

Aspergillus fumigatus fungus ball in the pleural cavity*

Bola fúngica por *Aspergillus fumigatus* em cavidade pleural

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Abstract

Objective: To report the cases of 6 patients with fungus ball caused by *Aspergillus fumigatus* (aspergilloma) in the pleural cavity. **Methods:** Between 1980 and 2009, 391 patients were diagnosed with aspergilloma at the Santa Casa Hospital Complex in Porto Alegre, Brazil. The diagnosis of aspergilloma in the pleural cavity was made through imaging tests revealing effusion and pleural thickening with air-fluid level; direct mycological examination revealing septate hyphae, consistent with *Aspergillus* sp.; and positive culture for *A. fumigatus* in the surgical specimen from the pleural cavity. **Results:** Of the 391 patients studied, 6 (2%) met the established diagnostic criteria. The mean age of those 6 patients was 48 years (range, 29-66 years), and 5 (83%) were male. The most common complaints were cough, expectoration, and hemoptysis. Four patients (67%) had a history of tuberculosis that had been clinically cured. All of the patients were submitted to surgical removal of the aspergilloma, followed by intrapleural instillation of amphotericin B, in 4; and 2 received systemic antifungal treatment p.o. There was clinical improvement in 5 patients, and 1 died after the surgery. **Conclusions:** In adult patients with a history of cavitary lung disease or pleural fistula, a careful investigation should be carried out and fungal infection, especially aspergilloma, should be taken into consideration. In such cases, laboratory testing represents the most efficient use of the resources available to elucidate the diagnosis.

Keywords: *Aspergillus fumigatus*; Tuberculosis; Empyema, pleural; Pleural effusion.

Resumo

Objetivo: Relatar os casos de 6 pacientes com bola fúngica (BF) na cavidade pleural por *Aspergillus fumigatus*. **Métodos:** Entre 1980 e 2009, foram diagnosticados 391 pacientes com BF aspergilar no Complexo Hospitalar Santa Casa de Porto Alegre (RS). O diagnóstico de BF na cavidade pleural foi definido com exames de imagem demonstrando derrame e espessamento pleural com nível líquido; exame micológico direto demonstrando hifas septadas, consistentes com *Aspergillus* sp.; e cultura positiva para *A. fumigatus* no espécime cirúrgico da cavidade pleural. **Resultados:** Dos 391 pacientes estudados, 6 (2%) preencheram os critérios diagnósticos estabelecidos. A média de idade desses 6 pacientes foi de 48 anos (variação, 29-66 anos), e 5 (83%) eram do sexo masculino. As queixas mais frequentes dos pacientes foram tosse, expectoração e hemoptise. Quatro (67%) dos pacientes tinham tuberculose curada. Todos os pacientes realizaram remoção cirúrgica da colonização fúngica, e houve infusão intrapleural com anfotericina B em 4; e 2 pacientes receberam tratamento antifúngico sistêmico v.o. Cinco pacientes melhoraram clinicamente, e um foi a óbito após a cirurgia. **Conclusões:** Em pacientes adultos com história de doença pulmonar cavitária ou fistula pleural, deve-se realizar uma investigação criteriosa levando em consideração a infecção fúngica, principalmente BF pulmonar. Portanto, a exploração laboratorial torna-se mais eficiente em relação aos recursos disponíveis para elucidação diagnóstica.

Descritores: *Aspergillus fumigatus*; Tuberculose; Empiema pleural; Derrame pleural.

* Study carried out at the Santa Casa Hospital Complex in Porto Alegre, Porto Alegre, Brazil.

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Introduction

A pulmonary fungus ball (aspergilloma) consists of a fungal mass, mucus, blood, inflammatory cells, and cell debris within a cavity. *Aspergillus fumigatus* is the most common etiologic agent, accounting for approximately 90% of all cases.⁽¹⁻³⁾ This clinical presentation can also progress to chronic necrotizing pulmonary aspergillosis (semi-invasive aspergillosis), when there is local invasion of the cavity wall in patients with immunosuppressive episodes. Among the causes of impaired local immunocompetence are interstitial lung disease, lung resection, sequelae of pulmonary tuberculosis, cystic fibrosis, pneumoconiosis, and COPD. Chief among the causes of impaired systemic immunocompetence are corticosteroid therapy, chemotherapy, and radiotherapy, as well as alcoholism, malnutrition, and diabetes.⁽⁴⁾ In addition, an aspergilloma can lead to invasive aspergillosis in severely immunocompromised patients (patients with neutropenia and transplant recipients); there is vascular tropism of the fungus and subsequent thrombosis and ischemic necrosis.⁽⁵⁾

