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ORIGINAL ARTICLE

Challenges, Characteristics, and Outcomes of Chronic Pulmonary Aspergillosis: A 11-Year Experience in A Middle-Income Country

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Abstract

Objectives Chronic pulmonary aspergillosis (CPA) is a research priority in fungal diseases with a need for new studies to reduce misdiagnosis with more common diseases, discuss improvement in diagnostic methods and better characterize gaps in antifungal and surgical treatments to improve clinical outcomes.

Methods In this retrospective study, we reviewed medical records of patients diagnosed with CPA from January 2010 to June 2021 at University of São Paulo, São Paulo, Brazil. We evaluated clinical characteristics, radiological findings, serology, treatment, and outcomes.

Results The study included 91 participants, with 43 (47.3%) patients who underwent surgery and 69 (75.8%) received antifungal therapy. We found a predominance of middle-aged adults (median 51 years), males (n = 58, 64%) with lower BMI (median 21.3 kg/m^2). The most common underlying lung disease was pulmonary tuberculosis (n = 70, 76.9%). The commonest symptoms were cough (n = 67, 74%), haemoptysis, and dyspnea (n = 63, 70%). The most common chest computerized tomography abnormalities were cavity (n = 86, 94.5%), with a predominance of mycetomas (n = 78, 91%). The serology was positive in 81% (61/75). The one-year mortality was low (3.3%). Clinical improvement and stability occurred in 89% of participants for constitucional symptoms and 86% for pulmonary symptoms.

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While serological improvement and stability occurred in 71%. Radiological improvement and stability occurred in 75%.
Conclusion We observed a good outcome after 1-year follow-up, in which the majority had improvement or stability of pulmonary and constitutional symptoms, decrease in CIE titers and low mortality.

Keywords Chronic pulmonary aspergillosis · Antifungal therapy · Surgery · Outcomes

Introduction

Aspergillosis is a disease caused by filamentous fungi of the genus *Aspergillus*, which are easily inhaled and deposited deep in the lungs, leading to a variety of pulmonary syndromes, based on host immune response and presence of lung comorbidities [1]. It can present as a progressive and chronic disease of the lung, called chronic pulmonary aspergillosis (CPA) [2, 3].

CPA affects 3 million people worldwide and consequently has been recognized as a global burden [4, 5]. Furthermore, contemporary series suggest 50–85% 5-year mortality [6]. Despite an elevated mortality, CPA is considered a neglected fungal disease [7].

As a neglected disease, CPA is a research priority in fungal diseases with a need for new studies [8] to reduce misdiagnosis with more common diseases, discuss improvement in diagnostic methods and better characterize gaps in antifungal and surgical treatments to improve clinical outcomes.

Materials and Methods

In this retrospective study, we reviewed medical records of patients diagnosed with CPA from January 2010 to June 2021 at Clinics Hospital of the University of São Paulo, São Paulo, Brazil. Ethical approval for the study was obtained from the local ethics committee.

Definition of CPA

The diagnosis of CPA was based on the updated criteria of the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the European Respiratory Society (ERS) guidelines for the management of chronic pulmonary aspergillosis [9].

All patients with proven CPA had the following characteristics: (1) the computerized tomography (CT) scan of the chest finds suggestive of aspergillosis (one or more cavities with or without a fungal ball present or nodules); (2) microbiological evidence of *Aspergillus* infection [microscopy or culture from sputum, bronchoalveolar lavage (BAL) or, biopsy, histology, positive serum or BAL GM] or serological evidence [positive serum immunodiffusion test (ID) and counterimmunoelectrophoresis (CIE)]; (3) All present for at least 3 months or at least a 1-month duration in subacute invasive aspergillosis (SAIA); (4) Exclusion of alternative diagnoses.

The diagnosis was established by a working group composed of members from professionals representing the disciplines of infectious diseases, pneumology, thoracic surgery, and radiology.

