Allergic Bronchopulmonary Aspergillosis in Brazil: a case report and integrative review

CASE REPORT

Abstract

Background: Prevalence of allergic bronchopulmonary Aspergillosis (ABPA) in asthmatic adults is estimated in 2,5%, what matches to more than 4.8 million of patients around the world; from those, more than 1.4 million are only in Latin America. Most patients with the disease are immunocompetent and present themselves with a poorly controlled asthma, secretive cough and recurrent pneumonia. It's curiously sensible to glucocorticoids, so early diagnosis and treatment may prevent bronchiectasis; otherwise, if it isn't recognized soon, may lead to ending stage pulmonary fibrosis. First described by Hinson in 1952, even after almost seven decades, it's still hardly recognized and treated.

Methods and Findings: A case report was performed through clinical follow up of a patient evaluated in a Brazilian hospital diagnosed with ABPA after four years of poorly controlled asthma after even being in ICU and mechanic ventilation support. The patient presented eosinophilia, high serum IgE, central bronchiectasis and positive prick test for *Aspergillus fumigatus*. There was also performed a integrative research of all the studies published in Brazil since the first case report in 1989. There were researched the platforms PubMed, BVS (that covers MedLine and LILACS bases), Scielo, Cochrane, JAMA, NEJM and LANCET using the descriptors "allergic bronchopulmonary Aspergillosis " and "Brazil". There were found 17 articles about ABPA, 10 meeting the inclusion criteria. Of those, only 4 covered clinical and epidemiological features of ABPA in asthmatic patients.

Conclusions: There are very few studies on ABPA in Brazil in the last 30 years. More research in the country is needed to make this diagnostic possibility part of severe asthma differential and lead the patients to earlier diagnosis.

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Introduction

Allergic Bronchopulmonary Aspergillosis is a pulmonary disease characterized by a hypersensitivity reaction to *Aspergillus* species airways colonization. Frequently, it occurs in addition to respiratory diseases such as asthma and cystic fibrosis, generating eosinophilia, increase of serum immunoglobulin E (IgE), pulmonary infiltrates and central bronchiectasis [1].

The fungal gender *Aspergillus* is common in environment; the inhalation of its spores is inevitable. The spores have size between 3-5µm, easily dropable in low airways. In immunocompetent individuals these particles can be easily eliminated with no associated morbidity. The *A. fumigatus* species, however, have considerable virulence and specific properties that may lead to increased deposit in susceptible populations –asthmatics and cystic fibrosis patients– who have abnormalities in airways defense, such as prejudice in mucociliary clearance and cellular epithelial function [2].

Prevalence of allergic bronchopulmonary Aspergillosis (ABPA) in asthmatic adults is estimated in 2.5%, what matches to more than 4.8 million of patients around the world; from those, more than 1.4 million are only in Latin America. Most patients with the disease are immunocompetent and present themselves with a poorly controlled asthma, secretive cough and recurrent pneumonia [3]. Despite the higher prevalence in asthma and cystic fibrosis, a few cases have been already reported in patients with chronic obstructive pulmonary disease (COPD), tuberculosis or lung transplant [4].

The special interest in ABPA occurs because this condition is curiously sensible to glucocorticoids, so early diagnosis and treatment may prevent bronchiectasis evolution. However, if it isn't recognized soon, the disease leads relentlessly to ending stage pulmonary fibrosis [5]. First described by Hinson [6] in 1952, even after almost seven decades, it's still hardly recognized and treated; many times patients

are diagnosed when already through pulmonary hypertension or respiratory failure [7].

The disease shall be suspected in patients with uncontrolled asthma despites the treatment, not being recommended routine tracking for asymptomatic patients with controlled asthma [4]. Besides increase of total serum IgE and eosinophilia, the diagnosis can be obtained by IgE and IgG specific serology for *A. fumigatus* [8] or cutaneous reactivity test. The radiographic findings include pulmonary opacities, central bronchiectasis and mucoid impaction [9].

ABPA has different classifications according to the conditions fulfilled by the patient. Asthmatic patients who fulfill minimal criteria but have no central or peripheral bronchiectasis are classified as Seropositive ABPA (S-ABPA). Patients who match minimal requirements and also the bronchiectasis are classified as Central Bronchiectasis ABPA (CB-ABPA). Finally, patients with severe asthma and fungal sensibility, but do not match the criteria are classified as Severe Asthma with Fungal Sensibility (SAFS) [10].

