

Acute pulmonary histoplasmosis: a case series from an outbreak in Southeastern Brazil

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ABSTRACT

Histoplasmosis is a systemic mycosis prevalent in the Americas. Humans become infected via the respiratory route by inhaling aerosols from soil contaminated with bird and bat excretions. Acute pulmonary histoplasmosis is usually asymptomatic and is more often a self-limiting illness. We report a series of seven acute pulmonary cases in adults during an outbreak in Nova Friburgo city, Rio de Janeiro State, Brazil, in a group of volunteers who were cleaning an old, abandoned house without using personal protective equipment. The patients had a favorable evolution after suitable treatment, but all required hospitalization.

KEYWORDS: Histoplasmosis. *Histoplasma capsulatum*. Diagnosis. Outbreak. Brazil.

INTRODUCTION

Histoplasmosis is a systemic mycosis present across the world. It is endemic in the Americas, Africa, and Asia. The actual incidence of histoplasmosis is unknown, owing to the fact that most of the studies carried out on the subject are limited to regions affected by outbreaks of the disease¹⁻³.

The etiological agent is the dimorphic fungus *Histoplasma capsulatum*, which is classified into two variants: *H. capsulatum* var. *capsulatum* and *H. capsulatum* var. *duboisii*. The fungus is found in moist soil, particularly with decaying matter. Bats carry the fungus in their gastrointestinal tract and birds carry it in their feathers, not being affected by it due to their high body temperature (40 °C). Occupational exposures are frequently implicated in histoplasmosis outbreaks⁴.

The disease manifests itself in two main types of presentation: pulmonary and disseminated forms². This mycosis occurs sporadically and usually emerges as an opportunistic infection among immunocompromised people who live in endemic areas of this fungus, having a higher propensity to develop a severe form of histoplasmosis^{2,5}.

The acute pulmonary form of histoplasmosis tends to be a self-limited and asymptomatic disease or with few symptoms without requiring any treatment. The main triggering factor for the acute symptomatic forms of this disease is the amount of inhaled fungal inoculum. Chest x-rays may show patchy pneumonia involving one or more lobes with adenopathy of the mediastinum or hilum^{6,7}.

This study presents a series of cases of acute pulmonary histoplasmosis from an outbreak in Nova Friburgo city, Rio de Janeiro State, Brazil, where more severe presentations of the disease required hospitalization and immediate treatment.

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CASE REPORTS

From the 4th to 11th October, 2022, seven adult patients admitted with a diagnosis of acute pulmonary histoplasmosis were followed during their hospitalization at Hospital Unimed Nova Friburgo (Nova Friburgo city, Rio de Janeiro State, Brazil). Written informed consent was obtained from all patients before their participation, and the ethics committee reviewed and approved the study (CAAE 66444622.4.0000.5243). Clinical data were collected from medical records during hospital stay and further information was obtained at post-discharge outpatient medical consultations.

The patients were part of the investigation of an outbreak that occurred in Nova Friburgo city, in which 40 patients had clinical manifestations indicative of histoplasmosis. The examination of the patients' medical history indicated that a group of volunteers was cleaning an old, abandoned house without using personal protective equipment (PPE). The house was located in the urban area, and bird and bat droppings were found on the walls and floor. According to bulletins issued by the city's surveillance service, 16 cases of the disease were confirmed, of which 7 are described in this manuscript.

Most participants were men (5, 71.4%). The mean age of the participants was 54 years old (ranging from 45 to 75 years old). All patients met the clinical and epidemiological criteria and the diagnosis was confirmed by detection of specific antibodies for histoplasmosis using enzyme immunoassay test (ELISA), qualitative type in serum samples (collected during hospitalization or at subsequent outpatient visits).

Patient 1

A 45-year-old man with hypertension and previous thromboembolism. Initial symptoms: myalgia, back pain and headache. Progressive symptoms: fever, sweating and severe dyspnea. Hospitalization: 18 days (5th to 22nd October, 2022), in the Intensive Care Unit (ICU). Treatment during hospitalization: Liposomal Amphotericin B (5 mg/kg/day – 15 days). Methylprednisolone (62.5 mg/day) was used in the first week. Post-discharge treatment: Itraconazole (200 mg/day) for 8 weeks. Resolution: Cured (clinically and radiologically).