Clinical Characteristics

We collected demographic data at the time of the diagnosis of CPA such as age, sex, and body mass index (BMI). As structural lung disease is a major risk factor for CPA, we collected data regarding pulmonary tuberculosis, nontuberculous mycobacterial (NTM) lung disease, asthma, chronic obstructive pulmonary disease (COPD), and thoracic surgery.

Other comorbidities that could lead to immunosuppression were collected such as diabetes mellitus, HIV infection, use of immunosuppressant drugs, smoking and alcoholism.

We evaluated the main symptoms at the clinical presentation: cough, haemoptysis, dyspnea, expectoration, weight loss, chest pain, night sweating, and fever. The duration of symptom onset was also collected.

Radiological Findings

Chest CT in all patients with CPA, which were evaluated by a radiologist experienced in lung

imaging. The following aspects were evaluated by the radiologist: number of cavities, cavity size, cavity location, presence of mycetoma, pericavitary or parenchymal infiltrates, lymphadenopathy, bronchiectasis, and hydroaeric level.

We classified the radiological presentation of the disease according to the ESCMID classification into simple aspergilloma (SA), chronic cavitary pulmonary aspergillosis (CCPA), chronic fibrosing pulmonary aspergillosis (CFPA), *Aspergillus* nodule and SAIA [9]. CPA is categorized as simple aspergilloma (ie, a fungal ball in a single thin-walled cavity without pericavitary infiltrates or pleural thickening), CCPA (ie, one or more cavities with surrounding fibrosis, infiltrates, or pleural thickening, possibly containing one or more aspergillomas), CFPA (ie, fibrosis of two or more lobes with cavities), *Aspergillus* nodule (ie, one or more nodules which may or may not cavitate), and SAIA (ie, variable radiological features including cavitation, nodules, progressive consolidation with "abscess formation") [9].

Serology

We evaluated serological assays by ID or CIE at the moment of CPA diagnosis. Both assays employed a culture filtrate of three isolates of *A. fumigatus* grown in sabouraud-dextrose broth. The ID test was performed in agar 1% gel in buffered saline (pH 6.9), containing sodium citrate 0.4% and glycine 7.5%. The antigen (12 µl) was placed in the central well and reference serum and patients' sera (12 µl) in the surrounding wells. The slides were incubated for 48 h, washed in saline, dried, and stained with Coomassie Brilliant Blue R (Sigma). The serum samples were tested undiluted. CIE was performed in agarose 1% gel with electrophoresis in veronal buffered saline, pH 8.2, at 120 V for 90 min. Serum samples were applied to the anodic side and the antigen to the cathodic side of the slide. The sera were diluted two-fold and tested from the undiluted sample. Samples that reacted at least undiluted were considered positive. These tests have been used routinely in our laboratories, ID being the test of choice for diagnosis and CIE used for diagnosis and follow-up of aspergillosis patients during treatment.

Treatment

We evaluated the treatment received, including antifungal therapy and/or surgery. We recorded if the patients received itraconazole or voriconazole. When surgery was performed, we evaluated the surgery indication, the surgical technique, and the surgical complications. We do not routinely perform therapeutic drug monitoring.

Outcomes

Our primary outcome was the one year mortality, defined as the number of deaths in one year follow up. As secondary outcomes we defined the clinical improvement, the serological improvement with the titers of CIE and the radiological improvement evaluated by the same radiologist. The data were collected at the start and 12 months following antifungal treatment and/or surgery.

Clinical outcome was evaluated by constitutional symptoms and pulmonary symptoms. Constitutional symptom improvement was considered as the disappearance or reduction of all constitutional symptoms (fever, weight gain and night sweats). Constitutional symptom stability was considered when there was no improvement in all constitutional symptoms, but stable. Constitutional symptom deterioration was defined by progression of systemic signs. Pulmonary symptom improvement was considered as disappearance or reduction of all pulmonary symptoms (cough, expectoration, hemoptysis, dyspnea and chest pain). Pulmonary symptom stability was considered when there was no improvement in all pulmonary symptoms, but stable. Pulmonary symptom deterioration was defined by progression of respiratory signs.