ABPA diagnosis is somewhat nebulous as it needs to fulfill a particular group of non-specific conditions. There isn't a unique serological pathognomonic test or radiographic characteristic that shows high sensibility, specificity or high positive or negative predictive value [2]. Several criteria have been created and modified – originally, there are the long Rosenberg-Patterson criteria [11]. and more modernly, the ISHAM modified criteria [12], exposed in the following **Table 1**

Greenberger [13] has also established even simpler diagnostic criteria containing only four points: previous asthma diagnostic, positive prick test to *A. fumigatus*, serum total IgE higher than 1000ng/ml and central bronchiectasis in absence of distal bronchiectasis. Those conditions became known as the Truly Minimal Criteria.

The need for strict criteria is because ABPA can mimic several diseases that involve airways and lung parenchyma. Before diagnosis it is important to dis-

Table 1. Modified ISHAM working group 2013 criteria for diagnosis of ABPA.

1	Predisposing condition		Asthma or CF
2	Obligatory criteria	a	IgE > 1000 IU/mL
		b	Positive immediate skin test or increased IgE antibody to <i>Aspergillus</i>
3	Supportive criteria (≥2)	a	Eosinophilia > 500
		b	Precipitins or increased IgG antibody to <i>Aspergillus</i>
		c	Consistent radiographic opacities

Source: adapted from Tracy et al (2016) [2]

card differentials such as: corticosteroid-dependent asthma without ABPA, severe asthma with fungal sensibility (SAFS), cystic fibrosis, bronchiectasis, acute and chronic eosinophilic pneumonia, Churg-Strauss syndrome, among other infectious conditions [14].

The standard treatment comprises a combination of systemic corticosteroids (to attenuate allergic response) associated or not to antifungals, generally imidazolic derivatives. However, recurrence is frequent by the end of the treatment and there is considerable preoccupation with the prolonged use of corticosteroids and their collateral effects [8]. Modernly the use of anti-IgE antibodies like omalizumab has also been used as experimental treatment with good response, having cost as major limitation [14, 15, 16].

As ABPA is extremely underdiagnosed in Brazil, one of the main objectives of this study is to improve the knowledge on the disease and address its suspicion in the differential diagnosis of hard-to-control asthma. To do that there will be performed a literature review of published articles in Brazil since the first ABPA case description. In addition, there will be shown a case report of an ABPA patient during her follow-up period in ambulatory and hospitalization, describing her evolution and diagnostic and therapeutic procedures, building a correlation with the accessible literature on the subject.

Methods

There is a descriptive, observational, cross-sectional, retrospective case report in which data is obtained through the follow up of a patient in a public hospital in the north of Brazil. There is also performed an exploratory and qualitative study of integrative review, searching in the literature published articles on ABPA in Brazil since the first case report in 1989 [17].

The casuistic corresponded to 01 (one) female patient in follow up at the Pneumology Clinic of Hospital Jean Bitar (HJB), Belém, Brazil, administrated by Instituto Nacional de Desenvolvimento Social e Humano (INDSH). The data evaluation comprised the period of her first appointment in the clinic until the ending of data collection of this research, running through diagnosis, as well as the start and early modifications of the treatment. The research was started after acceptance of the patient through signature of a consent term and the data collection was performed through medical record review and available exams obtained in the hospital or from the patient.

For literature review there were included articles published in english or portuguese language performed in Brazil until the study submission date in the allergic bronchopulmonary Aspergillosis (ABPA) subject. There were considered articles from the period of 1989 (first case related) until 2020 indexed in the platforms PubMed, BVS (that covers MedLine and LILACS bases), Scielo, Cochrane, JAMA, NEJM and LANCET using the descriptors "allergic bronchopulmonary Aspergillosis" and "Brazil", with their respective translations present in Medical Subject Headings (MeSH).

There were excluded duplicated articles found in more than one platform, the ones published in another foreign language, whose realization was not in Brazil or publishing in the format of letter to editor, book chapters or editorials. There were also excluded articles that cover exclusively physiopathology without clinical correlations or that mentions

ABPA but don't have relevant data on the subject along the article.