Patient 2

A 55-year-old man with diabetes mellitus, gastroesophageal reflux disease and dyslipidemia. Initial symptoms: fever, chills, syncope, arthralgia, and cough.

Progressive symptoms: moderate dyspnea, requiring nasal oxygen therapy. The patient suffered progressive worsening of breathing which required orotracheal intubation and transfer to the ICU. Hospitalization: 42 days (6th October, 2022 to 16th November, 2022). Intercurrences: Drug-induced hepatitis. Treatment during hospitalization: Liposomal Amphotericin B (5 mg/kg/day – 12 days). Methylprednisolone (62.5 mg/day) was used for two weeks. Post-discharge treatment: Itraconazole (200 mg/day) for 12 weeks. Resolution: Cured (clinically and radiologically).

Patient 3

A 52-year-old woman with gluten and lactose intolerance. Initial symptoms: fever, headache, myalgia, and arthralgia. Evolution of symptoms: persistent dry cough, abdominal pain, and petechial lesions on the trunk. Hospitalization: 12 days (4th to 15th October, 2022), uneventful. Treatment during hospitalization: Itraconazole (200 mg, three times a day). Post-discharge treatment: Itraconazole (200 mg/day) for 8 weeks. Resolution: Cured (clinically and radiologically).

Patient 4

A 46-year-old woman with hypothyroidism. Initial symptoms: fever, headache, myalgia, intense arthralgia, epigastralgia and nausea. Hospitalization: 7 days (8th to 14th October, 2022), uneventful. Treatment during hospitalization: Itraconazole (200 mg, three times a day). Post-discharge treatment: Itraconazole (200 mg/day) for 8 weeks. Resolution: Cured (clinically and radiologically).

Patient 5

A healthy 48-year-old male. Initial symptoms: high fever, headache, myalgia, productive cough,odynophagia, runny nose, and back pain. Evolution of symptoms: persistent fever and productive cough. Hospitalization: 6 days (5th to 11th October, 2022), uneventful. Treatment during hospitalization: Itraconazole (200 mg, three times a day). Post-discharge treatment: Itraconazole (200 mg/day) for 8 weeks. Resolution: Cured (clinically and radiologically).

Patient 6

A 75-year-old elderly man with hypertension, gastroesophageal reflux disease and chronic obstructive pulmonary disease (COPD). Initial symptoms: asthenia, mild dyspnea, and cough. Evolution of symptoms:

persistent cough and mild dyspnea. Hospitalization: 4 days (11th to 14th October, 2022), uneventful. Treatment during hospitalization: Itraconazole (200 mg, three times a day). Post-discharge treatment: Itraconazole (200 mg/day) for 8 weeks. Resolution: Cured (clinically and radiologically).

Patient 7

A 57-year-old man with hypertension and diabetes mellitus. Initial symptoms: myalgia, asthenia, and mild chest pain. Evolution of symptoms: persistent cough and mild dyspnea. Hospitalization: 5 days (10th to 14th October, 2022), uneventful. Treatment during hospitalization: Itraconazole (200 mg, three times a day). Post-discharge treatment: Itraconazole (200 mg/day) for 8 weeks. Resolution: Cured (clinically and radiologically).

Patients 1 and 2 evolved to more severe forms of the disease – progressive pulmonary impairment and respiratory failure – and required ICU care. Figure 1 shows the evolving pulmonary involvement of the two most severely affected patients.

All patients followed-up had the same radiological pattern on chest CT, showing a diffuse micronodular infectious process (ground-glass opacities). Images show symmetrically distributed nodules consistent with acute histoplasmosis, with a disseminated appearance in both

lungs (miliary opacities). Figure 2 shows lung images of five patients.

For most patients, there were no significant changes in hematological or biochemical parameters during hospitalization. Only patient 2 had a transient period of increased liver transaminases, but resolution occurred in less than a week without compromising the patient's treatment. The C-reactive protein was greatly increased in the acute phase of the disease for all patients followed up (normal up to 0.30 mg/dl) and the reduction of this biomarker is one of the positive criteria for hospital discharge. Patient 1 had a moderate increase in creatinine (normal for men 0.6~1.30 mg/dL), but without any repercussions on renal function. Table 1 shows the results of the main laboratory tests performed at hospital admission and discharge.