Serological improvement was considered when CIE titers decreased or became negative. Serological stability was considered when CIE titers remained the same as the diagnosis of CPA. Serological deterioration was defined by increased CIE titers.

Radiological improvement was considered as the disappearance or reduction of findings initially thought to be related to CPA. Radiological stability was considered when there was no significant change of findings. Radiological deterioration was defined by increased findings of CPA initially present and/or appearance of new chest CT abnormalities [3].

Total hospital length of stay and surgical complications were evaluated, respectively: bleeding, chest pain, empyema, pneumonia, pneumothorax, prolonged air leak, surgical site infections, respiratory failure requiring reintubation, bronchopleural fistula, pulmonary embolism, venous thromboembolism, atelectasis, acute kidney failure, arrhythmia, septic shock and cardiopulmonary arrest.

Statistical Analysis

Baseline and outcome data were described using median and range for continuous variables. Frequencies of categorical variables were calculated. We presented our data in summary tables.

Results

Demographic Characteristics and Underlying Diseases

This study recruited 91 participants with proven CPA. The baseline characteristics were shown at Table 1. We found a predominance of middle-aged adults, males with lower BMI.

The most common underlying lung disease was pulmonary tuberculosis (PTB). Most patients have had 1 (n = 49) or 2 (n = 13) previous treatments for PTB. However, we had in our sample one patient who had been treated for PTB 7 times. Another important condition was smoking, which patients had a history of more than 30 pack-years. The minority used immunosuppressant drugs.

Table 1 Clinical characteristics of patients with chronic pulmonary aspergillosis

Characteristics	Total (n = 91)
Age median (years)	51 (42–59)
Male	58 (64%)
BMI (kg/m^2)	21,3 (18,0–24,2)
Pulmonary TB	70 (76,9%)
NTM lung disease	8 (8.8%)
COPD	11 (12%)
Asthma	6 (6,6%)
Thoracic surgery	11 (12%)
HIV	3 (3,3%)
Immunosuppressant drugs	14 (15,3%)
Alcoholism	27 (30%)
Smoking	48 (52,7%)
Diabetes mellitus	16 (18%)
Symptoms	**Total (n = 91)**
Symptom onset (month)	12 (6–24)
Fever	8 (8.9%)
Cough	67 (74%)
Haemoptysis	63 (70%)
Dyspnea	63 (70%)
Expectoration	40 (44%)
Chest pain	11 (12%)
Weight loss	34 (38%)
Night sweating	9 (10%)

TB, tuberculosis; COPD, chronic obstructive pulmonary disease; NTM, nontuberculous mycobacterial

Symptoms

Symptoms were usually non-specific. The commonest symptoms were cough, haemoptysis, and dyspnea, while night sweating and fever were the least common (Table 1). Fourteen (15.4%) patients with massive haemoptysis underwent bronchial artery embolisation. The median duration of symptoms was 12 months at the diagnosis.

Radiological Findings and Serology

The most common CT abnormalities, summarized in Table 2, were cavity, with a predominance of mycetomas, and parenchymal infiltrate. The cavities were located mainly in the upper lobes. Less common radiological findings were emphysema, lymphadenopathy, and hydroaeric level.

All diagnosed CPA cases were classified into simple aspergilloma (27.5%, n = 25), CCPA (37.4%, n = 34), CFPA (19,8%, n = 18), SAIA (12%, n = 11) and *Aspergillus* nodule (3.3%, n = 3).

Seventy-five patients underwent ID and CIE, and it was positive in 81% (n = 61) of the cases tested. CIE titers at diagnosis ranged from 1/1 to 1/512, with most cases concentrating between 1/16 (n = 14) and 1/32 (n = 16) (Table 2).