Case Report

A 65-year-old woman, housewife, was hospitalized in 2020 July 02 for cough and dyspnea. She reported asthma diagnosis five years ago and complained that in the last six months, there was necessary to go to emergency weekly because of dyspnea. Symptoms were daily, even at rest. Besides, the patient waked up every night with shortness of breath despite absence of orthopnea. She also referred secretive hyaline cough, besides odynophagia, corize, headaches, insomnia, anxiety and lack of appetite, but denied fever.

The patient had hypertension, esophagitis, hiatal hernia, chronic rhinosinusitis and cholelithiasis; denied previous or actual smoking. She performed regular use of inhaled beclomethasone-formoterol three times a day (prescribed two times a day), nasal budesonide 50mcg 12/12h, olmesartan 40mg 1 dose/day and used, by her own, inhaled salbutamol 3 times daily (prescribed as-needed), without significant relief. The use of the devices was correct.

Four months before admission the patient presented exacerbation with fever, there was prescribed levofloxacin and prednisone with clinical improvement. Four years before she had pulmonary tuberculosis, treated for six months and her symptoms worsened ever since. Two years ago she was hospitalized for severe pneumonia, required intensive care and invasive mechanical ventilation.

The patient lived in a hot and not aired habitation, denied domestic animals and other occupational expositions. She presented anxious and referred paresthesia in hands for two years. She used to perform cardiologic follow-up and had inactive electrical zone in septal wall at electrocardiogram; denied diarrhea and abdominal pain.

On physical examination the patient presented diffuse sibilance, heart ratio of 132 beats per minute, peripheral oxygen saturation of 92% in ambient air and respiratory ratio of 24 incursions per minute. At hospital, she performed respiratory physiotherapy, received inhaled corticosteroids and bronchodilators, antibiotic therapy with piperacillin-tazobactam and metilprednisolone in the dose of 125mg for three days. She performed thorax computed tomography (CT) showing traction bronchiectasis in right superior lobe apical segment, tenuous ground-glass opacities dispersed bilaterally, mucous parietal perihilar bronchial thickening bilaterally, besides a large hiatal hernia. (Figure 1)

Figure 1: Thorax CT showing mucous parietal perihilar bronchial thickening bilaterally.

Source: patient's image exams.

The sinus CT has shown mucous thickening on maxillary sinus, ethmoidal cells and frontal sinus,

Table 2. Patient's blood count and total serum IgE during case investigation.

Exams	White cells	Neutrophils	Lymphocytes	Eosinophiles	Red cells	Platelets	Total IgE
Reference	4.000-11.000	48-66%	20-30%	2-4%	12-18	150,000-400,000	2-214
2 years before	7.500	53% (3990)	29% (2145)	10% (773)	13.5	315,000	137
1 year before	7.600	48% (3640)	26% (1968)	19% (1452)	13.1	276,000	-
Admission	10.100	39% (3949)	19% (1879)	36% (3656)	12.3	278,000	1484
3 days after	6.900	83% (5733)	12% (849)	1,5% (104)	11.3	242,000	11.3

Source: Research data.

besides pneumatized right middle nasal concha. The patient presented symptomatic improvement and reduction of sibilance after treatment. During hospitalization she performed laboratorial tests, showing increase of total serum IgE and important eosinophilia, which showed dramatic response to treatment, according to the next **Table 2**.

The patient also performed endoscopy to better evaluate the reflux complaint. The exam has shown active linear erosion, more than 5mm extension, in the esophagus, next to gastroesophageal junction besides a 4cm sliding hiatal hernia, resulting in erosive esophagitis and moderate proportions hiatal hernia.

Due to the dramatic response to systemic corticosteroid, the eosinophilia and high total serum IgE, conditions like ABPA and Churg-Strauss syndrome were suspected. As sinus CT had not shown nasal polyposis and there were no evidence of vasculitis, performing the ABPA was preferred. Those tests, however, were not covered by the public health system, so they were scheduled to patient's return after hospital discharge.

The patient continued to take oral prednisone 60mg/day until discharge at 2020 July 19. In discharge, asymptomatic, she received the prescription of prednisone 40mg/day, inhaled beclomethasone-formoterol 2 jets twice daily, nasal budesonide 50mcg 12/12h and inhaled salbutamol as-needed to the maximum of 4 times daily. After two months she returned to clinic, still asymptomatic

and brought positive prick test to *A. fumigatus*. She was performing regular use of medications and had no need for inhaled salbutamol. Prednisone was gradually reduced to 20mg/day.