The main predisposing factors for aspergilloma are a history of tuberculosis that has been clinically cured, bronchiectasis, emphysematous bullae, bronchial cysts, and cancer.⁽⁶⁻⁸⁾ In such aerated spaces, the defense mechanisms (phagocytosis) are impaired, allowing germination of conidia, which aggregate to form fungal colonies in a dynamic process of growth and death of fungal elements, which can result in degeneration of the aspergilloma.⁽¹⁾ Spontaneous lysis occurs in 5-10% of cases and is favored when there is associated bacterial infection.^(1,7,8)

The diagnosis is usually made in the fourth or fifth decade of life. The main symptoms are recurrent hemoptysis, cough, mucopurulent expectoration, weight loss, asthenia, chest pain, and dyspnea.^(1,9) On chest X-rays, a pulmonary aspergilloma appears as a solid, sometimes mobile, mass of varying size and shape, bordered by a crescent-shaped radiolucent shadow (air meniscus sign); there can also be pleural thickening and cavity wall thickening.^(7,8) Being more sensitive, conventional chest CT has the advantage of indicating the presence of an intracavitary mass when this mass is not evident on X-ray examination.^(1,6,7,10) On the basis of radiological findings, an aspergilloma is classified as simple, when the cavity wall is thin, with no surrounding

fibrosis in a healthy lung, or complex, when the cavity wall shows fibrosis, thickening, or the presence of severe sequelae of the subjacent or pleural parenchyma.^(1,7)

In rare cases, an aspergilloma can be located in the pleural space, being usually subsequent to surgical complications or concomitant with the presence of a bronchopleural fistula.⁽¹⁰⁻¹⁸⁾ The objective of the present study was to report and document cases of patients with pleural aspergilloma caused by *Aspergillus fumigatus*, determining the profile of those patients, and therefore to assist in raising clinical suspicion.

Methods

This was a retrospective descriptive study based on the analysis of the medical charts of the 391 patients diagnosed with aspergilloma caused by *Aspergillus* sp. at the Mycology Laboratory of the Santa Casa Hospital Complex in Porto Alegre, Brazil, between 1980 and 2009. We collected information on the following topics: demographics; clinical findings; predisposing conditions; laboratory and radiological test results; treatment; and outcome. The diagnosis of aspergilloma was made on the basis of clinical presentation, radiological and histopathological findings combined with mycological evaluation by double radial immunodiffusion, direct mycological examination (10% potassium hydroxide), and culture on Sabouraud medium with 1% chloramphenicol, incubated at 25 °C and at 35 °C.

We searched for cases of pleural aspergilloma, which was defined by the presence of aggregates of hyphal macrocolonies forming semi-solid masses in the pleural cavity.

This study was approved by the Research Ethics Committee of the Santa Casa Hospital Complex in Porto Alegre (Project no. 1461/06).

Results

Of the 391 patients analyzed, 6 (2.0%) met the diagnostic criteria for pleural aspergilloma. As shown in Table 1, 5 (83%) were male, and the mean age was 48 years (range, 29-66 years). The predisposing conditions were as follows: tuberculous empyema, in 4; bacterial empyema, in 1; and empyema with bronchopleural fistula, in 1. All of the patients were HIV-negative. The main clinical manifestations were cough, expectoration, and hemoptysis, in 4 patients (67%).

Table 1 – Description of the six cases of fungus ball caused by *Aspergillus fumigatus* (aspergilloma) in the pleural cavity.

Case	Age, years	Gender	Associated condition/ predisposing factor	Presentation	Pleural radiological findings	Pleural histopathological diagnosis ^a	Double radial immunodiffusion	Treatment/outcome
1	66	M	Lung resection for cancer/empyema with bronchopleural fistula, thoracostomy	Cough, expectoration, hemoptysis, dyspnea, and fever	Effusion and thickening on the left	Chronic inflammation and necrosis	Not performed	Open drainage and instillation of amphotericin B/hospital discharge
2	56	M	Lung resection for cancer; COPD/thoracostomy for tuberculous empyema	Cough, expectoration, hemoptysis, and fever	Effusion and thickening on the left	Chronic inflammation	Not performed	Itraconazole/hospital discharge
3	61	M	COPD/thoracostomy for tuberculous empyema	Cough, expectoration, hemoptysis, fever, and weight loss	Effusion and thickening on the right	Chronic inflammation and fibrosis	Negative	Open drainage and instillation of amphotericin B, followed by itraconazole/hospital discharge
4	53	F	Diabetes mellitus, arterial hypertension, and chronic renal failure/bacterial pleural empyema, osteomyelitis	Cough, expectoration, hemoptysis, fever, and a pleurocutaneous fistula	Effusion, thickening, and a mass with soft tissue density	Chronic inflammation and pleural fungal invasion/periostitis ossificans in the ribs	Negative	Open drainage and instillation of amphotericin B /death.
5	29	M	Thoracostomy for tuberculous empyema	Cough, expectoration, hemoptysis, fever, and chest pain	Effusion and thickening on the right	Chronic inflammation and fibrosis/foreign-body-type granuloma	Positive	Open drainage and instillation of amphotericin B, followed by decortication/hospital discharge
6	38	M	Thoracostomy for tuberculous empyema	Cough, expectoration, hemoptysis, fever, chest pain, and weight loss	Effusion and thickening on the right	Not performed	Not performed	Radical lobectomy/hospital discharge