Table 2 Chest computed tomography findings and serology assays

Radiological	Total (n = 91)
Cavity (or cavities) number	
1	45 (49%)
⩾ 2	41 (45%)
Cavity size, cm	6,1 (4.0–9.4)
Location of cavity	
Right upper lobe	31 (36%)
Left upper lobe	29 (34%)
Both upper lobe	21 (24%)
Mycetoma	78 (91%)
Parenchymal infiltrate	60 (66%)
Peracavity infiltrates	39 (43%)
Lymphadenopathy	21 (23%)
Bronchiectasis	82 (90%)
Emphysema	23 (26%)
Hydroaeric level	7 (8%)
Serological	**Total (n = 75)**
ID, reagent	61 (81%)
Titles CIE	
1/1	1 (1.3%)
1/2	2 (2.6%)
1/4	6 (8%)
1/8	7 (9.3%)
1/16	14 (19%)
1/32	16 (21,3%)
1/64	5 (6.6%)
1/128	2 (2.6%)
1/256	6 (8%)
1/512	2 (2.6%)

Antifungal Therapy

Among the 91 patients, 69 (75.8%) received antifungal therapy. The treatments used were itraconazole for 58 (84.1%) patients or voriconazole for 11 (15.9%) (Fig. 1). Oral itraconazole was administered at 200–400 mg per day. Oral voriconazole was administered at 200–600 mg per day. The treatment time was similar between the non-surgical and surgery treatment, with a median of 12 months [12 (IQR 10–12) vs. 12 (IQR 6.75–12); $p = 0.2$]. Twenty-two (24.2%) patients did not use antifungal treatment.

The antifungal therapy was changed in 10 patients: 6 for treatment failure, 2 for lack of medicine, 1 for intolerance and 1 for toxicity.

Surgery

Forty-three (47.3%) patients underwent surgery with 28 (65%) having a preoperative tissue diagnosis while 15 (35%) were confirmed post resection. We classified patients according to their preoperative risk complications based on ASA: I (23.3%, n = 10), II (30.2%, n = 13), III (44.2%, n = 19) and IV (2.3%, n = 1).

The indications for surgery included recurrent haemoptysis (53%, n = 30), simple aspergilloma (33%, n = 19), clinical treatment failure (10.5%, n = 6) and recurrent infection (3.5%, n = 2). The procedures included lobectomy (41.8%, n = 18), pneumonectomy (23.3%, n = 10), segmentectomy (16.3%, n = 7), lobectomy associated with segmentectomy (14%, n = 6), bilobectomy (2.3%, n = 1) and cavernostomy (2,3%, n = 1). The main surgical sites were: right upper lobectomy (30.2%, n = 13), left upper lobectomy (23.3%, n = 10), left pneumonectomy (20.9%, n = 9) and single S6 segmentectomy (7%, n = 3). The lung resections were performed with open thoracotomy (90.7%, n = 39) or video-assisted thoracoscopic surgery (VATS) access (9.3%, n = 4), according to the surgeon's preference. Only one (1.1%) patient was lost to follow-up before finalizing the outcome.

Primary Outcome

The outcomes were shown at Table 3. Overall, the one-year mortality was low (3.3%). One death occurred in-hospital related to post-operative septic shock, one death in the 30 days after discharge due to severe hemoptysis, and the last death up to a year after the diagnosis of the disease due to surgical site infection. All deaths were in the CCPA subtype. Thus, the mortality in the CCPA was 8.8% (3/34).

Secondary Outcomes

Clinical improvement and stability occurred in 89% of participants for constitucional symptoms and 86% for pulmonary symptoms. While serological improvement and stability occurred in 71% of participants.