DISCUSSION

Cases of histoplasmosis have been reported in all states of Brazil, mainly in the Midwestern, Northeastern, and Southeastern regions^{8,9}, and reports of histoplasmosis outbreaks are very common¹⁰. From 1958 to 2004, 26 outbreaks of histoplasmosis were reported, all occurring in one of eight Brazilian states (Rio de Janeiro, Rio Grande do Sul, Sao Paulo, Distrito Federal, Minas Gerais, Paraiba, Amazonas and Bahia States)¹¹.

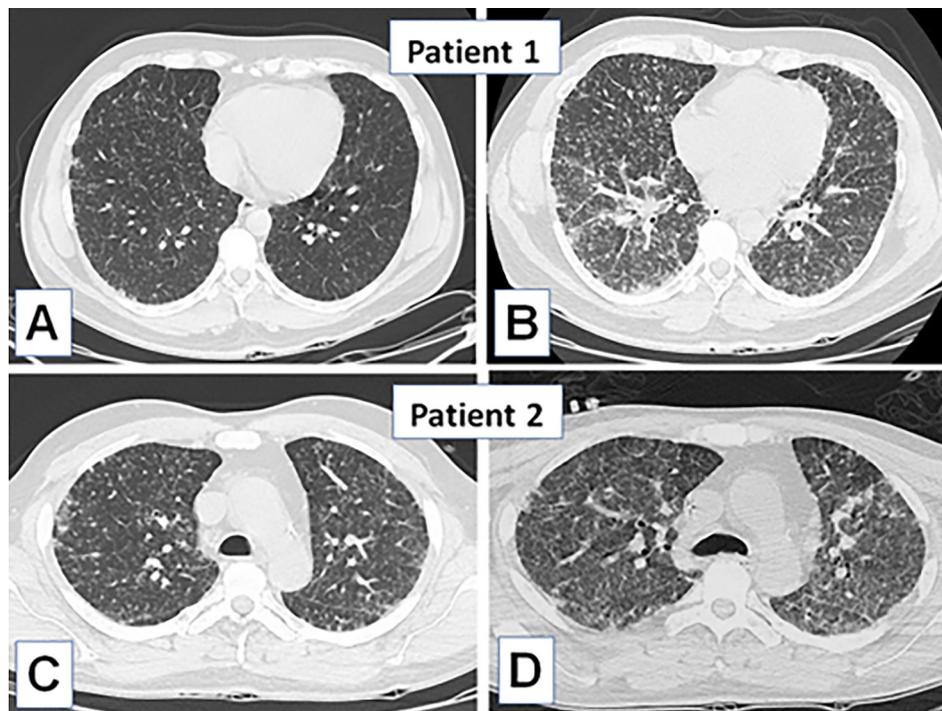


Figure 1 - Chest CT images showing the evolution of the pulmonary infectious process in two critically ill patients: A and B) Patient 1 with images of 4 days of evolution; C and D) Patient 2 with images of 14 days of evolution. The images show a granulomatous involvement in the form of micronodules, initially sparse, progressing to a disseminated form in the lungs (miliary opacities).

In 1997, Brazil (Minas Gerais State) experienced an outbreak in a group of people who had contact with a cave

inhabited by bats, but there were no reports of serious illness¹². In 2003, in Niteroi city (Rio de Janeiro State,