^aMycological diagnosis of pleural cavity content by direct examination (presence of septate branching hyphae arranged in the shape of an aspergilloma) and positive culture.

Radiologically, effusion and pleural thickening were identified in all of the patients; in case 4, a mass with soft tissue density was seen by conventional chest CT combined with X-ray. The diagnosis was made through direct mycological examination and culture of the clinical and surgical specimen of the pleural cavity content (Figure 1). *Aspergillus fumigatus* was the only etiologic agent identified. Double radial immunodiffusion was positive in 1 of 3 patients (33%). There was fungal invasion of the pleural wall in 1 patient (20%). The treatment instituted was open drainage of the cavity content and intrapleural instillation of amphotericin B, in 4 patients, followed by decortication, in 1; 2 patients (33%) received systemic antifungal treatment p.o. The patient who had fungal invasion of the pleura (case 4) was co-infected with *Klebsiella pneumoniae* and died in the postoperative period, without having received antifungal treatment. The other 5 patients (83%) had a favorable course, although 2 had infection secondary to lung resection for cancer.

We selected case 5 as an illustrative case: a 29-year-old male patient submitted to thoracostomy two years prior because of an empyema secondary to tuberculosis. He was an alcoholic and had dilated cardiomyopathy. The patient was hospitalized complaining of dyspnea and secretion at the thoracostomy site, which was partially closed. Physical examination revealed diminished breath sounds on the right, diminished vocal fremitus, thoracostomy with purulent secretion, and widespread purplish maculae. Cardiac auscultation revealed gallop rhythm. At the time, the infection resolved with antibiotic therapy. A chest X-ray (Figure 1A) revealed no secretion retention in the thoracostomy drainage bag on the right, as well as revealing thickening of the lateral costal pleura and of the pleura located medially to the aforementioned drainage bag, in addition

to cardiomegaly without left atrial enlargement; it was impossible to rule out pericardial effusion with certainty. The blood tests performed, all of which were within the range of reference values, were as follows: leukocyte count; platelet count; hematocrit; hemoglobin test; hemoglobin concentration of red blood cells; and alkaline phosphatase level. Six months later, because of an empyema, the patient underwent a second thoracostomy aided by resection of one more rib. An analysis of the pleural sample revealed chronic suppurative inflammation and fibrosis, as well as a foreign-body-type granuloma. As a result of the procedure, the patient achieved a satisfactory clinical improvement and was discharged from the hospital six days later. One year later, the patient again was hospitalized with complaints of right-sided chest pain and hemoptysis. He underwent assessment of the thoracostomy site under local anesthesia, and a specimen of parietal pleura was sent for bacteriological and mycological examination. The patient was discharged showing a better clinical status. He was readmitted with chest pain fifteen days later, at which point he underwent decortication of the lung (Figures 1B and 1C). The material collected for analysis showed fibrosis in the parietal pleura, chronic inflammation, and a foreign-body-type connective tissue granuloma. The material was sent to the laboratory for mycological evaluation. Direct examination detected the presence of septate branching hyphae (Figure 2) arranged in the shape of an aspergilloma, and *A. fumigatus* was isolated on culture (Sabouraud medium with chloramphenicol, incubated at 25 °C and at 35 °C). Double radial immunodiffusion was positive for this fungus. The treatment adopted was open drainage and instillation of amphotericin B, followed by pleural decortication. The patient was discharged from the hospital in good health.



Figure 1 – Chest X-rays. In A, open pleural cavity (time of pleural secretion collection when there was the finding of a fungal ball caused by *Aspergillus fumigatus*—aspergilloma—in the pleural cavity). In B, recovery after instillation of amphotericin B and decortication. In C, radiological evaluation at discharge.