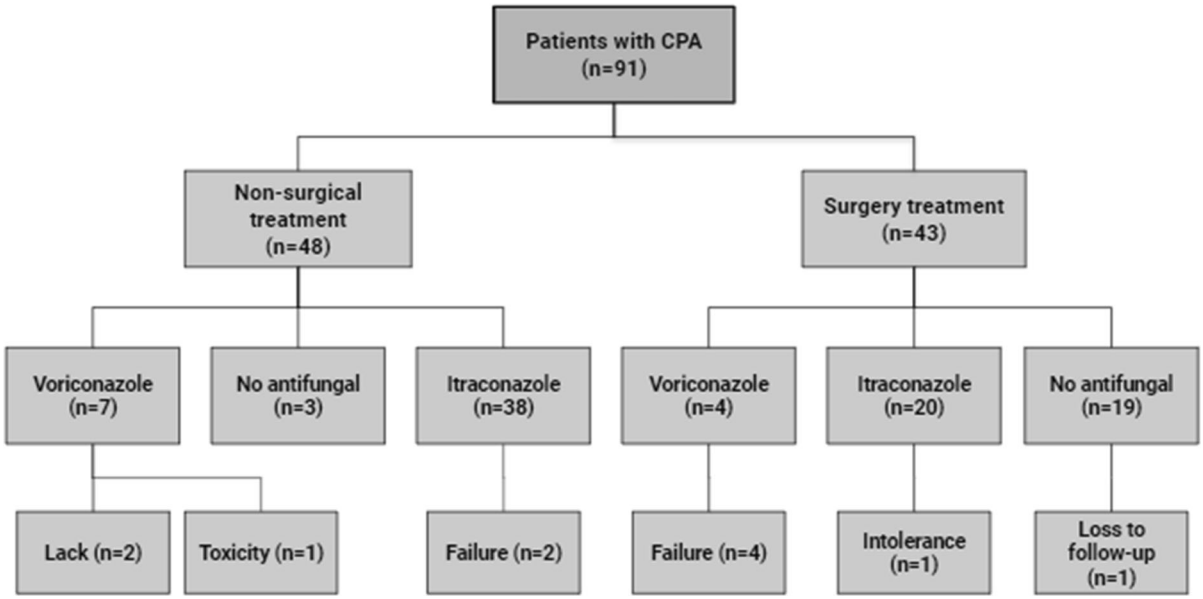

Fig. 1 Stratification of patients based on treatment

Table 3 Outcomes of patients with chronic pulmonary aspergillosis

Outcomes	Total
Total mortality, n = 90	3 (3.3%)
In-hospital mortality	1 (1.1%)
30-day mortality	1 (1.1%)
1-year mortality	1 (1.1%)
Constitutional symptoms, n = 76	
Improvement	51 (67%)
Stability	17 (22%)
Deterioration	8 (11%)
Pulmonary symptoms, n = 80	
Improvement	51 (58%)
Stability	25 (28%)
Deterioration	12 (14%)
Serology, n = 62	
Improvement	42 (68%)
Stability	2 (3%)
Deterioration	18 (29%)
Radiology, n = 51	
Improvement	7 (14%)
Stability	31 (61%)
Deterioration	13 (25%)

Table 4 Post-operative complications of patients with chronic pulmonary aspergillosis

Post-operative complications	Total
Total complications, n = 43	27 (62.8%)
Empyema	8 (29.6%)
Bleeding	7 (25.9%)
Surgical site infections	6 (22.2%)
Chest pain	6 (22.2%)
Prolonged air leak	3 (11.1%)
Respiratory failure requiring reintubation	3 (11.1%)
Pneumonia	3 (11.1%)
Acute kidney failure	3 (11.1%)
Bronchial fistula	2 (7.4%)
Pulmonary embolism	2 (7.4%)
Atelectasis	2 (7.4%)
Cardiopúlmonary arrest	2 (7.4%)
Septic shock	2 (7.4%)
Pneumothorax	1 (3.7%)
Venous thromboembolism	1 (3.7%)
Arrhythmia	1 (3.7%)

Lastly, radiological improvement and stability occurred in 75%.

Post-operative complications were observed in twenty-seven patients (27/43, 62.8%). The three most

common complications were empyema, bleeding, and surgical site infections (Table 4). Median hospital stay was 9.5 days (IQR 3–37).