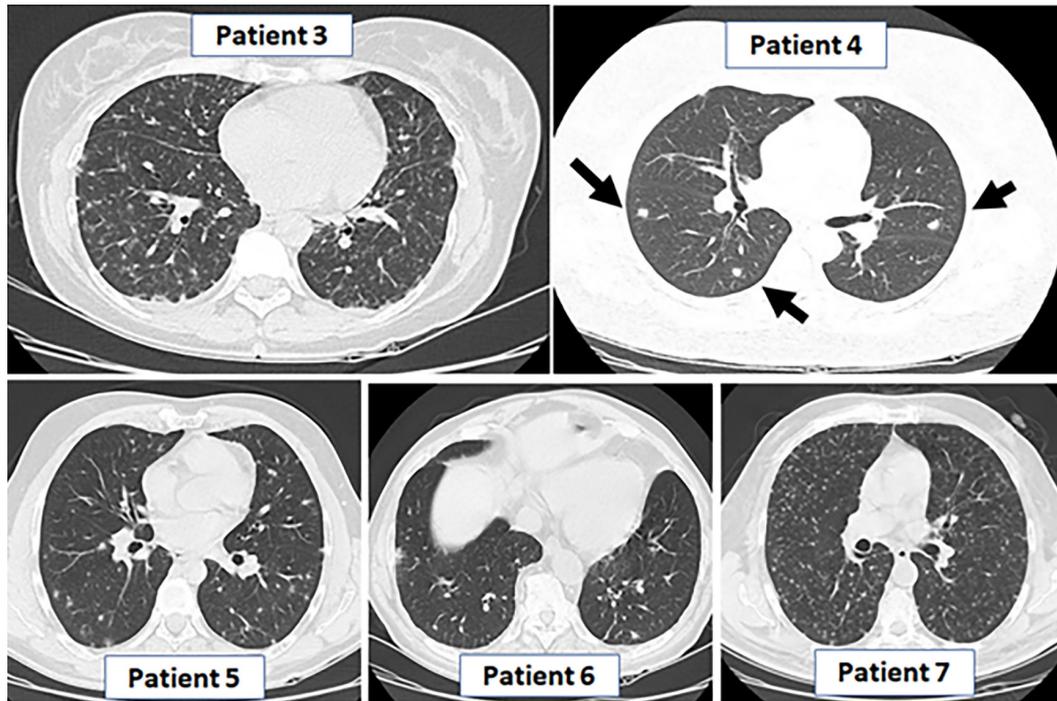


Figure 2 - Chest CT of five patients showing the pattern of a diffuse micronodular infectious process in the lungs (ground-glass opacities). Arrows show the presence of peripheral micronodules.

Table 1 - Laboratory tests performed during hospitalization, outbreak in Nova Friburgo city, Rio de Janeiro State, Brazil, 2022.

ADMISSION (1 to 7 days from symptom onset)							
Laboratory test	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Hemoglobin (g/dL)	15.6	13.2	12.5	13.6	14.1	11.7	11.4
Hematocrit (%)	45.0	39.0	36.0	40.0	41.0	35.0	34.0
WBC ($\times 10^3/\mu\text{L}$)	12,200	9,600	5,500	9,600	8,300	8,300	5,200
Platelets ($\times 10^3/\mu\text{L}$)	208,000	163,000	172,000	223,000	244,000	168,000	199,000
AST (IU/L)	60	50	17	23	NO	NO	23
ALT (IU/L)	71	74	14	35	NO	NO	34
Creatinine (mg/dL)	1.20	1.60	0.80	0.70	1.20	1.90	1.00
CRP (mg/dL)	435.80	81.30	174.70	103.00	23.50	25.40	69.20
ELISA test antibody histoplasmosis (after onset of symptoms)	Positive	Positive	Positive	Positive	Positive	Positive	Positive
	6 th day	10 th day	10 th day	10 th day	29 th day	3 rd day	10 th day
HOSPITAL DISCHARGE							
Laboratory test	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Hemoglobin (g/dL)	12.6	9.6	11.2	13.3	12.7	11.2	13.6
Hematocrit (%)	36.0	29.0	32.0	37.0	36.0	33.0	39.0
WBC ($\times 10^3/\mu\text{L}$)	15,500	6,800	8,600	14,700	14,900	11,800	10,100
Platelets ($\times 10^3/\mu\text{L}$)	317,000	282,000	279,000	361,000	276,000	246,000	240,000
AST (IU/L)	40	13	17	NO	NO	NO	NO
ALT (IU/L)	65	14	14	NO	NO	NO	NO
Creatinine (mg/dL)	2.40	1.70	0.90	1.10	1.00	2.10	NO
CRP (mg/dL)	0.10	52.30	2.00	8.40	11.40	NO	NO

WBC = White blood cells; AST = Alanine aminotransferase; ALT = Alkaline phosphatase; CRP = C-reactive protein; ESR = Erythrocyte sedimentation rate; NO = Not obtained.