Discussion

Accumulation of fluid in the pleural cavity is a common manifestation of pleural involvement. Empyema is defined by the presence of pus in the pleural space, resulting from a complication of pneumonia or as a consequence of surgical wound infection, lung abscess, or thoracic surgery.⁽¹⁹⁾ Fluid contamination is more common in patients with COPD and in patients undergoing surgery for suppurative disease, in which there is often persistent air leak, indicating prolonged use of chest tubes.^(20,21) The triad of symptoms characteristic of pleural effusion includes cough, chest pain, and dyspnea. Cough is usually dry, sporadic, and not very intense, being caused by inflammatory stimuli in the parietal pleura. Dyspnea is multifactorial and is more closely related to the time since the beginning of fluid accumulation and to the accumulation rate than to the volume of accumulated fluid.⁽¹⁹⁾ In general, chest pain, known as “pleuritic pain”, occurs only when breathing, is well localized, and is moderate in intensity. Other symptoms will depend on the underlying disease, symptoms such as fever and weight loss in patients with tuberculous pleural effusion, or such as productive cough, purulent expectoration, and fever in patients with parapneumonic effusion.⁽²⁰⁾ In the present study, all of the patients had fever.

In general, pleural infections are of bacterial etiology, which accounts for approximately 75% of all cases. Rarely are they of fungal etiology, and, in such cases, the genera *Candida*, *Aspergillus*, and *Cryptococcus* are noteworthy.⁽²²⁾ In one study, the proportions of 82%, 12%, and 4%, respectively,

were attributed to the genera *Candida*, *Aspergillus*, and *Cryptococcus* in 73 fungal isolates of clinically significant pleural effusion.⁽²³⁾

The fungal etiology of an empyema diagnosed by the presence of purulent fluid in the pleural cavity will be established on the basis of the following criteria: isolation of the fungus from an exudate; significant signs of infection, such as fever (body temperature > 38 °C) and leukocytosis (> 10,000 cells/ μ L); and isolation of the same agent from the pleural specimen in more than one occasion, or also from blood, sputum, or surgical wounds showing tissue invasion.^(21,23) Invasion of the pleural cavity by *Aspergillus* sp. is uncommon and usually results from a late complication: chronic empyema treated with thoracostomy or pneumothorax, this empyema being associated with bronchopleural fistula, previous pulmonary tuberculosis, cavernostomy, or complications of invasive aspergillosis.^(11,20)

In our study, the aspergilloma was located in the pleural cavity. Among the 6 patients, the predisposing factor was tuberculous empyema, in 4, bacterial empyema, in 1, and empyema with bronchopleural fistula, in 1. These findings are similar to those reported in previous studies.⁽¹²⁻¹⁴⁾ The present study was not different from other published experiences in terms of patient gender; most patients with pleural aspergilloma or with pulmonary aspergilloma were male.^(13,22) All of the patients had hemoptysis, cough, expectoration, and fever. Dyspnea was observed in 1 patient, and chest pain and weight loss were observed in 2, this being in accordance with most studies in terms of symptoms.^(10,12,13) However, one group of

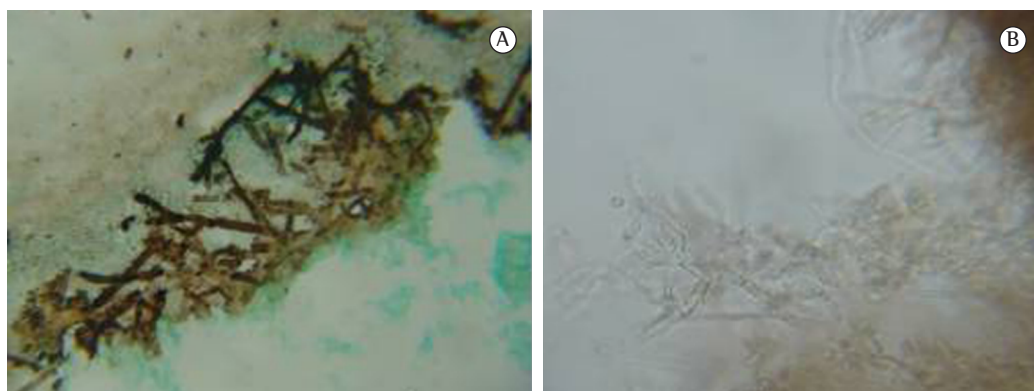


Figure 2 – In A, photomicrograph of a pleural secretion specimen showing a tangle of septate, dichotomously branching hyphae (Grocott-Gomori; magnification, $\times 40$). In B, photomicrograph of a fresh preparation showing hyaline hyphae (magnification, $\times 40$).

