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.
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 drop-pable 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 despite 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 Rosemberg-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.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Condition/Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predisposing condition</td>
<td>Asthma or CF</td>
</tr>
<tr>
<td>Obligatory criteria</td>
<td>a</td>
</tr>
<tr>
<td></td>
<td>b</td>
</tr>
<tr>
<td>Supportive criteria (≥2)</td>
<td>a</td>
</tr>
<tr>
<td></td>
<td>b</td>
</tr>
<tr>
<td></td>
<td>c</td>
</tr>
</tbody>
</table>

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

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.

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

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

**Source:** Research data.
Figure 2: Flowchart – Literature Review.

- Search Strategies (N = 41)
  - PubMed: 16
  - BVS: 15
  - Scielo: 10
  - Others: 0

- Excluded Studies
  - Duplicates: 6
  - After Reading Abstract: 18

- Studies with potential for inclusion: 17
- Studies excluded because they fit the exclusion criteria: 7
- Studies included in the review: 10

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

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

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

The patient in the report fulfills the modified IS-HAM 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.

Source: adapted from Gina[28]; Campos, Pereira [24].

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

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References