One month later the patient returned presenting cough, corize, effort dyspnea and sparse sibilance, without fever or vital sign alteration. A cold was suspected, but it could also relate to a relapse due to the reduction on oral prednisone. There was associated itraconazole 100mg/day as adjuvant therapy and ordered specific serum IgE to *A. fumigatus* to better address the diagnosis. In the next appointment, the patient was asymptomatic, however with specific IgE negative, probably because she had done already several treatment months.

Literature Review

For the literature review research there were carried out articles made in Brazil with the term "allergic bronchopulmonary Aspergillosis"; the results are organized according to the following **Figure 2**

Most studies included in the literature review were published between 2000 and 2009, with only one study registered in the 1990s. Few studies were found in the decade from 2010 to 2019, the same number was found between the years 1989, the year of the oldest record article, and 1990. (**Figure 3 & Table 3**)

Figure 2: Flowchart – Literature Review.

Source: Research Protocol.

Figure 3: Number of articles researched that discuss clinical and diagnostic aspects of ABPA in Brazil, for decades, since the first registered publication.

Source: Research Protocol.

Table 3. Characterization of studies by author and year of publication, title, type of study and study summary.

Author	Year	Ref	Title	Type of study	Study Summary
Londero, Guadalupe	1990	18	Pulmonary Aspergillosis	Literature Review	Three types of aspergillosis are described: bronchopulmonary allergic, invasive and colonization. Its pathophysiology, diagnosis and treatment are discussed.
Costa, Blanc, França	1995	19	Allergic bronchopulmonary aspergillosis (ABPA): comparative study of pulmonary radiographic changes	Case Series	Chest radiographs of 14 asthmatics are compared with those of 15 patients with ABPA.
Kalil	2006	20	Allergic bronchopulmonary aspergillosis presenting a glove-finger shadow in radiographic images	Case Report	A case of an asthmatic patient, who presented signs of opacity in "gloved finger" on the chest X-ray, suggestive of ABPA, is described.
Almeida, Bussamra, Rodrigues	2006	21	ABPA diagnosis in cystic fibrosis patients: the clinical utility of IgE specific to recombinant <i>Aspergillus fumigatus</i> allergens.	Prevalence Study	<i>Aspergillus fumigatus</i> sensitivity is investigated in 32 cystic fibrosis patients with suggestive ABPA characteristics using specific IgE against recombinant antigens.
Oliveira	2007	22	Allergic bronchopulmonary aspergillosis diagnosis remains a challenge	Prevalence study	There was investigated diagnosis of ABPA in 65 asthmatics with cutaneous sensitization to <i>Aspergillus</i> and it's compared with the specific serum IgE positivity, which is not very prevalent.
Carneiro	2008	23	Prevalence of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis in the state of Bahia, Brazil	Prevalence Study	ABPA prevalence is investigated among 74 patients with cystic fibrosis treated at a referral center.

Author	Year	Ref	Title	Type of study	Study Summary
Campos, Pereira	2008	24	Pulmonary eosinophilia	Literature Review	It discusses the differential diagnosis of pulmonary eosinophilia, including ABPA, Churg-Strauss syndrome, hypereosinophilic syndrome and eosinophilic pneumonia.
Armstead, Morris, Denning	2014	25	Multi-Country Estimate of Different Manifestations of Aspergillosis in Cystic Fibrosis	Literature review and prevalence study	There was estimated the number of patients with ABPA, <i>Aspergillus</i> sensitivity and <i>Aspergillus</i> bronchitis in several countries, including Brazil. The percentages of a British study[26] were compared to actual country notifications.
Aguiar, Damaceno, Fortec	2017	27	Tests to assess sensitization to <i>Aspergillus fumigatus</i> in cystic fibrosis	Prevalence Study	Examinations were carried out to assess sensitization to <i>A. fumigatus</i> in 86 patients with cystic fibrosis in a referral service.

Source: Research Protocol.

Discussion

The patient in the report fulfills the modified ISHAM working group criteria [12] and Greenberg's minimum criteria [13], exposed in the introduction. The therapeutic response to systemic corticosteroids and antifungals supports the diagnosis. The patient remains in follow-up, with the objective of minimizing the corticosteroids dose and fighting disease recurrences, preventing the bronchiectasis evolution.