authors reported, in a series of 13 cases of pleural aspergilloma, only 7 cases (54%) of symptomatic patients with hemoptysis, expectoration, and chest pain, whereas the remaining cases consisted of asymptomatic patients diagnosed only by routine chest X-ray,⁽¹³⁾ which differs from our clinical findings. In our study, similarly to another report,⁽¹⁶⁾ the radiographic diagnosis showed effusion and pleural thickening in 6 patients, indicating an exudative process. However, for a definitive diagnosis of the disease, it is necessary to perform a mycological evaluation, the positivity of which is determined by the microscopic finding of septate branching hyphae arranged in the shape of an aspergilloma and by the taxonomic identification of the fungus by culture of a specimen of the pleural cavity content. In 5 patients, histopathological examination revealed chronic inflammation, probably due to the underlying diseases (Table 1). Tissue invasion was observed in 1 case (16.7%).

Serological techniques have been extremely useful as adjuvant diagnostic tools. The presence of antibodies can be confirmed by double radial immunodiffusion, detecting approximately 98% of all cases of aspergilloma, because of the high levels of antigens found in immunocompetent patients.^(8,24) In the present study, the negative results of this test can be explained by the low quantity of circulating antibodies at the time of blood collection. As suggested by one group of authors, surgical removal of an aspergilloma leads to a progressive decrease in circulating antibodies and to its complete disappearance from the serum of patients.⁽²⁵⁾ In some phases, an aspergilloma can be completely devoid of living fungi, there being calcification with intracavitary residues. The absence of viable fungi could lead to loss of antigenic stimulation and, consequently, to the disappearance of antibodies circulating in the bloodstream.^(8,12,21,23,24) In the present study, we found negative results in 2 patients and positive results in 1; the test was not performed in 3 patients, probably because there was no suspicion of fungal disease before the onset of pleural effusion. More recent techniques, such as galactomannan antigenemia, nested PCR, and latex agglutination testing for *Aspergillus* sp. in aspergilloma samples, have lower sensitivity and a low diagnostic value.^(6,26)

The treatment of aspergilloma, consisting of surgery, antifungal treatment, or both, should be

tailored to each patient.^(1,9,10) The most common indication for surgery is a history of hemoptysis, which is a major cause of death, especially when the cavitary lesion colonized by the fungus is secondary to tuberculosis.⁽²⁷⁾ In this population of patients, there is significant potential for postoperative complications, especially in those who are symptomatic, when nutritional and functional status is poor; however, surgery should be considered in those cases in which hemoptysis becomes life-threatening.^(10,12)

The vascularization of the wall of the cavity that contains an aspergilloma comes primarily from the intercostal circulation rather than from the bronchial circulation, which results in two findings: early thickening of the wall of the colonized cavity, especially in its costal face, implying laborious and bloody extrapleural surgical detachment; and bronchial artery embolization, sometimes used in patients at risk of dying from hemoptysis, yielding fleeting and poor results.

In patients with decreased functional reserve for lung resection, a useful alternative is cavernostomy, which can be left open to the outside, maintaining a path, consisting of epithelium, to the skin.⁽²⁸⁾

Endobronchial/intracavitary antifungal instillation or oral administration of azole derivatives (e.g., itraconazole) can be considered the first-choice options in the antifungal treatment of aspergillomas in the pleural cavity because of the lipophilic characteristics of the drug, thereby resulting in high drug concentration in the cavity. Monitoring of itraconazole serum levels is useful for maintaining treatment efficacy.^(1,6,29) Intracavitary instillation of amphotericin B, which was performed in 4 patients in our sample, was considered an aid in the permanent eradication of aspergillomas in one study.⁽¹⁷⁾

One group of authors found a mortality rate ranging from 15-18% in patients with aspergilloma in the pleural cavity,^(13,14) a finding that is similar to that obtained in our sample.

In conclusion, surgical treatment of aspergilloma in the pleural cavity should be considered with caution because of its high morbidity and mortality, and it is necessary to make a careful decision on the basis of evaluation of the predisposing disease.⁽²⁹⁾ In the present study, open drainage followed by antifungal instillation was the most common treatment. In addition, it is essential that, in an attempt to elucidate the diagnosis of pleural effusion,

the patient be approached systematically, on the basis of clinical suspicion, signs, and symptoms. In such cases, laboratory testing represents the most efficient use of the resources available.

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