Discussion

In our retrospective cohort study from a Brazilian quaternary center, we found a low one-year mortality. Furthermore, the improvement and stability of clinical, serological and radiological outcomes were observed in the majority of patients analyzed with prolonged antifungal therapy and/or surgery.

PTB is an underlying condition among CPA cases [10], but the frequency is variable, based on the prevalence of tuberculosis in the countries [4]. Our study showed PTB was the main underlying comorbidity in patients diagnosed with CPA. The patient treated 7 times probably could have misdiagnosed TB many times, providing inadequate treatments. The diagnosis of CPA is often confused with PTB due to the presence of similar symptoms [11–13]. The most common symptoms in CPA are respiratory, such as cough, hemoptysis, and dyspnea. The presence of systemic symptoms is less common, like fever [14]. For this reason, CPA is an important differential diagnosis of what appears to be smear-negative tuberculosis [4]. Five (5.5%) patients in our sample had active tuberculosis at the time of diagnosis of Aspergillosis infection. This association has rarely been reported [15–17].

Forty-three patients underwent surgery, with 28 (65%) having a preoperative diagnosis, while 15 (35%) were confirmed post resection, compared with 76.7% of diagnoses made in the preoperative period in the UK study [18]. This shows the limitation of diagnostic tools for CPA.

Despite the frequent complications, surgical treatment had excellent outcomes reported in literature, with low mortality rates, ranging from 0 to 22.6% [18, 19]. Our study showed a total of three deaths (3.3%) during the period analyzed, only in patients that received surgical treatment. Probably, the lower rates of mortality and other outcomes can be explained by the combined use of surgical treatment with prolonged antifungal treatment. The patients who underwent surgical treatment received less antifungal agents, probably because some cases were diagnosed by histopathology after surgical resection.

Main guidelines recommend initially 6 months antifungal therapy [9, 20]. However, more recent studies have shown that treatment with itraconazole or voriconazole for at least 12 months is more effective, with better clinical and serological outcomes [21–23]. Prolonged treatment of antifungals commonly increases adverse effects, with the need to discontinue or replace the drug [24]. It is described in the literature a discontinuation in up to 30% of cases [22], although we didn't observe many adverse effects in our study. Antifungal therapy was changed in 10 (10.9%) patients, but only 2 patients changed treatment due to toxicity by voriconazole and intolerance by itraconazole. In most cases, the change in antifungal was due to therapeutic failure. Antifungal susceptibility testing was not performed in our study.

Our study better characterized the profile of patients with CPA in Brazil, for which we have little information. However, there are some limitations. It is a retrospective study, which made it difficult to access some information in medical records. We evaluated the clinical outcome subjectively, without using objective scores. Surgical and antifungal approaches were heterogeneous. Furthermore, the follow-up time was short, which may underestimate the relapse and mortality rates. On the other hand, we included a large number of cases, and despite having been done in a single center, this is the largest hospital complex in Latin America, with more than 2,400 beds, serving patients from all states of Brazil, including other countries.

Conclusion

We found many challenges in the management of CPA in our real-word data such as misdiagnosis with pulmonary tuberculosis, the difficulties diagnosis with some cases defined only after surgical resection, and the need of antifungal susceptibility testing in therapeutic failure.

We observed that previous tuberculosis was the main disease underlying CPA. Thus, patients

previously treated for tuberculosis and who later develop a new clinical manifestation of respiratory and constitutional symptoms should have CPA considered as a possible diagnostic hypothesis, especially if acid-fast bacilli microscopy is negative.

In general, we observed a good outcome after 1-year follow-up, in which the majority had improvement or stability of pulmonary and constitutional symptoms, decrease in CIE titers and low mortality, either with prolonged antifungal treatment or the combined use of surgical treatment with prolonged antifungal treatment.

Author Contribution VF, AN, AM, MM, and AK designed the study and analysed the data. VF wrote the first draft. All authors have approved the final manuscript draft.

Declarations

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Conflict of interest None declared.

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