A confusing factor in the patient's history is the antecedent of tuberculosis in 2017. An infectious sequel could explain bronchiectasis in the right upper lobe. However, in this case there was also bilateral perihilar bronchial thickening - this distribution is, therefore, more suggestive of early stage ABPA [20]. No research for serum IgG antibodies for *Aspergillus* was available in the city, which limited the etiological research to the prick-test and specific IgE.

The examination of the patient's specific IgE was negative; however, due to social conditions (performed privately) it was performed after more than 4 months of corticotherapy and already on antifungal therapy. Antibody fluctuation during treatment is well documented in the literature [22, 23]. There are prevalence studies in which no positivity for specific

serum preceptins was found, even in patients with full criteria to ABPA [23].

The patient has also other factors that can justify difficult-to-control asthma, such as the presence of gastroesophageal reflux disease (GERD) and hiatal hernia, environmental exposure, anxiety, rhinosinusitis and possibly infection of the airways [28]. Such factors alone, however, do not explain the extremely high eosinophilia and the other findings. **(Figure 4)**

During the research, a certain difficulty in the diagnosis of ABPA was noted, since even though the patient had been followed up in the pulmonology outpatient clinic for four years, there was a delay in the diagnostic suspicion, difficulty in carrying out tests by public health system and the need for a long time uncontrolled disease, even requiring mechanical ventilation.

The evidence that even after more than thirty years of diagnosis of the first case in Brazil, only 10 articles address its clinical-diagnostic process is evidence that the disease is underrated in the Brazilian scientific community. Of these articles, four address aspects of ABPA related to cystic fibrosis patients [21, 23, 25, 27]. One presents the disease within the multiple forms of *Aspergillus fumigatus*

Figure 4: Contributing factors with hard-to-control asthma.

presentation [18]; another discusses pathology in the differential diagnosis of pulmonary eosinophilia [24]. Only four articles discuss ABPA in asthmatics [17, 19, 20, 22].

Searching, only on PubMed, articles in English about ABPA in India in the last 10 years have already passed the mark of 100 published articles. Being one of the countries with the most scientific research on the subject, the occurrence of ABPA in patients from specialized clinics in India reaches 13%, high is the diagnostic suspicion [29, 30].

In world literature, the worldwide proportion of ABPA in asthmatics is around 1-3% [15] - the question is whether it is a reliable data or just an under diagnoses reflection in many countries. In the research, there was not possible to find an accurate prevalence of ABPA in Brazil. A multicenter study [25] analyzed ABPA in the context of cystic fibrosis patients. In Brazil, with a reported total of 1555 patients with cystic fibrosis, there was only a diagnosis of 15 cases of ABPA in 2010, right below the estimate of 65 patients estimated by the research methodology - comparative estimate with a large british cohort study [26].

Other brazilian studies of the review also point to the diagnostic difficulty of ABPA. There is mentioned that the criteria are nonspecific and very

difficult to be all present at the same time since during the natural evolution of the disease and the treatment; there are fluctuations in the levels of antibodies and in the presence of eosinophilia and pulmonary infiltrates. It is common to take years before the diagnosis is confirmed and at that time irreversible lung lesions appear [22].

Patients still without central bronchiectasis at diagnosis tend to maintain lung function despite occasional exacerbations. Early treatment with corticosteroids typically results in reduced secretion production and bronchospasm improvement, normalized specific antibodies levels, IgE reduction and radiological infiltrates resolution [5, 14].

Therefore, the objective of reporting a new brazilian case and reviewing the national literature is to value the ABPA suspicion in our country, in the context of the differential diagnosis of severe asthma in order to increase its clinical suspicion. It also intends, through the literature review, to promote greater knowledge about the disease, facilitating its early recognition and treatment. In this way, this study serves as a didactic and intellectual input for future research on this disease.

Conclusion

The case report reinforces the need for considering allergic bronchopulmonary aspergillosis as differential diagnosis in asthma patients, if they have eosinophilia or high IgE levels, since early diagnosis allows patient's life quality improvement after beginning the correct treatment. As few readings about the clinical and diagnostic features of ABPA were found in the last thirty years in Brazil, more scientific studies are needed to make this diagnosis stop being neglected.

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Contributions

Gabriel de Jesus da Fonseca Loureiro, Letícia Barbosa Barros: literature review, data interpretation, writing, translation and concept of the manuscript.

Roberta Santos Kahwage: concept and orientation regarding the manuscript, data acquisition and methodological review of the manuscript.

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Conflict of interest disclosures

The authors declare there are no conflicts of interest in this case report.

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