Brazil), an outbreak was described in 5 children who frequently played in a large deactivated coal oven. All children had the acute pulmonary form, but were cured without the need for antifungals¹³. In 2006, an outbreak was reported in the Santa Catarina State, in which two cases were reported and the fungus was isolated in the focus of the epidemic¹⁴. In our series of cases, the evidence of the outbreak was fundamental to establish the epidemiological diagnosis of the acute pulmonary disease, associated with radiological images suggestive of histoplasmosis. The association of serological tests, clinical data and epidemiological evidence helped to reach a diagnostic conclusion.

In 2019, in French Guiana, an outbreak of acute histoplasmosis was reported in Chinese mine workers, who were not using personal protective equipment (PPE) and were highly exposed to contaminated environments¹⁵. In this outbreak, 15 patients were identified, of which 7 had the diagnostic confirmation of histoplasmosis, and two died. The cases were related to contact with possibly contaminated soil and waste. Workers with long working hours and repeated entry into contaminated tunnels generally had an earlier onset of the disease and a more severe clinical course¹⁵. In the Nova Friburgo outbreak, two patients had severe respiratory compromise and an imminent risk of death. We assume that if the treatment measures were relaxed, deaths could have been recorded in this outbreak, which highlights the risk of lethal outcome even in immunocompetent patients.

Currently, the main drugs recommended for the treatment of histoplasmosis are Itraconazole and Amphotericin B. The latter is preferable for severe infection, in a short period of time (2 to 4 weeks), and requires maintenance from 2 to 4 months with Itraconazole¹⁶. In our series, Itraconazole was very effective for the treatment of uncomplicated cases and Amphotericin B proved to be an excellent option for the two patients with severe forms.

In acute infection, the inhalation of a large inoculum of *H. capsulatum* can occasionally lead to striking reticulonodular infiltrates with nodules. Symptoms may include fever with possible respiratory impairment, sweats, weight loss, headache and gastrointestinal complaints¹⁷. Isolation of *H. capsulatum* from clinical specimens is the gold standard for the diagnosis of histoplasmosis. The detection of anti-*H. capsulatum*-specific antibodies in serum samples may have helped for the diagnosis of histoplasmosis. After infection, a period from 4 to 8 weeks is required for the production of antibodies and a good humoral response by the host is required¹⁸. In our study, if the reported cases had not come from an outbreak investigation, we could hardly have taken into account the

initial hypothesis of diagnosis of histoplasmosis, thereby delaying the adequate or proper treatment. Outside of an outbreak, for acute lung infections, the main diagnostic hypotheses would be viral infections (such as Covid-19) or other fungal infections.

Radiologic findings can be helpful to distinguish acute histoplasmosis from bacterial/viral pneumonia, showed pulmonary nodules (typically multiple peripheric nodules with halo sign at computed tomography)¹⁷. In this series of cases, all patients had a disseminated and bilateral micronodular pattern, demonstrating a more aggressive presentation of the infectious process.

Although histoplasmosis is not in the national list of compulsory notification diseases in Brazil, the Rio de Janeiro State recommended it in a recent local list, considering the local epidemiological profile and need to improve surveillance of systemic mycoses¹⁹. The best protection for persons exposed to the risk of infection is proper protective equipment and soil moistening to minimize aerosols¹⁰. Unfortunately, there is no safe soil disinfectant that will kill the spores. People at risk of exposure (work or leisure) should receive adequate information about the risks of visiting a place that potentially contains spores of *H. capsulatum*. Healthcare professionals must be trained to identify suspected cases of this disease and to perform the appropriate treatment, avoiding fatal outcomes.

CONCLUSION

This case series expands the knowledge of the epidemiology of this mycosis in Brazil. Acute pulmonary histoplasmosis presents as isolated cases of difficult diagnosis or as outbreaks that are easier to diagnose. The benign course of this presentation depends on the degree of exposure to infectious propagules. Clinical and radiological findings must be analyzed in the differential diagnosis between bacterial and viral pneumonia. Early diagnostic suspicion and adequate treatment of acute pulmonary forms of histoplasmosis can prevent fatal outcomes.

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AUTHORS' CONTRIBUTIONS

DCS and EBM: conceived and designed; EBM, DCS, AARN, GMBM, MS, PLH and JO: data collection; EBM, DCS, RMCVV and SCF: data analysis; EBM, DCS, PLH,

BM, RMCVV and SCF: wrote the paper; BM, RMCVV and SCF: critically reviewed the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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