]
1981	São Gonçalo	RJ	Abandoned mine	Leisure	10	8	ND	(+) Soil and feces	Wanke, 1985[8]
1981	São Gonçalo	RJ	Abandoned mine	Study	4 **	4	ND	(+) Soil and feces	Wanke, 1985[8]
1981	Itaipava-Petrópolis	RJ	Abandoned mines	Leisure	10	9	ND	(+) Soil and feces	Wanke, 1985[8]
1982	São Gonçalo	RJ	Cave with bats	Leisure	6**	5	ND	NP	Verbicário *et al.*, 1993[11]
1982	Itaipava-Petrópolis	RJ	Abandoned mines	Leisure	5	2	ND	(+) Soil	Wanke, 1985[8]
1982	Niterói	RJ	Abandoned mine	Leisure	6 **	5	ND	(+) Soil	Wanke, 1985[8]
1984	PendotibaNiterói	RJ	Water pipe	Study	17	8	17	(+) Soil	Paula, Aidé, 1985[10]
1984	Tinguá	RJ	Hen house	Cleaning	12	ND	ND	ND	Paula, Aidé, 1985[10]
1986	Borborema	PB	Chimney with bats	Cleaning	6	4	5	(+) Bat feces	Fernandes *et al.*,1989[13]
1993	Taquari	RS	Hen house	Cleaning	2	2	ND	NP	Severo *et al.*, 1993[18]
1993	Manaus	AM	Cave with guano	Leisure	8	8	ND	NP	Suzaki *et al.*, 1995[14]
1997	Pedro Leopoldo	MG	Cave with bats	Leisure	4	3	ND	NP	Cury *et al.*, 2001[15]
2000	Jequié	BA	Basement with bats	Cleaning	4*	4	ND	NP	Martins *et al.*, 2000[16]
2003	Niterói	RJ	Out-of-use oven	Cleaning	5	5	ND	NP	Martins *et al.*, 2003[12]
			Total		181				

ND: no data; NP: not performed
*one case confirmed through histopathology; **one case confirmed through tuberculoid granuloma culture with caseous necrosis; *** cluster outbreaks

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